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Homeostasis, equilibrio y regulación en el marco de la Biología de Sistemas. Análisis histórico y conceptual desde una perspectiva filosófica

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Table of contents

RESUMEN

Resumen

Este proyecto de investigación consiste en una revisión conceptual de la noción de homeostasis y en una propuesta alternativa de su definición. Esta revisión será formulada desde un examen del papel de este concepto en filosofía de la biología, fisiología y medicina. El problema principal al respecto de este objetivo primario es la unificación de la idea original de homeostasis con los posteriores desarrollos del término.

Originalmente, la homeostasis tenía un claro papel de analizar a los seres vivos basándose en su organización típica. Este tipo de organización peculiar de los seres vivos da cuenta de sus especificaciones como organismos, como por ejemplo su unidad, así como su comportamiento general e individualidad. En cualquier caso, en posteriores desarrollos parte de su alcance epistemológico se perdió en favor de una explicación sobre los procesos constitutivos de auto-mantenimiento de los seres vivos, pero sin limitarse a esto. Este tipo de definición de homeostasis se queda corta cuando se aplica a fenómenos biológicos más complejos, como, por ejemplo, la regulación.

En este trabajo examinaré la literatura más relevante sobre la homeostasis, para así clarificar las diferentes definiciones de las que disponemos hoy día, analizarlas para determinar qué podría ser útil para la ciencia actual y la filosofía de la biología, y proponer de esta manera una definición que unifique los diferentes usos y definiciones del concepto. También se analizarán algunas de las posibles consecuencias que esta revisión de su definición podría tener para las diferentes áreas de conocimiento, como la filosofía de la medicina, el campo de la terapéutica o algunos debates abiertos en filosofía de la biología.

La investigación sobre la organización biológica como característica principal de los seres vivos comenzó con la observación de la estabilidad de los organismos. Los primeros registros sobre esta cuestión datan de la antigua Grecia, y la perspectiva sobre la misma no se vio modificada hasta que Claude Bernard presentó su propuesta. Para Bernard era muy importante estudiar los procesos orgánicos y los elementos de los

organismos cuando aún siguieran vivos, cambiando así los estudios fisiológicos a partir de entonces. El *milieu* interno definido por Bernard, que pertenece exclusivamente a los seres vivos, fue el paso previo en la aparición del concepto de homeostasis, creado por Walter Cannon.

Desde entonces, se ha dado una gran producción de investigaciones sobre la organización y la regulación en base a este concepto. Norbert Wiener incluso creó una disciplina inspirada, al menos en parte, en la noción de homeostasis, y varios investigadores le siguieron (Ashby 1952, 1956; Pask 1975, von Foerster 1960, 1979; Beer 1972, 1984; Bertalanffy 1950, 1968), buscando comprender los procesos biológicos de automantenimiento y regulación de los sistemas (vivos) desde una perspectiva mecanicista y a través de diferentes modelos. Dentro de la fisiología, los desarrollos sobre la homeostasis siguieron una línea diferente, centrándose en mejorar la teoría homeostática con contribuciones conceptuales para obtener así un conocimiento más profundo sobre el funcionamiento de los seres vivos (Selye 1973a, 1973b; Sterling and Eyer 1988, McEwen 1998, McEwen and Stellar 1993, Mrosovski 1990).

La homeostasis es definida, generalmente, como el mantenimiento de la estabilidad del cuerpo con la inversión mínima posible de energía. Cannon ligó la homeostasis con el *milieu* interno propuesto por Bernard, incluyendo así cada componente y proceso que mantiene la unidad del sistema biológico como un todo a la vez que se mantienen a sí mismos. Debido a que el *milieu* interior es exclusivo de los seres vivos, también puede entenderse como criterio de demarcación según su formulación original. Los desarrollos posteriores del concepto de homeostasis y el cierre que implica para el sistema, especialmente aquellos que enfatizaron la creación de modelos de la homeostasis, como la cibernética, sustrajeron las especificaciones biológicas de la homeostasis, perdiendo así su idoneidad para definir exclusivamente a los organismos, siendo utilizado para explicitar el funcionamiento de cualquier tipo de sistema automantenido.

Esto podría explicar por qué actualmente la homeostasis se entiende como un proceso mínimo de automantenimiento del cuerpo, incluso aunque su faceta más cualitativa, la de una metodología top-down, ya se conoce. Esto es tremendamente relevante para la posibilidad de una unificación entre las perspectivas dominantes en las ciencias biológicas de corte más reduccionista (metodología bottom-up), como la biología molecular, a través de una aproximación más amplia que permita conocer la unidad y la totalidad de la funcionalidad de un sistema biológico como un todo, que incluya cada componente, bien sea proceso o elemento, y que los integre en una explicación sobre el comportamiento del sistema.

Dicho de otra manera, la definición actual de homeostasis presenta un cierto cariz ambiguo debido a la tensión entre su definición primordial organicista y sus formulaciones más operacionalistas, que la convirtieron en un modelo de automantenimiento aplicable a cualquier sistema con tal característica. La definición operacionalista es sistemática y fiel a la especificidad de la ciencia, gracias a su carácter cuantitativo y reduccionista. En cualquier modo, la definición original de homeostasis, aun siendo de alcance holístico, estaba aún en su primera fase de definición, con lo cual su aplicación para la creación de modelos específicos en las ciencias biológicas, concretamente los organismos, podría haber sido prematura.

Esto se concibe así ya que Cannon, al formular el concepto de homeostasis, dejó en segundo plano el conjunto de interacciones del organismo con su medio ambiente, prestando atención casi exclusiva a las consecuencias de las influencias del ambiente externo en el interno (el *milieu* interior de Bernard). Este desequilibrio entre sus formulaciones cualitativas y las cuantitativas ha convertido a la noción de homeostasis en un concepto inestable e inadecuado para ser empleado en las investigaciones biológicas actuales.

Así que habría que ver, primero, si la noción de homeostasis podría ser adecuada para los proyectos organicistas, poniendo especial énfasis en el poder explicativo de su naturaleza holística, en caso de tenerlo. Si se revelara como adecuado, sería importante explorar qué clase de contribuciones podría hacer a las ciencias actuales, como la biología, la fisiología o la medicina, y cómo podría ser útil para construir un conocimiento más profundo sobre los fenómenos biológicos, en sus niveles macro, meso y micro. En relación a esto, sería importante ver si puede recuperar su papel original de criterio de demarcación entre lo vivo y lo inerte, con la idea de unificar su alcance explicativo original, incluyendo sus posteriores expansiones fisiológicas, con su derivación hacia desarrollos más operacionalistas.

Por ello, en este trabajo el principal objetivo es analizar la homeostasis para ver si es un término adecuado y útil para las ciencias modernas y, suponiendo que lo sea, analizar qué tipo de definición sería mejor y qué debería incluir. Asumiendo que, como principio unificador, debería incluir todos sus diferentes desarrollos, debe haber un modo de eliminar o debilitar las connotaciones negativas que se han ido asociando con el concepto de homeostasis, especialmente aquellos que lo enlazan con su vertiente más fuertemente matemática y de modelaje, y así incluir algunos de los componentes de la terminología fisiológica más avanzados, como la heterostasis o la alostasis.

Por todo ello, la principal hipótesis de este trabajo es que la homeostasis es un término adecuado para ser usado en las ciencias biológicas modernas si, y sólo si, puede superar siglos de desarrollos reduccionistas y recuperar su perspectiva más inclusiva y unificadora de su formulación original propuesta por Cannon y Bernard. Una vez conseguido esto, puede ofrecer una aproximación alternativa para las ciencias de la biología, así como contribuir a algunos de los debates abiertos en filosofía, como, por ejemplo, qué es un organismo, cómo definir la individuación de un sistema constantemente en cambio o cómo podemos caracterizar la salud y la enfermedad dentro de la filosofía de la medicina. Estos temas son mencionados en este trabajo, después del análisis del término de homeostasis.

.1.

Introduction

This research project consists in a conceptual revision of the notion of homeostasis and an alternative proposal of definition. This revision will be formulated from an examination of the role of this notion in philosophy of biology, physiology and medicine. The main issue regarding this primary goal is to unify the original notion of homeostasis with further developments of the term.

Originally, homeostasis had a clear role of analysing living beings based on their peculiar organization. This distinct organization accounted for their specificities as living systems, such as unity, as well as their general behaviour and individuality. However, in further developments some of this epistemological scope was lost to favour an explanation about the constituent processes of self-maintenance of living beings (but not only). This kind of definition of homeostasis falls short when applied to biological phenomena that are more complex, such as regulation.

In here, I will examine the relevant literature of homeostasis, in order to clarify the different definitions of it, analyse them to determine what can be useful for contemporary science and philosophy of biology, and propose a definition that unifies the different usages and definitions of the term. I will also explore some of the possible consequences that this revised definition could have for different fields such as philosophy of medicine, therapeutics, or some of the debates open in philosophy of biology.

1.1 Background and current state of the topic

As stated before, this project will examine the notion of homeostasis and its role in physiology, medicine or biology in relation with the study of living systems. Modern research has tried to include this notion in order to get an alternative perspective in the study of living beings. However, the outcomes were not as satisfactory as expected, since homeostasis is now an ambiguous term, in a similar form as organism or gene.

Homeostasis has deep roots in the history of the study of living beings and their stability. Starting in Ancient Greece when health was considered as a consequence of the internal balance of the body humours. These could be present in different amount, creating combinations that would explain someone's personality as well as their tendency towards some kind of diseases rather than others. Consequently, disease was perceived as an internal loss of harmony of humours.

This idea of equilibrium (pre-thermodynamics, hence still a synonym of stability as in its common usage) of the body, and concretely the internal state of the body, as equivalent to health, dominated the general scenario of medicine for centuries. Even nowadays the stereotypical perspective on health relates to a certain steadiness or reliability of the body and mind.

The notion of homeostasis appeared in a scientific context whose most relevant representative is Claude Bernard and, more specifically, in his studies on the particular nature of living beings, related to their unique organization (see Bernard 1865, 1878). Bernard's physiology enabled a new perspective in the study of living beings, as he postulated the existence of a *milieu intérieur* as the most salient peculiarity of the organization of living systems.

Briefly stated, the internal milieu differentiated organisms from the external environment and from any kind of non-living matter (*les corps bruts*). This difference is based in the characteristic organization of the internal milieu, aiming to maintain the processes of the body and its elements entangled in a way that supports their inner unity and inherent complexity, protecting the organism against the external milieu and enhancing its survival. In contrast, the external milieu is described as chaotic and as the main source of perturbations, which threat that balance of the living. Bernard conceived the internal milieu as an unbreakable unit, facing those perturbations as a whole.

Bernard's stance on the relevance of scientific analysis in physiology, that is the need to be clearly distinguished from any other approach, lead him to reformulate some cornerstone assumptions on physiology that would provoke a deep development of this discipline. That is one of the several reasons why mentioning Bernard is almost inevitable when talking about homeostasis. He changed the focus from the notion of vital force to a more feasible, scientifically manageable, element: the particular organisation of living beings and their self-maintenance. To this regard, he proposed both a methodology specific for physiology, and first foundations of the theoretical proposal that would inspire Walter Cannon's concept of homeostasis.

According to his perspective, science must advance through observation and experimentation. Anatomy shows itself to be insufficient to understand the mysteries of life, and that is why Bernard stressed with so much emphasis how experimentation, specially vivisection, complements biological studies. Observation was considered to be passive, and experimentation, active. Bernard examined the scientific method exhaustively and found that not every observation is passive, and not every experimentation can be considered active.

Besides the passive observation, Bernard exposed a kind of observation that is active, i.e. the one guided by a theoretical hypothesis to be tested (not as a stagnated preconception, but as a theoretical work framework). Similarly, Bernard divided experimentation into active and passive. This division, as Bernard notes, is just to be considered theoretical. But it serves to fulfil the exhaustiveness that he coveted for science, while avoiding dogmatism.

Together with his methodological proposals, Bernard ensured the theoretical distinction of physiology by defining organisms as entities with an organisation particular to them exclusively. Living beings exhibit certain immunity to the chaotic influences from their environments, and this peculiar characteristic allows them to keep living. This feature can be explained by analysing the organisation of living beings and including an enclosure within them to keep their vital processes protected.

This enclosure was named by Bernard as *milieu interieur*. The internal milieu can account for the difficulty to study internal living processes of organisms. It maintains a delicate stability amidst organs, fluids, and livings mechanisms at work. If the enclosure of the internal milieu is tampered, and we try to intrude their internal organisation, that delicate balance is most likely to be interrupted, stopping active living processes and causing the living entity to collapse and, ultimately, provoking its death.

Even considering this apparent fragility, the internal milieu has a wide capacity of resistance. The external milieu, unstable and chaotic as defined as opposed to the internal milieu and its harmony, it’s the main source of perturbations that can alter the organism’s health and living condition. The internal milieu, in this regard, is constantly operating so to resist the external milieu’s embrace.

This internal milieu also accounts for the different levels of complexity of organisms. Depending on how skilfully the internal milieu manages to withstand perturbations, the life of an entity exhibits different levels of independency, and an organism is placed lower or higher in the complexity hierarchy of living beings. Independence is to be understood as the ability of a living being to avoid being influenced by the external milieu. For instance, plants can be considered to be the lowest because they’re alive, but unable to escape adverse conditions and, always following the words of Bernard, humans are to be regarded as the most complex living entity, since humans have a greater competence eluding adverse conditions.

Walter Cannon (1932) followed Bernard's path and devised the notion of homeostasis. It is still within a context of inquiry whose main purpose is to find an explanation on the characteristic behaviour (as expression of organization) of the constituent processes and elements of living beings. However, his perspective already narrowed down the previous approach of Claude Bernard. The latter focused in organisms as unities, searching for an explanation of their maintenance and behaviour, distinct from that of the non-living, whilst Cannon focused specifically in the inner organization of organisms, putting aside their relationship with the external environment and describing the mechanisms able to account for that maintenance.

Those mechanisms are named *agencies* in *The Wisdom of the Body*, and they are activated just in emergency cases, since they take a great investment of resources and energy. Before they are called into action, an organism uses nutrients already present within its body, such as glucose or fat, to embrace the adverse influences from the external milieu. This response mechanism is constantly at work and stabilises minor deviations from the ideal medium point of the permitted oscillation. When resources within the body turn scarce, i.e., minimums necessary for the correct functioning of the body are threaten, agencies activate and balance the body back to a stable state.

Homeostasis is, as Cannon explains, an arrangement of economy of the body, and in charge of maintaining its stability. The degree of effectiveness of these mechanisms depends mostly on the evolutionary stage of the organism, implying that the complexity of an organism arises mainly from evolution, and that effectiveness is bounded to complexity. The more effective an organism, the less resources and mechanisms it needs to maintain itself within an acceptable range of oscillation.

These resources are also organised within the body and controlled by homeostasis. Depending on what element we focus when observing internal control of supplies, we can find different kinds of homeostasis. When homeostasis acts on materials, such as sugar, fat, and such, the body usually controls their concentration by inundation.

There is a threshold for materials, and when the requirements have been reached, the body gets rid of the excess. Materials can also be stored, to save an extra of available energy when agencies must act, or even if the oscillation does not activate them, but reaches a dangerous extreme. This storage must concentrate in some areas of the body and then be distributed when necessary, of can be present in the bloodstream and distributed but unused until needed.

While Bernard connected a higher evolutionary stage with a better sealed internal milieu, Cannon links it with a better management of the perturbations, that is, with a perfected organisation and performance from the control mechanisms or agencies. Another difference related to this is that Bernard does not explicit that his description of the internal milieu is a hermetically closed environment, but it is understood as more sealed than the conception of Cannon who clearly states that organisms are open systems.

Homeostasis must exhibit some characteristics to be considered as such. Change must be minimised by increasing the effectiveness of targeted mechanisms of the internal milieu. Constancy of the internal milieu is assured by the presence and action of agencies, and the maintenance of that stability is enough proof that those agencies exist.

Also, a homeostatic stable state is complex, so it is necessary for several factors to be active at the same time or consecutively in order to maintain it, cooperating to achieve the same goal. And lastly, homeostasis is so flexible because if there is a factor that can alter a homeostatic stable state, the body will automatise a mechanism of resistance, a control, that will allow to protect the organism spending less resources next time.

The idea of the necessary existence of some control mechanisms that could account for the organism's organization and regulation, inspired further developments of the idea, such as those from Cybernetics, in the hands of Norbert Wiener (1948), or William R. Ashby (1952, 1956). In their account, as well as in the one from Ludwig von Bertalanffy (1950, 1976) and his General Systems Theory, homeostasis is bounded to the notion of feedback loop.

Cybernetics is defined as the study of control mechanisms and communication on animals and machines. Wiener focused his interest on the agencies Cannon outlined. Formed strongly on mathematics, the aim for Wiener was to analyse living beings in order to procure a model that synthesised their main characteristics and use that model to build machines that could maintain themselves. To put it in another words, Wiener offered a model to explain the cycles present in nature.

He observed that both organisms and self-maintained machines sustain themselves on feedback loops. Feedback loop is a term coined by Wiener, circa 1950. He used it to define a mechanism responsible for the rectification of a trajectory deviated from the ideal pattern. It allows us to make predictions by quantifying the complexity of complex systems and controlling their behaviour, even correcting it if needed. They also account for the materialisation of boundaries. Feedback loops are a model of a self-maintained process whose paradigmatic case would be metabolism. They describe an automatized process that usually responds to a threshold "switch" (which activates and deactivates it).

The problem is that it would describe a minimum model of self-maintenance, but it no longer accounts for the unity and organization as a whole of organisms, since it is now diminished to be just a constituent part of that peculiar organization. Within this approach, homeostasis lost its status as demarcation criterion, and no longer defined biological organization, nor the relevant interactions of living systems.

Cybernetics exposed the complexity of self-maintained systems, being organisms the paradigmatic example of those. However, around the same time cybernetics appeared, Bertalanffy offered an alternative proposal on the study of the organisation of the living beings. Instead of focusing on understanding the functioning of the components of the system, Bertalanffy maintained a perspective that put special emphasis on the system as a whole instead.

For Bertalanffy the only way to significantly analyse organisation is through systems. In General Systems Theory (GST), a system is defined as a set of interacting parts. This organisation is specific of living beings, and it is generated from and for the system. Following this definition, structure would be defined as the special order of elements inside a system, and function is to be understood as the order of processes.

Interaction is the main condition for systems to be considered organised and is defined as a particular kind of relationship between the elements of a system that alters or modifies the behaviour of the elements inside the system. Bertalanffy considered systems to be dynamically open, in constant exchange with the external environment. This kind of system is self-maintained and self-regulated. Interactions between the elements of the system ground this regulation.

Bertalanffy’s proposal is based on the idea that the study of living beings has to maintain a systemic perspective, that is, a viewpoint from the system. From this standpoint, other analysis of life emerged. There was an attempt to model the minimum characteristics of a living system, based on Bertalanffy’s theory and cybernetics proposal, as well as the background of homeostasis and the internal milieu.

Bertalanffy’s studies on the living as open dynamic systems inspired the perspective of a relatively new approach to the subject. Systems Biology (Newman 2003, Kitano 2002, 2010; O'Malley and Dupré 2005) is a discipline that aims to collect theoretical and pragmatical resources from several specialties in order to overcome the slow advances on biological studies on the systemic perspective. It arose right after the great success of the Human Genome Project (HGP), and due to the limitations of its results.

The HGP brought a deep and exhaustive knowledge on the human genome since the complete sequence was decoded. Nonetheless, this immense amount of information of the human genome brought no further insights on preventing diseases, it did not broaden significatively the information available on the functioning of living beings, and we did not unveil the relationship between genotype and phenotype, just to name some of the unfulfilled outcomes expected from the results of the investigation of the HGP.

That is why, after the HGP ended, the next step in the scientific field was to look into the relations between the components of the living system disclosed on previous research. Those were known as Omic Sciences, that is, genomics, transcriptomics, proteomics, and metabolomics. These could be regarded as one of the most important starting points of Systems Biology, since they upgraded the genomic data and provided some insight on how the internal dynamics of living systems may work, at least at a molecular level.

The conceptual framework of Systems Biology is one of the best contexts to perform a revision of homeostasis. It enables homeostasis to merge its operationalist, reductionist developments and its most holistic, physiological ones. This is possible thanks to the different and integrative methodologies that Systems Biology cultivates (O'Malley and Dupré 2005). In addition, Systems Biology can take advantage of having a revised notion of homeostasis, since its final goal is to deepen the total understanding of biological systems, both in their micro and macro levels, and homeostasis can fully embrace both streams when the apparent opposition between holistic and reductionist is overcome.

To put it in other words, this biological framework seems to be a more fitting terrain to look into the stability and organisation of living beings, searching for understanding what makes them autonomous and independent, meaning a differentiated unit from its environment. It also was conceived to search for explanations on the behaviour of the processes and constitutive elements of a living system along many levels, specifying their interactions.

In addition, Systems Biology aims to include the analysis of the external environment they are embedded in, concretely a study of the perturbations, but on other possible influences from the external milieu that might affect the organism. This is a reasonably new contribution, since external influences on the living may not just be negative, but neutral, or even positive.

Anyhow, Systems Biology seems to lack a notion that includes the interactions inside and outside the system, as well as a concept that accounts for the interactions and behaviour of the system as a whole. The original formulation of homeostasis seemed to aim for that goal, to describe how biological systems differentiate from their environment and to describe their general behaviour, as this work tries to defend.

However, that original formulation, as seen earlier, was sometimes misinterpreted, sometimes modified, diffusing its meaning, and making it sensible to be confused with similar, but not equal, ideas. Self-maintenance and self-regulation are to be mentioned to this respect. This lax description may find its base on the indistinctly usage of some of the notions describing them, such as equilibrium, stability, or constancy.

1.2 General hypothesis

The main hypothesis of this work is that it is possible to use homeostasis to obtain an alternative approach in the study of living beings, which seems to have reached a breaking point. In order to achieve this goal, it is necessary to carry a revision of the notion, with the aim to integrate its physiological origins and its original epistemological scope with its more operationalist developments.

A secondary hypothesis is that this integration could be done more easily by using Systems Biology methodology, since it integrates the most relevant in the study of living beings, top-down and bottom- up. A bottom-up approach uses the concrete analysis of the low-level components of a system in order to induce from that data the general organization and behaviour of the system as a whole.

A top-down approach is the kind to start analysing the behaviour and organization of the system as a whole in order to find an explanation of the behaviour and organization of the constituent parts. Additionally, Systems Biology counts with another methodology, the middle-out, which complements the aforementioned traditional methodologies with its transversal approach in the analysis of living beings.

It is devised to permit the study of the different interactions and processes of a determined biological phenomenon across levels in any direction, and it can be understood as a bridge between top-down and bottom-up. The use of these methodologies would improve the chances to find an integrative definition for homeostasis, which constitutes the main goal.

A secondary goal of this thesis is to provide a theoretical framework to develop the full explanatory potential of the notion of homeostasis, by examining some of the most relevant scientific moments in its evolution, including its origins in the researches from Claude Bernard and its very first formulation by the hand of Walter Cannon.

This analysis will provide the grounds to revise critically further developments, concretely those that account for the current state of the notion of homeostasis. One important question is then why it is not yet as explanatory as needed, even if some original explanatory potential is to be developed yet.

With this purpose, the analysis from Cybernetics, particularized in the work of Norbert Wiener, William Ross Ashby, Stafford Beer or even Gordon-Pask, are as well present in this examination of the homeostatic tradition, trying to stress out which consequences those investigations had in the way we understand homeostasis today. In a similar line of research, but from physics field, the work of Ludwig von Bertalanffy, concretely his General Systems Theory, will be explored, in order to illustrate his contribution, if any, to the notion of homeostasis.

This study is based fundamentally in the works by Claude Bernard, Walter Cannon, Norbert Wiener, William Ross Ashby, Stafford Beer, Ludwig von Bertallanffy, John Dupré and Maureen O'Malley. This will grant that this project explores the different fields homeostasis has been used and transformed, like physiology, cybernetics, physics or biology.

1.3 Objectives

It is important to consider systems theory in relation to systems biology, and understand the theoretical approach that Systems Biology endorses about systems. In addition, as final step on the construction of this structure, which should allow for an alternative understanding of homeostasis, an examination of Systems Biology and the main features of its program are necessary to depict what kind of procedure could be more suitable for a reformulation of the concept of homeostasis.

Hence, this work will provide a critique of the current definition and usage of the notion of homeostasis, based on a meticulous analysis of its origins and evolution, to finally propose an alternative definition that integrates both its conceptual past and present. This definition will be tested in further applications of modern science, such as philosophy of biology or medicine. Therefore, this work should fulfil three main goals.

G1: First, to trace back the origins and evolution of the notion of homeostasis, in order to build the conceptual scheme and structure of its first formulation, the main source of it, and the changes it has undergone when applied to different fields of knowledge. Homeostasis arose within the field of physiology, and it is crucial to display the context that enabled its appearance. This is important since the scientific concerns that shaped the framework of homeostasis are still pertinent, especially in the fields of physiology, medicine, biology, and philosophy of biology.

By understanding its context and evolution, we are going to be able to discriminate amidst its definition gist and its different developments, making possible to approach the apparent paradox of being a holistic notion with a reductionist formulation, or a vitalist idea applied to non-vitalist descriptions. One of the arguments here is that this conceptual tension within the notion might be one of the main reasons why contemporary attempts to bring back the idea of homeostasis and use it to describe organism’s behaviour at every level cannot possibly be satisfactory enough.

G2: Second, carry a comparative analysis of the definitions and changes from the first point in order to build an explanation that articulates why the current conception of homeostasis is not fully satisfactory. la parallel to the study of the origins and changes of homeostasis, I will perform a comparative analysis of the consequences of the different changes in its formulation. I will display an explanation about the initial properties of the notion that got lost with that concrete re-definition.

In addition, I also will highlight some of the advantages that a concrete change brought to the term. Moreover, this comparative analysis will include as well how the different variations in the definition of homeostasis altered its relationship with its original field and those related. One of the early hypotheses at work would be that the notion needed further elaboration when applied to a field not related to biological systems strictly, and its affinities with the research program of mathematics, physics, and above all cybernetics, dragged homeostasis into quantifiable, operationalist formulations before it was time. It diminished from a notion whose goal was to explain the peculiarities of living beings to a notion that describes a model for the minimum self-maintenance (characteristic not limited to living beings).

G3: Third, and last, to propose an alternative approach for the description of homeostasis. Combine it and harmonize it with the previous work in its definition, within the framework of Systems Biology. The main proposal sustains that this revision of the notion has to bring together its operationalist developments while taking into account the final goal conceived for it, namely, to describe the distinctive characteristics of living beings according to their organization, and how does that explain their general behaviour. This implies a deeper examination of its holistic and organizational approach to the study of living beings for it to gain back its original epistemological scope, that is, make it able to use it as a demarcation criterion for living beings.

1.4 Methodology

The main methodology would be synthetic-deductive, since the idea is to ensemble the different notions of homeostasis, critically, and explore some consequences of the resulting definition. The concrete methodology regarded in this thesis corresponds to the methodologies endorsed by the philosophy of Systems Biology mentioned earlier, which are incorporated in the work of John Dupré and Maureen O'Malley (005).

First, there will be an examination of the conceptual changes in its definition and the nature of the experiments carried around the homeostatic conception, and to what extent they influence and shape the contemporary (un)definition and usage of the idea of homeostasis. Afterwards, the goal is to assemble the several and different characterizations of homeostasis, from its original physiological formulation to the last operational application in the shaping of mechanistic models. I will do so while using the mentioned methodology from SB, using the original holistic definition and the data from the bottom levels to build a definition that integrates both.

The contemporary state of the term has separated the two major constituent perspectives of the study of living beings:

> •A *physiological* one that shows a tendency towards an organicist, vitalist, and holistic approach to the study of living beings. This aims to build an explanation of the phenomena related to living beings as unified entities. In this work, this perspective is to be enriched with the analysis of the behaviour of their constituent processes and elements. This nature of the homeostatic explanation was neglected in further developments of both its theoretical and experimental approaches, at least partly.
>
> •An *operationalist*, reductionist approach, linking homeostasis to physics, mathematics, and engineering hence reducing the term to a theoretical representation of the models of feedback- based processes of the body. I will argue that the notion of homeostasis is underdeveloped, if considered not only its first physiological scope, but also its explanatory possibilities in current biological, medical, physiological and philosophical researches. For instance, the need for a holistic notion to strengthen their top-down approach, the conception of health and disease both in theoretical and practical medicine, the relevance of physiological studies, or even contribute to the debate about organism (some of these issues would be addressed in this work).

To that end, this methodology will be applied in relation to the previously stated goals:

M1: Firstly, a critical examination and analysis of the physiological, biological, and philosophical literature related to the origins and evolution of the notion of homeostasis, from its physiological origins to its current epistemological locus. To begin, I will examine the relevant literature from physiology from a philosophical perspective, starting from the seminal works that enabled the fabrication of the notion of homeostasis.

I will analyse the physiological background of the notion to extract the main goals of its original proposal. The same analysis and criticism will be applied to its further developments (cybernetics, physics). This part of the methodology is related to the first goal (**G1**), and it consists mainly in gathering the relevant data and analyse it in order to differentiate the original physiological context of homeostasis, its original definition and its further developments.

M2: Secondly, it will be carried a comparative analysis of the data collected and conceptual criticism of the advantages and disadvantages of the different (re)definitions of homeostasis. Study of the explanatory power of the current term and argue in favour of its epistemological potential. This comprehends a comparative analysis of the data gathered. It will include a philosophical evaluation of the different implications of the changes in the definition of homeostasis.

On these foundations, I will build an argument about the inadequacy of the term in its contemporary definition by highlighting the different epistemic and explanatory turns it has undergone. It will also constitute the grounds to argue about its original explanatory potential, comparing it to the current definition. For every change in the terms, an analysis in the alterations of its explanatory power will be displayed (see **G2**).

M3: Thirdly, a normative approach for a definition of homeostasis to use in contemporary Systems Biology, including physiological studies on the behaviour of living beings, with the aim of not neglecting previous developments of the term. References to previous attempts to display a definition that maintains its original physiological scope.

A last analysis will be done, this time about some of the developments of the term of homeostasis within physiology. This will allow me to build a definition of homeostasis, along with the previous work, while following the guidelines of Systems Biology methodology mentioned earlier (bottom-up, top-down). Finally, I will examine the resulting term in different scientific contexts that might be currently useful, such as philosophy of biology and medicine (see **G3**).

To sum it up, homeostasis was born as a hypothesis to find an explanation about what makes living beings alive. It is a specific way to look at organisms and study them. Concretely, homeostasis focuses on how living beings are organised. That is what Bernard first pointed out and what Cannon developed later.

Due to the complex nature of this kind of organisation, further developments of the same studies, such as cybernetics and the research for a minimum biological model, positioned homeostasis in a rather ambiguous level, rising debates whether it should refer exclusively to the most basic, metabolic processes of the body, or if it can be used to refer to the complete behaviour of the body as well as to regulatory processes maintaining it.

This work aims to demonstrate that applying homeostasis just to metabolic processes is a waste of potential, just as further physiological developments show, meaning mainly heterostasis, allostasis, and allostatic load. We may also try to clear the ambiguity ascribed to it, by clearing up the evolution of the term, and differentiating the uses made from the theoretical proposal that it offers.

This is relevant since this revision of the notion of homeostasis might make some contributions to some of the current biological researches like EVO-DEVO and, since it is a physiological term, may also open an alternative way to the medical practice, such as therapeutics or the relationship between doctors and their patients. Homeostasis has been not only used, but also criticized in the last years; still no known publication has proposed an alternative definition of homeostasis. In this work, I will venture a distinct, clearer definition by examining some steps to develop it conceptually starting from its seminal formulations.

1.5 Scope and sections

As stated earlier, the inquiry on biological organization as the main distinctive characteristic of living beings started with the observation of organisms' stability. First records are from Ancient Greece, and the approach did not change until Claude Bernard's proposal. He urged upon analysing living processes and elements while still alive, changing physiology and its methodologies forever. Bernard's internal milieu, which belongs exclusively to organisms, was the previous step in the creation of the notion of *homeostasis*, coined by Walter Cannon.

Since then, there has been an enormous production of research on organization and regulation based on the term. Norbert Wiener (1948) even created a discipline inspired, at least partly, on the concept of homeostasis, and several researchers followed in similar terms (Ashby 1952, 1956; Pask 1975, von Foerster 1960, 1979; Beer 1972, 1984; Bertalanffy 1950, 1968), aiming to understand biological processes of self-maintenance and regulation of (living) systems mechanically and through models. Within physiology, developments on homeostasis followed a different trend, focusing on enhancing homeostatic theory with conceptual contributions for a deeper understanding of how living systems function (Selye 1973a, 1973b; Sterling and Eyer 1988, McEwen 1998, McEwen and Stellar 1993, Mrosovski 1990).

Homeostasis is generally defined as the maintenance of the stability of the body with the minimum investment of energy possible. Lemoine and Pradeu (2018) refer to it just as a “dynamic equilibrium between essential parameters” (Lemoine and Pradeu, 2018: 237), distinguishing the term from what they refer to as different physiological phenomena with central explanatory power. This distinction they bestow follows an ongoing debate on the history of regulation (see Arminjon 2016), but in this work these “phenomena” (animal economy, autonomy from the external environment, and homeostasis) are not understood as separated objects of study, but as a continuum, ultimately assimilated under “homeostasis”.

Cannon linked homeostasis with the internal milieu of Bernard, and it includes every component and process maintaining itself as well as the defining unity of the system as a whole. Since the internal milieu is exclusive of living beings, homeostasis can be understood as a demarcation criterion in its original formulation. Further developments, especially those that emphasized on modelling homeostasis such as cybernetics of systems theory, subtracted biological specificities from homeostasis and it lost its suitability to define exclusively organisms to be used on every system that was self-maintained.

That might be an explanation on why nowadays homeostasis is understood as a minimum self-maintenance process within the body, even if its specific qualitative, top-down approach is still somehow recognised. This is extremely relevant since the search for a unification of the mostly dominant bottom-up approaches in biological sciences, such as molecular biology, with a wider perspective able to grasp the unity and wholeness of the functioning of the system as whole, that includes every component, either process or element, and integrates them in an explanation about the systems behaviour, in addition to explore the possibilities of downward causation (as defined by Sara Green, 2017).

To put it in another words, contemporary definition of homeostasis presents certain degree of ambiguity due to its original organicist formulation and its operationalist formulations that turned it into a model of self-maintenance applicable to any system with that concrete feature. The operationalist definition is systematic and akin with the specificity of science, due to its quantitative, reductionist character. However, the original formulation of the notion of homeostasis, even if holistic in scope, was conceptually unfinished or, at least, not ready yet for a modelling specific enough for biological sciences and, concretely, organisms. This is because Cannon, when formulating homeostasis, left aside the interactions between the organism and its environment, paying attention exclusively to the consequences of the influences of the external environment into the internal. This imbalance between its quantitative formulations and its qualitative definition makes the notion of homeostasis unstable and unsuitable to be used in modern biological research.

That is why it is argued that there is a certain ambiguity in the term homeostasis to be addressed before being appropriate for organicism recent approaches. This ambiguity is different from other scientific terms in the sense that it is not caused by a tension between an informal definition and a technical one, not even between different technical denotations of the same word, but between two different conceptual streams that defined homeostasis in diverse ways. Also, and instead of working on the concept of homeostasis, physiology, the field where the notion was born, built a conceptual network related to homeostasis, using the term as the base of a theoretical framework.

This theoretical framework encloses physiological studies related to the capacities of the body to maintain itself and their limitations, but it partly does so from a highly centralized functionality in the brain. Nevertheless, these latter physiological notions such as heterostasis, allostasis or rheostasis, could constitute the guidelines to widen homeostasis enough to include interactions with the external environment and, if analysed properly, do so in a way that includes as well the operationalist models of biological stability.

Given this, it would be necessary to establish whether if the notion of homeostasis is suitable for the organicist agenda, with special emphasis on exposing its holistic explanatory power, if any. If it is suitable, it would be important to explore what kind of contributions it could make for modern sciences such as biology, physiology, or medicine, and how can it help to build a better understanding of life phenomena. Related with that respect, a question to solve might be whether the term can gain back its original status of demarcation criterion between the living and the inert, or if it would be more useful to widen its applications to systems with similar characteristics. However, the most relevant question to address is whether if homeostasis can be the term to embed explanations on the behaviour of living beings in macro, micro, and meso levels, unifying the explanation scope of its origins and further physiological expansions with its more operationalist developmental stream.

That is why in this work the main aim is to test homeostasis, to examine if it is suitable for modern science and, supposing that it is, as it seems to be, to analyse what kind of definition would be better and what it should include. On the assumption that, as a unifying principle, it should unify its several developmental streams as well, there might be a way to eliminate or weaken negative meanings associated with the term of homeostasis, those that link it with its stronger mathematical, modelling side, and to include some of the components of advanced physiological terms such as heterostasis or allostasis.

The main hypothesis of this work is that homeostasis is a suitable term for modern sciences research on biological phenomena if, and only if, it can overcome centuries of reductionism and gain back its inclusive, unifying scope of its original formulation made by Bernard and Cannon. In doing so, it could provide an alternative approach not only for biological sciences, but also to some philosophical issues that are still in debate, such as what an organism is, how to define individuation of a constantly changing system, or how can we define health and disease within philosophy of medicine, for example. Some of those mentioned here will be addressed further in this work.

For the sake of clarity of exposure, there will be three main sections: one for analysing the origins of homeostasis, in chapters 2 and 3; another displaying a critical examination of the operationalists developments of the idea of homeostasis, composed of chapters 4 and 5; and another one that examines the organicist evolution of the study of living beings and homeostasis concretely, in chapters 6 and 7. Chapter 2 would be dedicated to the proposals of Claude Bernard, as well as his own conceptual scene, paying special attention to his idea of internal milieu and the relevance of the context. Chapter 3 belongs to Walter Cannon and the original proposal in homeostasis. In this chapter, there is a critical analysis on his proposal, highlighting what ambitions of the physiological program were intentionally abandoned or neglected in favour of a more exhaustive analysis on the internal milieu.

Chapters 4 and 5 belong to the operationalist drift of the notion of homeostasis, that is why chapter 4 will focus on Cybernetics, the engineering field that mixed homeostasis, control theory and information as its foundations, and it will be argued why it is considered in this work that homeostasis gets its well-known definition from cybernetics proposals. Chapter 5 analyses another modelling, the one by Ludwig von Bertalanffy. It will be argued that, even if closer to what kind of system an organism is, it is still to be considered an approach that might have influenced the turn of homeostasis into a physico-mathematical notion. Nevertheless, the description of a system will be considered, and it will be compared, along with some of the most relevant models of minimum life systems, with what it is considered here as the original idea of homeostasis.

Chapter 6 is dedicated to Systems Biology, as the most salient example of the organicist approach in modern science. Along with an analysis on its strengths and weaknesses, there will be a scrutiny on how the collaboration between Systems Biology and homeostasis could benefit both. Chapter 7 is exclusively consecrated to the analysis of physiological further proposals for homeostasis and how these developments are different from those transformations brought by more mechanist, operationalist approaches. Most of those contributions from physiology will be examined, to finally describe on the conclusions chapter what the proposal of revising is, and how a modern and revised notion of homeostasis can contribute to current biological studies. This critical examination will provide the foundations of the idea, procuring the necessary tools to settle the different steps in the evolution of homeostasis taken and how do they distinguish from each other. This will establish the bases not only for a necessary critical analysis, but as well as for a primer, or at least tentative, definition proposal of homeostasis able to fulfil an explanatory role on organisms' behaviour as individuated unities in present research on living phenomena.

.2.

The roots of homeostasis: *milieu intérieur*

Table of contents

When tracing back the origins of homeostasis it is almost impossible not to find the print of Claude Bernard (1813 – 1878) at some point. This French physiologist dedicated a good part of his life to study living beings, and in doing so, he also reviewed unverified notions and concepts earlier in medical studies and practices, by analysing their limitations and exploring alternative feasible approaches to biological investigation. It is important to underline that when Bernard made his proposals, the general medical scenario fluctuated between vitalist and mechanist approaches to the study of living beings.

Furthermore, there is a debate around the figure of Bernard on whether he was a vitalist or a mechanist. Vitalism, narrowed down to its basics, defends that there is a qualitative difference between living beings and inorganic bodies, including those made by human means. Mechanism relies for its explanations on the idea of living beings as complicated and complex wholes constituted by interacting parts, like human-built machines. Thus, there was this whole stream of thought, in Bernard times, which sustained that what makes living beings different is some sort of *élan vital*, a vital force that animates biological systems and plays the role of a demarcation criterion between the living and the inorganic bodies, in addition to be the foundations of the difference between vitalism and mechanism.

In this regard, Bernard can be found in between, since he did not think that any of them isolated were enough to account for living phenomena. On the one hand, he considered living beings and inorganic bodies to be qualitatively distinct, but in the other hand, he was looking for a demarcation criterion that could be expressed eventually in quantifiable terms, like physics and chemistry laws. He might be regarded as one of the firsts to look up for a mechanist explanation of living phenomena by focusing in the distinct kind of organization organisms have.

In his *Introduction to the Study of Experimental Medicine*, Bernard makes a strong statement against this vital force notion in several occasions. Even if his words are harsh when referring to vitalism, what bothers him the most is not the idea of a vital force telling apart living and not-living systems, but this idea of it being some untouchable dogma, or at least some notion not scientifically explored enough. Understood as a black box of sorts, the élan vital cannot be a scientific notion, for it is indeterminate and indeterminable, and that might be one of the main reasons Bernard devoted his life to the study of living beings and their differences from other kind of existence.

Bernard created an explanation for the prevailing idea of the body to have the ability to cure itself, derived from that of vital force, and this is the main reason why he denounced what he refers to as the dogma of vitalism. According to this, the role of the therapist consisted exclusively in helping the body to heal itself, enhancing its performance by means of changes in the diet or with the intake of herbal remedies, mostly. This perspective was on the table from Ancient Greece times, with some slight modifications when 18th Century was on its way to its end ad 19th was just starting.

In the 1976 Spanish version of the *Introduction*, Pi-Sunyer asserts that the issues Bernard addressed were the maintenance of health and the healing of the body. There are three main disciplines focused on the study of health preservation of biological bodies, the first one is physiology, understood as “el conocimiento de las causas de los fenómenos de la vida en el estado normal” (Pi-Sunyer, in Bernard, 1865/1976: 19 – 20). Physiology allows us to deepen our knowledge on mechanisms regulating phenomena related to health maintenance. It is the discipline that examines health maintenance and our knowledge about it, through the study of those internal mechanisms and/or phenomena in living bodies responsible of regulating body's stability. The second one is pathology, as the field of inquiry about diseases and their causes, primarily understood as some sort of disequilibrium on the body. This perspective is based on the notion that there is some internal stability and, when disturbed, it must be corrected since a loss in stability is perceived as problematic. Finally, the third one, derived from this last one, is therapeutics, the science devoted to medical practice and its main goal being healing living beings. It is the intervention on the body based on the assessment from pathology.

In this chapter, there is an analysis of some of Bernard's proposals that are seminal to Cannon's definition of homeostasis, with a specific stress on the internal milieu, which accounts for biological organization. There will be as well a critical review of his intellectual context to understand the roots of Bernard's proposal and his own perspective, which allowed him to create an alternative approach to the study of living beings. A special focus will be placed on Bernard's methodology, since it is crucial to comprehend his notion of biological organization. This might also give at subtle hint on why Bernard is considered "the father of physiology".

2.1. Introduction

It is widely understood that one of the very first observations about Nature made by humans was related to its stability in order to profit from its (cyclic) changes. This biological observation on the organization of nature applied to medical phenomena suggested a definition of health as a tendency towards an ideal point of equilibrium[1], that is some sort of stability or constancy. Some studies developed on stability are complemented with research on disease. Even in Ancient Greece, disease was already conceived as a type of internal instability of the organism's body, explaining it by means

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[1] It is important to keep in mind that equilibrium, in this context, is previous to thermodynamics definitions of equilibrium, stability, and related notions. That is why here equilibrium must not be understood as a stationary state, but as a notion associated to organisms' stability. Nevertheless, equilibrium loosely understood is used even after the distinction made by thermodynamics, which is not the same as basing a criticism on a wrongly assumed strict definition of the term (see also first note of last chapter).

of their humours' balance (referring to the four main fluids within the body which accounted for different body configurations and their health state).

Claude Bernard's formation, on the 19th century, still relayed on this perspective[2]. Though he can be considered as one of the very first physiologists to focus his research on finding an explanation about biological systems' maintenance within a state accepted as healthy. Emphasizing on unveiling those mechanisms involved on controlling the body's stability, he made a special effort in understanding the organization of organisms. This organization was conceived for Bernard as a *fixité*, a constancy, located in a fundamental part of organisms named *milieu intérieur*, or internal milieu, which encloses those vital processes and isolates them from the instability from outside, differentiating the organisms from their environment.

The relevance of that internal environment, as explained by Bernard, consists in using this concept as means of explanation of phenomena bounded exclusively to living beings, differentiating them from non-living beings. It also helps explaining their resistance to external environmental influences, or *general cosmic influence* (Bernard, 1865/1976: 59), source of disturbances responsible for alterations of the internal milieu of any organism. To wit, the external milieu is chaotic and random; the internal milieu is organized and necessarily stable.

He defended a distinction between biological and inorganic phenomena, but drastically rejecting any dogma related to it. He stressed out the terrible consequences these preconceptions have for investigation, such as the idea of an external vital force, which has no possible scientific analysis. Instead, he offered an alternative account for that distinction that does not rely on a barely analysable notion of vital force, understood as a metaphysical entity embedded from outside that infuses life into bodies. As he argues, if vital phenomena cannot be experimented on, "we should either have to recognize that

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[2] Sieck (2017) seems to be convinced about the thermodynamical background (concretely from Sadi Carnot) of Bernard's ideas. As he describes it, "Bernard applied equilibrium thermodynamics to medicine and physiology with his concept of feedback regulation of the internal milieu" (2018: 98). With no further elaboration of this argument, it is difficult to justify Bernard's proposal is *rooted* in thermodynamics. Nevertheless, Bernard did know about thermodynamics, and he used that knowledge in his experiments on the internal milieu (see, for instance, Bernard, 1876).

determinism is impossible in the phenomena of life, and this would be simply denying biological science; or else we should have to acknowledge that vital force must be studied by special methods, and that the science of life must rest on different principles from the science of inorganic bodies" (Bernard, 1865/1976: 60).

Bernard found a way of defining this difference between living beings and inorganic bodies consistent with his rigorous compromise with experimental methodology and the inescapable reflection on results and observations. He suggested to understand living beings as possessing something inorganic bodies do not, but instead of a hardly analysable notion such as *élan vital* he looked for something intrinsic to living beings, namely a specific kind of organization. This kind of organization shows and its defined by the conceptual and physical separation between the external and the internal milieu. This internal milieu is the part of the organism accounting for its stability despite constant and unpredictable influence of perturbations from the external environment, threatening its stability. The internal milieu is the one that confers to living beings their capacity of resilience when facing perturbations, since it isolates delicate vital processes and organs from the external randomness. On top of that, the internal milieu provides an account for organisms' independence, since the internal milieu demarcates life from non-living and inorganic bodies. This demarcation criterion defines life as a specific kind of organization, hence offering an alternative approach and more scientific perspective on the study of life.

Even so, Bernard is an historic figure whose alignment with vitalism and mechanism is still debated. This is so since Bernard severely criticized vitalist dogmas still at use on his time, for they were obscure and ineffable (at least as Bernard understood them), making impossible further investigation. His strong stances against the notion of this perception of vital force seem to position Bernard closer to the mechanistic stream of thought, as well as might point out to his experimental preferences and his insistence on the necessary determinism of natural phenomena. However, Bernard cannot be tagged as merely mechanist, since he also stands for vitalism. He considers vital phenomena as separated from those phenomena related to inorganic bodies, as qualitatively different. In any case, Bernard's proposal seems to offer a breakout for physiology, thanks to his re-conceptualization of life, modifying the original idea from an external force or influence to a determined, physical notion that could be studied and analysed, pushing physiology to the first place in the research about life phenomena, habilitating research specifically about them and not just from the analysis of body structure, like anatomy.

It might be really difficult to decide if Bernard can be considered closer to a mechanist or a vitalist perspective, but what we can say for sure is that he offers an alternative approach that makes life understandable through its organization. It might be said that Bernard bridges both perspectives, if we define vitalism as a perspective that upholds that there is a qualitative difference between living beings and inorganic bodies. Mechanism in this context should be understood as a perspective compromised to find scientific explanations for that difference. For instance, the contemporary work of William Bechtel aims to provide a definition of mechanism that supports a distinction between living beings and human-built machines, using the same models of explanation (for further reading, see Bechtel 2015f, 2016c, 2017c[3] , just to mention some of the latest ones).

Contemporary Systems Biology perspectives can be regarded as keen to Bernardian proposal. Bernard understood organisms as differentiated from their medium but, at the same time, focused on the relations between organisms and their ambient, and defined them as interdependent phenomena (while disclosing its constituent mechanisms by observation and experimentation). This can be regarded as some seminal perspective of Systems Biology, since this discipline stresses the importance of understanding biological interactions for a deeper understanding on the living. Nevertheless, Bernard might be considered a precursor of some ideas of Systems Biology, but he also inspired the work of a physiologist who is widely known nowadays for coining one of the most relevant notions on body’s health and general stability: Walter Cannon, disclosed on the next chapter.

2.2. Bernard’s medical and physiological inheritance

When Bernard worked as a pharmacist, he was responsible for the preparation of different remedies. Bernard soon realized that most of the remedies he made consisted

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[3] On his website, more of his latest works can be found: http://mechanism.ucsd.edu/~bill/

normally in master formulas that had no demonstrable causal relation with the re-establishment of a healthy state on patients, and that several mixes could be used for the preparation of remedies for considerably divergent ailments.

This practice in therapeutics is a consequence of the perspective on pathology of that time. The prevailing paradigm about disease and its causes was based on the body's capacity of healing itself, still based on the reaction of a still to be fully studied healing vital force, known as *vis medicatrix*. It is responsible to get the body back to its stable and healthy state, and the main and possibly only course of action for professional practitioners consisted in enhancing the possibilities of the body to restore health through the modification of diet and the addition of some mild remedies, such as herbal teas.

This is due to the prevailing model of medical science during mid-19th century that kept some of the ideas already present in humours theory from Ancient Greece, with little modifications, result of a wider knowledge on and accessibility to medical herbs and the effects of food on bodies. The idea of disease as a disequilibrium between humours within living beings was part of everyday medical practice. Bernard clearly shares the belief that instability is the real threat for living beings, and the fact that bodies tend to a certain stability in order to survive. This lead him to the conclusion that instability must come from outside the living body, and somehow affect it.

2.2.1. Medicine on the 19th century

Humour theory emerged from the necessity of explaining disease, even death, from a pragmatic, medical perspective. Since the beginning disease is understood as a loss of stability in the body, provoking an unhealthy state in the body, because of the influence of the chaotic external milieu (as main source of perturbations, which influence on the body is ultimately defined by the personal configuration of humours of each individual). Bernard agreed with that idea of stability, and he strongly linked it to the inner environment of organisms. This separation from the external environment and enclosure of the internal milieu makes it the main source and origin of living being's independence, even if this independence is just apparent, as Bernard understands it, is more like some sort of autonomy, since there is no life unless there is an external environment too.

In the Ancient Greece, when humour theory emerged, disease was considered a type of internal instability of the fluids (humours) that belongs in the body. Hippocrates, circa 420 B.C., was one of the first practitioners who focused on finding a better understanding on how the body is affected by the loss of humour stability and how to restore it. The usual procedure to restore body's stability consisted on treating patients by modifying their diet (since different foods could be transformed by digestion in different fluids) and prescribing them some exercise (to stabilise the humours already present in the body), in addition to several herbal preparations in the form of infusions, mists, or aromas. These alterations on levels of blood, black bile, yellow bile, and phlegm (the four humours or vital fluids) are considered responsible for these changes in functional performance of specific body organs, body's health, as well as personality traits. In its original Greek formulation, seasons' change was also considered to influence the stability of humours[4]. Consequently, some nutrition changes were usually prescribed along the year. One of the claims of 20th century organicism is precisely to take into consideration the relevance of the ambient context and its interactions with organisms, including the living phenomena it propitiates.

This perspective in the analysis of organisms and diseases did not change significantly in the years to come in physiology. Even so, some knowledge was developed on the organisms' structure and how it shapes or influences the performance of the organism. This paradigm proved itself quite useful, so, it was still maintained as main stream in medical practice even when Bernard fulfilled his physiological formation. This perspective defends the idea of the body holding an ability to heal itself, restoring its healthy state from whichever disease it may endure. Hence, the main goal of a practitioner should be to ease the way for the body to find its means to restore that lost equilibrium. Bernard would recognize as well that there is an observable tendency towards stability in organisms. However, the notion of vital force resisted to be defined and, consequently, it could not be analysed scientifically. Bernard always stood for experimental medicine, he recognised this issue and aimed to find a definition such to be able to experiment upon

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[4] The study of the consequences of cyclic change is followed by modern physiology, in the conceptual evolution of homeostasis crystallized in the notions of rheostasis and allostasis.

organisms' living condition. In order to achieve this, he studied the laws ruling healthy and diseased bodies, analysing organisms' complex organization of components and processes of the internal environment. This was meant to be one way to prevent and redefine organisms' states (Bernard, 1865/1976: 217), so he focused on finding an explanation on biological organization, including that idea of natural stability, to gain more information on how organisms' function.

Aristotle can be regarded as another historical contributor to the history of physiology. He used Hippocratic ideas and built connections between various elements from nature and those of the human body, hence pointing at the relevance of interactions. He approached the study of the living through anatomical studies, advocating for a preponderance of form over matter, emphasizing the connection between anatomy and function. This approach, meaning to find an explanation of life through anatomy first, will be one of Bernard's methodological starting points. He early realised in his analysis that living processes are not present in dead bodies, hence he concluded that life cannot be studied just through anatomy only. Another inspirational idea would be a proposal made by Galen, in 126 – 199 A.C., who widened the approach to the study of living beings by including experimentation. Before this, physiology was completely speculative. Galen contribution enabled the possibility for an experimental physiology, and Bernard himself pursued a balanced integration of experimentation with observation, through an exhaustive revision of physiological methodologies.

Thanks to Galen's research, the process of digestion was almost fully disclosed, by specifying its distinct phases, including nutrients distribution through the blood stream, among other contributions, like muscle control by the spinal cord, or bladder and kidneys functioning, to name a couple of them. His approach is interesting because it explains regular functionality of a healthy body, but he is still trapped within a framework that explains health, disease, and personality by metaphysical means, not humours, but three diverse types of spirit or pneuma, that influence the body and its behaviour in the same way.

It becomes evident that the complexity of biological phenomena pushed the pursue of an explanation from the scientific community, forcing it to use metaphors to describe phenomena that were still to be fully studied and named, aiming to enhance our knowledge on them. These metaphors were highly metaphysical, understanding life as something added to the body, otherwise inert[5]. This depiction of living bodies might be a consequence of the study of biological phenomena based just on anatomy. Bernard, realising the limitations of this approach, and using the technologic and scientific advances of his era, he emphasized on the necessity of vivisections. He proposed to do so to banish that allure of ineffability from those unexplained metaphors, with the aim to elucidate at least those biological phenomena related to the maintenance of stability and the peculiar organization of living systems and opening the possibility for them to be quantifiable in some way, to allow prediction. That is, to bring biological explanations closer to the scientific methodology.

On Middle Ages and Renaissance, knowledge on physiology kept a steady growth, mostly by analysing the behaviour of the human body. Nonetheless, theoretical context was still lacking and religion took the hypothesis on health and disease, since it was yet to be fully developed, and put a metaphysical twist on it, by linking diseases with the idea of some divine punishment for misbehaving, understood as some offence towards God. Avicenna (980 – 1037) tried to overcome these scientific limits and aimed to find ways to understand how to maintain body's stability, producing various methodical descriptions of diseases, like diabetes and its main characteristics. Even if Avicenna dedicated his efforts to find scientific explanations of body's stability, Jean Fernel (1497 – 1558) was the one giving the name *physiology* to this discipline dedicated to the study of living beings, by describing it as a scientific speciality that studies the behaviour of the living but based on the anatomical approach as Galen did. He compiled most of the medical knowledge achieved until his era and divided it in three main streams: 'Physiologia', 'Pathologia' y 'Therapeutica'. This division will be maintained, and they will constitute Bernard's three main branches of study, but establishing physiology as an independent discipline, prevalent among other disciplines when the focus is on the study of organisms and their health and disease conditions, their organisation and stability.

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[5] It might be relevant to underline that this kind of metaphysical metaphor was not due to a tendency towards obscurantism, but the scientific outcome to expect from the conceptual tools available.

Some of these metaphors created to fill the blanks, were interpreted sometimes as aiming to become licit descriptions, and the idea of animism spread since it was the easiest way to disdain vitalism as a legitimate scientific approach to the study of living beings and to mark vitalism as an irrational approach. Although it is not clear whether if this criticism started from the very beginning of vitalist metaphors, or if it was more like a setback critique. It is even difficult to deduce from Bernard's texts which one it is, since some pieces of his rabid critics to vitalism can be understood either as an attack to the impossibility of determinism, either as a total rejection to vitalism understood as animism.[6]

For instance, Georg Ernst Stahl (1659-1734) is sometimes considered as the founder of animism. He developed a medical theory used until mid-19th century in Europe, it established that every living body has a vital force which activity consists mostly in behaving like a *vis medicatrix naturae*. This force was already present in the humour theory, and it was responsible for restoring the loss of stability of living bodies when sick.

Within the hypothetical frame of animism, the *anima* or soul of living beings is in charge of embracing and confronting the external and destabilizing influences of disease, protecting itself and triggering all necessary actions to restore a healthy stability. That is why, as it happened in humour theoretical framework too, medical interventions should be reduced to its minimum, but enhancing the healing capacities of the body. One of the critics of this interpretation of vitalism pointed out that this is some sort of healing by expectation, taking away medical and scientific control, hence subordinating medicine to nature forces (Haller, 1981: 105[7]).

Stahl is often considered as a member of the medical School of Montpellier, where some of the greatest scientists and doctors from medical as well as other biological disciplines reunited. Sadly, there is no historical evidence that he really belonged to it,

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[6] Animism is the name given to the stream of thought that sustained the idea of an *anima* impregnating inert bodies, as noted before. Even if it is an undeniable part of vitalism history, vitalism itself is not depleted to it.

[7] J. S. Haller, author of *American medicine in transition 1840–1910*, and not Albrecht von Haller (1708-1777).

even if he enormously influenced one of the founding fathers of the School, Barthez. So, even if there is a debate on whether Stahl belonged or not to Montpellier, it is widely accepted that he was present, even if just through his ideas. That school forged some of the most relevant intellectual figures from the 18th Century and part of the 19th century, who are said to defend the necessity of a mechanist approach, but always as a support since it is not sufficient to understand biological phenomena.

This was the intellectual context where Bernard received his formation, and he resolved to find an explanation that accounted for those vital phenomena that resisted experimentation. As Bernard explains, "when a fact proves anything, the fact does not itself give the proof, but only the rational relation which it establishes between the phenomenon and its cause" (Bernard, 1865/1949: 53). Determinism is absolute, and if there is no cause to be found, "there must be error or insufficiency in the observation; for to accept a fact without a cause, that is, indeterminate in its necessary conditions, is neither more nor less than the negation of science" (Bernard, 1865/1949: 54).

2.3. Bernard's methodology and its relevance for physiology

One of the main reasons Bernard is considered to have transformed physiology in an independent discipline is due to his major revision of physiological methodology. Bernard's methodology is heir of the training received by his teacher François Magendie (1783 – 1855), but it was also influenced by the work of other specialists on the field, as mentioned earlier, as some of them have already been mentioned earlier. Hence, Bernard's methodology is partly indebted to previous and already existent techniques, but at the same time, he interpreted and used them in a way that brought a deep change in physiological practices.

Bernard was Magendie's disciple, and he owns him a good part of his ideas on methodology. Magendie was a prominent physiologist, because of his theories and discoveries, but most importantly due to his methodology. Magendie used to proceed with observations without preconceptions and with no clear goal either, working by compiling every bite of data he could find to analyse them afterwards to find an explanation for them. From Magendie, Bernard learned those techniques related to vivisection and experimentation, but they disagreed how to gather data from them. Bernard, contrary to what Magendie pleaded for, was convinced that vivisection and experimentation should be performed, for the sake of the progress of scientific knowledge, with the aim to contrast an idea or work hypothesis.

From Bernard's perspective, in the interest to be able to realise fruitful observations it is necessary to avoid prejudice-biased approaches. It is important to tell apart those ideas that might guide an investigation from (usually unquestioned) pre-established ideas, and how both relate with determinism. For starters, there are a set of ideas that usually lead observation and experimentation, the kind Magendie despised, that can be understood better as intuitions, "the *a priori* idea or the theory which serves as [their] starting point" (Bernard, 1865/1949: 53), that can lead a research in one direction or another, but never acting as prejudices that could limit observations in any sense.

Pre-established ideas are usually constructed upon a theory, and they are not negative if they are understood as *revisable notions*, and not as fixed truths, and they can be changeable if the evolution of investigation requires so. In another words, pre-established ideas are useful unless they are delimited as dogmas. Philosophical doubt might lead to scepticism if not controlled to some extent. Therefore, Bernard distinguishes unquestioned theories, namely dogmas, and the absolute scientific principle, "the determination of phenomena, which is as absolute in the phenomena of living bodies as in those of inorganic matter" (Bernard, 1865/1949: 52).

Before Bernard's revision, physiology was a discipline subject to anatomical studies, committed to a pure theoretical and speculative dimension, on the study of the origin and development of vital phenomena. This scission between physiological and anatomical studies did not happen earlier due to the difficulty of observing and manipulating living phenomena since they were no longer present in (already) inanimate bodies. Bernard emphasized on the necessary analysis made directly on living bodies, practice most known as vivisection, revising scientific methodology and, with this goal in mind, reshaping it through a deep update that ended in an exhaustive elicitation of those processes belonging to physiological experimental practice.

2.3.1. The novelty of Bernardian methodology

I take Bernard's sentence "observation shows, and experiment teaches" (Bernard, 1865/1949: 5) quite representative of Bernardian thought. Until Bernard's review, observation was considered somehow passive and experimentation active, but Bernard recognized some difficulties with this definition when trying to apply it to experimental practice, because he realized they were usually made spontaneously and simultaneously during the development of investigations. That is why he explains that observations and experiences can be active and passive, and describes them.

A *passive observation* would be the kind that happens by chance, with no preconceptions nor previous intentions bounded to it. *Active observation*, on the other hand, would be triggered by some previous ideas, and they serve these as means of checking their validity or usefulness. The same conceptual scheme applies to experiences. *Passive experiences* would be those happening hazardously and usually unexpected, while *active experiences* can be defined as those where the researcher engages in a kind of participation that looks for some modification or alteration of a phenomenon aiming for testing or even verifying a previous idea, what is customarily known as experimentation.

However, this differentiation is just theoretical, since he later claims that "the investigator himself must be analysed into observer and experimenter; not according to whether he is active or passive in producing phenomena, but according to whether he acts on them or not, to make himself their master" (Bernard, 1865/1949: 13). What is important is the exhaustiveness on understanding phenomena, which must let us provoke, modify, and test the legitimacy of them and the pre-established ideas we might have about them.

Everything stated until this point serves as means to establish some methodological base that Bernard might have acquired from his master Magendie, which would shape strongly his perspective on science, and to understand in what sense he criticized vitalism (or what kind of vitalism he really criticized) and what type of scientific approaches of is era he despised. This analysis is needed because there is a quiet debate about his "philosophical alignment", that is, some who study his figure consider him, for instance, a radical experimentalist, while others think he was more a vitalist, but his adscription to a determined alignment is not as clear as some might be claiming (for a good analysis on this debate, see Normandin, 2007).

Nevertheless, even if Bernard passionately defended vivisection as means to understand how living beings' function[8], he was also a thinker, so it must be considered that his researches were driven by two main streams evenly: experimentation and philosophy. A wisp of this can be found on his *Introduction*: "Philosophy and science, then, must be never be systematic: without trying to dominate one another, they must unite. Their separation could only be harmful to the progress of human knowledge. (…) solid union between science and philosophy is useful to both: it lifts the one and confines the other" (Bernard, 1865/1949: 224).

Bernard seems to have been quite fond of Renée Descartes (1596 – 1650), who is mentioned in his texts. Normandin, on his paper from 2007, explains that Bernard takes Descartes' mechanism and dualism as starting points, which shaped the theoretical framework of his time. Even on his *Introduction* they can be found two conditions for research that can be traced back to Descartes, namely, mind openness and philosophic doubt: "The first condition to be fulfilled by men of science, applying themselves to the investigation of natural phenomena, is to maintain absolute freedom of mind, based on philosophic doubt" (Bernard, 1865/1949: 35). The latter is especially relevant since it is keeping scientific practice away from untouchable dogmas, the kind Bernard was trying so hard to elucidate.

The problem with dogmatism is that it induces scientific theories to be understood as an *unquestionable* theoretical framework, and in combination with the idea of these being the only way to approach observation and experimentation, we end up with some blind approach to biological processes, confining our knowledge about them into a black box. That is why philosophical doubt must always be present, since it seems to be the best way to light up this black box and disclose what is inside of it, transcending what it is immediate in applied sciences and questioning stagnated dogmas to obtain useful

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[8] Because anatomy was unable to provide a description for the dynamics of living processes, being only useful to discover the static structure of living beings.

results and new knowledge through investigation. Actually, Bernard will defend that, given the complexity of biological phenomena, this philosophical doubt applied to the field of biology is not only important, but necessary, even to the extent to determine scientific progress: “In biological science, the role of method is even more important than in other sciences, because of the immense complexity of the phenomena and the countless sources of error which complexity brings into experimentation” (Bernard, 1865/1949: 35).

It is also important to make explicit that, to Bernard, scientific theories are not to be mistaken with determinism. He understood determinism as an absolute principle, ruling every single bit of universe. Scientific theories are defined as some sort of steps towards the truth, as relative principles to take into account just temporarily: “In scientific education it is very important to differentiate, as we shall do later, between determinism, which is the absolute principle of science, and theories which are only relative principles to which we should assign but temporary value in the search for truth” (Bernard, 1865/1949: 39). What Bernard had in mind on science can relate, in principle, to an epistemological realism of sorts, where science describes reality, but it is still pursuing the whole truth about what can be found within the universe, even if knowing it might never be reachable.

Bernard’s idea of determinism is sustained by the notion that biological organisms have their foundations on physico-chemical laws that are used to describe inorganic bodies as well. He embraced the idea of his time that living bodies were *alive* bodies, meaning that, first, they have a structure, as inorganic bodies do, and second, somehow living bodies shape their structure differently from inorganic bodies that enables them to act as a working mechanism controlled by life. Bernard was into eliciting the meaning of “life”, while adhering to the idea of mechanism: “The organism is merely a living machine so constructed that, on the one hand, the outer environment is in free communication with the inner organic environment, and, on the other hand, the organic units have protective functions, to place in reserve the materials of life and uninterruptedly to maintain the humidity, warmth and other conditions essential to vital activity"[9] (Bernard, 1865/1949: 76).

Is in this mechanist sense that Bernard rejected the idea of vital force as some sort of inexplicable mystery. In some paragraphs it might seem that he is in fact trying to describe vital phenomena from a purely physico-chemical perspective, by stating things like: "The experimental method necessarily turns aside from the chimerical search for a vital principle; vital force exists no more than mineral force exists, or, if you like, one exists quite as much as the other" (Bernard, 1865/1949: 66). However, what he is really against is to the indetermination of this idea, taken as it represents the essence of biological phenomena, when it is not anything else than a metaphor that must be disclosed as the analysable biological phenomenon it is: "The word, force, is merely an abstraction which we use for linguistic convenience. (…) As the essence of things must always remain unknown, we can learn only relations, and phenomena are merely the results of relations. The properties of living bodies are revealed only through reciprocal organic relations" (Bernard, 1865/1949: 66).

In another words, Bernard was against the idea of living beings completely independent of scientific determinism, that is completely alien to physico-chemical laws (since everything is made from the same elements). Nonetheless he was not against biological science having a distinctive object of study, that is organisms, subsumed under determinism: "If the above objections [life phenomena subjected just to separate laws and life force as an untouchable essence] were well founded, we should either have to recognize that determinism is impossible in the phenomena of life, and this would be simply denying biological science; or else we should have to acknowledge that vital force must be studied by special methods, and that the science of life must rest on different principles from the science of inorganic bodies" (Bernard, 1865/1949: 60).

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[9] This may be one of the paragraphs that lead some researchers to think that Bernard was kind of a radical mechanist. However, Bernard, as most of the scientists before the 19th century, is better understood when all of his scientific production is taken collectively, since some of these paragraphs lose their original character if isolated from the rest (which, most of the time, delimit and define each other meaning or purpose).

And even when he expresses so much resistance against vitalism, he does that because vitalism seems to avoid explaining its main phenomenon and, in the worst case scenario, it might be seen as compromised with the idea of an animist vital force, like an indecipherable essence, that precludes any chance of experimentation on living systems; but not because he does not think that there is a difference between living and inert, quite the contrary. The idea of internal milieu would have, most likely, grow from Bernard's ideas about biological organization, and this distinction he defended between the living and the inorganic is the one to bring Bernard closer to vitalism: "we are often duped by such words as life, death, health, disease, idiosyncrasy. We think we have explained when we say that a phenomenon is due to a vital influence, a morbid influence, or an individual idiosyncrasy. We must really learn, however, that vital phenomenon means only a phenomenon peculiar to living beings, whose cause we do not yet know; for I think that every phenomenon, called vital to-day, must eventually be reduced to definite properties of organized or organic matter" (Bernard, 1865/1949: 185). That is the goal of Physiology: learn about organisms whilst living to make explicit their determination.

2.3.2. Physiology independence

Physiology was not always an autonomous speciality. It was usually part of the studies program of anatomical education. This was the main discipline and physiology was a specialization within it. It was not until Bernard stressed out the necessity of study living beings while alive that the relevance of physiology was revised: "Physiologists also follow a different idea from the anatomists. The latter, as we have seen, try to infer the source of life exclusively from anatomy; they therefore adopt an anatomical plan. Physiologists adopt another plan and follow a different conception; instead of proceeding from the organ to the function, they start from the physiological phenomenon and seek its explanation in the organism" (Bernard, 1865/1949: 111).

Vivisection was not new in medical practice, but it was considered controversial for some. Thanks to the "invention" of anaesthesia in 1846 by William Thomas Green

Morton[10] some of the biological observations and experiments could be performed without that much pain for the subject, but it did not modify greatly biological experimentation, since anaesthesia can affect some physiological parameters and it is not always recommended when experimenting. Even so Bernard, as a scientist of his time, defended passionately the necessity of vivisection for the study of life phenomena (like, for instance, between pages 99 to 115 in his *Introduction*, 1865/1949), mainly due to the impossibility of deducing those from the static structure of living beings, that is, merely from anatomical studies.

Anatomy is heavily based on observation. Anatomical studies are indispensable to learn about the structure of living beings, through dissection of dead bodies, which is at the same time an important part on the study of relationships between structure and processes. Vivisection is necessary to complete the study on living beings, since in anatomical analysis the spontaneity of living beings disappears. Physiology is different from medicine, because the latter also includes the intervention on bodies with the aim to heal them, while physiology focuses on biological phenomena, and and realys on tools and knowledge from other disciplines in order to achieve this goal, just like a precursor of systems biology: “To solve the problem of life, physiologists therefore call to their aid all the sciences,—anatomy physics, chemistry, which are all allies serving as indispensable tools for investigation” (Bernard, 1865/1949: 111).

Bernard, in defending vivisection, alleged that it is necessary for the understanding of living beings’ processes and functions, namely biological phenomena, to observe and alter internal parts of organisms while still alive, same argument used by every vivisectionist. This links directly with the idea of Bernard that “observation shows, and experiment teaches” (ibid.), since “instruction comes only through experience” (Bernard, 1865/1949: 101). Nevertheless, there is a slight difficulty related to this, and it is the necessity to formalize that instruction by quantitative means, based on *principia* provided by mathematics or physics. The issue is that biological phenomena are

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[10] This is the date closer to the general introduction of anaesthesia in medical practice, but consider it just an indication. Anaesthetic effects of plants were probably already known since early human era, and there are even records of Chinese practitioners using it. The milestone attributed to Dr. Morton is the *painless* intervention and the more bearable recovery after surgery because of that.

tremendously complex, and to confine its qualitative nature to measurements made on a simplification of already limited knowledge is not really useful in the long term. Before we even attempt to quantify, we need to broaden our qualitative knowledge of them in order to understand the different layers of complexity life is composed of, to separate them properly and knowingly, and quantify them considering consciously the complex phenomena they are. As Berrnard says: "I believe that the most useful path for physiology and medicine to follow now is to seek to discover new facts instead of trying to reduce to equations the facts which science already possesses. This does not mean that I condemn the application of mathematics to biological phenomena, because the science will later be established by this alone; only I am convinced that, since a complete equation is impossible for the moment, qualitative must necessarily precede quantitative study of phenomena"[11] (Bernard, 1865/1949: 130). Not even a statistical approximation would do it, since it would be based on observed facts that are still indeterminate, on presuppositions, and it will never lead to determinism. They are only useful to the practitioner, but just if carried out by himself or herself (Bernard, 1865/1949: 130, 136-139).

To conclude, it is important to stress again that vivisection is an important mean to investigate biological phenomena, because it is necessary, as it has been implied earlier, to intervene by means of experimentation, using venoms and other means of disturbing the internal environment of an organism and widen our knowledge in the observance of the differences created by our intervention. Due to that complexity of living beings, the way to carry out an investigation about living systems is to start by considering their level of complexity to pick up some organism close enough to humans, the most complex biological system of them all. It might seem that Bernard, as it was the stream of thought of his time, conceived organisms as classified by their total complexity, from plants to humans. This complexity is based mostly on their ability to resist perturbations, that is, to

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[11] This will constitute one of the main arguments held in this work, for homeostasis is thought to have been quantified before it was fully "qualified", leading to a mathematical formalization by cybernetics of a notion of homeostasis that was still to be fully developed. This, additionally, implied the use of the term in that specific sense, that is, as a feedback loop, in further theorizations on biological systems, such as General Systems Theory.

enclose their internal environment. The more complex the organism, the more closed the internal milieu. On the lower level, just one step above inorganic bodies, we find plants. According to Bernard, they belong to this lower level because, even if we can tell apart when they are alive or not, they are completely subordinated to changes in the outer environment like, for instance, during winter, when most of them freeze and die. On the next level there are cold blood organisms, since they exhibit a little bit more independence from external changes, but still not as much as higher animals, that is hot-blooded animals, which possess the most complex internal milieu, and amongst them, the human being is on top of this complexity hierarchy (Bernard, 1878/1966: 65 – 124).

Physiology, then, it is an independent discipline since compromises to a field of study that should be not subsumed under any other discipline. This irreducibility comes from, besides the general field of study, a characteristic methodology and its practical application. It is also different from biology, since this one would provide the general framework while physiology would be keener to experimentation, to understand life with an interest on pathology and therapeutics, since physiology is the study of organisms in their normal state, hence complementing experimental medicine along with pathology and therapeutics (Bernard, 1865/1949: 1).

In conclusion, Bernard's methodology proposal for the physiological studies were a turning point for the physiological field. Thanks to his methodological proposition, for instance, those limits settled to science using metaphors and euphemisms for not well-defined ideas, like the one of vital force, are now highlighted, and have an opportunity to be analysed and made explicit through exhaustive research. It also changes the way to approach the study of living beings, basing hierarchy on complexity and not in some anthropocentric notion of nature, even if some remains can still be found. These definitions of complexity, autonomy, and resilience of internal milieu are the ones to inspire ulterior researchers looking for understand the way organisms work and how to explain their complexity, mostly focusing in their internal milieu, like those carried by Cannon or Wiener, to name two.

2.4. What is the milieu intérieur?

Internal milieu is a notion referring to the enclosed and protected maintenance elements and processes of an organism, that is, in other words, the peculiar organization of living systems. This is what makes organisms autonomous or independent as Bernard called them. The milieu intérieur is materialized on what we know now as intra- and extra-cellular fluid, namely blood, enclosed in our bodies. Bernard makes a description of the internal milieu as a liquid environment maintaining the heat of living systems (mammals, mostly, which are the paradigm of an organism according to Bernard). Further discoveries in the biological field over the years suggest us to include other extracellular fluids, that is, interstitial fluid and intracellular fluid, but in section will keep the focus on Bernard's proposal.

The complexity of living beings founds its basis on the internal milieu. Extensively, it is considered the demarcation criterion distinguishing living beings from inorganic bodies. That is why they can be explained by physics and chemistry in a basic level (since they are constituted by the same elements and a structure can be distinguished), but it is not enough to fully describe them. To get to understand living beings it is necessary to run an investigation on those phenomena typical of biology to build some laws belonging uniquely to physiology (as the science of the study of living beings as living). This idea sprouts from his texts, for instance: "In a word, biology has its own problem and its definite point of view; it borrows from other sciences only their help and their methods, not their theories. (...) That is why I think it proper to call the physico-chemical sciences allied sciences" (Bernard, 1865/1949: 95), and also: "Biology must borrow the experimental method of physico-chemical sciences, but keep its special phenomena and its own laws" (Bernard, 1865/1949: 69).

In addition, and as following some of Bernard's conceptions, organisms have three levels of study when approached from physiology. He does not call them levels, but conditions that are physiological and typical from animals: "In every experiment on living animals, three kinds of physiological conditions peculiar to the animal must be considered, apart from general cosmic conditions, to wit: anatomical operative conditions, physico-chemical conditions of the inner environment and organic conditions of units in the tissues." (Bernard, 1865/1949: 117). In this extract of his text, it is better understood how Bernard conceived the study of organisms, and how does it relate to physico-chemical sciences. This becomes especially important when considering there is a debate on Bernard whether he was a reductionist or not, but mainly it is relevant since it help us figure out how he was planning to make quantifiable the physiological knowledge of biological phenomena, bounded to its qualitative nature so far.

When talking about the internal milieu, it may surface the question about why this idea did not appear before in science history, or so does Bernard. His response is because science was trying to find an answer to another kind of problem, which is to find an explanation for first causes, the essence of phenomena, instead of looking into proximate causes[12]. In another words, this was not addressed like Bernard does before because science was demanding an answer for the reason why of phenomena, instead of looking for the how: "By the cause of a phenomenon we mean the constant and definite condition necessary to existence; we call this the relative determinism or the how of things, i.e., the immediate or determining cause" (Bernard, 1865/1949: 83). It is not

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[12] This was written by Bernard in 1865, in the first edition of his *Introduction*, about the different types of causes and their associated problematic, idea that years later, almost a century in fact (circa 1961), Mayr would make popular. Nonetheless, Mayr would credit John Baker for the very first distinction between final causes, as in teleology, and close causes, the ones explaining the origin and behaviour of a determined phenomenon, who did so while trying to build an explanation for bird migration.

Mayr's approach about kinds of causes is in tune with Bernard's idea about final and proximate causes. According to this, causes in biology can be classified into proximate causes, the kind Bernard calls functional, those that explain functions and the interactions of organisms. These are strongly linked to physics and chemistry, by using the same experimental methodology in their studies, and not for being reducible the one to the others.

On the other hand, we find final causes, those that Mayr consider the ones to focus on when trying to figure out the whole (hi)story of an organism, which he also calls evolutive causes. While proximate cause must find the how of phenomena, final causes must find the answer to the why. Even so, this distinction is based for pure explicative goals since, as Mayr himself states, it is necessary take them together to understand any biological cause that we aim to understand. As a curious fact, I might add that Mayr considers evolutive and genetic explanations to be included within the set of final causes; while physiological explanations would be understood as proximate causes, distinguishing between internal and external physiological causes (intrinsic and extrinsic, as he names them). This way, he keeps the distinction made by Bernard about internal and external milieu, defending the same perspective about physiology as occupied exclusively on the study of proximate causes.

necessary to know the essence of things to dominate them, but just their determination. Also, in his text from 1872, *L'expérimentation dans les Sciences de la Vie*, Bernard says "Il faut d'abord bien savoir qu'il ne s'agit pas de la cause première des choses: cette recherche n'est pas de notre domaine; les sciences expérimentales ne veulent et ne peuvent remonter qu'aux causes secondes ou prochaines des phénomènes" (Bernard, 1872: 488).

To say it in another words, science should undertake the study of those conditions or means that produce phenomena, aiming to be able to modify and produce them at will since that is one of the main and most important aim of science, as explained on the section about Bernardian methodology. In this specific point Bernard shows himself as a materialist[13], since he declares that it is necessary, for the study of these proximate causes, to turn to the study of matter and its properties, where this causes appear and from where they can be analysed by means of physico-chemical methodology.

One of the main reasons it is difficult to experiment on the internal milieu is because of the characteristic organization of living beings, because its parts cannot be easily separated while keeping their living properties, constituting an indivisible unit. This unity is due to the origin and the way they come to be, by means of production of the own body, and not made by the external milieu and put together by some external force. On top of that, living features depend on and sprout from the organization of those elements created by the organism itself. That is why, when extracted from the body, those components are still organic, but not organized anymore, i.e. they are no longer living because they lose their organization: "Anatomical units stand alone as organized living parts. These parts are irritable and, under the influence of various stimulants, exhibit properties exclusively characteristic of living beings. They live and nourish themselves, and their nourishment creates and preserves their properties, which means that they

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[13] Although, and at least in principle, Bernard shows some sort of aversion towards materialism as well as for spiritualism, for he considers both approaches as insufficient to grasp the deep complexity of physiological phenomena. That might be a reason why his texts swing between both perspectives, depending on what is the matter at stake: "For physiological experimenters, neither spiritualism nor materialism can exist" (Bernard, 1865/1949: 66).

cannot be cut off from the organism without rapidly losing their vitality" (Bernard, 1865/1949: 77).

This proposal adds to biological organization, already analysed in Ancient Greece, a new dimension. On top of living beings hierarchy, referred to the relation between diverse kinds of organisms formulated as their organization before, now biological organization accounts also for the relation between the parts that compose those organisms, and how those relations are responsible for that phenomena we call life: "As the essence of things must always remain unknown, we can learn only relations, and phenomena are merely the results of relations. The properties of living bodies are revealed only through reciprocal organic relations. A salivary gland, for instance, exists only because it is in relation with the digestive system, and because its histological units are in certain relations one with another and with the blood. Destroy these relations by isolating the units of the organism, one from another in thought, and the salivary gland simply ceases to be" (Bernard, 1865/1949: 66-67). This idea will have some intellectual echoes in General Systems Biology, firstly formulated by Bertalanffy and later inherited by Systems Biology, including the idea of life as an emergent property[14].

Those three types of elements of organisms mentioned before have the capacity to react physico-chemically to external influences, such as light, heat, or electricity. Despite this, living components, namely those organized anatomical elements, as Bernard calls them, are the only ones to have that property called *irritability*, meaning the capacity to react in a unique way, typical of living tissues, such as muscular contraction, nervous transmission, etc.[15]

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[14] This is one of the main streams of systems biology, where some of the basic and most important features of organisms are, amongst others, self-organization and self-regulation, or in another words, organization and regulation as a product of result of the very own living system. In this context, life is considered an emergent property, since it cannot be deduced from the purely material components of organisms.

[15] It was Albrecht von Haller (mentioned in another footnote) who popularized the term, allegedly coined by Glisson, of irritability, tightly related to investigations on body heat that were required in physiological studies when facing the analysis of living bodies' phenomena. Haller played one of the most relevant roles for experimental science because of his studies on irritability and sensibility. The latter is used to refer to the capacity of transmitting, and the former to the capacity to react to transmitted stimuli. Haller is indeed

To Bernard, "vital phenomena are the result of contact between the organic units of the body with the *inner physiological environment*" (Bernard, 1865/1949: 76). The physiological environment is the only environment where vital functions come to be. Bernard defines it as opposed to the external or cosmic milieu, the one who belongs, but not exclusively, to inorganic bodies. This cosmic milieu would refer to what we know now simply as environment or atmosphere, an in Bernard's point of view is a hostile milieu, main source of perturbations for the organism, which can resist its destabilising influence thanks on the internal milieu.

Nonetheless, inanimate objects, such as rock and the like, do not have this protective mean, and they are constantly and completely to the instability typical of the external milieu. For instance, the earth, as a substrate, cannot be considered alive, since it does not control at all its living conditions and its state depends fully on climate state, amongst other influences. On the other hand, internal milieu, exclusive of living beings, protects the organism and its vital functions, allowing it to resist the pressure of perturbations from the hostile external milieu.

Bernard's internal milieu works this way: for every single one of the disturbances coming from the external or cosmic milieu, the internal milieu acts as a damper to the impact of the alteration provoked for the negative influence of the external milieu. This kind of resistance concedes independence to organisms from the external environment[16]. Even so, this independence, as Bernard calls it, is just apparent since the internal milieu is in continuous interaction with the external milieu, and it is from that interaction that living phenomena come to be. That is what Bernard calls double condition of existence. Vital phenomena take place within the internal milieu, but they would not

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one of the researchers to take into account within the vitalist framework that appear just before Bernard in history.

[16] Internal milieu is the reason why living organisms can be considered robust, if we are to link Bernard's proposal with some of the notions from systems biology of the last years. Robustness is referred, generally, to the property of living beings that makes them able to resist perturbations that could endanger organism's functions. It could be defined as a reaction from the organism, or the internal milieu if preferred, that opposes at the same time and with the same strength or intensity to the perturbation coming from the external milieu.

be possible if the external milieu would not exist, which provides the organism with the indispensable conditions for it: "The phenomena of life, as well as those of inorganic bodies, are thus doubly conditioned. On the one hand, we have the organism in which vital phenomena happen; on the other hand, the cosmic environment in which living bodies, like inorganic bodies, find the conditions essential to the appearance of their phenomena. The conditions necessary to life are found neither in the organism nor in the outer environment, but in both at once" (Bernard, 1865/1949: 74-75).

Jose Luis Barona, a Spanish scientific historian specialized on Bernard, explains how the internal milieu confers independence to living beings in one of his works: "Cada ser vivo, mediante la regulación de las condiciones energéticas y materiales de su medio interno particular, es capaz de mantener las condiciones precisas para su existencia, estableciendo así una forma particular de *determinismo* en los fenómenos que se producen en su interior. Ese determinismo interior regulado por el propio ser vivo constituye, en definitiva, una forma única de asociación entre determinismo y libertad, puesto que el aparente indeterminismo que muestra el ser vivo con respecto a su medio exterior no es más que la consecuencia de un determinismo interior regulado por él mismo, para lograr la constancia y el equilibrio de su universo propio" (Barona, 1989: 12).

Bernard, in his *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux* from 1878 (just a few years after his *Introduction*), he stresses out again how important it is to not mistake Leibnizian determinism with the kind of determinism he is trying to outline. For Bernard, Leibniz is a complete materialist (term that Bernard seems to use indistinctly with the one of mechanist – Bernard, 1878/1966: 42) who defends the racial and total separation between body and soul, having each one their own and independent dynamics, stressing out limitations to those approaches to the study of living beings both mechanist and spiritualist: "En recourant ainsi alternativement aux deux hypothèses spiritualiste et matérialiste, Descartes et Leibnitz ont en quelque sorte implicitement reconnu l'insuffisance de l'une et de l'autre pour expliquer les phénomènes de la vie" (Bernard, 1878/1966: 42).

That is why he confronts the physiological determinism against philosophical determinism. Bernard defines physiological determinism as a strict affirmation of laws, understood as physico-chemical laws that rule every type of existing matter on Earth.

Thus, following these laws, we can predict how a phenomenon is going to be determined, and we can know in advance its relations and conditions of existence, allowing us to control it completely, creating it, destroying it, or simply modifying it (Bernard, 1878; in Barona's anthology, 1989: 151).

Bernard considers this determinism as an indispensable condition for freedom. Following the rules strictly implies there is no restriction: what it *is* is what *exists*, because laws establish it that way. That is why Bernard's idea of determinism could be considered the same way as constrictions in cybernetics (further in this work there is a chapter on cybernetics), according to which an element is what it is because some laws that establish that those are the characteristics of that element. According to Ashby, any object must be taken as a constriction. The fact that and object constitutes a sole unity, and not a mere collection of independent parts is due to the presence of a constriction, and it is this constriction that allows us to make predictions (Ashby, 1972: 181-182). Contrary as those defended by Leibniz, there is no difference between free and determined, for they are the same. Even Bernard stated that freedom could not be based on indeterminism, quite the contrary, since it is within physiological determinism that freedom can be found (Bernard, 1878).

I would like to stress out that all these deterministic presuppositions, as a strict application of laws, absolutely belong to the internal milieu according to Bernard. It displays and organizes physico-chemical elements that constitute it so they make a living entity. In opposition to this internal milieu, Bernard opposes the external milieu, which is random, chaotic, constantly changing. It is the main source of perturbations and, as Bichat had already remarked before on his texts, a force that conflicts with life and denies it. To this respect, Bernard may be considered as a little less radical, taking the external milieu more likely to a later definition, the one provided by cybernetics, i.e. as a root for entropy, of change, in conflict with the organizing force of living systems.

Summarizing, Bernard considers the internal milieu as the physiological milieu, the one from which to recognize the external environment over its influences on the internal milieu, and to know the internal milieu itself, for its own actions triggered by the influences from the cosmic milieu. As Bernard says, "[t]he general cosmic environment is common to living and to inorganic bodies; but the inner environment created by an organism is special to each living being. (Bernard, 1865/1949: 76)[17].

2.5. Final remarks

Claude Bernard proposed an approach to the study of living beings with the goal to unite mechanism and vitalism streams, not happy with the limitations of both when trying to account for vital phenomena. One of the most important premises for Bernard was the one related to organization when studying living beings. To him, investigations concerning to this concrete matter of physiology should be going in two directions, due to the complexity of organisms: first, to decompose the phenomenon under study into the simplest parts possible. Second, to compose back the phenomenon from those smallest parts. This, at least in principle, should provide us enough knowledge about existence conditions of a phenomenon, as well as the determination of the existing relation between a body that manifests the properties of a phenomenon and the proximate cause of that relation (Bernard, 1865/1949: 73).

This procedure has as a final aim the formalization of some laws that belong exclusively to nature, by mathematical criteria. Laws of nature, just like any other scientific law, must be able to be expressed in quantitative terms, the kind that not only allows prediction and control of those phenomena they explicit, but also that allows us to calculate the intensity of those relations between phenomena. However, before that formalization there must be a deep qualitative analysis about the conditions of those phenomena to know which variables consider (Bernard, 1865/1949: 129-130).

To achieve that formalization, he created his methodological system, and new tools were revealed to face some of the old issues about living beings. Taking into consideration that living beings display a series of phenomena that are *qualitatively* distinct, and unique, from those that can be observed in the realm of the inorganic, he

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[17] There is a criticism to this respect, that is, to the idea that the external environment is the same for every living system, if looked closer. If every internal environment is peculiar for every living being it is to expect that the reactions to the external environment and its perturbations are dependent of each organism configuration. Some of the physiological elaborations on homeostasis will further develop this critique.

starts his research on these phenomena by the search for a common, integrative, and exclusive element of living systems. This component is defined by Bernard as opposite to external environment and locates it inside of living beings.

This inner integral part is the internal milieu, where it can be settled a starting point for building explanations about those characteristics belonging exclusively to organisms like, for instance, individuality, autonomy, and independence, to name some. These peculiarities are all due to the stability of the internal milieu, conceived as a kind of, in his own words, *fixité*, as the most plausible explanation for its constancy, but that *fixité* is not to be understood as some sort of stagnation. That would imply that there is no interaction between the internal and the external environment, which Bernard said not; and that the internal environment is uniform and static. Even so, and that what is meant here by *fixité*, when describing the intercourse of the internal environment with the external, he does it in terms of resisting the incoming randomness with the steadiness arising from the complex organization in the internal milieu. The organism stays the same even in the face of an unstable external environment. The dynamics of life would be, in Bernard's account, in the intersection between the internal and the external environment: the internal milieu preserves its activity to resist the randomness of the external milieu, so it can maintain itself stable. The delicate unity of the internal milieu is so fragile that either it resists or succumbs when it is menaced by external perturbations. That is why it is so difficult to experiment on organisms, and that is what is meant when pointing to the fixity of living systems: their unique capacity of stay the same even if in hostility to the external environment.

Through this internal milieu and its study, we might know the internal material structure of organisms, which determines what kind of functions are to manifest in living matter "The properties of living matter can be learned only through their relation to the properties of inorganic matter; it follows that the biological sciences must have as their necessary foundation the physico-chemical sciences from which they borrow their means of analysis and their methods of investigation" (Bernard, 1865/1949: 71–72). It is important to remember that Bernard considers insufficient for a comprehensive understanding of living beings the sole approach of anatomical studies, but at the same time, he considers them as one of the most important steps in the analysis of organisms.

Also, vital phenomena as such, that is the laws determining every single living being, are defined as relationships between concrete bodies and to be dependent of their own organization. Vital phenomena sprout from the relationship between the internal and the external milieu, and the complexity of that relation is what defines the situation of a concrete organism within the hierarchical scale of living beings.

This seems to point out that Bernard, even if it was said in an implicit and a little bit obscure manner, establishes some sort of distinction between phenomena and function, the same way as it is distinguished between structure and organization. It may seem like he was following the trace of the philosophical debate between form and function, but without making it explicit any time, nor either a deep analysis. What it seems relevant to underline is the importance he concedes to relations for the determination of vital phenomena. Moreover, how he points out that the direction to explicit those relationships is the path to unravel and understand those problems related to a definition, clear and in opposition to the inorganic entities, of organism as an entity with characteristics of its own, and with its own peculiarities of its pathological states and its healthy stable states. Bernard pointed out that the main distinction of living beings is their organization and complexity and opened a way to approach their study even despite the intrinsic difficulties of experimenting on them.

Even so, it seems like Bernard somehow biased his own investigation, since he limited the focus of his research to adult, fully grown individuals, and to the analysis of how these restore their equilibrium, lost by the influence of a determined disease. The problem with this notion is that it does not consider individuals' development and, consequently, not exploring probable sources of variety that would be also interesting to explore, since some stability seems to be required for growth, for instance. The internal milieu independence is based on its resistance to external influences, usually random and harmful, but that might not include developing organisms, that need not to stay the same but change to survive. This is an issue that Cannon's homeostasis did not solve, even if it added some flexibility to organisms, and Ashby tried to mathematically overcome (further in this work).

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Homeostasis: the foundation

Table of contents

The kind of analysis on the organization of living beings and their self-maintenance started by Bernard found its heir on Walter Cannon (1871 – 1945). This American physiologist is the one to credit for the original term and notion of homeostasis, which will be a central notion, a reference concept for further investigations about biological organization and regulation. Concretely, homeostasis is a term coined to refer to the processes and elements of the body constantly maintained to keep itself stable. Cannon will specifically talk about "agencies", understood as what will be further understood as control mechanisms, as one of the key elements in biological regulation. These control mechanisms are specifically described as enabling homeostasis, and so they established the grounds of a long-lasting tradition in the study of biological organization and regulation.

When Cannon received Bernard's theories about the functioning of organisms, he considered that, even if it is true that organisms show a great resilience capacity when facing perturbations, they do not resist by just repelling external perturbations, building up a better, stronger barrier against the external milieu. Quite the contrary, they fluctuate within a certain spectrum, and even if sometimes provoked by those outer influences, it does not always imply a crisis, such as a significant loss of stability that necessarily imply a transition to a pathological state, or even death. Instead of resisting, living beings use their flexibility to reduce the negative impact of external perturbations. The do not damper their effects, but let themselves oscillate within a “safe” range around their idea stable state.

This observation allowed Cannon to think about the possibility for the internal milieu not to be as rigid as Bernard thought, but resilient: it could be understood that those processes in charge of the stability of the internal milieu can have a little “deviation” from the regular limited range and still let the internal milieu to be considered as relatively stable. The maintenance within a narrow oscillatory range around an ideal point, while keeping a minimum waste of energy, is what Cannon calls homeostasis. Instead of considering stability in absolute terms, Cannon introduces the idea of a certain extent of oscillation that enhances body’s chances of survival. He does so by introducing limits of that stable state, where oscillatory controls fail, and the organism goes to a wider oscillation that the usual, wherewith the energetic costs rise due to the additional effort of the body to get back to a narrower oscillatory range, closer to the ideal point. Cannon’s proposal points out that living beings do not collapse because just of the perfection of their organization and complexity, but they also show some flexibility which allows them to embrace some perturbations without dying (but spending extra energy).

This chapter will focus consistently in describing Cannon’s proposal, with the aim to clarify what was his original formulation of the concept, to differentiate it from Bernardian origins and formulations on the investigations about biological organization and its implications (such as stability or regulation). It is displayed some of the most relevant steps that Cannon took in his process to define homeostasis, to be able to comprehend what he was aiming to account for and, most importantly, how the forthcoming disciplines unveiled the meaning of homeostasis, and how did that affect to the notion and the biological (physiological) investigation agenda.

A critical display of the various kinds of homeostasis Cannon classifies, and how those can be related to our current concepts on regulation and the diverse levels of organization that constitute it will be included in this chapter as well. This can be traced forward to those modern debates on how the individual is determined by means of regular development of its self-regulatory processes, or what is to be called an organism, and what kind of individuality it constitutes, in the sense that homeostasis might be a powerful tool to approach them in an alternative way.

3.1. Introduction

Cannon’s homeostasis springs from Bernard’s internal milieu which, as mentioned before, can be considered as a material, physical space: an enclosed nucleus that every single living being on Earth has, that maintains itself invariable even if in constant contact with an unstable, perpetually changing environment. What Cannon focused on was the set of processes take place within this invariable internal milieu, which are meant to maintain stability (such as body heat constancy or sugar processing), working at several levels of efficiency. Cannon thought that such efficiency cannot be explained without adding to the equation some sort of flexibility that enables that performance while avoiding the system to collapse, as well as the changes that the body undergoes, following alterations that might not be necessarily pernicious, such as digestion, for instance.

Homeostasis was conceived as a term that accounted for this narrow range of oscillation, and more than a physical nucleus present in every living being, it is a way to give an explanation about how that characteristic and exclusive nucleus of living beings works. It also enables the study of the influences of the external milieu to the internal milieu in terms that do not imply necessarily a life or death situation but a way to understand better the internal milieu as it is, that is, as regulating and maintaining itself.

There might be even a subtle differentiation in Cannon’s proposal that can be elicited from his work *The Wisdom of the body*, not deeply explored in the text, but that may be interesting to analyse. Cannon seem to point towards a distinction between a more basic, or metabolic, homeostasis, which would be in charge of the maintenance of (generally) involuntary basic body processes of minimum maintenance, such as heartbeat or breathing, and a properly regulatory homeostasis. The latter can be identified as those homeostatic control systems triggered exclusively when the oscillatory range begins to get close to the limits. These control systems, that Cannon names agencies[18], are only activated when facing specific perturbations like, for instance, the appearance of a pathogen agent influencing the body, since it drives the body to a higher energetic regime.

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[18] For the current definition of control system we have to wait for the appearance of cybernetics and the results of their investigations on control mechanisms and their functions within a self-maintained system.

As Cannon will define it, homeostasis is a conservative regime of energy, just like the *oeconomie animale* from 18th - 19th centuries' vitalism: "So long as it is kept uniform, a large number of special devices for maintaining constancy in the workings of the various organs of the body are unnecessary. The steadiness of the "milieu interne", therefore, may be regarded as an arrangement of economy" (Cannon, 1932/1967: 287).

Within this context, the oscillatory range is limited, on the one side by the energy invested and on the other side by the energy available, or the maximum energy that is possible to invest in the organism maintenance without triggering and internal irreversible crisis. With the aim of preserving its stability, if a perturbation is strong enough, it pushes the internal milieu to an increased investment of energy, forcing the body to sacrifice part of the energy invested in basic maintenance to resist the perturbation and to bring back the body to its original energetic regime. If that energetic investment compromises the usual development of maintenance processes of the internal milieu, then we can consider that the homeostatic system has passed from a metabolic, with minimum investment of energy, of basic processes of maintenance, to one specifically regulatory, with higher investment of energy, and complex coordination of maintenance processes.

3.2. Describing homeostasis: the original proposal

Cannon proposes the notion of homeostasis to refer unequivocally to the maintenance of stability exclusive of living organisms (Cannon, 1932/1967: 24). In a seminal work, published in 1929, just two years before his The Wisdom, explains profusely the reason that pushed him to choose the term homeostasis. This word is the union of two Greek concepts. One of them is stasis, which might point out something that is maintained and can be easily linked with "static". However, Cannon stresses out another aspect of it, which is its meaning as a condition (Cannon, 1929: 400 – 401). This distinction allows Cannon to introduce the idea of oscillation, conceding more flexibility to the internal milieu and more plasticity to the resistance of organisms to the influence of perturbations from the external milieu. The other Greek term forming the concept of "homeostasis" is homeo, preferred over the one of homo, which means "same", "equal". Homeo, on the other hand, means "similar" or "alike", which permits certain flexibility that homo forbids. This is a clear indicator that, to Cannon, it is important to underline that homeostasis is not a stagnation in a fixed state, as Bernard defined his internal milieu, but a stable state, and flexible.

Even if Cannon follows Bernard's idea of the fixité by proposing an ideal middle point as a reference for the allowed oscillation, the internal milieu now has a wider parameter within which can oscillate and still be considered stable. So much so, when taking the perspective of the field of statics within mechanics discipline, a better term to refer to what he wants to express would be *homeostatics*, since statics is based in creating a stable state by the action of several forces (Cannon, 1929: 401), avoiding that implicit meaning of stasis, implying something stagnated or immobile.

Cannon credits Bernard for the idea of the internal milieu necessarily being subject to the control of certain agencies responsible of maintaining it stable, when he says "He early pointed out that the milieu interne not only is a vehicle for carrying nourishment to cells hidden away in the deep tissues, far from the surfaces of contact with the world outside, and for bringing away from these cells refuse for excretion, but also that it is under control of agencies which keep it remarkably constant. He clearly perceived that just as far as that constancy is maintained, the organism is free from external vicissitudes" (Cannon, 1932/1967: 38; as well as in 1929: 399 – 400). Bernard committed himself to the study and analysis of processes accountable for organism's stability to find out what makes them different from inorganic bodies, and why these entities and not others are able to maintain their stability. Cannon deduced the necessaru existence of some sort of control mechanisms intervening on the protection of the internal milieu, aiming to understand those processes in charge of the behaviour of living systems.

Cannon used the notion of agency in a philosophical sense that implies control mechanisms. Even so, he was not the first one to discuss about control mechanisms: classical control theory studied the structural stability of dynamical systems before, as it is summarised in Maxwell's On Governors (1868) where a study on self-oscillation can be found. Nevertheless, the closest this control theory got to any biological related matter was thanks to the Lotka-Volterra equations of population biology, which started to be formulated circa 1910 but were not definitely bounded to predator-prey interactions until 1925 with the publication of *Elements of Physical Biology* by Lotka. Cannon might be regarded as a pioneer in considering that there might exist control mechanisms that are to withhold biological systems within a range of existence that keeps them stable and are triggered just in case of necessity, since they are expensive in terms of energetic resources.

Some distinctions need to be underlined between the proposal of Cannon and the one from Bernard regarding the organization and self-maintenance of the body. Those can be articulated in two key theoretical remarks. On the one hand, the flexibility of Cannon's homeostasis for the internal milieu. While for Bernard seemed to be a binary condition of yes/no, Cannon includes in stability the possibility of not being just in a concrete stable state but a dynamic flow of relatively stable states.

On the other hand, there is an important insight in Cannon regarding the control mechanisms of the body. Even if Bernard mentions a keen idea (because of the determination of biological phenomena), Cannon builds the foundation for a properly biological theory of control. For Bernard, an internal milieu exists and maintains itself, necessarily protected from external, destabilizer influences. To do so, the confinement of the internal milieu needs to be strong enough. For Cannon, it does not matter that much how strong the barrier between the internal and the external milieu is, but how does it cope with those destabilizers while keeping itself stable.

Cannon explains that some nutrients necessary for the organism, such as glucose, fat, or proteins, can be found normally within the body in a moderately stable state. When some oscillations happen, these oscillations occur within some narrow margin. Thus, they do not pose a risk on survival nor health of the living being[19], that is, they do not trigger any alarm and they do not surpass those limits, meaning they do not need a special investment of energy and resources from the body.

Exceeding those limits can be problematic for the organism and it might bring some disastrous consequences with it. Before reaching the extreme, which implies a real menace to the well-being of the living system, those agencies act and, as Cannon

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[19] I would like to underline here that Cannon developed his observations on the base of animal experimenting, which would keep alive with a relatively equilibrated diet, or which he would deprive of a concrete nutrient or motion, while keeping the rest of the variants relatively stable. In this concrete case, it can be pointed out a possible distinction between reactions by excess or reactions by deficiency. That excess must be understood as way much greater that the one explicated in the section on different kinds of homeostasis, a kind of excess based on a massive, unnecessary, and sustained ingest of food like, for instance, what happens in some contemporary First World societies.

repeatedly says, they draw in the organism to the original stable state, before it endures the deleterious effects of the perturbation. “Before those extremes are reached, agencies are automatically called into service which act to bring back towards the mean position the state which has been disturbed” (Cannon, 1932/1967: 39).

These agencies are control mechanisms that Cannon introduces in the field of study about the organism’s stability. In the same way as Bernard’s internal milieu, these mechanisms or agencies are built from and for the organism itself. That means they are constantly reacting to the necessities of the body and, at the same time, ensuring those necessities are fulfilled. This does not take over the relevance of organization, quite the contrary, since he links it with the achievement of stability just like Bernard. To Cannon, the way to know how systems organize themselves to gain and maintain stability goes through the study of functions carried out by the nervous system. As he argues, “[t]he possibility of obtaining further insight into the organization which makes for resilience and endurance in spite of the fell blows of circumstance lies in an examination of the ways in which stability is achieved” (Cannon, 1932/1967: 244).

These functions can be classified, even if just theoretically as Cannon forewarns, in exterofective and interofective, whether if they project their action towards the external environment, or if they do it towards the inner environment. This distinction is just theoretical because “in normal existence the two divisions are not separable” (Cannon, 1932/1967: 244). Exterofective functions are those whose realization is intentional, they are “arranged for altering the external environment or the position of the organism in that environment by labouring, running or fighting” (Cannon, 1932/1967: 249). Interofective are all involuntary and disengaged from voluntary muscular control, “known also as the ‘vegetative’ or ‘autonomic’ system: ‘vegetative’ because it is concerned largely with the nutrition of the organism rather than with the animal functions of locomotion and prehension; and ‘autonomic’ because it acts automatically, without direction from the cerebral cortex” (Cannon, 1932/1967: 249).

This functional division separates the internal milieu from the external milieu, since exterofective functions are to influence the external environment for the organism’s own benefit, and interofective functions are those taking place in the internal environment, also in benefit of the whole organism. Cannon did not disclose fully the analysis of these influences from the organism on the external environment to focus in the exterofective homeostasis understood as the influences from the external milieu, but even so, and as Arminjon points out: "Regulative *exterofective actions* extend regulation to the external world (Cannon, 1932, pp. 235 – 236). They correspond to voluntary modifications of the environment by means of labour, flight or fight" (Arminjon 2016: 402 – 403). This way, Cannon established a relationship between the internal and the external milieu that was not necessarily confrontational.

Cannon conceives the stability of the internal environment as a matter of economy of the organism[20]. While the internal milieu keeps itself stable, it is not necessary for the mechanisms in charge of resisting the perturbations to be active. Just in the one case when the organism receives an external perturbation, those mechanisms of stability preservation, present but dormant, would be activated. The degree of effectiveness of those management mechanisms of the internal milieu would depend on the evolutionary stage of the organism itself, understanding evolutionary stage as "the more evolved, the more complex, hence the more effective" motto[21]. In superior organisms, as Cannon states, we can appreciate how evolution implied a crescent control over the functions of the internal milieu "as an environmental and conditioning agency" (Cannon, 1932/1967: 287). That might as well imply that those superior mechanisms of control are present just in complex organisms.

To sum it up, homeostasis is an arrangement of economy of the body that ensures the maintenance of the body's stability with the minimum investment of energy and material resources. However, as it was display here, two kind of functions are responsible for that maintenance. This may suggest the idea of homeostasis operating in two different "levels": one basic, automatic, in charge of the fundamental maintenance processes of the internal milieu; and another dedicated to the relationships between the internal and

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[20] "As an interofective system exerting its influence on the activities of the viscera the autonomic must necessarily be intimately involved in the preservation of that stability and constancy of the internal economy of the organism which we have called homeostasis" (Cannon, 1932/1967: 261). It is important to underline that Cannon says "intimately", and under no circumstance "exclusively".

[21] Actually, Cannon is citing a text from Léon Fredericq from 1885 (Cannon, 1932/1967: 21), but he seems to be a supporter of this same idea, just as Bernard, but instead of defending the relevance of the enclosure, he is stressing that evolutionary aspect of homeostatic control mechanisms.

external environment, which would require a superior energy investment[22]. This might be so because the body cannot predict fully the consequences of whatever perturbation from the external milieu disturbing it (unless is a repeated or cyclic kind, in which case the predictions can become more accurate). This also implies an extra energy investment since it might need to act upon the conditions from the external milieu, and not only on the purely internal homeostasis. Those conditions cannot be completely controlled but ameliorated at best. That means that homeostatic processes might cost more energy and resources because their leaning towards the outside.

3.3. Homeostatic organization

To follow the previous distinction, it is safe to assert that there are two main ambits where homeostasis can be displayed. Nonetheless, Cannon focuses mainly on the internal functionality of the body, to know "how the uniformity of the fluid matrix is preserved" (Cannon, 1932/1967: 288). The diverse types of internal homeostasis appear depending on the item regulated, that is, if it is about materials or processes (Cannon, 1932/1967: 290). At the same time, homeostasis of materials is divided in two subcategories, since they can act by overflow or by storage. In addition, material storage can be twofold, depending on the time-scale it is operating within. The first one would be temporary storage, the kind to use the materials acquired in a brief amount of time, and the other would be permanent storage. In the concrete case of glucose (ibid.), for instance, temporary storage can turn into permanent storage if it does not have an immediate use.

Complementary to these kinds of storage, we can find reserves concentrated in "cells or in special places" (Cannon 1932/1967: 291), which is called storage by segregation, or simply flowing around the body, "either in the blood or in the fluids of the alveolar connective tissue" (Cannon, 1932/1967: 290), also known as storage by inundation. The storage by inundation is connected to make substances available through the blood stream to those parts of the body where they can be required. This system does not count on any control mechanism that could be considered very sophisticated, since it "just" acts on substance concentration within the organism. Storage by segregation is

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[22] "So long as it is kept uniform, a large number of special devices for maintaining constancy in the workings of the various organs of the body are unnecessary" (Cannon, 1932/1967: 287).

constituted by storage of fat or proteins like calcium, for instance, and targets specific areas where nutrients may be needed. Storage by segregation separates from storage by inundation because of the control mechanism in charge of sending the signal of the element needed and the area in need, which is a nervous or neurohumoral government in this case.

Another kind of homeostasis with the aim to ensure the stability of the internal milieu is the regulation of materials by overflow. This type of regulation establishes a limit on the ascendant variation of substance in the blood stream (Cannon, 1932/1967: 293). Material excess, like sugar or water excess, are released through the action of kidneys. All of those are threshold substances, i.e. when blood filters through the kidneys, these give in return the amount of necessary materials for the maintenance of the organism, back to the blood stream. If there is any other surplus, it is usually expelled through the urine, or as Cannon says, if those normal quantities are surpassed, the material leftovers are to be rejected by means of overflow (Cannon, 1932/1967: 293). The peculiar characteristic is that not only deleterious materials are to be ejected, but also some of those profitable that can be found in excess.

Back to the main classification on types of internal homeostasis, another general kind if the one of processes, regulated by means of controlling their speed, only to maintain stable the internal milieu and its conditions. Normally these processes are not under control of the cortex, because these are usually automatic processes, as materials management, and that is why there are more likely to be controlled by the sympathetic-adrenal division. The best example of this kind of regulation is control of body temperature. The system in charge of the control of the temperature is based in negative feedback mechanisms, since its main action is to counteract those performances that lead towards instability. Body temperature can be altered because of internal generation of heat, that is, from the internal milieu itself; as well as environmental changes in temperature, meaning it can be affected by changes in temperature of the external milieu. The autonomous system is the main controller of body heat, and skin is the principal mean of its purpose: if it is settled in a temperature higher than the one of the external ambient, it eliminates the excess of heat; and if it is in a lower temperature, it can enhance its ability to keep the heat inside.

Different functionalities regulating temperature are classified according to their final goal and its main physiological mechanism. In the one hand, we can find compensations of normal fluctuations of temperature, where functions are to maintain the body within an acceptable range of heat for the body to be considered healthy. On the other hand, there are functions counteracting possible abrupt changes in temperature in the outside that might compromise homeostasis and threaten the survival and well-being of the organism. These are part of the exterofective homeostasis mentioned before. Regarding this, it is important to note that Cannon did not really explored the relationship between the internal and the external environment but focused exclusively in the inner mechanisms of the body managing the changes of the external environment. To express it differently, Cannon did not explore the voluntary actions to take when, for instance, external temperature drops down, such as putting on a jacket, but only the influences of the external milieu in the internal.

For that reason, when reading Cannon, it is easy to conclude that the "exterofective" functions are controlled as well by the sympatho-adrenal system, and that there is not really a difference to be considered. Quite the contrary, there is a specific paragraph that highlights this concrete issue, when Cannon writes that

> We have already learned, however[23], that exterofective activities must produce coincident changes in the internal environment, as in the utilization of blood sugar and the discharge of acid waste and extra heat into the streaming blood. In these circumstances, the "involuntary nervous system" plays its part by influencing the heart, and the muscles and glands of other viscera, in such ways as will preserve the fitness of the internal environment for continued exterofective action. This inwardly directed functioning of the involuntary nervous system justifies calling it the interofective system. We shall now consider its organization. (Cannon, 1932/1967: 250)

Consequently, Cannon did not fathom the study of the interaction between the internal and the external because he was mostly concerned with the consequences for the internal environment of that interaction, for the reason that "We are separated from that atmosphere [the atmosphere which surrounds us] by a layer of dead cells or by a film of

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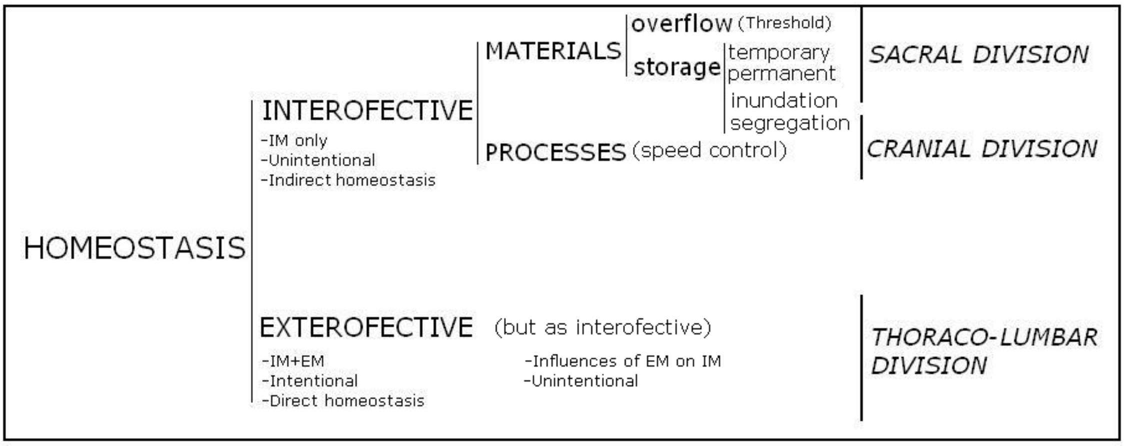
[23] He is previously talking about the voluntary moves that the body takes to preserve itself, controlled by the cerebrospinal nervous system, whose action is mediated by sensitive exterofectors and the different possibilities of voluntary movement that some muscles offer.

mucus or of salt solution. All that is alive within these lifeless surfaces is immersed in the fluids of the body, the blood and the lymph, which form an internal environment" (Cannon, 1932/1967: 263). Still, Cannon acknowledges, like Bernard, that there is an external environment, but contrary to him, Cannon does not believe it plays a relevant role when studying living systems, but the interaction of the internal with the external milieu and the internal consequences of this interaction.



Cannon's proposal for homeostasis (1932)

Table 1 – Representation of Cannon's homeostasis according to his work from 1932. It represents the different divisions of homeostasis, differentiated by several criteria, such as what is mainly affected (internal and/or external milieu, materials or processes), if it is voluntary or not, and how does it function, as well as what body part is considered to be mainly responsible for it.

3.4. Main characteristics of Cannon's homeostasis

The first time that Cannon lists those minimum characteristics homeostasis must have is in a work of his published in 1926, where there can be found six basic features of it, together with a description. These six are still present on his text from 1929, *Organization for Physiological Homeostasis*. Even so, three years later he would publish *The Wisdom of the Body* (1932), where two of those six "tentative propositions concerned with steady states in the body, and with the maintenance of these states, that are pertinent in the present consideration of the general features of homeostasis" (Cannon, 1932/1967:

299) have disappeared from the list, leaving only four[24]. Because of this, here the four basic characteristics of homeostasis:

First, “In an open system such as our bodies represent, compounded of unstable material and subjected continually to disturbing conditions, constancy is in itself evidence that agencies are acting, or ready to act, to maintain this constancy” (Cannon, 1929: 424). In another words, open dynamic systems tend to chaos, and those elements composing this kind of systems are as well inclined to chaotic behaviour, and their interactions are completely random (at least in principle). The fact that some sort of order prevails should be considered prove enough of the real existence of those control mechanisms Cannon is explaining, and that they act with the main goal of maintaining the necessary stability for an organism to be alive.

Second, “If a state remains steady it does so because any tendency towards change is automatically met by increased effectiveness of the factor or factors which resist the change” (Cannon, 1929: 425). This is the main characteristic of homeostasis, the one about resistance to change, if change is to be understood as those perturbations the organism endures along its existence. The problem is that, formulated this way, seems excessively general, and it could be interpreted as the organism resisting also to development or growth processes, for instance. It could be relatively easy to solve this matter if we leave aside from the homeostatic framework this feature typical of organisms, but the aim of this work is to include, ideally, those growth processes within the homeostasis definition, even if as an extreme case, if it must be understood that way.

Third, “The regulating system which determines a homeostatic state may comprise a number of cooperating factors brought into action at the same time or successively” (Cannon, 1929: 426). This point is referring to the complexity of a homeostatic stable state, which cannot be controlled or maintained by just one factor, due to the same complexity of self-regulated systems. That is why it is necessary to several

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[24] Cannon mentions quickly that he had thought about six characteristics, but switched to four without any kind of explanation on which could have been his motives. That is why it seems reasonable to think that, in a determined revision of his work, he decided to subsume some of the original ideas on the six characteristics in just four points, or even that it is no necessary to disclosure six characteristics to understand homeostasis properly.

elements or factors to exist and cooperate, at the same time and speed or in temporal scales connected, that is consecutive, that keep the system stability through time.

Fourth, “When a factor is known which can shift a homeostatic state in one direction it is reasonable to look for automatic control of that factor or for a factor or factors having an opposite effect” (Cannon, 1929: 426). Theoretically, if we consider just as Cannon does, that homeostasis is a resistance or opposition to change, homeostatic system must have that characteristic that enables it to offset that change with the same intensity, to revoke the power of that change with the same intensity, to invalidate its effects and protect this way the organism. Still, in practice it results really complicated to determine which and how many of those factors are at play, mostly because of these random interactions and inherent complexity of open dynamical systems.

Just for the sake of philosophical curiosity, these are the two characteristics that Cannon discarded, explained as he originally defined them. First, “Any factor which operates to maintain a steady state by action in one direction does not also act at the same point in the opposite direction” (Cannon, 1929: 425). When Cannon wrote this, he did not consider that some processes might be reversible, and that those very same processes might be using the same factors used to alter that original state of the system.

And second, “Homeostatic agents, antagonistic in one region of the body, may be cooperative in another region” (Cannon, 1929: 425). Even on the paper where this point is to be found, Cannon does not seem sure about how those agencies would work within the homeostatic maintenance of stability. It seems difficult to try to explain, and even to trace, the action and consequences of some body parts, or organs, in the wider set of the organism as a unit for its maintenance. This complexity might have been the main reason for Cannon to take this one out from his definite list from 1932.

3.5. Final remarks

The main aim of this chapter was to clarify what Cannon meant by homeostasis when he proposed it, and in what context it arose. Briefly stated, physiology, after Bernard’s breakthrough, searched to comprehend the phenomena of life through the study of organisms, and more concretely in the case of Cannon, to understand the peculiar organization of living beings that make them different from the rest of entities. In this sense, Cannon considered that it was not necessary to study anything else than the internal milieu and its constitutive processes and elements when analysing life. To this respect, the work of Cannon departs from Bernard. Even if Bernard considered that the phenomena of life could be only found inside the internal milieu, as Cannon does, he underlined the relevance of the existence of the external milieu. He acknowledged that life can be found in the boundary between the internal and the external, and that there will be no life without that friction. Cannon did not disregard the relevance of that interaction but he focused on a deep study on the constituent mechanisms responsible for the organization and stability of living beings.

This led him to define homeostasis as a set of internal control mechanisms, rising from the organization of the organism, which perform several functions depending on the internal milieu necessities. That means that within a biological system there are controls dedicated to the constant maintenance of certain minimums necessary for the body to persist, such as the management of materials and processes, as well as a set of controls dedicated to respond to specific perturbations coming from the external milieu. This specificity is defined in terms of energetic and resources investment, for homeostasis is an arrangement of economy of the body. Most of the perturbations from outside the organism can be handled by basic control mechanisms, but some of those perturbations that require a more complicated response.

One of the issues of Cannon's proposal addressed in further researches, such as cybernetics, is related to this last remark. The limits of the homeostatic oscillation are defined as narrow, and around an ideal, medium point. From this definition, two main problematic matters arise: one concerning the definition of that medium point. The other is related to the limits of that oscillation. Cannon aimed to establish a definition for both through experimentation, inspired by the factor of safety from Meltzer[25] (Cannon, 1932: 231). He experimented with different components of the internal milieu, recording the changes of concentration in blood of those elements (like sugar, calcium, blood pressure, or the carriage of oxygen) and the consequences for the body. This way he could define an ideal concentration, where the body functioning was optimal, and the amount of concentration where the body started to feel the shortage, named the deficiency threshold.

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[25] It was a term already used in engineering to refer to the maximum amount of stress a machine could bare while at work, but Meltzer wrote an article applying it to biological entities (see Meltzer, 1907).

This threshold is controlled by the control mechanisms of the body, which constitute "A noteworthy prime assurance against extensive shifts in the status of the fluid matrix is the provision of sensitive automatic indicators or sentinels, the function of which is to set corrective processes in motion at the very beginning of a disturbance" (Cannon, 1932/1967: 288). The problem is that, to know when those agencies are to be activated, we need to know the limits of the homeostatic oscillation. Even if not the limits, since limit can be defined also as collapse or death, but the gradation, or medium "limits" within the oscillation that activate different emergency control mechanisms to re-stabilize the body before surpassing a point of no return.

These limits of the definition of homeostasis, together with the overall limitation of being restricted only to the internal milieu, will determine further researches based on homeostasis and agencies proposal. It is important to stress out that Cannon not only focussed just in the internal milieu, but within the internal milieu he studied mostly mechanisms programmed and controlled by the adreno-sympathetic system, i.e. the functionality of the spinal cord. As some of the forthcoming critiques will likewise underline, the role of the brain must be included in a full-developed notion of homeostasis, as well as the relationship between systems. This means to include the formulations from Bernard about the interaction between the internal and the external milieu, deepening in its characteristic features to enable the creation of a model that can be used widely on biological interactions. That is why it is needed to define biological systems (as in General Systems Theory and, later, Systems Biology), clarify how those control mechanisms of the body work and relate to each other (like in the explanatory proposal by cybernetics), and to include higher, more complex, controls from the body, such as the brain, to fully disclose homeostasis (that can be found in further physiological developments on the matter).

First Stream:
The Operationalist Turn

.4.

Control Mechanisms and Information

Table of contents

Cannon's agencies and his explanation on how a system maintains itself, inspired Norbert Wiener (1894 – 1964) to deepen the analysis on control mechanisms. Keeping the focus on understanding living beings and how they function, his approach to the subject was strongly characterised by his mathematical cultivation. Thanks to it, he was able to propose one of the first mathematization and modelling of self-maintenance or stability of a system related to homeostasis.

His aim for making homeostasis a quantitatively tractable hypothesis would lead him to formulate a new field of study, strongly linked to information theory and control theory, which he would baptise as *cybernetics*. The main object of this new discipline is to analyse regulatory systems, considering biological cases as paradigmatic; as well as their structure and organization. Even if cybernetics might follow the most relevant traits of the previous physiological researches, it does so roughly, since there are some primary differences with the formulations from Bernard and Cannon. First, we find that there is no longer interest on the specificity of the features of living beings, but just as models of regulated systems and, concretely, as self-regulated systems. The definitory unity of living beings and how they establish relationships with their external environment is not a central issue in cybernetics, but the controls that enable self-maintenance. In other words, focus switches from the study of organisms as they behave and maintain themselves as unities to the search on the biological mechanisms that sustain them.

This points to the second divergence from Cannon's and Bernard's previous approaches. The specificity of physiological and biological terms of the study of stability of living beings is compromised, due to that mathematization and modelling. Organisms are referred to as systems, and their behaviour is explained in terms of separated mechanisms. This is not inherently negative, but it can be considered as such when the biological tone of the study on organism's organization is compromised. This gives rise to justified accusations of reductionism of biological phenomena to mathematical and physical descriptions. This will mark one of the main streams of the conceptual development of homeostasis, which will take the role of being the main, if not the only, definition considered when aiming for scientific explanations based on homeostasis. Yet again, this is not intrinsically counterproductive, but the gap created between the definition provided by this cybernetic approach and the proposal raised from physiology confers to homeostasis certain ambiguity in modern research about organisms that makes difficult, if not completely unable, to be used as a holistic notion for organisms and their functioning.

Consequently, homeostasis defined as a property maintained by feedback loops loses its biological particularity. Therefore, the line between living beings and inorganic bodies, or *corps bruts* as Bernard called them, becomes even more ambiguous. That is why it can be said that homeostasis categorically loses its character of demarcation criteria. Surely feedback loops (and extensively a great part of cybernetics) can be understood either in informational terms or dynamical terms. This informational side of cybernetics will constitute the explanatory core of this chapter, since this quantitative unfolding is held responsible in this work for the current ambiguity of homeostasis. Dynamical, more qualitative descriptions will be used only when explanations of dynamical feedback differ significantly from homeostasis as posed by Cannon[26].

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[26] To clarify, this does not mean that homeostasis is exhausted by the description provided by the feedback model: feedback, described in cybernetic dynamical terms, can be just referred univocally to an

In any case, Wiener's work helped to widen our knowledge on system's organization and control mechanisms, so much so it initiated a novel field of study, a discipline that started with a completely new line of research. William Ross Ashby (1903 – 1972), following Wiener's work (some even say he was his disciple), used the theoretical work of Wiener to develop a formula that allowed him to build a machine capable of self-maintenance. He called it *homeostat*, and to build it he took into consideration the preceding idea of feedback loops, complementing and developing feedback theory with experimentation. This led him to create a formula called *Ashby's law of requisite variety.* This formula allows calculating the amount of variation a system can endure, opening the possibility of creating artificial response mechanisms to be confronted to perturbations.

From Ashby's contributions, cybernetics starts to modify slightly its focus as well, going from a strong interest on the structures behind self-regulated systems to pursuit how information is transmitted and maintained, that is to say, it starts to focus on the study of systems as perception, action interpretation, and communication centres (von Foerster, 1969, in Livet, 2006: 261); to wit, their learning and communicating capacities. This change would have a principal part in the distinction of two kinds of cybernetics. On the one hand, the first order cybernetics, focused in descriptions of constitutive processes and minimum control mechanisms, tightly related to control theory. On the other hand, second order cybernetics, extremely concerned on widening this perspective through the study of informational fluxes, using feedback loops as "building blocks" (as it is further developed in this chapter) for complex systems.

One of the most influential figures of this second order cybernetics is Stafford Beer (1926 – 2002) who dedicated his work to make explicit the organization of various levels of feedback loops and control mechanisms that constitute self-regulated systems. The work of both researchers can help in the matter of understanding relationships between those control mechanisms, the hierarchical levels that emerge from those relationships, and how they coordinate with each other. That is mostly why these

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interofective type of homeostasis, homeostasis of processes, where the body controls their speed to self-regulate. The dynamics of the feedback model are more difficult to apply to homeostasis of materials or even exterofective homeostasis.

investigations indicate a possibility of development of the analysis of organization and complexity in living systems.

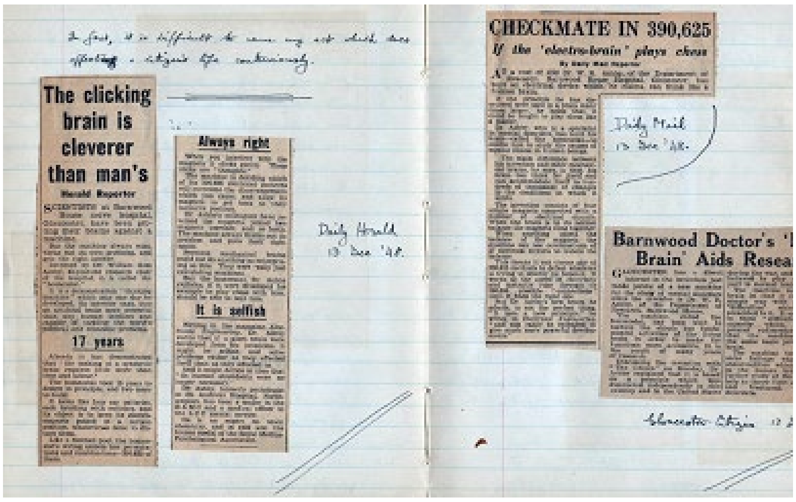
The main goal in this chapter is to stress out the pros and cons of the developments of the idea of homeostasis under this cybernetics light, namely, understanding quantitatively the stability of the internal milieu. This is done by means of making explicit the structure of the process underneath, often in informational terms because, as Collier (2003: 292) expressed, "information is a central aspect of organisation". However, since homeostatic self-regulation is more than just structure, as Bernard already pointed out when demanding vivisections, another goal in this work is to argue that the homeostatic model defined through feedback loops is not fully satisfactory when applied to higher levels of complexity in biological systems. This can be considered the conceptual twist that makes the notion of homeostasis ambiguous nowadays. Forasmuch as it was conceived as a specifically biological (or physiological) notion that describes biological organization as a distinctive feature, this operational turn, which was remarkably popular and successful, marked the notion in a way that makes difficult for it to connect again with its (underdeveloped) qualitative definition, leading to this tension found in modern research related to the acknowledgement of its holistic, unifying potential while using its operational, more reductionist, developmental stream. However, there were researchers trying to build bridges between qualitative and quantitative descriptions, like J.S. Haldane (1860 – 1936), who aimed for the creation of a common ground where living systems and machines could be tell apart, while keeping a mechanistic explanation about biological being's behaviour.

4.1. Introduction

The origins of cybernetics are based on the shared idea of searching for an explanation and emulation of regulatory mechanisms, together with their control systems. Wiener was not the only one to develop a theory on control systems. He had a German homologous, Hermann Schmidt (1894 – 1968), but his proposal was slightly different since Schmidt relied vehemently on a strong technical perspective of engineering. For him, control is to be defined as the last stage of human technological evolution that means it is in the most complex historical moment of its development, since it involves every previous evolutionary phase of technology. Wiener, contrary to Schmidt, thought that there was a clear difference between human and machine, while for Schmidt machines were an uninterrupted extension of human beings and their activity. Wiener had in mind a more pragmatic goal, which is to solve mathematical problems and technical issues of regulation and control, trying to underline the difference between human being and machine. Notwithstanding, he could not avoid being accused of not differentiating those two enough, a probable cause for his reductionist approach, which holds him in a micro-perspective, centred in constitutive processes but not including a holistic perspective to complete his description.

One of the main ideas that inspired Wiener was, as mentioned before, Cannon's configuration of the notion of homeostasis as processes to maintain stable a system by means of the internal milieu, where the mechanisms of control and self-maintenance are the main concepts leading to deepen our knowledge about regulation. Since it was just a part of Cannon's theories and not really a continuation of them, the study of these ideas got a new name from Wiener, that is, *cybernetics* to refer to the study of control mechanisms and communication on animals and machines. With that designation he was trying to stress out the self-government of complex systems that rely on a set of control mechanisms to maintain their stability.

William Ross Ashby is another important figure in cybernetics that is to be highlighted when approaching the matter of self-regulation and biological organization. Even if he is widely known for applying Wiener's original ideas to the field of artificial intelligence, what it is interesting for the investigation at hand is his law of requisite variety, which allows us to calculate with a minimum margin of error the amount of variety a control system can withstand. This calculation explains quantitatively the dynamics of a system, whether human-made or biological, that allows it to maintain itself stable. Aiming to test this law, Ashby built an apparatus that worked by following the principles of Cannon's homeostasis, called *homeostat*, and which resulted to be highly popular on the press back then, since it was one of the first machines to be constructed that could maintain itself through homeostatic regulation of some sort, that is to say, that it was able to oppose the same amount of variety of the perturbation against it from within, hence persisting without any necessity of human intervention.



The clicking brain is cleverer than man's

Herald Reporter

17 years

Always right

It is selfish

Daily Herald
13 Dec '48.

CHECKMATE IN 390,625

If the 'electro-brain' plays chess

Daily Mail
13 Dec '48.

Barnwood Doctor's '
Brain' Aids Resea

Gloucester Citizen

Figure 1 - Ashby kept newspaper clips in his journals about the homeostat. Image courtesy of The Estate of W. Ross Ashby. Copyright 1972, 2008 © Found in rossashby.info

The observed behaviour of Ashby's machine offers a hint on what could be considered as limits for the oscillatory range that Cannon stated as dangerous for the stability of the system, even if Ashby never built a specific explanation to that respect since he was more interested on building an automaton exhibiting an organism-like autonomy. In any case, it can be inferred that the allowed oscillatory range depends on the amount of complexity of the system: the more complex it is, the more variety it can resist, making its resilience against perturbations stronger. It is not clear, anyway, how could that make the oscillatory range peculiar for every self-regulated system, in the case it is not just to be applied to an evolutionary scale of complexity, justifying this way a biological hierarchy. However, thanks to cybernetics we have an explanation on why a system enters a critical state and collapses, or how does it manage to avoid reaching that critical state and why.

4.2. First-order cybernetics analysis of cycles

As stated some lines above, Wiener was the one to come with the name of cybernetics, and he did so with a special interest on the research, study and quantification of control mechanisms present in both living beings and human-built machines. The main question Wiener might have asked himself about organized systems was *how* they work, that is, how homeostasis works, what mechanisms make possible those processes that enhance their characteristic self-maintenance, and their functioning.

Wiener established a parallelism between animals and machines based on their functioning. As he points out in his proposal, the idea that links both is that of feedback loop. This proposal explains how homeostatic processes work, while comprising an explanation as well on why those processes, as much as every biological process, mostly, follow a cyclic structure, and how it is maintained. In another words, feedback loops offer an explanation, through modelling, on why cycles are present in nature, while justifying themselves at the same time by naturalizing their existence (see appendix on feedback).

The idea of feedback loop emerges directly from Cannon's theories about control systems. The interest was on Cannon's agencies, to analyse them to discover how they function, and how they control homeostasis, keeping the stability of the system. One of the most interesting studies from cybernetics is their inquiry on how control mechanisms make possible the maintenance of a system, building a model suitable for every system that sustains its stability in a homeostatic, or self-regulated way, regardless of its origins.

Informational theory, which Wiener used as groundwork as well to elaborate his theories, has some implications and ramifications in several disciplines and theories, such as computational theory, engineering, etc.; but in this work the focus is consciously set on feedback loops and their relationship with homeostasis and its conceptual changes. A simplified way to start understanding feedback mechanisms is through the widely known structure of emitter, message, and receiver. Just for the sake of clearness, emitter would be the control system that triggers a reaction for a perturbation, sending a signal (a "message") to be decoded by the receptor, the mechanism responsible for taking into action the response necessary to maintain homeostasis.

In dynamical terms, feedback is characterised by using as input the previous outcome from the system, routed back to it. In its simplest representation, that input is pictured as going back immediately, but usually it does so after being modified, at least to some extent, influencing back the system and modifying its functioning and behaviour if necessary. When such a modification occurs, there are two ways the system can be influenced, by increasing its performance, or by decreasing it. Positive feedback raises the gain of the system. Negative feedback reduces it, by means of correcting it to make it able to meet the needs of a concrete situation or, as Rosenblueth et al. (1943) describe it, "the behaviour of an object is controlled by the margin of error at which the object stands at a given time with reference to a relatively specific goal (…) to restrict outputs that would otherwise go beyond the goal" (Rosenblueth et al., 1943: 19). In the case of biological systems, for example, feedback loops are defined as to maintain a stable state, either by accelerating its processes (positive feedback) or by slowing them down (negative feedback).

Back to informational theory, the interest Wiener has on it comes from the fact that he was thinking about the matters relative to control engineering and communication engineering to be inseparably bounded to each other, since both share their focus on the idea of message[27]. The relevance of it is rooted on the accuracy of predictions: any future prediction of a message is based on a past operator, and the method to get optimum predictions is to statistically analyse the messages, i.e. the predictable time series, to find the predictive error and fix it (Wiener, 1948/1985: 9). These notions (message, operator, etc.) constitute basic concepts from informational and communication theory, from which the idea of feedback was build. A deep understanding of the theoretical framework from which cybernetics principles were established would make easier a posterior specification of those parallelisms that are to be found within the machines performance, from a cybernetics perspective, and the behaviour of living beings, within physiology and biology.

4.2.1. Feedback loops

The notion of feedback is the cornerstone of the cybernetics discipline, since it is applicable to systems that exhibit a closed information loop only, or to pose it differently, a dynamic loop (which is ultimately reducible to informational terms within this discipline), such as biological systems, for instance. This implies that the action of the system leap back on the very same system, creating this way a causal closure. Feedback

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[27] "The message is a discrete or continuous sequence of measurable events distributed in time – precisely what is called a time series by the statisticians" (Wiener, 1948/1985: 8-9).

is no more no less than a mechanism that deviates part of its output, or final product, back to the inside of the system, to control and regulate its own behaviour and activity.

That output can be used as a mere resource, e.g. food, or as information. Regarding those feedback mechanisms of living systems, Wiener writes: “We thus see that for effective action on the outer world it is not only essential that we possess good effectors, but that the performance of this effectors be properly monitored back to the central nervous system, and that the reading of the monitors be properly combined with the other information coming in from the sense organs to produce a properly proportioned output to the effectors” (Wiener, 1948/1985: 96).

In the specific case of homeostasis, the kind of feedback that characterizes it the most is negative feedback. When this type of feedback is present, the system, using the information available, reduces the output or activity of any organ or subsystem, getting it back to its normal range of activity, contrary to the positive feedback, which is a source of change and variability, negative feedback enhances the possibilities of survival of the system by means of preservation of stability and the increasing of its resistance. even if in biological systems, both types of feedback can be found, homeostasis is usually understood as to correct deviated parameters, to take back the system to the allowed oscillation range[28].

Wiener comments about this kind of feedback that “the feedback tends to oppose what the system is already doing, and is thus negative” (Wiener, 1948/1985: 97). Typical examples of this kind of regulation are temperature, velocity, or position regulation (Wiener, 1948/1985:97), all of them examples applicable to both animals and machines created by human beings. Regarding temperature regulation, and just for the sake to enhance the understanding of the matter at hand, if body temperature increases, the hypothalamus activates those control mechanisms in charge for temperature regulation and triggers the sweating process. As soon as body temperature goes back to the normal range, it sends a signal towards the hypothalamus to cancel the action of those sweating

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[28] This can be regarded as the regular usage whitin medicine nowadays. Homeostasis applied to medicine describes disease as a departure from the established oscillation, focusing the role of medicine on correcting that drift. Further in this work there is an analysis on this conception.

mechanisms, inhibiting this way that activity and avoiding dehydration for excessive sweating.

Wiener mentions homeostasis from a cybernetics perspective, considering it as a physiological application of the feedback principles. As he points out, “A great group of cases in which some sort of feedback is not only exemplified in physiological phenomena but is absolutely essential for the continuation of life is found in what is known as *homeostasis*. The conditions under which life, especially healthy life, can continue in the higher animals are quite narrow. A variation of one-half degree centigrade in the body temperature is generally a sign of illness, and a permanent variation of five degrees is scarcely consistent with life. (…) In short, our inner economy must contain an assembly of thermostats, automatic hydrogen-ion-concentration controls, governors, and the like, which would be adequate for a great chemical plant. These are what we know collectively as our homeostatic mechanism” (Wiener, 1948/1985: 114 – 115).

Those mechanisms for homeostasis are slower in comparison to those mechanisms responsible for the voluntary movement or postural but for heart movements, as he punctuates. This is mostly because normal effectors of homeostasis, like smooth muscles and glands, are a slower mean of transmission than stripped muscles, those used in voluntary and postural activity. This implies that homeostasis does not use nervous channels, but hormones or carbon dioxide in blood, which are slower than the nervous system communications. That is why homeostatic oscillations do not usually imply dangerous consequences for the organism, since homeostatic mechanisms absorb the impact of perturbations by slowing them down.

This definition is what it is currently understood as homeostasis. It is opposed to voluntary movements of the body, following the focus Cannon posed on the internal environment homeostasis. The main difference between these two conceptions is that homeostasis in cybernetics is reduced to the internal, automatic responses from the body, what can be regarded as metabolic maintenance; while Cannon’s proposal, even if disregarding the importance of exterofective homeostasis for the study of self-regulated organisms, still considers homeostasis as a holistic notion for system’s organisation and regulation.

4.2.2. A formalization of homeostatic oscillations

Ashby also mentions that capacity of systems to resist perturbations, but also from a quantitative perspective, in line with the concretion drive of cybernetics. In his theoretical approach, he explains that a deterministic dynamical system will always tend to a state of stability. That is why every state that takes it away from that goal would be ignored or eliminated. This tendency towards stability is a constriction, or as Ashby names them, a *constraint*[29] that it is of its own, and which implies a dependency relationship, or a coordination between the different subsystems or elements that form the system.

Ashby built the first apparatus based on the formulas he ideated for measuring variation, with the goal of testing his *law of requisite variety* and see to what extent a self-regulated system built, meaning not born, could be able to persist on existing. It was constructed circa 1950, close to the year that Wiener coined the term of cybernetics, and he called it *homeostat*, as recognition for Cannon's investigations.

Extremely simplifying the idea of Ashby, and in order to be able to understand how the homeostat works, the machine functions according to negative feedback, fighting against the disturbances imposed by the experimenter from the outside with the goal of keeping itself stable and keep going, testing if it is true that it can be calculated the quantity of variety that a system can endure by means of his law of requisite variety, as a system's stability criteria.

It establishes a relationship between the internal variety with the external one, arguing that, in order to resist the different kinds of perturbations, a system must face along its existence, system's regulator must be able to manage the same level of variety of the very same perturbations, keeping the system within the range of normal physiological states (Ashby, 1952/1999: 202ʃʃ).

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[29] This notion of constraint refers to a series of boundary conditions that, by narrowing down the degree of freedom of a system, increases the possibility of a determined process or trait to happen. This definition would be used by the organizational account developed by Álvaro Moreno, amongst others.

4.2.3. Law of requisite variety

Ashby's law of requisite variety is defined from a remarkably simple table game, where a series of combinations are given between D and R, and progressively complicating it. After offering several versions of it, a first attempt of definition of this law is: "If V_D is given and fixed, $V_D - V_R$ can be lessened only by a corresponding increase in V_R. Thus, the variety in the outcomes, if minimal, can be decreased further only by a corresponding increase in that of R"[30] (Ashby, 1952/1999: 207).

Moreover, he continues: "This is the law of Requisite Variety. To put it more picturesquely: *only variety in R can force down the variety due to D*; **variety can destroy variety**" (Ashby, 1952/1999: 207). In this case, as in a good part of the book, R refers to regulator, D to disturbances, and V is used as a substitute for variety. Ashby formulated this law when reading Cannon's *Wisdom*, trying to find some means to calculate the amount of regulation achieved, but sometimes Ashby seems to take as synonyms complexity and regulation, and even if they are tightly related, they are not the same. For instance, when talking about regulation as a process instead to take it from the biological point of view, he says that we must thus find "ways of measuring the amount or degree of regulation achieved, and we shall show that this amount has an upper limit" (Ashby, 1952/1999: 202). It might seem that Ashby follows the idea of "the more complex, the better the regulation" as well, based on his definition of variety (further on).

Nevertheless, the role of requisite variety that is quite remarkable is the one of constraint of regulation, defined as the limits of the amount of information or control manageable by the regulator. After distinguishing between the size and amount of variety

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[30] Where D and R are players, being D the first one in moving, by choosing a row, thus conditioning R's responses, which searches a determined result in within the columns (in the case shown on the original text, that being "a"). For instance, if the input it is 1, the job for R to do is to find "a" within that row. In case there was not any to be found, it should be choosing the closest result to the original one, in this case "b", or "c" of there was not any "a" or "b", and so on. The main goal of this simplification is to explain, by progressively complicating the game until reaching the formulation of the law of requisite variety, how regulatory systems work when faced to perturbations from the external milieu, opposing the same amount of variety from the inside to the one coming from outside; and also how control systems are conditioned by disturbances. There is a fragment in this work that goes deeply in this idea.

of a system[31], "It now follows that when the system T is very large and the regulator R very much smaller (a common case in biology), the law of Requisite Variety is likely to play a dominating part. Its importance is that, if R is fixed in its channel capacity, the law places an absolute limit to the amount of regulation (or control) that can be achieved by R, no matter how R is re-arranged internally, or how great the opportunity in T" (Ashby, 1952/1999: 245)[32].

Hence, when the explanation through that simple game reaches a determined level of complexity, Ashby considers he can offer a definition of what can be considered as regulation: "There is first a set of disturbances D, that start in the world outside the organism, often far from it, and that threaten, if the regulator R does nothing, to drive the essential variables E outside their proper range of values. The values of E correspond to the "outcomes" of the previous sections. Of all these E-values only a few (h) are compatible with the organism's life, or are unobjectionable, so that the regulator R, to be successful, must take its value in a way so related to that of D that the outcome is, if possible, always within the acceptable set 17, i.e. within physiological limits" (Ashby, 1952/1999: 209).

Consequently, the main feature for a regulator to be a good one is to block perturbations, just as Bernard said, but described in another words, and from a quantitative perspective: "In general, then, an essential feature of the good regulator is that it blocks the flow of variety from disturbances to essential variables" (Ashby, 1952/1999: 201). In fact, further in his writings, he distinguishes two ways of blocking that variety. There is a passive one, consisting in placing a barrier, whether material it must be built, between the disturbance and the essential variables, just as, for instance, a tortoise carapace. This basic kind of resistance was more likely the one that Bernard had

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[31] The size of the system does not account for the level of complexity it holds within, but the variety is: "What is usually the main cause of difficulty is the variety in the disturbances that must be regulated against" (Ashby, 1952/1999: 244).

[32] Here it can be found an implied distinction between regulation and control. *T* refers here, and also in the rest of the text, to every single possible state, that might be also called outputs, that a system can find itself from the very second the effects of perturbations are triggered by the action of the regulator, to its evolution to a concrete and determined state.

in mind when proposing the *fixité* of the internal milieu, namely, the internal milieu avoiding being influenced by the chaos from the external environment.

The other kind of resistance to perturbations consists in taking the information available and used it to build a defence, this being composed of an opposing force against the disturbance, which can only be done with the necessary information about the perturbation coming, in order to get ready for it and offset its influence before it becomes a problem; the so-called “skilled counter action”. These two are not the only cases, but the extreme cases of a range of possibilities (Ashby, 1952/1999: 201). They also can be understood as extreme cases of diverse kinds of biological regulation, being the first one the closer to what a metabolic maintenance looks like, and the second as the upper possible level in biological proper regulation.

We have been talking about blocking variety, but not how that variety reaches the system. Further on, Ashby talks about that in terms that might be understood as evolutionary, almost: “There is that which threatens the survival of the gene-pattern — the direct transmission by T from D to E. This part must be blocked at all costs. And there is that which, while it may threaten the gene-pattern, can be transformed (or re-coded) through the regulator R and used to block the effect of the remainder (in T). This information is useful and should (if the regulator can be provided) be made as large as possible; for, by the law of Requisite Variety, the amount of disturbance that reaches the gene-pattern can be diminished only by the amount of information so transmitted. That is the importance of the law in biology” (Ashby, 1952/1999: 212).

Therefore, the regulator is to obey Ashby’s law precepts, but it needs a controller to be able to block the perturbations. The way it seems to work is by influencing the regulator, with the result that it has two independent sources of information, namely perturbations and the very same control, in order to control the results of interaction between regulator and perturbation, with the final object, at least in principle, of keeping the organism within the limits of what he calls “normal physiological boundaries”, trying to avoid at all costs any influence from disturbances. This kind of correction of deviated oscillations seems close to Cannon’s notion of homeostasis.

For the sake of clearness, let us share the example Ashby's uses: "Suppose now that R is a perfect regulator. If C sets a as the target, then (through R's agency) E will take the value a, *whatever value D may take*. Similarly, if C sets b as target, b will appear as outcome whatever value D may take. And so on. And if C sets a particular sequence —a, b, a. c, c, a, say— as sequential or compound target, then that sequence will be produced, regardless of D's values during the sequence. (It is assumed for convenience that the components move in step.) Thus, the fact that R is a perfect regulator gives C complete control over the output, in spite of the entrance of disturbing effects by way of D. Thus, *perfect* **regulation** *of the outcome by R makes possible a complete* **control** *over the outcome by C*" (Ashby, 1952/1999: 213 - 214). As it can be seen, the success of the controller depends highly (necessarily, as Ashby would say) on a successful performance of the regulator, and that is why they are to be understood as tightly related to each other.

An interesting proposal derived from that law of requisite variety, and exclusively referred to biological systems, is an especial type of regulation, which Ashby calls regulation by error. It is called this way because, contrary to the perfect regulator explained before, this error-controlled regulator does not react directly to perturbations, like, for instance, the red blood cells rising when facing a decreasing availability of oxygen (like happens to people living in high mountains): "This regulation draws its information from the harmful effect (the lack of oxygen) itself, not from the cause (D) of the heart disease, or from the decision to live at a higher altitude" (Ashby, 1952/1999: 222).

From a perspective closer to the informational theory, Ashby calls it "error-controlled servomechanism" or "closed loop regulator", and it is said to appear just when "the information available to R is forced to take an even longer route, so that R is affected only by the actual effect at E" (Ashby, 1952/1999: 223).

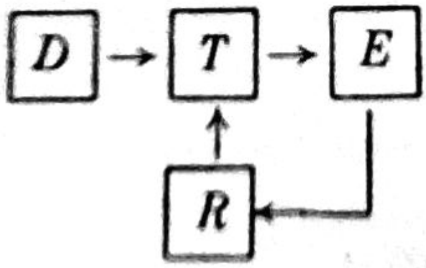

Figure 2 - Ashby's regulation by error layout (Ashby, 1957: 223). Disturbances D influence the system T, producing the error variable E, which constitute the element that informs the regulator R in this case. The more successful the regulator, the smaller the range of error. This type of regulation occurs when there is no information about D, or that information does not suffice for a complete blockage from R, such as living systems: they can count on "channels of information, through eyes and ears for instance, that supply them with information about D before the chain of cause and effect goes so far as to cause actual error" (Ashby, 1958: 91)

What allows this type of regulation to be viable is continuity. The regulator acquires information on these errors progressively, to avoid further and serious problems, enabling this way the persistence of the entire system: "Fortunately, in many cases complete regulation is not necessary. So far, we have rather assumed that the states of the essential variables E were sharply divided into "normal" (η) and "lethal", so occurrence of the "undesirable" states was wholly incompatible with regulation" (Ashby, 1952/1999: 224). But regulation by error explains how a system with a regulator unable to block every perturbation completely is still capable to survive. The question might be if it cannot be considered normal a system with such a regulator, since it seems to be the (paradigmatic) case of biological systems, for instance. In any case, the continuity that allows a system regulated by error to maintain itself is related as well with the teleology of this kind of systems. As Ashby puts it,

> As is now well known, a system around a state of equilibrium behaves as if "goal-seeking", the state being the goal. A corresponding phenomenon appears in the Markovian case. Here, instead of the system going determinately to the goal, it seems to wander, indeterminately, among the states, consistently moving to another when not at the state of equilibrium and equally consistently stopping there when it chances upon that state. The state still appears to have the relation of "goal" to the system, but the system seems to get there by trying a random sequence of states and then moving or sticking according to the state it has arrived at. Thus, the objective properties of getting

> success by trial and error are shown when a Markovian machine moves to a state of equilibrium (Ashby, 1952/1999: 230)[33].

This tendency towards equilibrium is an idea that is present as well in General Systems Theory (next chapter) and explains how (biological) systems persist despite perturbations not being completely avoided or blocked, as well as the basic dynamics of these kind of systems. Biological systems are no longer understood to avoid the influence of perturbations, but to use them, as far as possible, to strengthen their own resistance to future perturbations.

4.2.4. Some considerations on first-order cybernetics

Cybernetics helped quantifying the ideas on homeostasis, by formalizing Cannon's agencies and modelling those processes necessarily needed for a stabilizing process like homeostasis, allowing us to calculate, with a minimum margin of error, the capacity of a system to endure the perturbations coming from the external milieu. To this respect, feedback loops expressed by Wiener offer to us the possibility to picture how cycles observable in nature work. On the other hand, Ashby's law of requisite variety clarifies how a system resists perturbation, even if new, since it establishes a parallelism between the level of complexity of a system and the amount of variation that the internal milieu of an organism can resist. It also permits calculating what would be the margin of error of a system when getting in a critical state or collapsing[34].

However, and as it was pointed out earlier, as much as we can calculate the level of variety that a system faces, and even if we can display the amount of variation for a system to reach a critical state, it is still difficult to define the boundaries of that range of

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[33] A Markov chain, in probabilistic theory, is a special kind of discrete stochastic process, where the probability of an event to happen depends exclusively on the previous event.

[34] Cybernetics in Ashby's hands transmutes from the search of an explanation about processes of creation and maintenance of that stability with a drift towards equilibrium in any kind of system from Wiener, to an attempt to emulate the processes of nature for the sake of human being well-being (but avowing the difference between biological and human-made systems: so far as this work is concerned, the only author consulted that brought them closer was Schmidt, by considering technology as an extension of human being definition.

action that Cannon thought about. The closer we get is through Ashby's idea that states the more the information transmitted, the more complex the system, so the greater the possibility of failure, and the greater as well the amount of entropy.

In other words, to resist disturbances, the regulating mechanism must be able to counter its action with the same amount of variety. That is why, the harder the perturbation, the more the need for a system with an important level of complexity equal to the complexity of perturbation. The problem, which Stafford Beer would try to solve later, is that the higher the level of variety, or if preferred the more the information to work with, the easier it is for an error to occur, so the regulator must use more informational and energetic resources to remove the errors and rectify the deviated trajectory of the system.

Consequently, homeostasis defined as an arrangement of economy can be understood, in this framework, only within the limited margins of a minimum maintenance such as the one described by feedback loops, since more complex regulation would require higher energy investment. The problem mentioned also points to the difficulties on defining the allowed range of oscillation, which was underdefined in Cannon's formulations. According to cybernetics proposal, complexity can ideally grow indefinitely given enough variety to push the system to "learn" without collapsing and enough time. This gives the oscillation range a dynamic that did not have originally, that is, growing complexity. Consequently, the allowed range of oscillation might no longer be limited to a (pre)established configuration, and might not be static anymore, but changing and evolving as the body gathers experiences (faces perturbations).

This is linked with another main issue with theoretical formulation of cybernetics on the calculation of variation. The problem is that it offers no qualitative information about the system. What is implied here is that it is possible to know when and why a system has fall into a critical state, but it is not possible to know what kind of system it is, if biological or artificial, not even if the values provided of that system are universally valid or if they are context (system) dependent. One of the most relevant implications of this is that the limits of the homeostatic oscillation range are not, or cannot be, defined yet, nor be predicted when the self-regulation of the system will enter a critical state, either pathological – if referring to organisms-, or final, inevitably collapsing.

An important feature of living systems that is lost in cybernetics proposal or may suppose a relevant difficulty is that human-built machines are not only made of detachable parts, but it is also known the chain of states it has undergone through. This turns hard to know when facing biological organisms, since it can be known a state in a determined moment, but never completely since there are an undisclosed number of unknown variables. This is difficult for a conception that it is based on Markovian terms. As mentioned, a state cannot be fully disclosed due to its complexity, and because that complexity is not something fabricated nor controlled. This makes extremely complicated, if not impossible, to predict what next states of an organism would be, and it cannot be used neither to know a posteriori, unless assumed that the variables known are either the most relevant or the ones we do not know are not influential.

It could be considered this indeterminacy about the system is to be held responsible for the loss of one of the most important implicit features of homeostasis, since it seems to consider that qualities of a system are not relevant to know about its organisation but just its quantitative features. However, Bernard thought the internal milieu as the unique feature of living beings, distinct from inorganic bodies. From that idea Cannon devised homeostasis. The problem is not to apply the model of homeostasis to other kinds of systems, even Cannon applied homeostasis to social organisation. The problem is that homeostasis needs to be fully developed and, ideally, complemented with modern knowledge before being quantified and modelled to be applied to any self-regulated system. For instance, it is important to explore the role of the external environment and its relationship with the internal, at least because it defines a great part of how the body adapts to new situations and general perturbations and regulates itself.

Nonetheless, the modelling and formalization devised by Wiener and Ashby on feedback loops and homeostasis have been tremendously useful for the understanding of biological cycles, and it also widened this notion to be used to refer to any type of self-maintained system, and not exclusively those from the natural realm. This could be pointed out as one of the main reasons why the notion of homeostasis has lost its unifying, holistic perspective that gave significance to it, in addition of depriving it of its character of demarcation criteria.

4.3. Second-order cybernetics analysis on interactions

There is a distinction between first and second order cybernetics, difference ascribed to Mead (1968), even if the name was given by von Foerster (1974, 1979). There are two distinct positions regarding this distinction. The first one states that there is no such thing as a differentiation between them, since what it is called second order cybernetics can be easily understood as natural development of the discipline, or shortly stated, same matter, same methodology, further results (see for instance Cariani, 2017; Heylighen, 2001). The second one is better known, which defines second order cybernetics as a brand-new approach to the study of systems, not only limited to the analysis of their constitutive mechanisms. In addition to this analysis of mechanisms, second order cybernetics widened its perspective by including the several levels of control of systems, and how do they relate to each other in the general scheme, through the figure of the observer and its influence.

One of the issues in this chapter is the analysis of that distinction, to argue if it is justified enough, and in doing so they will be displayed some of the arguments that plead for that distinction to be legit. The position held here is that there is a reason for that distinction between the first and the second-order cybernetics, and it is not just a historical one (Cariani, 2017), but a little more elaborated. However, there are several issues that make difficult to defend it. Some of the literature consulted defends Ashby as the first second-order cyberneticist, while others consider him responsible of triggering it, but not part of it. In any case, there seems to be some agreement on the approximate date when it was born that is circa 1970.

Second-order cybernetics emerges directly from the investigations related to the recursive mechanisms belonging exclusively to self-maintained and self-organized systems, such as feedback mechanisms, but it is sometimes differentiated because of its interest on relationships between systems, as mentioned before. For instance, one of the issues questioned in this period is the role of the observer, together with its situation and of the system under study within the universe, as the context. It is from these second-order cybernetics that emerges the idea of a super system that comprehends every existing system and starts dealing with the issues related to the relations between these systems and subsystems aiming to establish a hierarchy based on control mechanisms and functions. In another words, while first-order cybernetics used circularity to explain natural cycles and display the means of using them in our benefit, second-order cybernetics went further and analysed the consequences of that circularity when dealing with more complex systems.

As Drack and Pouvreau pointed out, “this field [cybernetics] was initially rather technical, providing mathematical tools for the study of regulation. In this regard, it is often referred to as first order cybernetics. A few years after this endeavour started, the field was extended by applying the recursive character of regulation also to the interaction between the observed thing and the observer. Hence an epistemological approach, called second order cybernetics, emerged, which is tightly linked to concepts of first order cybernetics” (Drack y Pouvreau, 2015: 526). Second-order cybernetics, then, used the glossary and conceptual work from first-order cybernetics, such as feedback loops, and applied them to the study of the observer as designer of control devices (Kauffman and Umpleby, 2017). For instance, Beer will call feedback loops “building bricks” when speaking about the control mechanisms implied in his viable system model.

4.3.1. Relations between control systems explained

One of the names to consider when approaching second order cybernetics is Stafford Beer, who is considered as one of its main representatives. He defended a perspective that favours the idea of being us, observers, who organize things[35]. The awareness of the world being constituted by complex systems, albeit at diverse levels of complexity, is addressed differently by both cybernetics. While for the first-order the organization is a characteristic feature of the observed system, and our role as agents consists exclusively in accounting for the characteristics of that organization, for the second-order cybernetics the role of the observer and its influence on the observed are

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[35] Basic ideas of Beer’s approach are mostly taken from the recording of a conference that he gave in Monterrey Tec, uploaded on January 2011, and named *The intelligent organization*, available on https://www.youtube.com/watch?v=7COX-b3HK50.

questioned. Concretely, second-order cybernetics raises the question about how much of the observer is on the observation, and how does this influence affect the observed system.

Beer is one of the cyberneticists that took interest in understanding the relationship between systems and the hierarchy that is naturally established among them. According to Beer's perspective, the organization of systems (social, biological, etc.) is distributed at various levels. Five distinct (sub)systems can be distinguished, each of them with a characteristic and specific function for the maintenance of stability, hence regulation. As he points out, within the local environments there can be found several processes, such as digestion or breathing in mammals, to name a couple of them. These processes are controlled necessarily by some management mechanisms, as Beer calls them, like the autonomous nervous system[36].

The first, basic system, system1, relates with other systems 1 by a negative feedback mechanism, like those described by Wiener, and the unity they constitute thanks to that feedback determines them as "building blocks" of complex systems, i.e. they are the parts that constitute the most fundamental organization of systems. These blocks are easily destabilized by perturbations or variations, that is, they oscillate aimlessly unless there is a system 2. This second system is consequently necessary for the stability of system(s) 1 and it controls they are properly functioning through the control of their production. If systems 1 can be understood as the most basic metabolic processes in the body, system 2 would be regarded as their threshold (inhibiting their productivity or enabling it). One of system's 2 functions would be, for instance, to control that the stomach does not produce more acid that the necessary to transform food into nourishment

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[36] It is important to understand that Beer upholds that the scheme he is presenting can be applied to any kind of system, at any given level.

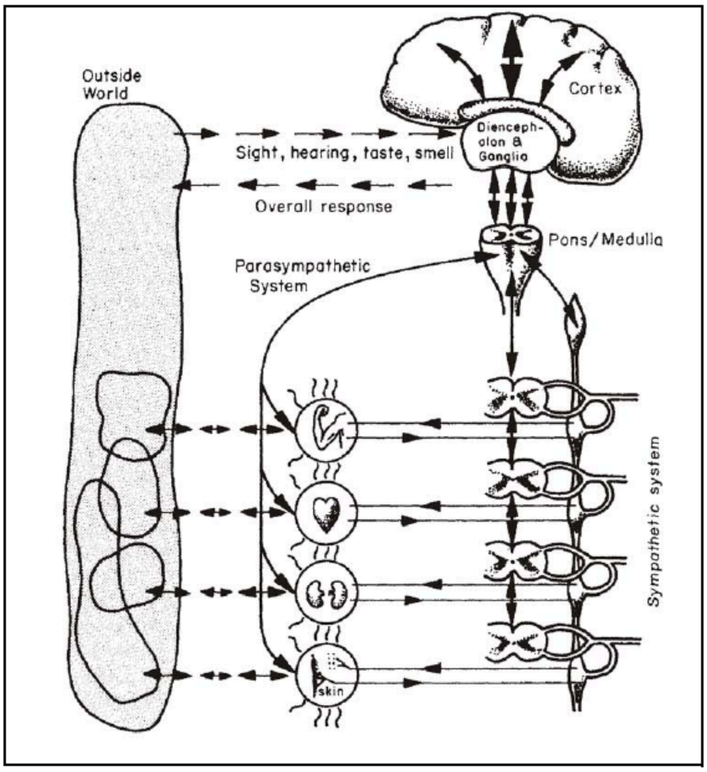

Figure 3 - Stafford Beer (1985): Viable system model in human beings

Nonetheless, this system 2 just controls that set of systems 1 in a quantitative way, that is why it is needed another system that veils for the interconnection of the functions of these lower systems, by monitoring and levelling qualitatively their state. To put it in another words, it is necessary the existence of a level responsible for the coherence of the (sub)systems at work, and that is why Beer introduces system 3. This is linked with management units of (sub)systems 1, and accounts for their well-functioning. It should be understood as the control in charge of the breathing to keep going while digesting food.

All those systems mentioned so far are basic crisis control systems. If a parallelism should be established between Beer's and Bernard's proposals, Beer's controls mentioned up to this point behave according to the dynamics described by Bernard of the internal milieu: either they hinder the perturbation or succumb to it. On top of that, they govern, as mentioned before, metabolic processes, and they are time-limited: the act when they receive the influence of a perturbation, immediately, and they are bounded to correct momentary deviations, constricted to react to brief alterations. Accordingly, they are not complex enough to resist by themselves high variety perturbations, let alone to predict them.

That is why it is necessary to include a fourth (sub)system to describe complex systems, which connects the internal milieu with the external and acts as a mediator. The external environment referred here by Beer is the same as the cosmic milieu of Bernard. It includes external conditions from the entire universe, which is to be understood as the general environment for every (sub)system defined by Beer. In the description of this system 4, Beer includes prediction by adding the condition of future. This system is responsible of monitoring the external milieu and to use that information to harmonise the internal milieu correspondingly. It does so by influencing system 3 and 2 (consequently 1 as well) to modify their action according to needs and challenges resulting from the interaction with the external environment, examining the adjustment of the internal milieu to the external.

These four systems together constitute a system that it is not centralized. This decentralization is what keeps away the system from collapsing, for instance, enabling the heart to beat without the need of a conscious effort for it, but independently. But centralization is needed for the system to constitute a unity, a whole, such as organisms. Consequently, it is necessary to add one last control, system 5, which is responsible of harmonising and balancing decentralization and centralization. This would enable constitutive processes and functions to work independently but coordinated. This last system would account for the stability of the final resulted system, which is called *viable system*, since it is the system that makes possible the maintenance of an independent existence. That independence is not absolute, for it stresses out the importance of the relationship with other systems and their mutual dependence. But system 5 introduces the necessary coherence for the system to constitute a unity, hence making possible to define an identity.

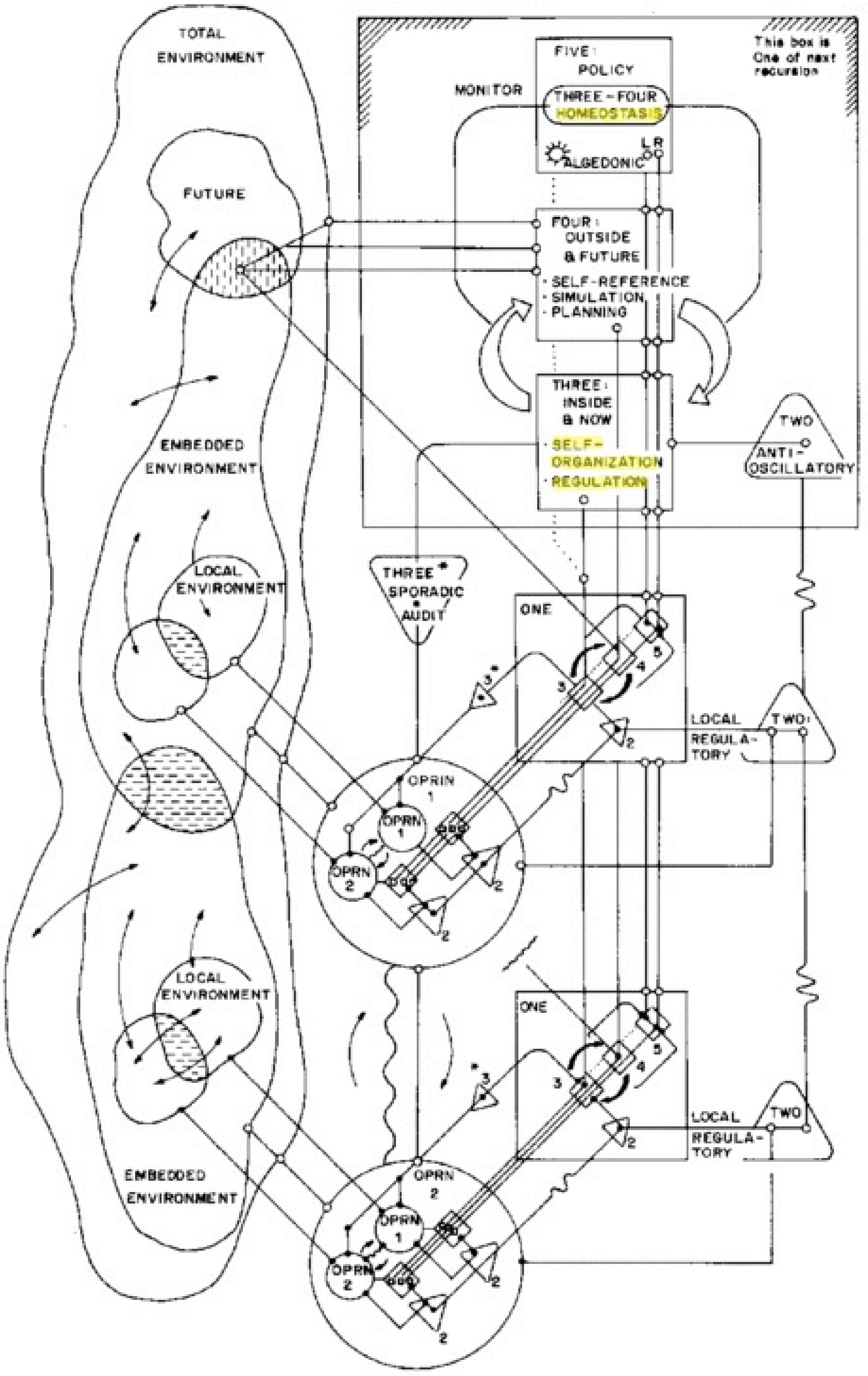

Figure 4 - Beer's viable system model. On the left, a graph of the interconnection of different environments is depicted. On the right, zooming out, are represented the different systems and how they relate to each other. Note how homeostasis is used here as a coordination of mutual constrictions between the external and the internal milieus, and note that self-organisation and regulation belong in the internal milieu (Beer, 1984)

To sum it up, Beer's proposal goes one step further from the theories from first-order cybernetics while still using its concepts, such as feedback loop, as "building blocks" to devise a model for a complex self-regulated system and describe how different controls are necessary to maintain it. Besides Beer, other second-cyberneticists explored systems' relationships and deepened the study on the concepts proposed earlier within the discipline, such as Pask (1975), widening the differences between first and second-order cybernetics. In von Foerster's own words, first-order cybernetics is the cybernetic of the observed systems, while second-order cybernetics is the cybernetics of the observing systems (von Foerster, 1974; in Drack y Pouvreau, 2015: 530). Then, for second-order cybernetics, a system would be "a set of elements and relations, or operations on these elements, that is specified by an observer. Alternatively, a system is a set of variables specified by an observer" (Drack y Pouvreau, 2015: 530-531). Even if the focus of study is relatively displaced, and both cybernetics should be distinguished on that behalf, this distinction should be considered as belonging to the same discipline, and not as two separated fields of study.

4.3.2. Some considerations on second-order cybernetics

The contributions of cybernetics to the study of living beings follow the original idea of Cannon inasmuch they focus in the internal sustenance of the body. Cybernetics quantify those processes and models the controls in charge of the maintenance of the internal stability of a system, but at the same time disengage the notion of homeostasis and the one of biological regulation, as well as from the field of physiology and any other specific area of study on living systems. Once again, it would be advisory to remember Bernard's words, when he argued that qualitative knowledge must precede quantitative knowledge (Bernard, 1865/1976: 150). Implications of cybernetics approach influence harshly further developments of the term to the extent that nowadays homeostasis needs a thoughtful conceptual revision to get rid of its ambiguity and to bring it back to the specific realm of natural phenomena. In doing so, it is important to enhance it with a qualitative development that matches the extent and degree of the quantitative reached by cybernetics. Hence, the problem is not the quantitative development carried by cybernetics per se, but the gap created between homeostasis quantitative formulations and its qualitative definition. Qualitative analysis on homeostasis was starting to be expanded within physiology when second-order cybernetics was defined as a differentiated stream of cybernetics, and the twenty years separating the first quantification to the first qualitative analysis made a difference.

Regarding the analysis of the presumed difference between the first-order and the second-order cybernetics, it does not seem to be so clear that there is a sharp difference, as suggested earlier. For instance, Peter Cariani (2017) points out that those differences between the both cybernetics are better understood as the evolution of the very same discipline, instead than a conceptual and epistemological significant distinction. He defends that this supposed "cut" between both cybernetics is based in sociological reasons, and that the change of perspective was mostly due to the withdraw of foundation from the government[37]. Cariani stresses out two negative aspects of this radical distinction between them, while defending that both are strongly related. The first one is related with the area of philosophy of science, and more precisely with the debates between realism and pragmatism. The second one is a reminder that, in scientific practice, it is usually some awareness of the perspective of the observer, by considering methodology and purposes. First-order cyberneticists could be better defined as pragmatic operationalists: "A realist says "say how it is", and Heinz von Foerster replies "it is how you say it" (§27 and table 3), but a pragmatist-operationalist would say "you will see it this way, if you construct these lenses for observing it"" (Cariani, 2016: 473).

In summary, it does not seem to be a definite distinction between first-order and second-order cybernetics, but rather their differences are grounded in what can be understood as a development of the original theory from the same discipline, marked undoubtedly by the influence of sociological and financial aspects and, consequently, modifying the scope of research. If a parallelism with homeostasis might be set up, first-order cybernetics would correspond to interofective homeostasis, and second-order

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[37] This might seem a little bit unrelated, but Cariani explanation blames it on Manfield's amendment, which explicitly forbidden the founding of any kind of research not related to military purposes, with the obligation to justify such relation.

cybernetics would be closer to exterofective homeostasis. However, both are homeostasis and should not be separated drastically.

Even so, second order cybernetics does imply a change of approach to the study of systems. As mentioned before, while first-order cybernetics was concerned about the analysis of constitutive systems' controls, second-order cybernetics widens its perspective and tries to get back that holistic account for system's behaviour by taking into consideration the relationships between systems and building them from the bottom. Unfortunately, it is extremely complicated to use low level explanations, such as the feedback loop model, as building blocks like Beer's proposed. This is because they are mostly constructed on a highly abstracted model of basic biological cycles, like it is the model of feedback, and a mere addition of control systems will hardly suffice for an explanation about any system's behaviour as a whole.

4.4. Final remarks

In this chapter, two central issues about cybernetics were displayed. Firstly, an analysis on the relation between cybernetics and homeostasis and how did it affect to the concept. Secondarily, an examination of one of the debates around the existence of two clearly differentiated cybernetics. It might seem that there is no consensus on whether we should consider second order cybernetics as a separated discipline from its originator or just as a further development of it. For instance, Francis Heylighen and Cliff Joslyn (2001), both cyberneticists, consider that there is no clear separation between them; hence, we should just talk about cybernetics. But Gordon Pask himself made a list of some of the outstanding differences between the first and the second order cybernetics, claiming that, even if it is the same discipline, the huge development that it embraced from the 50's brought a "*new* paradigm", even if as an evolution of the first order cybernetics (Gordon Pask, 1992: 25). Some of those differences include a change of the notion of control, previously focused on the external variation and then more interested in a distinction between the increase and decrease of variation; also, the treatment of communication, formerly understood as sending data and then as a conversation (To consult the complete tabular comparison he makes, see Gordon Pask, 1992: 24-25).

Ranulph Glanville, in the same line as Pask, makes an exhaustive list of differences in an article from 2004. For instance, purpose on first order cybernetics (FOC) could be even imposed by the external observer, while in second order cybernetics (SOC), purpose is naturalized within the system. The perspective on control changes as well, since on FOC there is a clear difference between control and controller, one subsumed to the other, but in SOC control and controller are mutually controlled, which also changes the dynamics and the way communication goes, constraining each other. It might seem that the big issue in SOC is circularity. In second-order cybernetics observer and observed are mutually influenced by each other, not only by an exchange of information but also an exchange of energy (Glanville, 2004). This circularity was historically conceived as problematic, but second-order cybernetics highlighted the relevance of circular causality for regulatory processes. As Louis H. Kauffman and Stuart A. Umpleby point out, "circular causality is essential in every regulatory process. A thermostat regulating the heat in a room, a driver steering a car on a road, or a manager working to maintain the profitability of a firm are all engaged in a circular process. In each case the regulator affects the system being regulated, observes the results of actions and the formulates another course of action. Note that this sequence of observation and formulation is not only circular, it is more simultaneous that sequential" (Kauffman and Umpleby, 2017: 3).

This inclusion of the observer, that can be tracked down to the work of Heinz Von Foerster, was considered problematic by some, but for instance Von Foerster (one of the advocates to distinguish first from second-order cybernetics instead of considering some cybernetic post-modernism) thought it could be even helpful when trying to understand and widen our knowledge on systems relationships. More concretely, he defended a position that shown that form and content are inextricably interrelated, just as Bateson advocated for the unity of mind and body. Even if Humberto Maturana coined it, this sentence could be attributed either way to Von Foerster, according to Glanville: "Everything said is said by an observer" (Glanville, 2009: 69). Another issue related to circularity is recursion. The peculiarity of recursion is that we learn by constantly "re-distinguishing the distinction" (Glanville, 2009: 70) by recursive observation, which is the tool we use to construct our reality. For instance, it is crucial for Beer's viable system, since hierarchy in his model is based on structural recursion.

Linking back with the idea of homeostasis and organisms, another issue to address in a qualitative manner rather than the quantitative one offered by cybernetics, is the one about the relations between systems. According to Beer, hierarchical structure is formed by setting up relationships between control (sub)systems by feedback, positioned according to the type and amount of information that they handle or, if preferred, to the type of system they control. But those systems are completely detachable from each other, but for the last one, system 5, created ad hoc to give coherence to the ensemble of control systems. Biological systems are not made of detachable systems, and the interconnection and interdependence of the constituent systems of an organism is hardly represented in cybernetics.

While cybernetics developed its main activity, almost simultaneously Ludwig von Bertalanffy delved into the study of biological systems from a strongly linked to physics approach. The explanatory power of cybernetics and the simplicity of their model proposed, together with the treatment of homeostasis by Bertalanffy (chapter 4), confined homeostasis into the definition known nowadays, that is, as a minimum maintenance cycle within the body. Along with the gap between the quantitative and qualitative developments of homeostasis, the gap between interofective and exterofective homeostasis grew, making extremely difficult to recover its holistic side to use it for explanations on the behaviour of the entire system as a unity. In the case of cybernetics, it is clear the elegance of the feedback model eased the way to set an equivalence with homeostasis, but it was posterior usage of homeostasis in this sense, primarily by Bertalanffy, that merged it inseparably from feedback, changing the notion permanently.

Appendix: Feedback

The notion of feedback is central for the understanding of the scientific development of the last century. As mentioned before, Norbert Wiener coined the concept, circa 1950, with the aim in mind of unveiling the nature of the processes involved in the maintenance carried out by complex, dynamic systems, such as organisms, for instance. He started a new discipline, inaugurating a way to understand complex systems that will enable us to build self-maintained, and even learning, systems. Feedback allows us to make predictions on the behaviour of complex systems by quantifying that complexity and offer the tools to control that behaviour and correct it if needed.

One of the recognized sources of his proposal is the idea of homeostasis proposed by Walter Cannon. To be more precise, Wiener focused on his notion of *agency*, understood as some sort of regulator of the behaviour of the organism. He says that he borrowed the term from control engineering, looking for a specific word to express a way to correct or adjust behaviour, being especially relevant in voluntary motion.

A. What is feedback

An early definition of the term of feedback can be found at the very beginning of what it is considered one of the most important references within the realm of cybernetics, namely *Cybernetics: or Control and Communication in the Animal and the Machine*. This definition explicates what feedback aims to, that is, to correct a trajectory when deviated from the ideal pattern. According to Wiener, “when we desire a motion to follow a given pattern the difference between this pattern and the actually performed motion is used as a new input to cause the part regulated to move in such a way as to bring its motion closer to that given by the pattern” (Wiener, 1948: 6-7).

Further, he defines feedback as the transmission and return of information, through the most widely known example of what feedback is: “Another example of a purely mechanical feedback system – the one originally treated by Clerk Maxwell – is that of the governor of a team engine, which serves to regulate its velocity under varying conditions of load. In the original form designed by Watt, it consists of two balls attached to pendulum rods and swinging on opposite sides of a rotating shaft. They are kept down by their own weight or by a spring, and they are swung upward by a centrifugal action dependent on the angular velocity of the shaft. They thus assume a compromised position likewise dependent on the angular velocity. This position is transmitted by other rods to a collar about the shaft, which actuates a member which serves to open the intake valves of the cylinder when the engine slows down and the balls fall, and to close them when the engine speeds up and the balls rise. Notice that the feedback tends to oppose what the system is already doing, and is thus negative" (Wiener, 1948: 97).

Feedback loops also account for the appearance of boundaries. For instance, one of the simplest control systems is the linear, which implies that the output of an effector as well as the inputs are managed by a linear operator, within what it is known as a feedback chain. If feedback is linearly controlled, it will divide the plane in two regions, consistent in a set of external points, a set of internal points, and the limit points of the exterior points of the curve of feedback, which constitute the *effective boundary* (Wiener, 1948: 101). This strongly relates to the distinction proposed by Claude Bernard of the internal and the external environment and explains how boundaries are to be in a self-maintained and homeostatic system. All these previous examples are about a compensation control by just one feedback, but usually complex systems require more feedback systems of control, such as postural feedbacks in the human being.

But just adding feedback control systems one on top of another is not sustainable, even if it might have some benefits as Wiener says, even if he did not mention an explicit example of any (Wiener, 1948: 108). One of the reasons why is related to the energy needed to perform work, and the one needed to coordinate all those feedback loops. This can be linked to the idea, within the organicism and vitalism, of *oeconomie animale*, that was mentioned earlier in this work, and explains why in complex systems, such as living organisms, the internal organization, including task coordination and coherence in the general performance just to mention two, is shaped in that determined way. Feedback plays a relevant role in the structural organization of complex systems, for it is as well a minimum model of self-maintenance.

What Wiener does explain is that the amount of feedback is strongly related to the frequency of the oscillation a system might show. For instance, linear system would oscillate in a sinusoidal form, while non-linear systems will not. "Another really significant difference between linear and non-linear oscillations is that in the first the amplitude of oscillation is completely independent of the frequency; while in the latter, there is generally only one amplitude, or at most a discrete set of amplitudes, for which the system will oscillate at a given frequency, as well as a discrete set of frequencies for which the system will oscillate" (Wiener, 1948: 109).

The usefulness of feedback systems of control and compensation systems is related to the characteristics of the effector, even if feedback systems are relatively independent of the characteristics and changes in those characteristics of the effector. There will be cases where a combination of both shall be more suitable. One of the simplest ways to do so is:

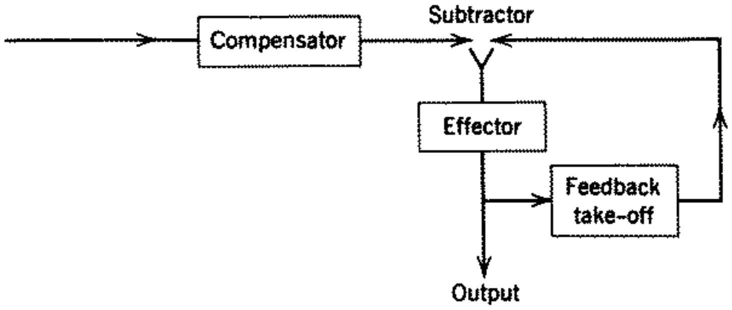

FIG. 4.

Figure 5 - Wiener, 1948

… Where the feedback systems might be regarded as an enlarged effector, where the role of the compensator is to compensate the average characteristic of the feedback system. They can also be arranged like:

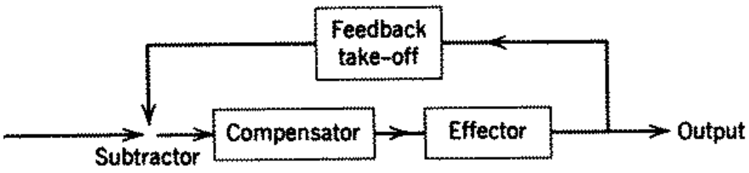

FIG. 5.

Figure 6 - Wiener, 1948

… Where *both* compensator and feedback system are combined in a larger effector. This shape will alter the maximum feedback admissible, but it will improve the performance of the system, where the compensator takes the role of an anticipator or predictor. This is the type found in human and animal reflexes (Wiener, 1948: 112 – 113).

Another kind of feedback system can be defined by the example of driving on an icy surface, where a correct performance depends almost entirely on previous knowledge about the slippery-ness of the surface. This type is called control by informative feedback, and it is characterized by a superimpose of a weak high-frequency input on the incoming message and separating the output of that high frequency from the general output, and by exploring their amplitude-phase relations it can be obtained the performances characteristics of the effector. This will allow modifying in the right sense the characteristics of the compensator. The flowchart would be as follows (Wiener, 1948: 113):

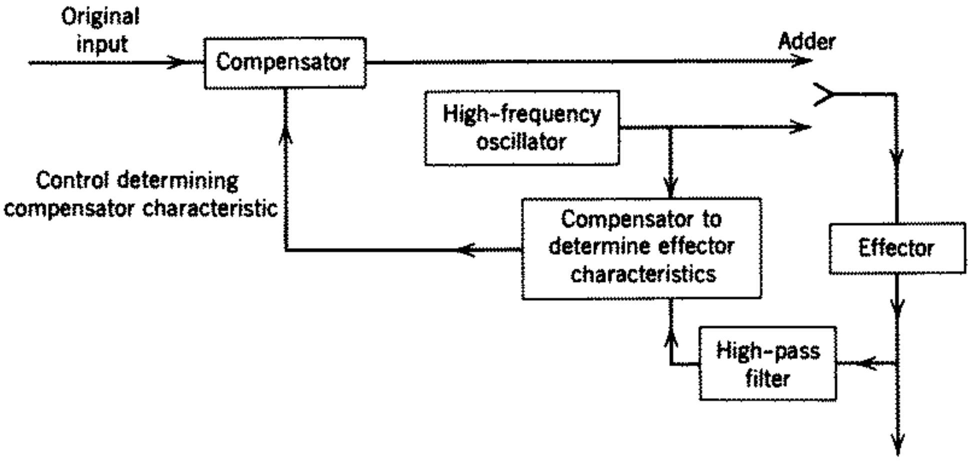

FIG. 6.

Figure 7 - Wiener, 1948

To put the core of this explanation in another perspective, the quality of the performance of feedback is related to the management of the information available. In management theory, feedback is widely used, and it is defined as the information about the gap between the actual level and the reference level used to alter that same gap in any kind of way (Ramaprasad, 1983: 4). *Actual level* can be understood as the current "state of affairs", the concrete, existing performance of the system or subsystem under analysis. *Reference level*, on the other hand, is to be understood as the ideal performance, transmission of information or, more precisely, the parameter taken as reference from that same system or subsystem. This can be correlated to Cannon's proposal of homeostasis, since he also said there was some ideal state that physiological systems tend towards, and generally (at least) slightly different from the "real" behaviour of the organism.

Within this framework, then, in order to designate something as feedback, three requirements need to be fulfilled: first, there has to be data concerning the *reference* level; second, but similar, it is necessary the existence of data on the *actual* level; and finally, some mechanism or mechanisms have to exist that provide information about the gap between the first and the second (Ramaprasad, 1983: 5). Within this field it is not really important whether the measurement is quantitative or qualitative; but it is important to keep in mind, if the measurements taken are to be qualitative, that "is necessary to use methods to generate consensus, taking into account that differences may arise concerning the nature of the gap and the magnitude (roughly) of the gap" (Ramaprasad, 1983: 7).

Furthermore, the usefulness of feedback systems can be divided in four main levels of performance, depending on the accuracy of the data gathered from the actual level and the reference level. If the data (information) obtained on the reference level and on the actual level is accurate, then the feedback process can be saying to be producing the expected result, that is, it can be described as efficacious. When the opposite case happens, that is, when the information is not valid or correct, feedback has no meaning and it is not useful at all.

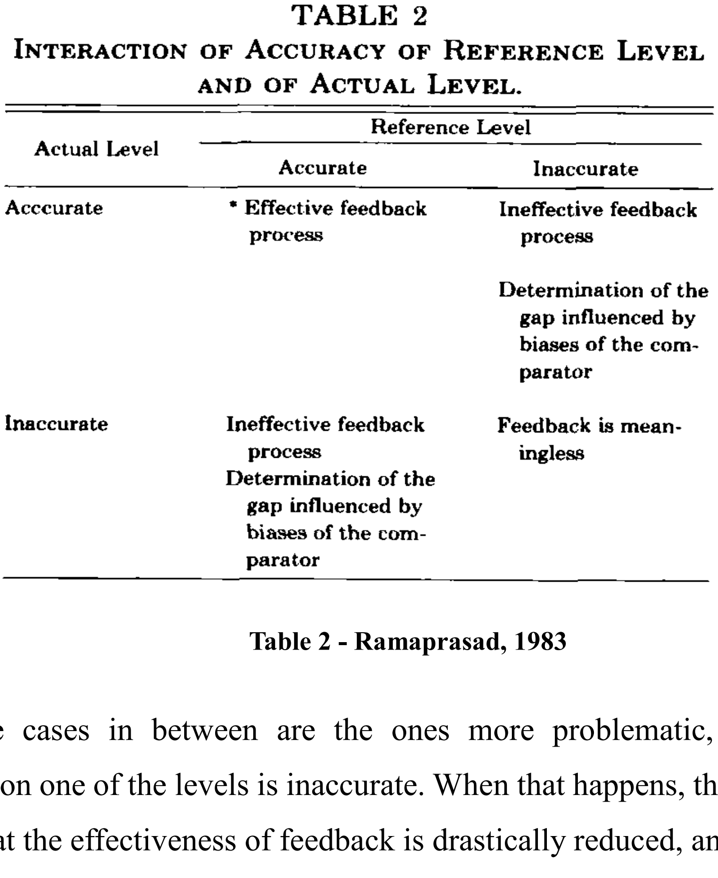

TABLE 2
INTERACTION OF ACCURACY OF REFERENCE LEVEL AND OF ACTUAL LEVEL.

Actual Level	Reference Level	
	Accurate	Inaccurate
Acccurate	* Effective feedback process	Ineffective feedback process Determination of the gap influenced by biases of the comparator
Inaccurate	Ineffective feedback process Determination of the gap influenced by biases of the comparator	Feedback is meaningless

Table 2 - Ramaprasad, 1983

The cases in between are the ones more problematic, when the data or information on one of the levels is inaccurate. When that happens, the main consequence would be that the effectiveness of feedback is drastically reduced, and that "the biases of the comparator[38] will affect the measurement of the gap between the actual and reference levels" (including the table, Ramaprasad, 1983: 11).

B. Further developments and applications of feedback

Since its original formulation, the idea of feedback has been used in several fields, as well as in researches and experiments. For instance, one of the most famous applications of the notion defined by Wiener was the creation of the *homeostat* by Ashby, an automaton able to maintain itself and even capable of some sort of "learning" from earlier perturbations. Further on, but still within the field of cybernetics, Stafford Beer (second order cyberneticist) call this kind of feedback loops "building blocks", as basic units of complex, self-maintained systems.

Wiener considered homeostasis to be a physiological application of feedback. In this context, one characteristic that tells apart homeostatic feedback from other kinds of feedback in the body, like voluntary or postural feedbacks, is that in homeostasis feedback loops tend to be comparatively slower. The reason for him to make such an affirmation is that, usually, "[t]here are very few changes in physiological homeostasis –not even cerebral anaemia- that produce serious or permanent damage in a small fraction of a second" (Wiener, 1948: 115).

The notion of feedback implied an important triggering in the study of complex (living) systems. It provided a mean to analyse biological systems from the bottom and start decomposing what it would seem exceedingly difficult to approach otherwise, that is, their behaviour and extensively their structure. However, the notion of feedback was also used for the study of other systems, as a tool to ensure the maintenance of the stability of a system. For instance, in a paper from 1982, John M. Ivanovich and J. Timothy McMahon published some of the results of an investigation they carried on organizational behaviour within the framework of management theory.

Their study brings out the influence of goal setting and the differences between external feedback and self-generated feedback in the performance of an individual within a company. Even if their work is focused in the direction from the individual outwards,

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[38] The comparator refers to the mechanism or mechanisms described earlier which are responsible to measure the gap between the reference level and the actual level.

namely on behalf of the company, it is easy to set up a parallelism to use the results of their research in the analysis of the individual inwards, that means, as a whole, as a system on its own. The only thing to change in their discourse is the psychological terms involved, such as motivation, for energetic economy, and their goal being their own maintenance and existence instead of the enhancement of productivity within the company.

That said, their study is relevant for the case at hand in this work since it proves that it is better for organizational behaviour to set a goal than to have none and, similarly, that it is better for the overall performance to have feedback than not to have any. Finally, they say that to get the best result, a self-generated feedback with a goal should be enhancing the behaviour of the system significantly (for further information on their research, see Ivancevich and McMahon, 1982).

It might be relevant to mention at this point a paper by Rosenblueth, Wiener and Bigelow, where they make explicit and clear several issues related to feedback that might be useful to understand deeper the research of Ivancevich and McMahon when talking about goals and non-feedback. In that paper, it is offered a series of definitions related to feedback that can be rewritten in a schematic form to make the classification even more explicit. They start by defining behaviour (of a system) as any change of an entity with respect to its surroundings, and that this change can be active or passive.

If active, it could be further unravelled in two kinds, depending on if this action is directed to a goal or not. They call them purposeless if the behaviour is random, and purposeful if "the act or behaviour may be interpreted as directed to the attainment of a goal" (Rosenblueth, Wiener, and Bigelow; 1943: 18)[39]. Likewise, this purposeful active behaviour "may be subdivided into two classes: "feedback" (or "teleological") and "non-feedback" (or "non-teleological")" (Rosenblueth, Wiener, and Bigelow; 1943: 19).

While positive feedback adds energy to the input, by returning some of the output energy *as input*; negative feedback corrects the behaviour of a system, that is to say, that

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[39] It is highly relevant not to misunderstand the idea of purpose. Within this framework exclusively refers to the tendency towards a goal, as explained, and it is not to be mistaken with the also extended usage, which is closer to the fields of cognition and psychology, that is intimately related to the intention of an agent.

it accounts for “the behaviour of an object (that) is controlled by the margin of error at which the object stands at a given time with reference to a relatively specific goal” (Rosenblueth, Wiener, and Bigelow; 1943: 19). One of the reasons why negative feedback is an active *purposeful* behaviour is because it is a way to restrict the output and ensure it does not go beyond the goal, as it should do otherwise.

Positive feedback, apparently, it is not really considered purposeful (When talking about negative feedback: “It is this second meaning of the term feed-back that is used here”; and also: “All purposeful behaviour might be considered to require negative feedback” - Rosenblueth, Wiener, and Bigelow; 1943: 19). Thus, when talking about feedback (as proper purposeful behaviour) and the possible predictions about it, or rather the behaviour of the system, there can be distinguished two kinds as well.

On the one hand, it can be a non-predictive behaviour, like tropisms[40]; and on the other hand, it can be predictive, based on receptors and internal organization, and using at least two coordinates as space and time. According to the intermediate steps that need to be predicted to act, there can be told apart different levels of prediction, from first-order predictions to n-order predictions.

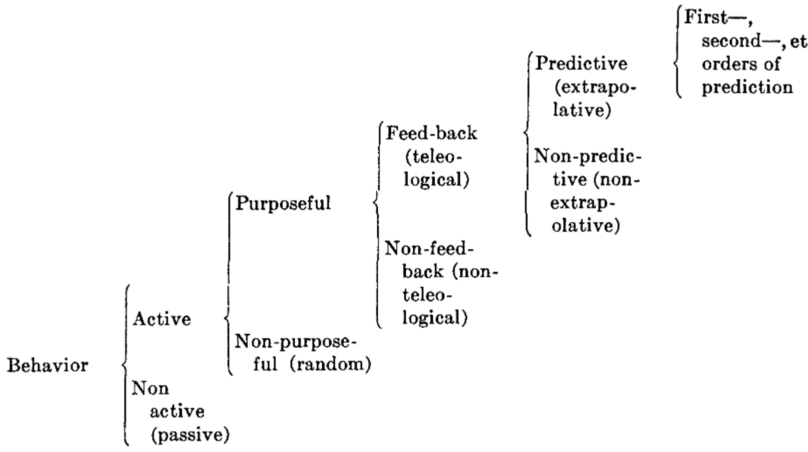

Table 3 - The classification of behaviour (Rosenblueth, Wiener and Bigelow, 1943)

The examples provided in the original text are quite revealing: “The cat chasing the mouse is an instance of first-order prediction; the cat merely predicts the path of the

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[40] “The amoeba merely follows the source to which it reacts; there is no evidence that it extrapolates the path of a moving source” (Rosenblueth, Wiener, and Bigelow; 1943: 20).

mouse. Throwing a stone at a moving target requires a second-order prediction; the paths of the target and the stone should be foreseen. Examples of predictions of higher order are shooting with a sling or with a bow and arrow" (Rosenblueth, Wiener, and Bigelow; 1943: 20-21).

That is quite to consider when embracing some of the further theoretical developments of the ideas triggered by cybernetics, like, for instance, the study of self-maintenance in cells, autocatalytic chemical reactions, or its role in regulation within a biological organization, just to mention some. Any current study about complex systems shall be familiar, at least, with what feedback is, and how does it relate to the system under study. Even if Wiener tried to keep separated human-built machines and organisms, it was a distinction difficult to maintain, since feedback loops act the same way in both, and some of the strongest mechanistic ramifications directly obviated it or tried to overcome it in one sense or another.

.5.

El análisis teórico de los sistemas biológicos

Tabla de contenido

Con una diferencia de escasos años, Ludwig von Bertalanffy (1901 – 1972) con su teoría general de sistemas (TGS) se centró, así como la cibernética en sus orígenes, en desarrollar investigaciones relacionadas con las propuestas de Bernard y Cannon sobre la organización de los organismos. Sin embargo, aunque tanto la TGS como la cibernética contribuyeron a ampliar la comprensión de su funcionamiento, ambas lo hacen desde una perspectiva de tendencia reduccionista: mientras la cibernética se centra primordialmente en una explicación sobre los procesos constitutivos de la estabilidad homeostática del medio interior, la teoría general de sistemas busca una definición del tipo de sistema que debería considerarse un sistema biológico, si bien con una inclinación hacia descripciones de corte físico. En ambas perspectivas las especificaciones propiamente biológicas pasan a un segundo plano. Ambas aproximaciones están fuertemente marcadas por una fundamentación última cuantitativa, donde las descripciones cualitativas de los sistemas biológicos se reducen según principios fisicomatemáticos, y ambas relegan el rol de la homeostasis a un nivel muy básico de manutención del cuerpo.

Aun así, cabe señalar que una de las diferencias entre ambas disciplinas radica en que la TGS, en sus investigaciones sobre los diferentes tipos de sistemas, mantiene una perspectiva relativamente organicista, si bien la homeostasis está definida según criterios altamente influenciados por la cibernética y el uso que hacen del término. Se desvanece la necesidad de la homeostasis como término específico biológico y como descriptor de la manutención de la estabilidad en los organismos, debido a que esa estabilidad se explica según unos modelos aplicables a cualquier sistema auto-mantenido, sea biológico o no. Sin embargo, cuando Bertalanffy explicita las relaciones (jerárquicas) entre los sistemas, se acerca a las formulaciones primeras de Bernard y Cannon, y a una definición completa de homeostasis, aunque debido al sesgo (muy probablemente, proveniente de la primera cibernética) acerca de esta, desdice la propuesta de Beer y vuelve a rebajar la homeostasis a la categoría de simple bucle de feedback, si bien la describe en otros términos.

La TGS abrió un nuevo campo de investigación que se ha analizado desde la perspectiva de diferentes disciplinas, como por ejemplo Mario Bunge y su sistemismo según el cual todo es un sistema o parte de un sistema. Sin embargo, este capítulo se centra exclusivamente en las propuestas de Bertalanffy relacionadas con la fisiología y la biología, señalando las diferencias y similitudes con la propuesta homeostática, en su primera mitad. En la segunda mitad el foco se centrará en analizar algunas de las propuestas sobre sistemas mínimos automantenidos que se desarrollaron posteriormente, en concreto sobre aquellas propuestas más cercanas a la búsqueda de una definición de lo que puede ser considerado como un sistema mínimo de *vida* o cómo se individua un sistema. Todas esas propuestas buscan encontrar precisamente un modelo de tales sistemas, pero mantienen una perspectiva similar a la cibernética y a la TGS en lo tocante a la homeostasis.

Así que, por un lado, se ofrece un análisis de las nociones propuestas por Bertalanffy para la teoría general de sistemas, contrastándolas con la homeostasis y su marco teórico, con el fin de argumentar a favor de la propuesta de esta tesis, a saber, que se ha trabajado la homeostasis de una manera cuantitativo-reduccionista, propiciando el sesgo conceptual examinado en el capítulo anterior, fortaleciendo la ambigüedad del término y separándolo aún más de su vertiente más holística. Por otro lado, y para ilustrar parte de las consecuencias de algunas nociones de Bertalanffy sobre el estudio de los organismos, mencionaré algunas de las tentativas actuales de describir, analizar y modelar un sistema regulatorio que dé cuenta de las características mínimas que se supone deben exhibir los sistemas biológicos. Para ello, hablaré de las investigaciones llevadas a cabo por Gánti, Maturana y Varela, y Moreno, Mossio, et al.

5.1. El análisis de Bertalanffy

Al analizar la noción de homeostasis en búsqueda de una redefinición que le devuelva la potencialidad explicativa que sea capaz de dar cuenta de las especificaciones biológicas de los organismos, ofreciendo una aproximación alternativa a la problemática relacionada con las definiciones de organismo y, por extensión, de salud y enfermedad, por caso, es de obligada mención la teoría general de sistemas ideada por Bertalanffy. Su propuesta sobre el estudio de los sistemas biológicos se centra en las interacciones entre sistemas (la cual está íntimamente relacionada con la homeostasis exterofectiva), mientras, curiosamente, critica la homeostasis como innecesaria o irrelevante para este tipo de análisis.

La teoría general de sistemas, según insiste Bertalanffy, fue ideada mucho antes de que surgiera la cibernética. Aunque su libro *Teoría general de sistemas* no apareciera hasta 1968, al parecer presentó un primer esbozo de sus hipótesis en una conferencia en la Universidad de Chicago en 1937. De cualquier manera, Bertalanffy dedica una buena parte de sus esfuerzos a diferenciarse de la cibernética, definiendo los sistemas cibernéticos como parte de la teoría general de sistemas, subordinando así la cibernética a la TGS mediante la descripción de diferentes niveles de organización de los sistemas y la vinculación a la definición de Wiener de la homeostasis.

La propuesta de Bertalanffy parte del afán de dar una respuesta al reduccionismo imperante en la investigación científica, desde una reivindicación de la necesidad de regresar a una perspectiva más holista, que permita mantener cierta perspectiva al estudiarse los diferentes elementos que componen a los seres vivos. Así, su propuesta apunta a ofrecer una teoría general de sistemas que sirva para los sistemas biológicos y, por extensión, para cualquier campo, como por ejemplo la psicología y la psiquiatría, los estudios sociales o la física y la matemática. En este sentido, la propuesta de Bertalanffy cae en la misma problemática que la cibernética: al optar por definir un modelo de sistema automantenido de modo que este sea aplicable a todo sistema de este tipo, y por mucho que parta del análisis de los sistemas biológicos, esta intención o punto de partida no son lo suficientemente vinculantes, ni específicos de los organismos y demás sistemas biológicos. Esta insistencia en la proyección de un modelo, incluso estando fundado sobre una base biológica, a ámbitos de la realidad distintos mediante generalizaciones y el uso de metáforas que oscurecen las carencias cualitativas de la definición de homeostasis, no es intrínsecamente negativo. Pero como se mencionaba en capítulos anteriores, carecen de la profundidad cualitativa como para dar cuenta del comportamiento de los sistemas biológicos específicamente, a la vez que niegan la posibilidad de hacerlo desde la homeostasis por relegarla a un término secundario, si no prescindible, en este tipo de análisis.

La propuesta de Bertalanffy que más se acerca a los planteamientos de Cannon es su concepción de la realidad como constituida por diferentes sistemas, conformados por procesos y elementos en constante interacción, que mantienen una relación jerárquica clara. En palabras de Drack, Bertalanffy creó una teoría sistémica de la vida, que también puede entenderse como biología organísmica (Drack, 2009: 563). Por ello, la hipótesis aquí sostenida es la de que Bertalanffy desdeñó la homeostasis, de un carácter organicista similar, debido a que o bien entendió la propuesta de Cannon del mismo modo que la cibernética o su noción de homeostasis proviene primordialmente de la cibernética.

5.1.1. La teoría general de sistemas

Así como lo describe Bertalanffy, para los estudios acerca de los sistemas pueden distinguirse tres ámbitos. El primero lo llama "ciencia de los sistemas" y lo define como "la exploración y explicación científicas de los "sistemas" de las varias ciencias (física, biología, psicología, ciencias sociales...), con la teoría general de los sistemas como doctrina de principios aplicables a todos los sistemas (o a subclases definidas de ellos)" (Bertalanffy, 1968/1976: XIII). El segundo es la "tecnología de los sistemas", que se encarga de analizar los "problemas que surgen en la tecnología y la sociedad modernas y que comprenden tanto el *hardware* de computadoras, automación, maquinaria autorregulatoria, etc., como el *software* de los nuevos adelantos y disciplinas teóricos" (Bertalanffy, 1968/1976: XIV).

En esta línea su propuesta señala a la "filosofía de los sistemas" como una de las partes más relevantes del estudio. Según la define en su tratado sobre los sistemas, la filosofía de los sistemas se encarga de "la reorientación del pensamiento y la visión del mundo resultante de la introducción del "sistema" como nuevo paradigma científico (en contraste con el paradigma analítico mecanicista, unidireccionalmente causal, de la ciencia clásica)" (Bertalanffy, 1968/1976: XV). En ese paradigma analítico mecanicista incluye a la cibernética, a la que acusa de llevar un análisis reduccionista de los sistemas biológicos, y la critica por no llevar más allá sus estudios. Cabe decir que, por lo que escribe Bertalanffy, la cibernética que parece estar criticando principalmente es la que aquí se ha descrito como cibernética de primer orden (ya que menciona principalmente a Wiener y Ashby) y no tanto las propuestas de Beer, por ejemplo.

Bertalanffy concebía los sistemas como medio de aproximación al estudio de la organización: "el único modo significativo de estudiar la organización es estudiarla como sistema" (Bertalanffy, 1968/1976: 7; citando y secundando a Scott, 1963). Los sistemas, en este contexto, y en un primer esbozo de la definición, están formados por partes en interacción organizada. Así, la estructura quedaría definida como el orden de los elementos de un sistema, mientras que la función debería entenderse como el orden de los procesos. Y añade: "(...) en el mundo biológico las estructuras son expresión de una corriente de procesos" (Bertalanffy, 1968/1976: 26). En este sentido se puede establecer un paralelismo más que evidente con las propuestas de Bernard, quien ya distinguió entre el estudio de la estructura (anatomía) y el estudio de los procesos vitales en acción (fisiología). Bertalanffy, a lo largo de su trabajo, mantiene una aproximación al estudio de los sistemas que se centra más en definir y especificar "sistema" en general (es decir, como una definición que se pueda aplicar a sistemas no exclusivamente biológicos) para luego explicitar las peculiaridades de tales sistemas en lo biológico. Por ello se defiende aquí que, aunque Bertalanffy sostenga que su objetivo principal es describir sistemas biológicos, el sistema que utiliza para tal fin se parece a la aproximación cibernética.

En *Perspectivas en la teoría general de sistemas*, la definición de sistema que ofrece es la de "un complejo de partes interactuantes", lo que constituye un "concepto absolutamente formal de sistema" (Bertalanffy, 1975/1986: 110). Y más adelante: "cabe definir un sistema como un conjunto de elementos que se relacionan entre ellos y con el medio" (Bertalanffy, 1975/1986: 142). Esta definición es un primer esbozo, porque más adelante se nos dice que "un sistema puede ser definido como un complejo de elementos interactuantes" (Bertalanffy, 1975/1986: 56), entendiendo la interacción como una relación que altera o modifica el comportamiento de los elementos implicados. En concreto, los sistemas biológicos, según la teoría general de sistemas, son sistemas dinámicos abiertos, en constante intercambio con el medio exterior.

Estos sistemas dinámicos abiertos son sistemas auto-mantenidos y auto-regulados. Esta regulación se basa en su nivel más básico en la dinámica de las interacciones entre los componentes de un sistema. Aquí Bertalanffy distingue dos niveles constitutivos de los sistemas, diferenciación que aprovechará también para distinguirse de la cibernética. Por un lado, encontramos las "regulaciones primarias", que son aquellas más fundamentales y primitivas, formadas por interacciones dinámicas de procesos como, por ejemplo, el caso de las regulaciones embrionarias guiadas por procesos equifinales. Estas interacciones dinámicas son del tipo propio de sistemas dinámicos abiertos: "Se basan en el hecho de que el organismo vivo sea un sistema abierto que se mantiene en estado uniforme o se acerca a él" (Bertalanffy, 1968/1976: 44).

Por otro lado, y superpuestas a las regulaciones primarias, encontramos las regulaciones secundarias, controladas por lo que Bertalanffy denomina *disposiciones fijas* que surgen del dinamismo del primer nivel y que son especialmente del tipo de la retroalimentación (Bertalanffy, 1968/1976: 44). Este nivel se organiza gracias a un principio general que Bertalanffy denominó *mecanización progresiva*. Esta mecanización progresiva no es otra cosa que el proceso que lleva a los componentes de un sistema de un estado donde se encuentran totalmente sometidos a las leyes de la dinámica a un estado donde se consolidan una serie de procesos, por repetición. Este cambio no afecta solamente a los componentes del sistema, sino también al comportamiento del sistema como un todo. A medida que se generan repeticiones en el comportamiento, se van generando disposiciones fijas y lo que Bertalanffy llamó *condiciones de restricción*. Estas condiciones de restricción y disposiciones fijas hay que entenderlas como las constricciones que definía Ashby[41]. El resultado de la aparición de las restricciones y las disposiciones fijas es la pérdida de equipotencialidad de los sistemas. La equipotencialidad no es otra cosa que la pérdida de grados de libertad de los sistemas o el aumento de probabilidad de que se dé un tipo de sistema, elemento o comportamiento por encima de otro.

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[41] Ese retorno al estado de equilibrio, en Ashby, se debe a una serie de constricciones (mencionadas un poco más arriba) que delimitan los estados posibles en los que un sistema sobrevive, entendiendo siempre supervivencia como estabilidad (1972:268). Para él, el hecho de que algo constituya una unidad y no una mera colección de partes se debe, primordialmente, a la presencia de una constricción.

Sin embargo, Bertalanffy se desmarca de la cibernética y denuncia el reduccionismo imperante de la ciencia proponiendo que la organización es un principio que cumple una función integradora en la teoría general de sistemas, acercándose a través de esa concepción de la organización a las ideas de Bernard y Cannon. En vez de hacer toda ciencia reducible a las leyes de la física, lo que Bertalanffy defiende es que existe cierto isomorfismo entre las leyes de diferentes campos de estudio. Bertalanffy propone el perspectivismo como antídoto contra ese reduccionismo imperante en la ciencia clásica (Bertalanffy, 1968/1976: 49). Sin embargo, cabe preguntarse hasta qué punto evita el reduccionismo con esta propuesta. Más bien, parece que da un rodeo argumental para justificar el uso de las leyes físicas, como se hace en aproximaciones reduccionistas. Con ello su perspectivismo parece más cercano a un reduccionismo argumentado que a una alternativa real al mismo (ver Bertalanffy, 1975/1986: 82 - 88).

Volviendo al argumento principal, en el desarrollo de un sistema se dan diferentes estadios. Partiendo de un estado de totalidad, donde los elementos de un sistema interactúan entre sí, el siguiente estadio consiste en la segregación progresiva. Esto es así porque las interacciones entre los constituyentes decrecen con el tiempo, llevando a un estado de independencia de los elementos, que se dividen en varias "cadenas causales independientes" (Bertalanffy, 1975/1986: 74). En ese punto se establece una clara diferencia entre los sistemas biológicos y las máquinas: mientras que una máquina constituye una suma de partes independientes entre sí, en los sistemas biológicos se parte de un todo que se va escindiendo en sus diferentes partes (Bertalanffy, 1975/1986: 70 - 71). Este proceso se separación se llama "segregación progresiva", que viene acompañado de una "mecanización progresiva", que es lo que hace que los organismos estén constituidos por partes independientes, ya que se refiere a la especialización funcional de cada una de sus partes.

Para evitar la pérdida de poder regulatorio, análogo al proceso de mecanización progresiva, se da una centralización progresiva, que unifica esas partes y complejiza los sistemas biológicos. Esta complejización se entiende aquí en el sentido que Bernard había señalado, dificultando la manipulación y experimentación sobre organismos vivos, potenciando su indivisibilidad; dificultades que Kant ya había señalado (1790/2007) cuando definió la diferencia entre organismos y máquinas según la habilidad de autoproducirse de las primeras, que explica su imposibilidad de ser descompuestas atómicamente sin que las partes separadas pierdan sus propiedades vitales[42]. Esta centralización progresiva se constituye mediante la “formación de partes conductoras mediada por el tiempo” (Bertalanffy, 1975/1986: 74) y es lo que configura al individuo, pero entendido como una individualización progresiva debido a una centralización dominante. No hay individuación tal que se aísle el sistema, ya que lo más habitual es que este tipo de sistema descrito aquí sea una parte en el sistema inmediato inferior. La individuación así entendida se da por una centralización más marcada dentro de una jerarquía de sistemas y subsistemas.

5.1.2. Desarrollando las ideas de Cannon

La organización de los organismos es un tipo de organización específico que se genera desde y para el organismo, también conocida como autoorganización. Esta autoorganización cuenta con dos momentos clave. En primer lugar, y como ya explicaba Bertalanffy, el momento en el que se inicia el proceso en el que las partes interactuantes empiezan a desplegar repeticiones creando disposiciones fijas, aumentando la complejidad y autonomía del sistema. En segundo lugar, la aparición de un control central que permita la coordinación de esos subsistemas y sus procesos, ya altamente complejizados, con una importante capacidad de gestionar altos niveles de complejidad. Este requisito es indispensable para un (sub)sistema central ya que, a mayor cantidad de información y de carácter más heterogéneo, más necesita procesar y coordinar el sistema central.

Como organismos metabolizantes, los sistemas biológicos son sistemas abiertos que mantienen un estado uniforme. Ese estado se mantiene por la resolución de dos

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[42] “En una producción de la naturaleza de esta especie, cada parte será concebida como no existiendo más que por las demás y por el todo, del mismo modo que cada una no existe más que para las otras, es decir, que se la concebirá como un órgano. Mas esta condición no basta (porque es también del arte y de todo fin en general). Es necesario, además, que cada parte sea un órgano que produzca las demás partes (y recíprocamente). No hay, en efecto, instrumento del arte que llene esta condición; no hay más que la naturaleza, la cual suministra a los órganos (aun a los del arte) toda su materia. Es, pues, en tanto que ser organizado y organizándose por sí mismo, como una producción podría llamarse un fin de la naturaleza” (Kant, 1790/2007: 124 – 125).

actividades típicas de los sistemas autoorganizados. Por un lado, tenemos los procesos periódicos, que se generan desde el sistema y para el sistema, con lo cual son procesos autónomos. En esta clasificación encontramos, por ejemplo, la respiración o el latir del corazón. Por otro lado, nos encontramos con lo que ya Bernard había denominado "perturbaciones". Debido a cambios temporales en el medio, el organismo reacciona mediante fluctuaciones que consigan devolverle a su estado estable inicial. A este respecto, Bertalanffy ofrece un avance que cuenta con su homólogo en el terreno de la fisiología y sus posteriores desarrollos sobre homeostasis, esto es, la inclusión de un análisis sobre la dimensión temporal de la homeostasis y sus alteraciones. Bertalanffy dice: "Si después del "estímulo" retorna la constante de catabolismo a su valor normal, el sistema regresará al estado original. Pero si persiste la perturbación y con ello el cambio de ritmo catabólico, se establecerá un nuevo estado uniforme" (Bertalanffy, 1986: 135).

En otras palabras, Bertalanffy abre una vía hacia una explicación de cómo es posible que un sistema biológico cambie y evolucione a través de la propuesta de Cannon del rango oscilatorio permitido. Al percibir una perturbación, el sistema pone en marcha los mecanismos específicos de respuesta, y una activación sostenida de los mismos modifica el rango oscilatorio habitual, cambiando el régimen mantenido hasta el momento por el sistema. Esta propuesta de Bertalanffy se puede enlazar con las propuestas cualitativas posteriores hechas en fisiología (ver capítulo 6). La descripción de comportamiento de los sistemas de Bertalanffy pone sobre la mesa un tipo de adaptación que se ejemplifica de manera fácil en la *Biston Betularia*. De manera muy resumida, esta es una polilla que cambia de color según el color de la corteza del abedul, usualmente de cierto tono blanquecino, pero que se ve fácilmente afectado por los residuos de la polución, volviéndose visiblemente más oscuro. Bertalanffy explica las oscilaciones que sufre esta clase de polilla provocadas por los cambios del medio en el que habita.

5.2. Sistemas en modelos mínimos

La teoría general de sistemas de Bertalanffy, así como las teorías de la cibernética (concretamente los bucles de retroalimentación), inspiraron una serie de propuestas que también exploraron, desde el modelaje, cuáles deberían ser las características mínimas de lo que debe entenderse como un sistema vivo. Estas propuestas, aunque sus raíces se encuentren en dichos marcos teóricos, guardan cierto paralelismo con la propuesta de la homeostasis, en tanto que buscan analizar cuáles son las características mínimas necesarias y suficientes para distinguir a los sistemas vivos. Dicho de otro modo, tres investigadores, Tibor Gánti, por un lado[43], y Humberto Maturana y Francisco Varela por otro, propusieron cada uno una explicación partiendo de la pregunta acerca de cuáles serían los rasgos mínimos para poder decir que un sistema es un sistema autoorganizado, es decir, que se mantiene a sí mismo y su equilibrio al mismo tiempo que se desarrolla y organiza: los requisitos mínimos para la vida.

En esta sección se explican sus propuestas de modelos mínimos, por un lado, la de Gánti, el quimiotón, y por otro la de Maturana y Varela, la autopoiesis. Ambas aspiran a desglosar las características estrictamente necesarias de un sistema para exhibir esa independencia de la que hablaba Bernard, hoy entendida como autonomía, que está presente en los seres vivos debido a su tipo de organización, y que además los define como tales.

Parafraseando a Maturana y Varela en *El árbol del conocimiento* (1996), el hecho de que reconozcamos algo tiene que ver, al menos parcialmente, con la aprehensión por nuestra parte de que cierta organización conforma aquello que reconocemos. En este caso, los autores usan el concepto de organización como piedra puntal para su explicación sobre las características que distinguen a los seres vivos, con el fin de evitar largas listas de propiedades y la problemática que conlleva el aspirar siquiera a una categorización estricta.

Según Maturana y Varela, la perspectiva común a la hora de considerar a los seres vivos es la de seguir como criterio de demarcación una lista de propiedades que lo distinguen del resto de entidades físicas que pueblan el planeta. Entre esas características se encuentra, comúnmente, la capacidad de reproducirse. Sin embargo, el ejemplo de la mula que ponen estos autores da una idea intuitiva de que en realidad esa no es una

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[43] "The conception of the chemoton model had at least two motivations: first, to understand the organization of life in its minimal form, and second, to apply it to the problems of natural and artificial biogenesis" (Griesemer and Szathmary, 2008: 482)

característica que forme parte de lo que se tiene que definir *sensu estricto* como un ser vivo. La explicación más teórica acerca de esto se basa en la centralidad de la organización de lo vivo, que es decir lo mismo, pero desde otra perspectiva. Usando sus propias palabras: "la reproducción no puede ser parte de la organización del ser vivo porque, para reproducir algo, *primero* es necesario que ese algo esté constituido como unidad y tenga una organización que lo defina" (Maturana y Varela, 1996: 49).

Gracias a este ejemplo se entiende que las listas de propiedades no pueden tomarse como criterio de demarcación, ya que los fenómenos biológicos no pueden explicarse en "términos estáticos o mecanismos no autopoiéticos", que se usan para explicar sistemas "que no producen una unidad autopoiética en el espacio físico". Las explicaciones biológicas deben entrar en el ámbito fenomenológico biológico, y por ello los sistemas autopoiéticos solo pueden explicarse "en términos de procesos subordinados a la autopoiesis de los organismos participantes" (2004: 108).

Esta perspectiva que prima la organización por encima de cualquier otro criterio pertenece a una corriente de pensamiento en filosofía de la biología que ha dedicado sus esfuerzos a comprender y delimitar los sistemas vivos y su origen desde la base de esta organización característica y única de los sistemas biológicos. Esto ha llevado a la creación de varios modelos que intentan abstraer[44] las características mínimas que deberían constar en cualquier sistema vivo y que permiten, a la vez, distinguirlo de otras entidades. Entre ellos, algunos de los más nombrados son el quemotón de Gánti y la máquina autopoiética de Maturana y Varela, de los cuales hablaremos un poco más adelante, tras definir qué es la autoorganización, según la tradición filosófica del término y los desarrollos contemporáneos del término por parte de Álvaro Moreno y los miembros y colaboradores de su equipo de investigación.

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[44] Es mejor usar el concepto de abstracción en vez del de idealización en este caso, y en todos los casos similares, por la diferencia de connotación semántica que conllevan. Abstraer consiste en seleccionar las características de un caso real que interesan en el estudio que se esté realizando a cabo, elegir los rasgos más importantes. Sin embargo, en las idealizaciones se asumen con frecuencia premisas falsas con el fin de simplificar las explicaciones.

5.2.1. Autoorganización

Evelyn Fox Keller (2007) nos dice que la autoorganización ya fue mencionada como característica distintiva de los seres vivos por Kant en su *Crítica del juicio*, donde expone que la organización de los seres vivos forma un tipo de entidad[45] "en la cual todo es fin, y, recíprocamente, también medio" (2007:308). Kant está hablando de un tipo de organización en el que las partes tienen una finalidad propia, que es la de mantenerse a sí mismas, pero a la vez contribuyen al mantenimiento del sistema total mediante el mantenimiento de las otras partes que forman parte de este.

En un sistema del tipo dinámico abierto no lineal, el surgimiento de orden es espontáneo. Sin embargo, siguiendo el comentario que hace Keller sobre Weaver, el análisis de estos sistemas dinámicos muestra lo sencillo que es la aparición de la complejidad, pero no distingue entre el surgimiento y la organización de complejidad. La organización de esa complejidad es especial en los organismos y marca la diferencia.

Bechtel también sigue la corriente según la cual la organización de los seres vivos es la base de las características distintivas de los mismos. La idea que plantea en su artículo (2007) es que el mecanicismo, en principio, podría dar cuenta de explicaciones de carácter global desde una perspectiva mecanicista, a pesar de las críticas holistas recibidas. La cuestión es que los sistemas naturales siguen una dinámica no lineal, pero algunas de esas dinámicas ya cuentan con una explicación mecanicista, como el *feedback* (o retroalimentación, o realimentación) negativo, el *feedback* positivo o la organización cíclica tan característica de los organismos.

Kaufmann ya señaló la capacidad de los seres vivos en no disipar la energía, sino en reutilizarla en su propio provecho, al menos en parte. Esta capacidad viene dada por la presencia de una limitación o *constraint*, según el apelativo inglés, global, que

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[45] Siguiendo a Maturana y Varela en *El árbol del conocimiento*: "Se entiende por *organización* a las relaciones que deben darse entre los componentes de algo para que se lo reconozca como miembro de una clase específica. Se entiende por *estructura* de algo a los componentes y relaciones que concretamente constituyen una unidad particular realizando su organización". Editorial Debate S.A., Madrid, 1996. P. 40.

constituye la identidad de un sistema, el "auto" (*self*)[46] en la autoorganización que menciona Fox Keller. No es sólo importante la composición de los sistemas, su estructura, y las relaciones de producción que mantienen, sino que también es importante saber en qué ámbito se producen. Esta idea puede enlazarse con la de la importancia del contexto para las interacciones, según la cual, para poder tener una visión más completa del funcionamiento de un sistema (biológico), además de tener en cuenta los elementos que lo componen, las relaciones de estos y los efectos de esas relaciones sobre el sistema, hay que añadir a la cualidad estructural la importancia del lugar donde se encuentran para poder explicar su función y procesos con mayor profundidad.

Lo que Keller encuentra interesante acerca de los organismos y cómo diferenciarlas de las máquinas no es la emergencia de complejidad, sino la organización de esta. Así que, hecha esta distinción, defiende que, si consideramos a los componentes como agentes/*selves*, se podría dar cuenta de cómo se ha organizado esa complejidad. El problema que preocupa a esta autora es el paso de una estructura o patrón, que surge espontáneamente de las interacciones químicas y/o de la base física de los componentes, a esa aparición de los agentes o *selves*, como esa clase de organización especial y específica de los sistemas biológicos. Eric Karsenti, en su artículo "Self-organization in cell biology: a brief history", menciona esta idea de los agentes como una definición usada actualmente por los científicos. Según esta idea, la "organización dinámica surge del comportamiento colectivo de 'agentes', cuyas propiedades individuales no pueden dar cuenta de las propiedades del patrón dinámico final" (2008:255).

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[46] "Auto" en el contexto de este trabajo y de la tradición en la que se incluye, se refiere a la creación y mantenimiento de las partes de un sistema para el sistema tanto como para sí mismas, en un sentido kantiano, como se ha mencionado antes. Es decir, los seres vivos se producen a sí mismos y sus partes, manteniéndose entre sí y a sí mismos, formando una unidad indivisible en tanto que, una vez separadas del cuerpo, las partes dejan de estar vivas (aunque sigan siendo productos orgánicos, como ya señaló Bernard). Como escribe Fox Keller al analizar la propuesta de Kant: "An organism is not merely self-steering, self-governing, and self-maintaining; it is also self-organizing. More, it is self-generating", y también: "a "self"—an entity that, even though not hermetically sealed (or perhaps because it is not hermetically sealed), achieves both autonomy and the capacity for self-generation." (Fox Keller, 2008: 49). En resumen, el "auto", o "self", es lo que distingue organismos de máquinas.

Según Karsenti, puede que esta sea una definición bastante general, pero que cuenta con la ventaja de permitirnos estudiar el surgimiento de las funciones por separado y que también apunta a cómo estudiar los sistemas autoorganizados: "el objetivo de la ciencia de la autoorganización es el de identificar los principios y mecanismos por los cuales un conjunto de agentes en interacción evoluciona hacia un patrón dinámico particular espacial o temporal" (2008:256).

En la entrada de la *Encyclopedia of systems biology*, Etxeberria y Umerez distinguen tres maneras de entender las explicaciones acerca de la organización. Por un lado, está la organización abstracta o lógica, del tipo que Maturana y Varela defienden. En este tipo de explicación, el material de que están compuestas las máquinas organizadas no es lo relevante (aspecto que varios autores han encontrado problemático), sino el hecho de que autodefinen su identidad en el espacio de interacciones que la componen.

Por otro lado, encontramos la organización mecanicista, que defiende que hay que tomar en cuenta "tanto las capacidades del todo como las partes estructurales de las partes para poder explicar la organización" (2013:1614). Así entendida, podría considerarse que es una explicación sobre la organización que intenta unir las tradiciones reduccionista y holista (aunque este es un campo por debatir). Según esta aproximación, "las propiedades estructurales de las partes dan cuenta de la organización de los todos, aunque los últimos no pueden ser reducidos a las primeras" (2013:1614).

Por último, nos hablan de la organización restringida ("constrained organization"). Esta vertiente considera que incluso los sistemas abstractos deberían tener propiedades materiales o estructurales para poder ser capaces de obtener una definición de vida. "En este sentido, aunque la organización no puede ser reducida a las propiedades de las partes, necesita estar restringida por algún parámetro empírico" (2013:1614).

Según Mossio y Moreno, los organismos tienen una complejidad que no tienen las estructuras disipativas, y lo que distingue a unos de otros es el modo en que se auto-mantienen, esto es, los sistemas biológicos se mantienen mediante una organización de restricciones ("constraints"). Mossio y Moreno lo definen como "un régimen de causación distintivo, que se ve como emergente sobre las leyes fundamentales de la física y la química. En particular, *el auto-mantenimiento es el resultado de restricciones locales*" (2010:271).

Un poco más adelante ambos autores precisan más la cuestión: "¿Qué implicamos con organización de restricciones? La idea principal es que los sistemas biológicos son capaces de mantenerse a sí mismos constituyendo una red de estructuras que ejerzan acciones mutuamente restrictivas en sus condiciones limítrofes ["boundary conditions"], tales que la red al completo se auto-mantiene colectivamente. La dependencia mutua entre un conjunto de restricciones es lo que llamamos *cierre organizacional*" (2010:276).

Como puede verse, hay varias aproximaciones para explicar la autoorganización como característica distintiva de los seres vivos. De cualquier modo, como señala Karsenti, "los principios de la autoorganización nos dicen que si hay un conjunto de productos que pueden interactuar dinámicamente para alcanzar un estado funcional estable, lo harán robustamente al menos bajo ciertas condiciones" (2008:260). Y prosigue diciendo que la diversidad existente en el universo de lo vivo, desde la perspectiva de la autoorganización, más que depender de la selección, parece depender de "las propiedades intrínsecas de la materia viva y la combinación de varios módulos funcionales autoorganizados" (2008:261).

Esta perspectiva se recoge en el concepto de auto-ensamblaje, el cual justifica la aparición de organizaciones modulares en la naturaleza. Según nos dice Keller sobre Simon, la idea de que sistemas heterogéneos relativamente simples y estables se unen en sistemas que son, a su vez, estables en todos los sentidos, estos sistemas compuestos pueden constituirse como bloques de construcción para futuros ensamblajes. "Mediante repetición, el proceso da lugar a una estructura jerárquica y modular que Simon dice que es la marca de sistemas con complejidad organizada" (2007:312-313).

Dos de los modelos surgidos desde las investigaciones cuyo objetivo era explicar cómo funciona la organización de los sistemas biológicos son el quimiotón y el sistema autopoiético, que ofrecen diferentes perspectivas sobre las características mínimas que debe tener un sistema para ser considerado vivo. Estos modelos no son solo importantes para saber cómo funcionan los mecanismos de los organismos y obtener una definición de vida, sino que, además, por ser sistemas simplificados al máximo, también han servido de herramienta en las investigaciones sobre el origen de la vida. Aquí lo que más nos interesa es estudiar estos modelos con el fin de descubrir los posibles paralelismos entre el automantenimiento explicado de sus sistemas mínimos y la homeostasis.

5.2.2. El quimiotón

Bechtel nos dice de Gánti que desarrolló un modo de representar las relaciones estequiométricas dentro de los ciclos para rastrear el flujo de materia y energía que atraviesa esos sistemas. "Desde este punto de partida, Gánti continuó articulando una explicación sobre cómo la organización cíclica puede ser usada para ofrecer el núcleo de una máquina química mínima que exhiba las propiedades fundamentales de un organismo viviente" (Bechtel, 2007:274). Dicho de otro modo, el modelo de Gánti recoge la organización cíclica (no lineal) para explicar el funcionamiento de los seres vivos.

Gánti formuló por primera vez la idea del quimiotón en 1952, pero la formulación definitiva es de 1978, que fue revisada y se mantiene hasta hoy. El libro de Gánti donde aparecen sus teorías sobre el quimiotón no fue traducido al inglés hasta el 2003. El quimiotón es un modelo creado para explicar cómo funciona un sistema vivo, ateniéndonos a las características básicas con las que Gánti supone que debe contar. Este lo describe como un modelo mínimo de las ciencias naturales que sirve como punto de partida para el estudio de la naturaleza de la vida, y sus orígenes. Para ello empieza estableciendo las diferencias entre los productos de la naturaleza y los productos del hombre, al más puro estilo kantiano. Una de las diferencias que resalta es el hecho de que el trabajo de los unos y de los otros difiere en que el trabajo de la naturaleza no está dirigido, no cuenta con una meta preestablecida. "To get from random to directed work, the flow of energy must be manipulated along a series of forced trajectories within the system" (Gánti, 2003: 2).

Otra diferencia, y más importante, relacionada con la anterior, es que "The driving force of living systems is chemical energy." (Gánti, 2003:2). O como dice más adelante, manipulan la energía mediante métodos químicos. En otras palabras, los seres vivos son seres constituidos a base de reacciones químicas, de las que extraen la energía necesaria para su manutención y supervivencia. Debido a eso, solo pueden trabajar estando en fase fluida, motivo por el cual se les llama “autómatas flexibles” (“soft automata” en el original inglés).

La manutención del equilibrio químico corre a cuenta de la retroalimentación estequiométrica, que es el tipo de realimentación típico de los ciclos químicos. Esta clase de realimentación es importante, ya que el objetivo final de un ser vivo no es otro que el de superar el embate de las distintas perturbaciones que amenazan su pervivencia y a las que se ve sometido a lo largo de su existencia. Esto se logra con el control interno del flujo de materia y energía que atraviesa el quimiotón.

Gánti (2003) continúa precisando lo siguiente sobre las reacciones y transformaciones químicas: “The direction of the reactions depends on the reactants. There are cases in which the directions of the subsequent reaction pathways change in such a way that eventually we arrive at our starting point, i.e. after several or many chemical transformations we have the same chemical compound with which we started. This can be interpreted as going round a circle in the chemical state field, and this is what is meant by stoichiometric feedback. In chemistry these processes are simply called chemical cycles” (Gánti, 2003:22).

Este control de la energía, controlada para el mejor aprovechamiento de los materiales en la propia manutención, supone una diferencia con respecto a las máquinas homeostáticas en un sentido cibernético con el tipo de autómata que describe Gánti. Y es que, para los autómatas del primer tipo, esa canalización de energía viene dada desde arriba, mientras que para los autómatas fluidos el control de esa energía se reparte por todo el sistema, gracias a las reacciones químicas (DiFrisco, 2014: 517).

Un ejemplo de autómata fluido que podemos encontrar en la naturaleza es el del citoplasma celular: “Cell cytoplasm operates completely normally during this swirling process. Thus the cytoplasm is a machine whose operation is not disturbed by stirring, whose internal organization is not destroyed, and whose regulated character is not ruined by chaotic wandering of its components. Thus cytoplasm is a fluid automaton, similar to an oscillatory chemical system” (Gánti, 2003:17).

El modelo mínimo de vida que ideó Gánti consta de tres características básicas y necesarias, que se relacionan con los tres ciclos autocatalíticos de los que consta el modelo: La primera de ellas es que debe funcionar bajo la dirección de un programa. “The essential point is that life is a specifically operating system which also operates in a program controlled manner. Consequently, a living system should necessarily comprise at least two systems, of which one is the controlling unit and the other is the controlled part. Neither system is living if the other system is absent". (Gánti, 2003:15).

Ese programa de control apareció después del sistema: "This is because a machine can exist without program control, and even without any program at all, but the converse is not true" (Gánti, 2003:16). El segundo requisito es que debe ser capaz de reproducirse a sí mismo, y el tercero es que su descendencia debe estar separada del medio ambiente (Gánti, 2003:3). "Living systems are self-reproducing systems since their basic property is their ability to proliferate" (Gánti, 2003:25). Aunque, como dice más adelante, esta característica de proliferar por sí sola no es suficiente para considerar que un sistema esté vivo. Es necesario un programa de codificación, también llamado material genético (Gánti, 2003:35).

Si citamos el texto de Gánti, nos encontramos con esta definición de quimiotón [*chemoton*, en inglés]: "The chemoton model is an abstract model. By using it we can understand how it is possible to organize a chemical supersystem from several autocatalytic subsystems, which are directed by a central program, and which can reproduce itself" (Gánti, 2003:5)[47]. El mecanismo descrito por Gánti es relativamente sencillo: consiste en tres subsistemas acoplados estequiométricamente que contribuyen al mantenimiento del sistema al completo.

El primero de todos ellos es el citoplasma, el cual lleva a cabo un ciclo metabólico autocatalítico, también denominado por Gánti como máquina química auto-reproductora. Este es el subsistema dedicado a sintetizar componentes químicos, haciendo compuestos para mantenerse a sí mismo y contribuir al mantenimiento de los otros subsistemas, y, por lo tanto, al sistema entero. Produce moléculas complejas a partir de las simples con gran carga energética. Es el motor químico del quimiotón y tiene que contar con una organización interna estable.

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[47] Un supersistema no es otra cosa que la unión de los tres subsistemas que componen el quimiotón trabajando juntos para el mantenimiento de la unidad, o supersistema, que conforman, tal y como se explica en la cita.

El segundo es una membrana fluida bidimensional, que sirve para el propósito de separar espacialmente el ambiente interno del quimiotón del externo que le rodea o, dicho de otro modo, mantiene los materiales internos del sistema dentro del mismo. Tiene que ser permeable a sustancias químicas, tales como los nutrientes y los materiales de desecho y ser capaz de crecer en la presencia de sus materias primas, siendo estas los compuestos producidos por el primer subsistema.

El tercero y último es la subunidad de control, capaz de almacenar y usar información, habilitándolo para controlar los otros dos subsistemas mediante acoplamiento estequiométrico exclusivamente. Produce macromoléculas usando plantillas de policondensación, sirviéndose de los compuestos producidos por el primer subsistema. Los productos de este ciclo se usan en la formación de componentes de la membrana. "This contains a large number of polymer molecules with a double-stranded structure which, at a given monomer concentration, are capable of separating into individual strands, each of which serves as a template for polymerization. (…) The consumption of monomers in a polymerization cycle (and thus the amount of condensation product formed) is unambiguously determined by the number and length of the template molecules" (Gánti, 2003:36 - 37).

Gánti (2003) describe el quimiotón mediante tres subsistemas: "A chemoton consists of three different autocatalytic (i.e. reproductive) fluid automata, which are connected with each other stoichiometrically. The first is the metabolic subsystem, which is a reaction network (optionally complicated) of chemical compounds with mostly low molecular weight. This must be able to produce not only all the compounds needed to reproduce itself, but also the compounds needed to reproduce the other two subsystems. The second subsystem is a two-dimensional fluid membrane, which has the capacity for autocatalytic growth using the compounds produced by the first subsystem. The third subsystem is a reaction system which is able to produce macromolecules by template polycondensation using the compounds synthesized by the metabolic subsystem" (Gánti, 2003:4).

Explicado de un modo muy escueto, el quimiotón funciona de la siguiente manera: tomando como punto de partida el momento de división, cuando el quimiotón ha desarrollado plenamente la forma esférica que le es propia y se encuentra en perfecto equilibrio osmótico con su ambiente, los nutrientes se propagan continuamente dentro del sistema a través de la membrana a un ritmo muy rápido.

Así como los nutrientes van entrando en el quimiotón, reaccionan con los materiales provenientes de la red de reacción autocatalítica, creando material interno, que no es más que “los precursores de las moléculas que formarán la membrana y las materias primas de las plantillas de control (los monómeros). De cualquier modo, estos monómeros no pueden polimerizar, ya que las plantillas se encuentran todavía en su forma de doble hebra y se cubren mutuamente las superficies” (Gánti, 2003:37).

El quimiotón tiene un umbral de activación. Cuando se alcanza cierto grado de concentración de los productos metabólicos, el subsistema de patrones inicia la producción de la membrana: “Cuando la concentración de monómeros alcanza el valor en el cual la estructura de doble hebra se torna inestable, las hebras de la plantilla son separadas y la polimerización (o, más precisamente, policondensación) de los monómeros empieza en cada una de las hebras. Nuevas hebras poliméricas son construidas sobre las hebras de plantilla y la mayor parte de los monómeros se usa, con lo cual la concentración de monómeros desciende” (Gánti, 2003:38).

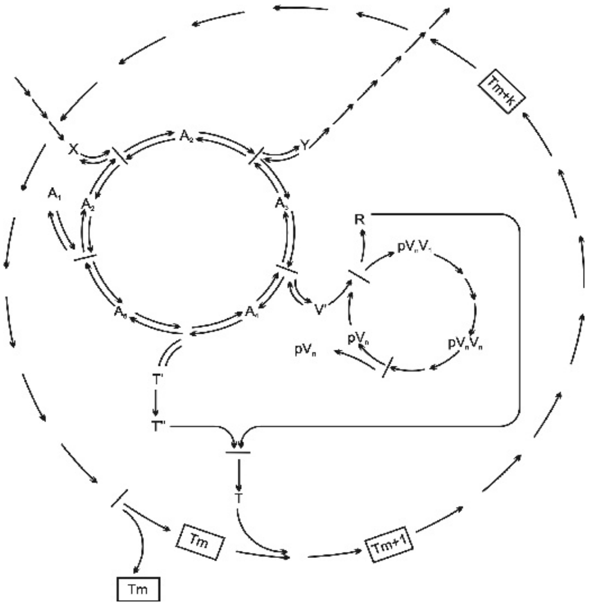

Figure 8 - ***Gánti: Modelo de Quimiotón:*** **"Minimum model of chemotons. Three self-producing systems are coupled together stoichiometrically: cycle A → 2A′, template polycondensation pV n → 2pV n′ and membrane formation T m → 2T m. This coupling results in a proliferating program-controlled fluid automaton, known as the chemoton" (Gánti 2003: 5)**

Esta es una forma de regulación en la que el sistema reacciona a la presión interna alargando la membrana para evitar el colapso, haciendo al sistema más estable ante cualquier tipo de variación. "Estas [las moléculas creadas tras la policondensación] son entonces incorporadas en la membrana, la cual empieza a crecer y el volumen que contiene también aumenta. Entonces un vacío osmótico se crea y la esfera de la membrana se alarga. Un cuello se forma en el medio, y la esfera se divide en dos esferas idénticas, conteniendo cada una de ellas la mitad de las moléculas del ciclo autocatalítico y la mitad de las moléculas de plantilla (template molecules)" (Gánti, 2003:38).

Este modelo de Gánti intenta recoger las características mínimas de los seres vivos desde un punto de vista mecanicista (no animista o vitalista), basándose en la organización cíclica de los procesos de los entes vivientes. Sin embargo, y quizá debido a su perspectiva holista, presenta ciertos problemas en cuanto se aplica a los seres vivos naturales. James Griesemer y Eörs Szathmáry son los revisionistas del quemotón más destacados y Bechtel recoge algunos de sus comentarios al respecto en "Biological mechanisms: organized to maintain autonomy" (2007), incluso antes de que publicaran su trabajo.

Uno de los comentarios del propio Bechtel al respecto es que esta clase de sistema es extremadamente sensible a las perturbaciones. Funciona mientras el equilibrio de inputs y outputs se mantenga invariable, y siempre y cuando ninguna perturbación altere el ciclo metabólico y/o la membrana. Esto se debe principalmente a la mutua dependencia entre el ciclo metabólico y la producción de membrana, dada por la estequiometria de su relación. Si se altera el metabolismo, la membrana se resiente, y viceversa.

Esta dependencia estequiométrica asegura la unión entre operaciones, pero impide que se puedan modificar los elementos implicados por separado (Bechtel, 2007: 289), ya que la alteración de una de las partes afectaría irremisiblemente al comportamiento general del sistema. La propuesta de Griesemer y Szathmáry consiste en proponer la libertad estequiométrica como el modo más eficaz de mantener la coherencia en un sistema dotando de cierta independencia a sus partes componentes a través de cierta modularidad. Tal y como la definen, la libertad estequiométrica es "a *chemically* emergent property of molecules in infra- or protobiological systems on the way to autonomous or autopoietic living systems. Such chemical properties may constitute intermediate steps or stages to biologically emergent system behaviour" (Griesemer and Szathmáry, 2008: 504), lo cual otorgaría mayor plasticidad al quimiootón, y como consecuencia una mayor resistencia a las perturbaciones. Griesemer y Szathmáry señalan que es gracias a la introducción del subsistema de información del quemotón que se puede obtener libertad estequiométrica sin grandes modificaciones del modelo original.

La libertad estequiométrica es una propiedad químicamente emergente de las moléculas que actúa como paso intermedio entre los sistemas protobiológicos y los plenamente autónomos (Griesemer y Szathmáry, 2009: 504). Para aplicarla al quimiotón, bastaría con que, en la formación de los polímeros que conforman la membrana, en vez de una molécula, participaran dos o más. El proceso de formación de polímeros y por ende de la membrana seguirían siendo estequiométricos, pero la secuencia de los monómeros en el polímero sería estequiométricamente libre (Bechtel, 2007: 289-290).

Esto le otorga al modelo mínimo de Gánti de una modularidad que permite modificar una parte sin alterar las demás. Esto implica que las causas de los cambios de propiedad del sistema pueden descomponerse en cambios de las partes componentes. Dicho de otro modo, los efectos de los cambios se producen a nivel local, evitando así las consecuencias a nivel global o sistémico (Griesemer y Szathmáry, 2009:506) y otorgando al sistema una mayor plasticidad y resistencia a perturbaciones.

5.2.3. El modelo autopoiético

Otra idea elaborada, desde una perspectiva mecanicista, con el fin de obtener la misma respuesta que Gánti buscaba acerca de las características mínimas necesarias para la vida, es el de autopoiesis. Humberto Maturana y Francisco Varela resaltan especialmente la importancia de la organización de los seres vivos por encima de cualquier otro criterio. Dice Maturana: "En 1965 yo señalé este modo de ser autónomo del ser vivo hablando de una 'organización circular' de transformaciones y de producciones moleculares, indicando que el ser vivo es y existe como ente molecular sólo en tanto permanece en la conservación de tal organización" (Maturana y Varela, 2004:16).

En relación a la organización estos autores subrayan lo siguiente: "En tanto que es la organización lo que define la identidad de clase de un sistema, y es la estructura lo que lo realiza como un caso particular de la clase que su organización define (ver Maturana, 1975; y Maturana y Varela, 1985), los sistemas existen solamente en la dinámica de su organización de una estructura" (Maturana y Varela, 2004: 19-20). Estos autores se centran en los procesos y las relaciones que se establecen entre ellos, y no tanto en los componentes, que solo se consideran en tanto que medios para la realización de esos procesos, sin importar cuál sea su realización material.

Ellos definen el concepto de organización como "aquellas relaciones que tienen que existir o tienen que darse para que ese algo sea" (Maturana y Varela, 1996: 36). La organización define a qué clase pertenece una unidad, y la organización autopoiética es la que caracteriza a los seres vivos. Lo representativo de esta organización es que permite a los organismos reproducirse continuamente a sí mismos (Maturana y Varela, 1996: 36).

La autopoiesis es un tipo de organización que constituye a los sistemas como unidades, entendidas como individuos, y definidas por actos de distinciones, en los que se separa lo señalado del fondo en el que se halla (Maturana y Varela, 1996: 34). En palabras de Maturana y Varela, "una máquina autopoiética es una máquina organizada como un sistema de procesos de producción de componentes concatenados de tal manera que producen componentes que: i) generan los procesos (relaciones) de producción que los producen a través de sus continuas interacciones y transformaciones, y ii) constituyen a la máquina como una unidad en el espacio físico" (Maturana y Varela, 2004: 69).

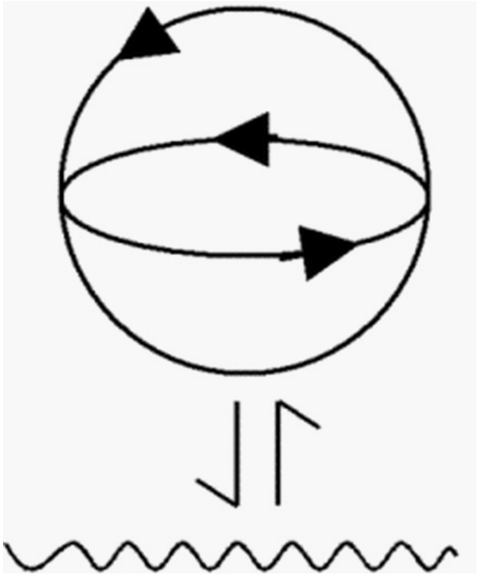

Figure 9 - Modelo autopoiético incluido sistema nervioso (Maturana y Varela, 1996)

Son máquinas homeostáticas que tienen "a su propia organización como la variable que mantiene(n) constante" (Maturana y Varela, 1996: 69). Son homeostáticas porque se mantienen estables a pesar de (y gracias a) el intercambio constante de materia y energía con el exterior. Que su organización sea definida como una variable viene de los escritos de Walter Cannon, también. Hay que recordar que este concibió la homeostasis no como un estado fijo, sino como una condición, implicando así que el sistema podía sobrevivir dentro de un rango de estados posibles, pero que si se sobrepasaban esos límites el sistema colapsaría (Cannon, 1963).

Más adelante, explicitan que "una organización autopoiética constituye un dominio cerrado de relaciones especificadas solamente con respecto a la organización autopoiética que ellas componen, determinando así un espacio donde puede materializarse esta organización como sistema concreto, espacio cuyas dimensiones son las relaciones de producción de los componentes que los constituyen"(Maturana y Varela, 2004: 79), que son las relaciones constitutivas, que dan forma material al sistema, las relaciones de especificidad, que determinan los componentes participantes en la autopoiesis, y las relaciones de orden, relativas a las relaciones entre componentes según la autopoiesis del sistema.

La insistencia en la definición de lo que constituye una máquina autopoiética y su tipo de organización característica resulta en una clara subordinación de la reproducción a la misma. Siguiendo la lógica desplegada, los autores explican que, antes de poder hablar de reproducción, hay que disponer primero de una unidad[48], tal y como ellos la definen, plenamente desarrollada. La reproducción, como tal, la consideran una complicación de la unidad, término que ellos mismos usan para describirla.

Nos dicen que hay tres tipos de generar unidades: por réplica, que consiste en la producción de entidades idénticas entre sí, pero distintas operacionalmente al productor. El ejemplo que ponen es el de una fábrica de coches, con el fin de ilustrar también la independencia de los productos entre sí y con respecto al productor. Evidentemente, una fábrica de coches hace todos los coches de modo idéntico, pero el hecho de que el coche de un particular se estropee, no afecta en absoluto a la fábrica (Maturana y Varela, 1996: 50).

Otro tipo de generación de unidades es la copia, en la que existe una unidad que sirve de modelo para la creación de otras unidades. Aquí se pueden dar dos tipos de producción: una en la que las copias son históricamente independientes, puesto que son todas copias del "original", y otra en la que sí son dependientes históricamente, según la cual se hacen copias sucesivas de las copias, supuesto bajo el cual esas copias van cambiando a medida que se repite el proceso (Maturana y Varela, 1996:52).

Para terminar, nos encontramos con la reproducción. Esta la definen en términos de "fractura" de un original, que da lugar a otra unidad, pero conservando elementos de la entidad original. Sin embargo, nos advierten, para hablar propiamente de reproducción,

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[48] "Una *unidad* (entidad, objeto) queda definida por un acto de distinción. Cada vez que hacemos referencia a una unidad en nuestras descripciones implicamos la operación de distinción que la define y hace posible". Y también, como señalaba un poco más arriba: "El acto de señalar cualquier ente, objeto, cosa o unidad está asociado a que uno realice un *acto de distinción* que separa a lo señalado como distinto de un fondo. Cada vez que hacemos referencia a algo, implícita o explícitamente, estamos especificando un *criterio de distinción* que señala aquello de que hablamos y especifica sus propiedades como ente, unidad u objeto" (Maturana y Varela, 1996: 34)

"la estructura de la unidad tiene que realizar su organización de forma *distribuida* y no compartimentalizada" (Maturana y Varela, 1996:53). Esto debe ser así para que ambas partes fragmentadas dispongan de una estructura que pueda llevar a cabo la misma organización original.

Este es el tipo de generación de unidades que puede observarse en la naturaleza, el que llevan a cabo las células (que, al fin y al cabo, son las consideradas como unidad básica por Maturana y Varela). En este tipo de generación, lo importante para ambos es que "todo ocurre en la unidad como *parte* de ella y no hay separación entre el sistema reproductor y el sistema reproducido" (1996:55).

Hay una diferencia clara entre esta concepción de reproducción y la descrita por Gánti, y es que la reproducción de unidades autopoiéticas no da lugar a dos sistemas idénticos como sucedía en la división del quimiotón, sino que tienen peculiaridades estructurales diferentes entre las unidades producidas y el productor, aunque mantienen la misma organización. "Esto no sólo porque son más pequeñas, son también porque sus estructuras derivan directamente de la estructura de la unidad original en el momento de la reproducción y reciben al formarse distintos componentes de ella que no están uniformemente distribuidos y que son función de su historia individual de cambio estructural" (1996: 55).

5.3. Consideraciones finales

En el análisis que hace Drack de la teoría y de la postura general de Bertalanffy, subraya los esfuerzos de este por evitar el debate entre el mecanicismo y el vitalismo, tomando una postura organicista en su lugar, al menos como marco teórico. De hecho, Drack afirma que en los textos de Bertalanffy hay una evitación tan recalcitrante contra este debate que, en vez de usar el término "holismo", por su supuesta carga metafísica-vitalista, lo sustituye por el de "integridad" o "completud"[*].

En otro orden de cosas, Bertalanffy llevó un trabajo crítico sobre la cibernética, con la intención de desmarcarse de sus propuestas y enfatizar sus concepciones sobre los

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[*] El término original es "wholeness", que se traduce literalmente como "integridad", pero en el sentido de partes integradas, totalidad o, como decía arriba, completud.

sistemas. Uno de los puntos clave en donde ambos paradigmas se distinguían es, precisamente, en la aproximación al estudio de los sistemas que llevan a cabo. Mientras que la cibernética tiene un carácter más constructivista, derivada sobre todo de la segunda cibernética, Bertalanffy defendió para la TGS una aproximación perspectivista (según Drack, 2015: 532-535).

Ambos modelos de los mínimos recogidos aquí son abstracciones para describir un mismo fenómeno, pero desde perspectivas diferentes. Quizá el mejor modo de expresar esa diferencia sea recurriendo a la distinción entre las distintas metodologías disponibles para investigar a los seres vivos. El quimiotón de Gánti parte de una metodología bottom-up, o de abajo arriba, como él mismo dice[49]. Sin embargo, el modelo autopoiético toma la perspectiva contraria. DiFrisco (2014) añade a esta distinción otro criterio clasificatorio, distinguiendo entre descriptivo y constructivo. Lamentablemente no ofrece una descripción de tales criterios, y la distinción entre ambos queda en una intuición más que en una descripción clara.

Por otro lado, ninguno de estos modelos tiene en cuenta la influencia del ambiente, salvo en la forma de perturbaciones. A lo que trato de referirme aquí es a la influencia del medio en la formación y desarrollo de un sistema biológico. El medio puede afectar a la organización de estos sistemas, como la expresión o inhibición de un fenotipo en determinadas circunstancias (polifenismo), y no por el hecho de que se ha sufrido una perturbación puntual de la que el sistema se recupera o por el cual colapsa. Por ejemplo, la altura de un organismo, ya sea planta o humano, depende en parte del bagaje genético, pero también, en gran medida, de la disponibilidad de los nutrientes necesarios para su desarrollo.

En cualquier caso, ambos son los modelos por antonomasia de lo que, clásicamente, y al menos en principio, se puede considerar un modelo de un sistema mínimo que se autoorganiza y automantiene, y probablemente muchas de sus limitaciones podrían ser superadas con la inclusión de las nociones de la cibernética acerca de la

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[49] Según aparece en Gánti (2003), el quimiotón ha sido “diseñado desde abajo, comenzando por la dirección de las reacciones químicas” (2003: 5).

cantidad de variedad que puede soportar un sistema y cómo puede sobrevivir a las perturbaciones que la traen consigo.

Se hace necesaria una definición de sistema capaz de abarcar la complejidad total de los seres vivos a partir de la cual construir un concepto de organismo que nos permita definir con mayor precisión el objeto de estudio y que también nos permita determinar las variables útiles para el análisis de los sistemas biológicos. Las carencias que presentan los distintos modelos que han aparecido en este capítulo se manifiestan por haber elegido una serie de variables que se han considerado indispensables. Además, y como se ha intentado demostrar, algunos modelos tienen un componente marcadamente físico que limita la posibilidad de incluir algunos factores biológicos definitorios.

Lo que podría enriquecer estas propuestas es una perspectiva integrativa que una todo el conocimiento que se ha ido acumulando sobre el estudio de los sistemas biológicos desde las diferentes disciplinas, para formar un nuevo cuerpo epistemológico que abra la posibilidad de mantener el objetivo de estudio a la vez que se despliegan nuevas formas de aproximarse al problema. Por ello, en el siguiente apartado se presenta la biología de sistemas, una nueva disciplina que recupera el espíritu original de las pesquisas de Bernard y Cannon, en unión con los análisis realizados sobre la materia desde diferentes disciplinas, junto a los últimos avances tecnológicos.

.6.

El estudio interdisciplinar de los sistemas biológicos

Tabla de contenido

La disciplina denominada biología de sistemas se refiere a un área de investigación y estudio sobre los sistemas biológicos cuya idea es aunar diferentes disciplinas con el objetivo de superar el reduccionismo y el determinismo genético que marcaron fuertemente la investigación biológica durante décadas y conseguir una serie de normas que, además de ser exhaustivas cualitativamente, nos permitan hacer predicciones basándonos en cálculos cuantitativos. Esta superación del reduccionismo no implica en absoluto el abandono de esta perspectiva, sino que el objetivo final es el de complementar esta perspectiva con unas aproximaciones de carácter claramente holístico, que nos permitan comprender el comportamiento del sistema como un todo. Dicho de otro modo, el objetivo primordial de la biología de sistemas es la de dar una explicación a la vez cualitativa y cuantitativa, poner en relación los niveles macro y micro del universo biológico.

Esta complementariedad surge naturalmente de la necesidad de continuar y ampliar los estudios sobre los seres vivos que pretende superar las limitaciones implicadas en planteamientos de corte reduccionista en los estudios biológicos. Un buen ejemplo de esas limitaciones es el Proyecto Genoma Humano: se decodificó la secuencia completa del código del genoma humano, pero estos datos se mostraron insuficientes a la hora de prevenir enfermedades, comprender mejor el funcionamiento del organismo, la relación entre genotipo y fenotipo o incluso alcanzar un conocimiento más profundo de la vida, por nombrar algunas cuestiones relevantes que surgieron, incluso disponiendo de la completud de los datos a nivel micro.

Por ello surgieron las ciencias ómicas, profundizando en el filón de conocimiento abierto tras el Proyecto Genoma Humano. Estas aproximaciones científicas aparecieron ante la necesidad patente del análisis y del estudio de las diferentes relaciones entre los elementos y demás componentes de los sistemas orgánicos vivos, abriendo el paso hacia la actual meta, que es la de estudiar los sistemas, además de como un compendio de moléculas e interacciones, como una totalidad que dé cuenta de su autonomía e independencia, meta que ya se habían propuesto, como decía en los correspondientes capítulos, Bernard con su medio interior y Cannon con su idea de homeostasis. En otras palabras, las ciencias ómicas abrieron de nuevo las cuestiones acerca de la relevancia de las interacciones y de la búsqueda de explicación sobre los fenómenos biológicos, en especial de aquellos relacionados con el comportamiento y la constitución de los organismos como unidades organizadas.

Esta disciplina cuenta con dos aproximaciones principales que han surgido en el estudio de los seres vivos que se corresponden con dos aproximaciones distintas, la pragmática y la teórica, cada una de las cuales se adecua a la obtención de diferentes resultados. Ambas aproximaciones se sirven de tres metodologías distintas que se superponen y se complementan con el fin de obtener la información necesaria del modo más exhaustivo posible.

6.1. Introducción

La biología de sistemas es, por definición y necesidad, una disciplina que aúna los recursos teóricos y prácticos de varias especialidades, entre ellas la matemática, la bioinformática, la filosofía y la fisiología, por mencionar algunas. Esa necesidad surge, por un lado, de la comprensión de que la biología por si sola no basta para gestionar y manejar la cantidad de datos (cuantitativos) generados a lo largo de la historia y, en concreto, de la genética (sobre todo por el proyecto genoma y de las ciencias ómicas).

Por otro lado, también surge en un contexto en el que se comenzó a tomar mayor conciencia acerca de la importancia de complementar y aunar todos esos datos con una aproximación de carácter más holista o, si se prefiere, organicista. Cada una de estas disciplinas juega un rol inalienable en el desarrollo de las investigaciones en esta rama de la biología, cuyo objetivo principal es el de “capture the dynamic complexity of living systems through the combination of mathematical, computational and experimental strategies” (Green, 2017: 1; citando a Kitano, 2001).

La biología de sistemas es algo más que la mera heredera de las ciencias ómicas. Aunque la narrativa científica pueda hacer que parezca así, la biología de sistemas se fundamenta en varias tradiciones disciplinares que se han dedicado, en mayor o menor medida, al estudio de los sistemas biológicos. A eso hay que añadir, como también sostiene Green (2013: 555), que la biología de sistemas puede aplicarse a un buen rango de prácticas y no solo a formulaciones teóricas. En cualquier caso, la biología de sistemas parece el marco conceptual más apropiado para desarrollar la revisión de la noción de homeostasis que nos permita eliminar su ambigüedad, si bien solo práctica, y también que nos permita dilucidar hasta qué punto podría tomarse como noción holista que la propia perspectiva más organicista de la biología de sistemas necesita. Esto es suscitado por la perspectiva de la biología sistémica que defiende un punto de vista holista de los organismos, pero sin obviar los elementos y procesos que los componen, integrando ambas aproximaciones mediante diferentes metodologías con el fin de comprender mejor y de forma más precisa el comportamiento de los sistemas biológicos, al menos en su formación primordial.

Otro motivo por el cual considerar la biología de sistemas como un marco más adecuado resulta más pertinente es que armoniza con la idea original de la homeostasis, esto es, la idea de buscar una explicación de la estabilidad y organización de los organismos que les otorgan su autonomía e independencia, constituyéndolos como una unidad diferenciada del resto de su entorno, buscando las explicaciones sobre el comportamiento de sus procesos y elementos a diferentes niveles, especificando los distintos tipos de interacciones que mantienen. Sin embargo, la biología de sistemas aspira a incluir un análisis del ambiente o del contexto en el que se encuentran los organismos, añadiendo al estudio sobre las perturbaciones provenientes del exterior otro sobre distintos tipos de relaciones e influencias entre el organismo y el medio. Por decirlo de otra manera: al contrario que en las formulaciones bernardianas, el contexto no es solo fuente de perturbaciones, sino que además es una suma o un conjunto de factores que pueden ser positivos o neutros.

6.2. Pluralidad y cohesión metodológica

La biología de sistemas recoge distintas metodologías tradicionales de la investigación científica y las convierte en constitutivas de su propia práctica disciplinar. Además, complementa ambas con una metodología específica de especial relevancia para el tipo de investigación que la biología de sistemas aspira a desarrollar. Durante mucho tiempo, la aproximación científica al análisis de los diferentes fenómenos bajo estudio consistía en aislar y observar esas partes y elementos separados del resto, con el fin de comprender su estructura y funcionamiento. Esta metodología se conoce como “bottom-up” o, en otras palabras, la metodología que va del detalle a lo general. La idea principal de esta aproximación es la de deducir el comportamiento de los sistemas biológicos como un todo mediante la anexión de todos esos fenómenos y elementos aislados. Esta estrategia ha resultado altamente prolífica a lo largo de la historia de la ciencia, pero, sin embargo, tras la finalización del Proyecto Genoma Humano, se confirmaron las sospechas de que esta metodología por sí sola presentaba ciertas limitaciones a la hora de analizar el comportamiento de los organismos como un todo.

Esto se debe, por un lado, a la cantidad de datos provenientes de la biología molecular. Tras el Proyecto Genoma Humano y el desarrollo de las ciencias ómicas, la cantidad de información acumulada se hizo difícil de cotejar y manipular. Esta gran cantidad de información, en cierto modo, impulsó las ciencias de la computación hacia la creación de computadoras lo suficientemente potentes como para compilar esa base de datos y, a la vez, contribuyó a la mejora de sistemas de programación con respecto al ámbito biológico, creando programas específicos con algoritmos afines a los procesos y elementos organísmicos y a su comportamiento. Este tipo de computación se conoce hoy día como la disciplina de la bioinformática.

No obstante, esta recopilación de datos, dado que son sobre todo datos a nivel de composición molecular, nos dice mucho del comportamiento molecular, pero no es especialmente reveladora en el nivel del sistema en su conjunto y su comportamiento.

Como dice Noble: “las estructuras y los procesos característicos de los niveles superiores no resultan visibles a nivel molecular” (Noble, 2008: 96-97).

Para ejemplificar mejor esta metodología científica, se puede decir que la perspectiva científica más afín a este tipo de metodología es la reduccionista. Con el fin de superar las limitaciones inherentes a esta metodología, la biología de sistemas incluye otra metodología para complementar la atención al detalle que conlleva el reduccionismo, la “top-down”, que abre la posibilidad de estudiar los seres vivos desde la perspectiva unitaria del organismo. Este procedimiento parte del estudio del sistema como un todo para luego poder comprender hasta qué punto los niveles superiores determinan el comportamiento de las partes que los componen. Esta estrategia aparece en el ámbito de la fisiología, por ejemplo, en las disquisiciones de Bernard sobre el organismo (de las que ya se ha tratado en este trabajo de investigación en capítulos anteriores), que le llevaron fundamentalmente a la distinción del organismo con respecto a su medio, en función de su organización interna, dando cuenta así de su autonomía, sin entrar necesariamente en detalles del estudio de las partes que lo componen, salvo para tratar de descubrir cómo se determinaban mutuamente el organismo y su autonomía con sus partes y la autonomía de estas.

El problema es que esta metodología, tomada de manera aislada, tampoco resulta suficiente para el estudio completo de los seres vivos, ya que el análisis de las partes se limita a su relación con el todo que constituyen. El principal inconveniente es, en palabra de Noble: “una vez que hemos conseguido horadar el sistema atravesando la totalidad de los niveles que lo componen, hasta alcanzar los elementos constitutivos de menor tamaño, a saber, las moléculas, resulta preciso reconstruir nuevamente todo el conjunto *en términos cuantitativos* si deseamos entenderlo cabalmente a nivel sistémico” (Noble, 2008: 98).

Precisamente debido a su naturaleza antagónica la fusión de ambas resulta enriquecedora a la hora de investigar cualquier fenómeno biológico. Sin embargo, el análisis de los sistemas biológicos aún puede enriquecerse con una metodología adicional, una que no constriña la investigación a los niveles superiores o inferiores de los organismos, sino que cuente con una flexibilidad tal que permita establecer las bases del análisis en función del nivel de estudio de interés. Esta idea se condensa en lo que podría denominarse la metodología más característica y propia de la biología de sistemas, la “middle-out”. Esta última metodología se hace necesaria, ya que complementa y pone en relación las dos mencionadas anteriormente, mediante el análisis de los diferentes niveles *y sus relaciones*. Esta última metodología sirve de puente y cohesión entre todas las posibles aproximaciones metodológicas en biología.

Para utilizar esta estrategia es preciso elegir un nivel del que se conozcan bien las funciones biológicas, esto es, cualitativa y cuantitativamente. Para poder comprender la potencia de este método hay que tener en cuenta que las metodologías anteriores, la top-down tanto como la bottom-up, parecen encorsetarnos en la idea de que existe una jerarquía estricta y vertical en todo sistema biológico. Sin embargo, gracias a la middle-out, esa jerarquía pierde la verticalidad estricta, abriendo el análisis y posibilitando explicitaciones biológicas que recojan interacciones de elementos y procesos en varios niveles a la vez, modificando esa estructura jerárquica, de tal modo que adopta la forma de una red de interacciones en función de la necesidades del organismo y no tanto según un orden jerárquico inflexible.

La táctica middle-out resulta imprescindible, porque como dice Noble: “Cuando se trata de redes de interacciones entre elementos que pertenecen a diferentes niveles, es evidente que no cabe otra alternativa” (Noble, 2008: 99). La cuestión más importante es conocer bien el punto desde el cual se inicia la investigación y, a partir de ahí, se va navegando entre niveles, tomando de cada uno aquello que resulte más relevante en el trabajo que se tenga entre manos. “De este modo, los niveles inferiores se examinan a través del filtro que supone el nivel superior en el que se integran. Esto nos permite entresacar lo más relevante de entre la ingente masa de datos existente a ese nivel, de forma que se reduce en gran medida la cantidad de información que es necesario trasladar de un nivel de análisis al siguiente” (Noble, 2008: 100).

En resumen, para una práctica científica que aspire a consumar las aspiraciones teóricas de la biología de sistemas es necesario aunar diferentes metodologías para recoger la complejidad de los sistemas biológicos y así analizarla en toda su extensión. Para ello se combinan las metodologías bottom-up y top-down, siendo esto posible por ser compatibles, a pesar de su naturaleza aparentemente antagónica. Ambas se complementan asimismo con el método middle-out, que nos permite seleccionar el nivel a investigar y habilitar el análisis de las relaciones entre niveles, mediante la discriminación de los elementos y procesos relevantes para el estudio en cuestión que se desee realizar.

6.3. Dos vertientes principales

Estas tres metodologías se relacionan con dos diferentes perspectivas en la biología de sistemas. Esta diferenciación se la debemos a O'Malley y Dupré, quienes se han dedicado al estudio de la biología de sistemas desde la perspectiva filosófica prácticamente desde sus inicios. De acuerdo con el análisis que hacen de la disciplina, pueden distinguirse dos corrientes principales dentro de la propia biología de sistemas.

La primera de ellas es la biología de sistemas pragmática, a la que también denominan "biología de sistemas biológica". Esta vertiente busca la integración de datos de distintos niveles y con procedencia de diferentes fuentes. Se ocupa con mayor preferencia del estudio de las interacciones moleculares a gran escala y se centra con más intensidad en el análisis de las funciones de los sistemas biológicos. De esta forma su propósito primordial es el estudio de los sistemas como un todo compuesto de fenómenos interconectados (O'Malley, Dupré, 2005: 1271).

Para ello, este enfoque utiliza prioritariamente la metodología bottom-up y también la middle-out esporádicamente, con el fin de realizar sus modelajes por ordenador. En el contexto de esta aproximación es importante contar con datos moleculares exhaustivos, además de necesitar herramientas capaces de manejar grandes cantidades de datos y de integrarlos a través de la inclusión en el modelaje de las interacciones que mantienen entre sí los diferentes elementos del sistema, para construir así una imagen más global del mismo, partiendo de sus componentes, de sus relaciones, de la manera en como se estructuran en la formación del todo y de sus interrelaciones.

Por otro lado, nos encontramos con una aproximación a los fenómenos biológicos dentro de la biología de sistemas que mantiene una perspectiva top-down. O'Malley y Dupré la llaman "systems-theoretic biology" o, lo que es lo mismo, biología teorética de sistemas. Esta rama conceptual de la biología de sistemas parte del estudio de las funciones del sistema global y sus propiedades, sobre todo, tomando en consideración las emergentes. La idea principal es la de encontrar los principios y las leyes que rigen los sistemas biológicos, basando esta investigación en la dinámica que les es propia (O'Malley y Dupré, 2005: 1271).

Las diferentes metodologías que marcan la línea divisoria entre ambas aproximaciones se deben también al origen ideológico del cual parte cada una de las perspectivas de la biología de sistemas. Mientras que, por un lado, la vertiente pragmática bebe directamente de la herencia de la biología molecular y las ciencias ómicas, con especial énfasis en la genómica; la corriente teorético-sistémica guarda más relación con disciplinas como la ingeniería teórica, la teoría de sistemas de Bertalanffy o la fisiología clásica de Bernard y Cannon, entre otros (Green, 2015: 636).

Aunque se puedan distinguir dos corrientes de investigación dentro de la biología de sistemas, es importante señalar que, al igual que las diferentes metodologías, no son incompatibles entre sí. De hecho, la biología de sistemas pragmática aspira en última instancia a encontrar principios básicos de comportamiento de sistemas globales, del mismo modo que la biología de sistemas teorética debe incluir en sus pesquisas los diferentes niveles que componen el sistema total, con sus componentes e interacciones, para justificar esos principios generales de los que parte. Además, al aunar las diferentes perspectivas, es mucho más probable que podamos forjar una definición de sistema más estricta que con la que se trabaja actualmente que, según O'Malley y Dupré, es algo como "complex structures of *interdependent* and subordinate *components* whose relationships and properties are largely determined by their function in the whole" (O'Malley y Dupré, 2005: 1271).

6.4. Debates filosóficos sobre biología de sistemas

La biología de sistemas no es sólo una colaboración entre un conjunto de disciplinas, sino que su carácter intrínseco es interdisciplinar. La biología es el marco general de estudio, pero no sería plenamente de sistemas si no se contara con la matemática para traducir los elementos y relaciones de los organismos en datos cuantificables, que sirvan de base para el modelaje por ordenador. También es necesaria la bioinformática, que tiene la tarea de recoger esa información y compilarla en simulaciones por ordenador, además de la ya mencionada construcción de modelos.

Incluso la biología cambia de perspectiva, desplazándose desde un planteamiento molecular hacia niveles superiores de organización para incluir puntos de vista más holistas, que no pierdan de vista el sistema al completo bajo estudio y que pongan en relación las funciones presentes en los diferentes niveles, con el fin de dar cuenta de la complejidad intrínseca de los seres vivos. Esta perspectiva nos permite analizar los sistemas como una red de interacciones, con lo cual nos obliga a buscar una explicación acerca del tipo de jerarquía que ostenta, cómo se justifica y cuál es la base sobre la que se construye.

Otra cuestión que resulta relavante señalar acerca de la biología de sistemas es el tratamiento y uso de las nociones recogidas por los binomios vitalismo/mecanicismo y holismo/reduccionismo. Por un lado, reconcilia las dos perspectivas que, en la concepción clásica, parecían no tener terreno en común sobre el que asentarse, que son el holismo y el reduccionismo. No volveré sobre esto, ya que lo he explicado ampliamente en secciones previas, pero sí subrayaré que esto ha sido posible gracias a una redefinición de las nociones clásicas de vitalismo y de mecanicismo, donde el vitalismo pierde su fundamentación metafísica para convertirse en un criterio de demarcación entre lo vivo y lo no vivo y donde el mecanicismo se transforma en el estudio de los procesos y los elementos de los sistemas en funcionamiento, sin necesidad de mantener la analogía entre los seres vivos y las máquinas.

Una de las preocupaciones de las que se hacía eco Newman en los primeros años de la biología de sistemas era relativa al desarrollo tecnológico y conceptual. Por un lado, señalaba que la cantidad de datos a manejar era inmensa y que a principios del siglo XX aún no se contaba con la tecnología necesaria para compilarlos y cotejarlos de manera que quedara reflejada la compleja red de interacciones que se establecen entre ellos. Por otro, subrayaba que algunas de las nociones necesarias para una profunda comprensión de los fenómenos biológicos hacía relativamente poco tiempo que habían empezado a desarrollarse, como, por ejemplo, las leyes de comportamiento de materiales complejos, "such as living tissues, [which] requires, in addition to genetic information, an understanding of chemical dynamics, including oscillations, pattern forming processes, and chaotic behaviour" (Newman, 2003: 12).

Otra de las cuestiones de la biología de sistemas desde la perspectiva filosófica sería la de comprobar qué grado o clase de validez tienen los experimentos por ordenador, como señalan O’Malley y Dupré. En este punto parece necesario comprobar si nos pueden llegar a ofrecer el mismo grado de información que los experimentos en vivo y también es fundamental pensar si sería menester que los resultados de la experimentación por ordenador están respaldados por resultados experimentales “reales” (O’Malley y Dupré, 2005: 1274. Las comillas son del texto original).

Otra de las preocupaciones sobre la biología de sistemas, pero esta vez en su aplicación en el ámbito de la medicina y de la farmacología por extensión, es qué aportación ofrece a estos aspectos prácticos de la biología. Desde luego que una aplicación de la biología de sistemas en la práctica cotidiana de la medicina cambiaría de manera importante la relación entre médico y paciente, además de la perspectiva del profesional acerca del tratamiento y aproximación a las enfermedades. Por ejemplo, una influencia positiva sería la necesidad ineludible de tomar en cuenta el historial del paciente a la hora de realizar diagnósticos. Otro aspecto reseñable que señala Kitano es el de la importancia para la medicina de que la biología de sistemas, mediante sus técnicas de modelaje, cree “a detailed model of cell regulation, focused on particular signal-transduction cascades and molecules to provide system-level insights into mechanism-based drug model. Such models may help to identify feedback mechanisms that offset the effects of drugs and predict systemic side effects” (Kitano, 2002: 1664).

El mayor problema de la biología de sistemas actualmente es que se ha desarrollado enormemente su aspecto más técnico y reduccionista. No se trata de que haya cambiado sus planteamientos o sus aspiraciones, sino de que su vertiente más organicista ha pasado a segundo plano ante la aplastante producción de trabajos a nivel molecular del estudio de los seres vivos. Esto puede deberse a una causa doble. Por un lado, los datos y las metodologías de este tipo estaban mucho más avanzados y desarrollados. Por otro lado, y quizá como causa de lo anterior, es difícil modificar las prácticas establecidas sin un trabajo consciente de deconstrucción. En cualquier caso, la biología de sistemas necesita recuperar las propuestas de su vertiente más organicista, y quizá sea más sencilla esa tarea si utilizamos la noción de homeostasis revisada, a modo de elemento unificador.

6.5. Consideraciones finales

El nacimiento de la biología de sistemas y el de la fisiología guardan ciertos paralelismos. Por un lado, la biología de sistemas surgió como consecuencia necesaria de un periodo prolífico de estudios moleculares que llegó al límite de su potencial, alcanzando la subsiguiente ralentización en la producción de resultados novedosos. La biología de sistemas surgió de la necesidad de ampliar las miras de la investigación acerca de los sistemas biológicos, con el objetivo de salir de ese parón y seguir obteniendo respuestas acerca de su funcionamiento.

Por otro lado, nos encontramos con la fisiología moderna. Esta, por su parte, también surgió como reacción intelectual subsecuente ante la falta de explicaciones satisfactorias acerca del funcionamiento de los organismos. La anatomía, que era la aproximación por excelencia al estudio de los seres vivos, se mostraba limitada a la hora de responder a la pregunta acerca de los procesos, los elementos y sus interacciones, que conforman el todo que es un sistema biológico. Así, tras una revisión profunda de los métodos de investigación, se propuso pasar del estudio de la estructura de los seres vivos al estudio acerca de su funcionamiento, entendido como conjunto de procesos e interacciones entre elementos.

En resumen, un punto en común entre ambas ramas de la ciencia es que puede decirse que surgieron por la necesidad de complementar a la perspectiva científica imperante y sus limitaciones, tras haber explorado al límite los recursos de esa vía de investigación, proponiendo una alternativa de análisis. Pero los paralelismos que pueden establecerse entre fisiología y biología de sistemas deben también limitarse. La biología de sistemas y la fisiología son dos disciplinas distintas, como algunos debates apuntan, por propio derecho. La biología de sistemas no es una suerte de nueva fisiología. Sin embargo, Kevin Strange dice al respecto: “Physiology and systems biology thus share the goal of understanding the integrated function of complex, multicomponent biological systems. In my opinion, physiology and systems biology are synonymous” (Strange, 2004: C968).

Por poner otro ejemplo, Denis Noble también compara la biología de sistemas y la fisiología en un artículo de 2008, donde defiende que la fisiología es la disciplina donde situar el origen de la biología de sistemas. A través de las ideas de Bernard acerca de los métodos de investigación y de dónde centrar la atención en dichos estudios, desarrolla la idea de que ambos buscan principios generales y que ambos defienden que el comportamiento general del sistema puede llegar a comprenderse no mediante el estudio de los elementos que los componen de manera aislada, sino cuando se encuentran en interacción en el interior del organismo.

Aun así, parece que Noble va un poco más allá, si bien no del todo explícitamente, definiendo la fisiología como lo que pudo ser una biología de sistemas, pero que no fue, debido a las constricciones "prácticas y temporales": "The control of the *milieu interieur* meant not that the individual molecules is anything different from waht they would do in non-living systems, but rather that the *ensemble* behaves in a controlled way, the controls being those that maintain the constancy of the internal environment. (…) Physical scientists had long since used mathematics to formalize their theories. Could that also be done in physiology? Bernard's answer is "yes, but not yet". (…) His caution, therefore, was purely practical and temporal" (Noble, 2008: 17).

Para Joyner y Pedersen la relación entre la biología de sistemas y la fisiología tiene un cariz completamente opuesto. Para ellos es la fisiología la disciplina que tiene un carácter más integrador, mientras que el papel de la biología de sistemas es poco más que el de haber señalado las limitaciones del reduccionismo: "So, while systems biology should be applauded for recognizing the limits of reductionism that underpinned molecular biology and genetics, it continues to fail to recognize that a variety of integrating functions between cells, organs, systems, the entire organism and the environment are required to generate a fully functional and highly adaptive animal. This is clearly one area that distinguishes integrative physiology from systems biology" (Joyner y Pedersen, 2011: 1020).

Existe también una disciplina "intermedia" a considerar y es lo que se ha venido llamando "fisiología de sistemas", que tuvo su apogeo hacia el final de la mitad del siglo veinte (Buchman, 2002: 251). Ya que desde sus orígenes la fisiología pertenece al ámbito de la medicina, la idea es que la fisiología de sistemas se constituya como una subdisciplina de la biología de sistemas que se encargue de las aplicaciones prácticas de los preceptos y resultados de esta en el campo de la medicina y de la farmacología, o como dice Buchman: "to promote the integrity of the self, suggesting that a deeper understanding may yield new therapies" (Buchman, 2002: 251).

Kitano, por su parte, la define como "an integrated discipline. It combines experimental, computational, and theoretical studies to advance our understanding of the physiology of human and other living creatures. In other words, systems physiology is systems biology with a physiology (i.e., functionally)-centered view" (Kitano, 2010: 1). De cualquier manera, Kitano defiende la fisiología de sistemas como subcategoría de la biología de sistemas centrada en el estudio y en el modelaje de los elementos que componen los sistemas biológicos y sus interacciones.

Quizá un modo de aproximarse a esta problemática sea considerando la homeostasis como una noción propiamente fisiológica. En cualquier caso, este concepto resulta afín a la biología de sistemas en tanto que esta disciplina mantiene un carácter organicista. Este apunte es importante. No significa que la homeostasis no pueda ser utilizada en las investigaciones de corte más operacionalista, sino que la homeostasis, idealmente, tiene el potencial para unir los desarrollos de este tipo con los estudios organicistas, salvando la escisión, al menos aparente, entre ambos aspectos de la misma disciplina.

Lo que sí está claro es que la noción de homeostasis necesita de la biología de sistemas y de sus estrategias y metodologías de investigación, en concreto las bottom-up y middle-out, ya que fue formulada siguiendo los principios de la fisiología, es decir, buscando la percepción global de los sistemas y su comportamiento.

El análisis y la revisión sobre la homeostasis podrían realizarse con mayor facilidad dentro del marco de estudio que ofrece la biología de sistemas. Por un lado, porque la biología de sistemas puede complementar la perspectiva holista de la fisiología con sus tres estrategias metodológicas combinadas, ofreciendo así el análisis exhaustivo que pretendía Bernard del funcionamiento del medio interior de los organismos y los mecanismos que intervienen en el mantenimiento de su estabilidad intrínseca. Por otro lado, a la biología de sistemas le falta un concepto paraguas bajo el cual aunar los estudios realizados con respecto al comportamiento de los niveles superiores, como el del organismo como un todo, el comportamiento de los demás niveles y la integración total en cada uno de los sistemas biológicos.

.7.

Homeostasis analyzed

Table of contents

Heretofore, this work has displayed the origins and some developments of the notion of homeostasis. From its seminal formulation to the contemporary interest for the current studies within systems biology field, with the aim of examining how is it understood nowadays, mostly due to its operationalist developments, and why might be considered an interesting approach to the study of living beings and their behaviour, if highlighting its origins.

Nevertheless, there is an alternative epistemological path, where homeostasis is not as much needed to be quantified, but specified or deepened, that is, to be developed qualitatively. Within the field of physiology, homeostasis was understood as an interesting notion, but yet to be fully developed: “In my vision, there is no reason to abandon the concept of homeostasis. It is firmly entrenched, as it should be, in our scientific lexicon, and we can continue to expand its meaning. It does, however, begin to strain our conceptual framework for understanding bodily adaptation” (Schulkin, 2004: 12). Even if agreeing with the words of Schulkin, there is an ambiguity in the contemporary usage of homeostasis that needs to be analysed. This ambiguity is quite likely derived from the tension between the holistic, organicist origins of homeostasis, which aimed to describe living phenomena as specific of living beings, and the operationalist, reductionist developments of it, which modelled a notion of stability by sacrificing its exclusive circumscription to the biological realm. That is why it becomes necessary, if not urgent, to revise and re-define the notion of homeostasis for the current biological research.

In this chapter, the notion of homeostasis is to be sharply distinguished from related notions, such as regulation or stability, which have been used sometimes as synonyms. This final clarification will be based on the conceptual background displayer in earlier chapters. It is needed since that undisguisable usage of stability, regulation, etc. as synonyms for homeostasis disregard the inner tension of the homeostatic tradition and may complicate further understanding of the criticism. After clarifying what homeostasis is not, the focus will come back on homeostasis or, to be more precise, on the criticism that homeostasis has encountered, and how it inspired other physiologists to enhance the homeostatic project with their own proposals. This last analysis, together with the previous work, should be suitable for a revision of the notion of homeostasis and its related concepts, as well as their role in modern sciences.

7.1. Introduction

It has already mentioned that homeostasis was born from the idea of living beings exhibiting a peculiar kind of organization. While in previous chapters some approaches have been followed that stress the necessity of quantifying and modelling that organization for it to be applied on predictions relative to robustness or self-regulation, in this chapter the main focus is placed on the qualitative approach to homeostasis, that is, the notions developed from other perspectives rather than those from fields like physics or maths, with their interest placed on a description of stability of living beings within the idea of homeostasis as main attribute maintaining it.

There is a criticism in physiology that cannot be found in quantitative developments of homeostasis, for they are focused on finding more suitable ways to *calculate* predictions on regulation and self-maintenance. Contrarily, the physiological unfolding of the notion of homeostasis is centred in enhancing the core of this notion. Hence, evaluations are directed towards possible deficiencies in its formulation that might not make it appropriate enough to describe living phenomena, in a qualitative mode. For instance, one of the recurrent critiques to homeostasis is that of it being excessively static, or the one around the problematic of defining the set point of oscillatory homeostatic range (Bailey, 1984; Sterling and Eyer, 1988; Mrosovsky, 1990; McEwen, 1998; Torday, 2015; among others).

Besides these essential reviews, there are other underlying issues regarding the terminology used to describe it. Terms borrowed from other disciplines, such as equilibrium and stability, are used interchangeably, as well as self-organization, self-maintenance, regulation, metabolism, etc. This is a problem since each one of those concepts has a precise meaning within their fields that might not (as usually happens) match the specifications of biological denotations, especially those related to the formulation of homeostasis. Due to this, some descriptions of homeostasis seem to loose part of its explanatory strength in biological description, favouring a model that could be used in several fields not necessarily related to biology, this is problematic since those fields have notions of their own to refer to stability and organisation, and biology could use a term as homeostasis as it was initially conceived.

7.2. What homeostasis is not

There appears to be certain agreement to understand homeostasis as some sort of balanced state, related to living beings, even if not really defined but through its ideal modelling. This reduced definition of the term, in addition to the theoretical approach derived from cybernetics, make the term homeostasis diffuse and prone to be confused with similar ideas, like self-maintenance, or self-regulation; and this confusion is extended to a lack of distinction between some concepts that define it, such as equilibrium, stability, or constancy.

When Bernard proposed his concept of internal milieu he was describing a *constancy*, observable in living beings, produced and maintained from inside, that accounted for their resistance to changes coming from the outside in the form of disturbances. That notion of constancy is to be understood as the capacity of living beings of staying the same while resisting the surrounding unstable environment. The distinction amongst constancy, stability or equilibrium was not clear yet, until thermodynamics. Even if Bernard’s conceptualization was sometimes misunderstood as being closer to an idea of equilibrium, in a thermodynamic sense (Bailey, 1984), it might be due to a past negligence on the historical and conceptual context.

In the same stream, homeostasis has also been confused as a synonym for feedback loop[50]: “There is indeed a large number of biological phenomena which correspond to the feedback model. First, there is the phenomenon of so-called homeostasis, or maintenance of balance in the living organism, the prototype of which is thermoregulation in warm blooded animals” (Bertalanffy, 1968: 43). Even if Bertalanffy is right to say that the body’s temperature regulation *is* homeostasis, he is leaving aside the kind of homeostasis that Cannon already talked about and that inspired the creation of notions like heterostasis or allostasis (further in this section). To put it in other words, homeostasis comprises the basic, minimum maintenance processes like blood pressure or thermoregulation, but also other processes that entail regulation, such as influencing the surrounding environment to change it on one own benefit. Moreover, even if Bertalanffy is the chosen one to illustrate the idea, that same formula can be found in cybernetic accounts, as well as in physics and chemistry, economics, or sociology (see Bailey, 1984).

To conclude, and as means of general clarification, it is imperative to stress that homeostasis *is not* (just) a feedback loop because it falls short in the definition, *neither* a stable state as in physics since it misrepresents the amount of flexibility biological systems exhibit, *nor even* (just) an automatized compensation when unbalance occurs since it is not just resistance for a perturbation but an active destruction or adaptation to it. *It is not* just a case of self-maintenance for the last comment, and it *is not* just self-regulation even if it might be the most paradigmatic case. It cannot be defined by terms like *equilibrium*, which does not account for biological dynamics, even if in literature

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[50] This happens more often than not. For instance, Sieck (2017) makes an effort to justify that Bernard “applied equilibrium thermodynamics to medicine and physiology with *his concept of feedback regulation* of the internal milieu” (italics not in the original) by bringing out Nicolas Sadi Carnot, a brilliant French engineer regarded as “the father of thermodynamics”, who wrote *Reflections on the Motive Power of Fire* on 1824. It might be relevant to remember that his book got little attention until Clausius and Kelvin used it to base their thermodynamics theory, but it was not until 1850 that a seminal idea of the second law of thermodynamics was devised (*On the Moving Source of Heat* by Rudolf Clausius) and it was not until 1865, the same year Bernard published his *Introduction* (not his first publication, that happened in 1843-1844), that they defined entropy. I find difficult to accept the idea that Bernard was effectively founding his research on thermodynamic terms when seminal works on thermodynamics were barely known, set aside developed.

It is worth to mention that the relationship between pressure, temperature and volume was studied long before, and it is of course considered as the roots of thermodynamics. Names such as Otto von Guericke, Robert Boyle or Robert Hooke can be traced back up to the 17th century.

they have been used widely as synonyms. For instance, within sociology, Bailey says: "as a number of writers have pointed out, equilibrium theorists in sociology have tended to merge the concepts of equilibrium and homeostasis, even to the point of using the two terms interchangeably" (Bailey, 1984: 26). Homeostasis includes most of these cases and must aim to describe the ongoing process of living of organisms, by substituting, or at least defining sharply, these notions from other disciplines for biological terms and taking the role of explaining that kind of stability and organization observable in nature that accounts for the characteristic behaviour of living beings. To start understanding what homeostasis is, it might be useful to examine physiology itself, since it developed the idea of homeostasis gathering the importance of considering the context to understand the behaviour of a system as a whole, looking forward to understanding how internal and external interactions could affect it and shape its integral and integrated behaviour.

7.3. Developments in physiology

Within physiology, expectations for homeostasis were different from the enthusiastic quantitative ones. Instead of looking for a useful (and relatively fast) implementation of it, the main interest was directed towards the limits and explanatory power of homeostasis in its very same formulation – even if ultimately was to be applied in physiological, biological, and medical praxis. Physiological developments on homeostasis analysed the relationship between the internal and the external environment and how it affects the general behaviour of the system. For instance, one of the main questions raised to homeostasis was about the alterations that the internal environment goes through by the homeostatic definition, which are usually considered temporary, like a cold or a "fight or flight"[51] response when facing a predator. However, what happens if that alteration is not just temporary?

This difference in the analysis responds to the need for a qualitative development of the term, which implicitly (and sometimes not so implicitly) points to one of the work hypothesis held in this work, namely, that homeostasis needed additional development of its core description on the research branches that arose from Cannon's theory, and even

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[51] Cannon also devised the "fight or flight" response. He studied the alterations that a body goes through when facing a potentially dangerous situation that could suppose a threat to life. It is to be understood as the kind of situation that triggers those specific control mechanisms (in this case, we could use the term "stressors" for them) when facing a determined perturbation (the predator).

if that original formulation from Cannon was enough for some of the most important advances in more quantitative, technical sciences (physics, maths, chemistry that enabled cybernetics and systems theory to arise), it can be said that it falls short when applied to explanations about complex phenomena, such as physiological and biological, and definitely in need of some deep insights for improvement within an organicist framework.

7.3.1. Heterostasis

There are pathogens that are not easily dismissed, or stressful situations that stand much longer than the ambush of a predator. Homeostasis, as defined by Cannon, is conceptualized as an arrangement of economy, which means responsive to punctual perturbations that briefly alter the regular oscillation of a system by spending the least resources possible. If a perturbation lasts longer, and especially if it is needed the intervention of the higher control mechanisms, the energy investment would seize all the body activity to focus on that perturbation and deplete rapidly and completely every source and trace of stamina left, pushing the system towards a breakdown. That would be the case, of course, if we were completely subjugated to the action of those control mechanisms, and there was no other, higher, control mechanism monitoring the maintenance and survival of the system as an indivisible unity.

Therefore, when tending to collapse in these long-sustained stressful case scenarios, a homeostatic resource of the body is *heterostasis*. This concept was coined by Hans Selye (1907 – 1982), who is best known by his researches on stress. In Selye's perspective, stress is a non-specific demand for the body to readjust itself when facing a specific perturbation. This general demand is made on top of the specific response to specific perturbations, and it is non-specific in the sense that it refers to a requirement of enhancing the body's performance to adapt to any kind of problem (Selye, 1973: 693). There are three indexes of stress, three steps in the process that are subsumed by the notion of General Adaption Syndrome, or G.A.S., also known as biologic stress syndrome (Selye, 1973: 694). The first one is an alarm reaction. The body gets ready to defence itself against whatever perturbation it must face, and it is usually turned off relatively quickly, that is, when the menace is gone.

Nevertheless, if there is a perturbation capable of trigger this kind of reaction, and it does not fade after a reasonable timespan, the second response to stress is activated, since no body can hold the state of alarm for a long time. This second stage builds some resistance to the perturbation, or adaptation, and it is endocrinologically opposite to the previous stage. The resistance built would seem to maintain the body for as long as it lives, but that is not quite the case. When the perturbation, or stressor, still holds, there is a moment when the adaptation obtained fades away, leading the organism to the next and last stage of the G.A.S., exhaustion. Selye recognizes they do not know what is it that is lost, but he explains that: "just as any other inanimate machine gradually wears out, so does the human machine sooner or later become the victim of constant wear and tear" (Selye, 1973: 695)[52].

The state of resistance is the paradigmatic case of homeostasis (Selye, 1976: 31), "even though the primary reaction of alarm is also driven by homeostatic mechanisms", and to maintain stability it mainly uses two types of reactions. On one hand, there are syntoxic actions, directed to enhance the tolerance to those menacing stressors or pathogens of the body, creating a state of harmony between the organism and the perturbation. One of the most effective syntoxic agents of the body are corticoids, for instance, that have an anti-inflammatory effect, letting pathogens get into the bloodstream when the risk is not that high, or maybe when the cost of terminating the invasion is higher than to aim to an agreement. Another reaction, on the other hand, is to find and destroy the pathogen, by the production of extra enzymes, with the goal to accelerate the metabolic degradation (Selye, 1973: 697).

Still sometimes homeostasis is not enough[53]. A longer exposure to a hazardous situation, or stronger demands of whatever nature, would require a stronger response. Heterostasis is a homeostatic resort not only including a protective response, but also introducing the possibility of resetting the adjustment point of homeostatic oscillation, to adapt to the new environment, as a sort of pathological state turned into the regular one. As Selye puts it:

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[52] Selye would argue that one of the important secondary outcomes from his study was to prove that the body has limited energy for adaptation, "since, under constant stress, exhaustion eventually ensues" (Selye, 1973: 695).

[53] It might be important to clarify something that might be lost in the midst of the argument and the very nature of language. When saying that homeostasis is not enough it refers specifically to regulatory homeostasis, that is, the set of agencies that trigger their action when facing specific perturbations, in this case, stressors. Metabolic homeostasis is included just to the extent that enhances the activation of regulatory homeostasis.

> The salient feature of these adaptive mechanisms is therefore not that they attack only substances foreign to the body but that they establish a new equilibrium between the body and an unusually high level of the potential pathogen, either by destroying the excess (catatoxic action) or by making tissues tolerant to it (syntoxic action).
>
> When such an abnormal equilibrium must be established to protect against potential pathogens, I propose to speak of *heterostasis* (heteros = other; stasis = fixity) as the establishment of a new steady state by exogenous (pharmacologic) stimulation of adaptive mechanisms through the development and maintenance of dormant defensive tissue reactions (Selye, 1975: 26).

The "pharmacologic" remark is within parenthesis because the peculiarity of heterostasis is not only resetting the adjustment points, but also doing so by enhancing the performance of those syntoxic and catatoxic response mechanisms. It can be achieved by natural means, of course, but it might be more common to reach that altered stated by means of medical treatment. The drugs applied must aim only to enhance the performance of the responsiveness of the organisms, and not to the destruction of the pathogens themselves. In this sense, heterostasis can be considered an external favourable influence on internal mechanisms of balance, a homeostasis enhancer.

An important statement must be made explicit: adaptation (the maintenance of a living system – as in Selye) can be reached not only by these means exposed here, but also by interventions that not require the internal environment to participate actively. In the case of deficiencies, a substitute can be provided, or in the case of a clearly demarcated problematic body part, it could be mechanically removed. For instance, in some cases of anaemia, when not finding the causes of it, or even while doing so, it is common to provide pills enriched with the element absent or scarce in the body; in some cases of cancer it is necessary to sever a whole part of the body. In the cases when pathogens are involved, the internal milieu has no role to play if the treatment is directed straight to the pathogen. These are neither homeostatic nor heterostatic mechanisms, and the differences between this kind of adaptations and those directed to the pathology is that, for homeostasis and heterostasis, the internal environment has to play a major role by restoring its balance by its own means: "Both in homeostasis and heterostasis, the *milieu intérieur* participates actively" (Selye, 1976: 31).

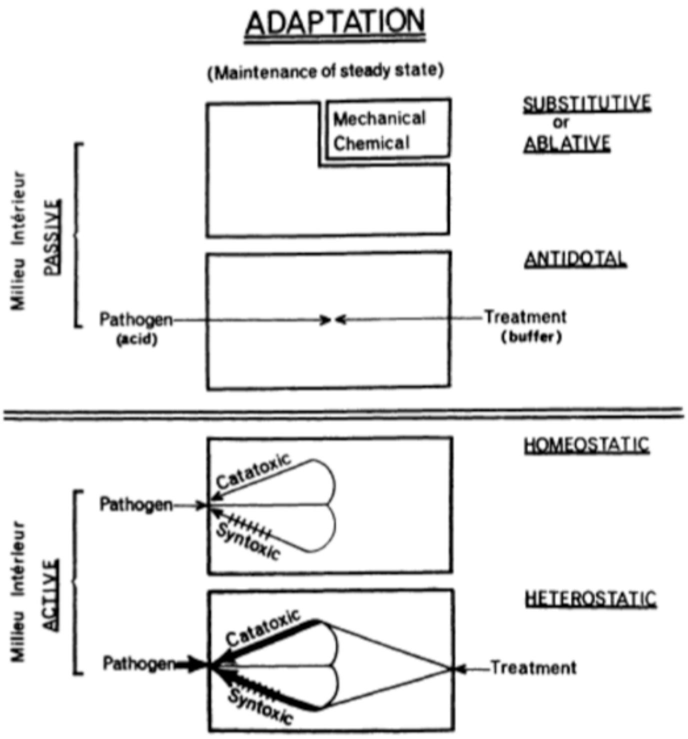

Figure 1

Hans Selye, 1973: 698

Figure 10 - Distinction between homeostasis, heterostasis, and passive maintenance of stability

Hence, heterostasis can be understood as a revision of homeostasis within therapeutics framework. By defining the behaviour of the homeostatic mechanisms activated when facing a perturbation and explaining how they change through time when the exposure to that disturbance is sustained and not a punctual situation of "fight or flight", the idea of homeostasis widens and ameliorates. However, the main issue with Selye proposal is that it keeps holding to an ideal point[54] to oscillate around, even if now some extra flexibility has been added to homeostatic mechanisms since that ideal point is no longer a constant, but a variable. Still, this possibility of change opens a question about organisms keeping some sort or record of past alterations and uncovers what would be another of the most relevant contributions to the development of the notion of

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[54] It might be useful to remember that the main issue of defining a middle reference point is that it cannot be described without appealing to either an abstract ideal, or a statistically found medium. In both cases, the former implicitly and the latter explicitly, that medium point is based in an abstraction of what it is observable, hence establishing what it is *normal* and what is not, with all the philosophical implications that it implies.

homeostasis, that is, the possibility of organisms to change more than once, and to be stable across every change.

7.3.2. Allostasis

That is what belongs to the idea of allostasis, the notion of some past records of previous adaptations to the external environment based on the interactions between the organism and its context, hence "the stability of the organism through change" (Sterling and Eyer, 1988: 636). Peter Sterling and Joseph Eyer observed that, in some cases, after ending the perturbation that altered the body in the first place, the arousal did not come back to the previous, expected stable state: "when the arousing stimulus is made chronic and removed only after a rather long period, the [blood] pressure may remain elevated" (Sterling and Eyer, 1988: 633). Their analysis of the data available about physiological changes caused by behavioural states showed that not only blood pressure, as shown in the previous quote, but every physiological parameter is altered when a stressful situation occurs; and this is a physiological norm relevant to every living system:

> [T]he contextual fluctuation of blood pressure (...) is not exceptional. Rather, it exemplifies a critical principle of physiology: to maintain stability an organism must *vary* all the parameters of its internal milieu and match them appropriately to environmental demands. We refer to this principle as allostasis, meaning "stability through change" (Sterling and Eyer, 1988: 636).

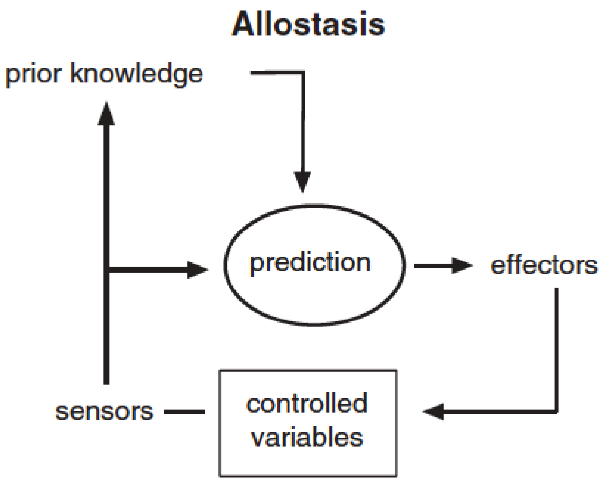

Fig. 5. Allostasis model. The brain integrates prior knowledge with sensory data to predict what resources will most likely be needed. The brain then directs effectors to optimize the distribution of resources in space and time. An arrow leads from “sensors” to "prior knowledge" because the brain integrates – and stores in compressed format – lessons from today's sensing – so that they can become tomorrow's “prior knowledge.

Figure 11 - How does allostasis work. Sterling (2011)

Of course, some sort of higher mechanism must control these kinds of connections between parameters, to coordinate and regulate them. The brain is the organ that qualifies, since it has connections with every part of the body, and it can communicate with each one of them while receiving signals from each one of them. This neural control is multileveled, and the action is displayed in different time stages, as in a cascade. For example, it can be observed through the action of hormones, which can trigger different kinds of processes at diverse parts of the body at different timescales. Allostasis, due to the central control of the brain of all the mechanisms within the body at the same time, not only involves the whole brain, but also the whole body. In this sense, the allostatic proposal is a possible holistic approach to the study of living beings and their pathological states.

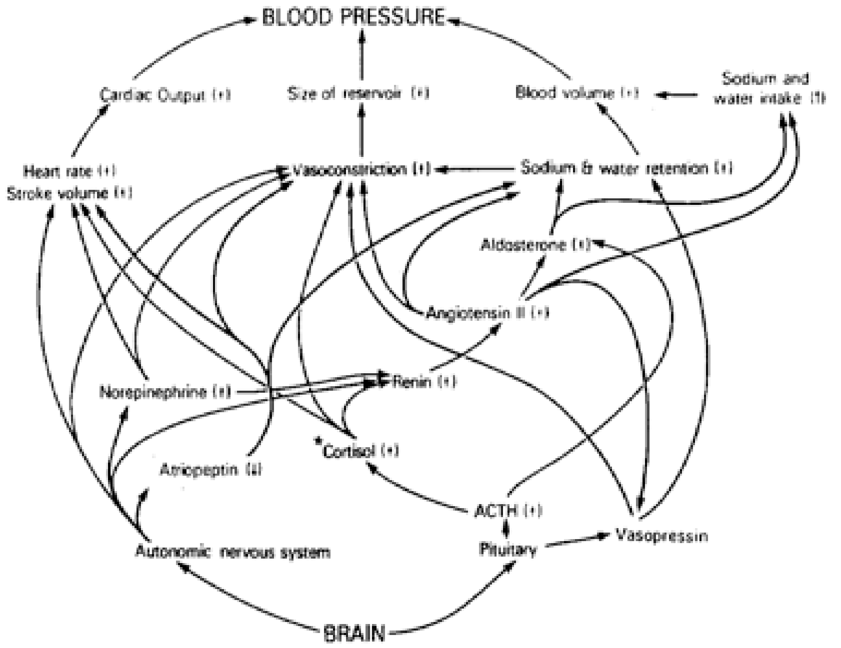

FIG. 34.3 Multiple, mutually reinforcing mechanisms to raise blood pressure during arousal. Negative feedbacks reset or overridden. (*Indicates that cortisol acts indirectly by enhancing receptor binding of norepinephrine.)

Sterling and Eyer. 1988: 635

Figure 12 - Allostasis in blood pressure. Sterling and Eyer (1988)

There are some advantages to embrace allostasis instead of homeostasis, as the original text implies. For starters, "allostasis provides for continuous re-evaluation of need and continuous readjustment of all parameters toward new setpoints" (Sterling and Eyer, 1988: 637). Contrary to homeostasis, which stays around a determined set point as the ideal trajectory, allostasis allows a higher, most controlled kind of regulation, since every signal sent to the brain is twice evaluated, at least: once by the receptor, locally; another one by the brain, in the big scheme of things. This dialog between brain and body improves to its best the usage of the organism's resources, since the brain can distribute them according to the overall necessities, avoiding the risk of putting too many resources at one point while neglecting other(s). It also offers and explanation on how homeostasis is not limited to the action of the control agencies of the homeostatic regulation. To achieve that, it is necessary for the brain to hold a buffer capacity that allows it to store all the information and handle it to obtain the best performance available. This feature also enables another advantage of allostasis, that is, "*anticipating* altered need and achieving the necessary adjustments in advance" (Sterling and Eyer, 1988: 637; also, Sterling, 2011: 3 - 4). This leads us to the final and the most cheered characteristic peculiar to allostasis (even if all of them are intrinsically related): historicity, or the capacity to keep a record of past states of stress.

Nonetheless, when the external demands are higher than the average, usually an altered state of regulation follows[55]. The features of allostasis mentioned right above, such as predictability, control, and the communication between mind and body (as feedback); they are useful to reduce the level of arousal, but sometimes the demands from the external milieu are severe enough to override the action of them and alter the regulatory regime. What it is new from the allostatic proposal in comparison with the heterostasis one is that the former is strongly oriented to holistic therapeutics, while the latter is more concerned about describing the mechanisms that are activated from within the organism to resist pathogens and how to enhance their performance. Alternatively, allostasis tries to find central regulation mechanisms. This will allow the body to leave the arousal regulation and go back to a stable state, including not only the physiological level as in heterostasis, but also behavioural and emotional levels. It does so by pulling an approximation to altered states that have to cope with the system as a whole, and not just with the effects of a determined pathogen (even if Selye described diseases as to be in most of the cases multicaused – Selye, 1973: 696).

In that sense, Sterling and Eyer propose that, after catabolism must follow an anabolism state, that meaning after an arousal period, it is required a relaxed period where all parameters should go back to the previous state of average regulation. However, it can be the case that this does not happen, and the regulation of arousal does not disappear when its performance is no longer required and becomes chronic. This can happen for several reasons, for instance, "the body becomes addicted to its own catabolic hormones" (Sterling and Eyer, 1988: 641), requiring a higher dose of the elements involved, such as hormones, whose receptors downward their regulation if aroused for long enough. This arousal state can be self-maintained but cannot last forever since the parameters of the body are settled higher than the body performance, and if sustained for long periods of time, it leads to the wear and tear of the body, and if made chronic, it might as well entail death. Nevertheless, one of the consequences of the allostatic model is that no parameters

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[55] Just as heterostasis, which is implicitly referred to through Selye in the introduction of Sterling and Eyer's paper from 1988 as an early study of what they call regulation of arousal, linked to homeostasis, and it is missed in the ensuing argumentation. Same as for Sterling, 2011.

are to have any kind of normal values in the sense of that ideal point that Cannon used to describe homeostasis, since from this model:

> (...) health is a state of responsiveness. A parameter with values outside the normal range is not considered “inappropriate” because every parameter is controlled by a multitude of mutually reinforcing signals. If a parameter has a value above or below normal, most likely, there are multiple mechanisms forcing it there, and most likely the ultimate source of these signals is the brain (Sterling and Eyer, 1988: 645).

This allostatic proposal seems to face some difficulties. There is one already mentioned, but not developed, in Sterling and Eyer’s quoted paper. If nothing is inappropriate within an allostatic regime, how is it even possible to determine that it is needed a treatment? What can be considered as pathological? They offer a holistic treatment against the regulatory arousal, namely to slow down a little bit and relax, “placating spirits (including our own) through maintaining communal relationships”, in proportion to the amount of work. Still, it seems difficult to determine when that should happen. It might create the impression that they want to get rid of the homeostatic idea of an adjustment point, but they seem to rely implicitly on it: “The therapy suggested by the allostatic model is to reduce arousal” (Sterling and Eyer, 1988: 645). Note that to define arousal it is needed a setting point, to use a reference to state there has been an alteration, as well as a limit threshold were to start reckoning it is dangerous to keep that kind of high performance.

There are yet some other difficulties not mentioned in their proposal, namely to reduce demand and “to enhance predictability, control and feedback”, through communal life. The latter, for instance, might be counterproductive for some. Introverts and, in general, people that suffer of social anxiety tend to activate their stressors when facing social scenarios. Also, and without the need to recur to a specific part of the population, social meetings are not always pleasant enough to reduce arousal or stress and can produce quite the opposite effect. This conception seems to relay on a perception of human social gatherings as necessarily ensuing (not enough justified) inherent goodness. Without going too deep in this issue, it can be observed that whatever goodness social gatherings bring depends on a set of conditioning variables multiplied by every social individual present in the intercourse at that moment, in addition to some secondary conditions that may as well influence the outcome.

Regarding the second issue, “to enhance predictability, control and feedback”, the main concern seems to be that, to improve them, it might be compulsory to go through some arousal, cope with it, and finally learn something new. Variety, mostly, comes from that adaptive process of the organism triggered when facing changes in its environment. This idea is reinforced by the paragraph where they state: “Allostasis provides for continuous re-evaluation of need and for continuous readjustment of all parameters toward new setpoints” (ibid). From past situations, the internal milieu can learn, and avoid reaching a dangerous point *again*, but what it is difficult to imagine from this perspective, left aside to conceptualize, is to foretell when a state or situation is going to be dangerous without previously experiencing it. That would leave a certain percentage of secure failure of the system, on top of that brought by violent unexpected accidents. It seems more plausible to limit the capacity of prediction of a system to its ultimate, extreme (in the sense of close to the limits of oscillation) experiences and maybe, in the case of higher cognitive capacities available, conceptual combination of them to face new situations, but that should be called *anticipation*, rather than prediction[56]. Therefore, it would not seem impossible to conclude that the only way to enhance predictability, control and feedback for personal profit is through our own experiences, and sharing with others can enhance ultimately that predictability and control, but mediated by anticipation, that could be as much beneficial to that respect as detrimental.

The last difficulty addressed here is the requirement to reduce demand. There is a kind of dangerous understatement implicit in here that challenges the limits of the individual responsibility in the own well-being. An individual can withstand a determined amount of stress. That limit can be said that is settled by its own configuration[57] and amount of variation, or if preferred, by its ultimate experiences on adaptation. The problem of pointing out the individual as if responsible of controlling the demands of the environment is that it plainly cannot. The amount of variety of the external environment,

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[56] The main difference among these is that prediction needs to be performed on a determined kind of knowledge about the relevant variables (which are those, or their quality and quantity, for instance). Anticipation relies mostly as an expectation, a general state of alert of the body in this case, established by the construction of some parallelisms between a previous situation and an event to come, evaluated as similar from (generally) a subjective perspective.

[57] This configuration is shaped as well by the specific features of each species. As Sieck points out, “Welch and colleagues discuss how energy homeostasis in these animals [vertebrate nectanivores] is achieved despite high sugar loads and huge differences in aerobic demands from hovering, long-distance migration, and non-foraging periods. Elevated sugar intake, especially free fructose, is a known contributor to the development of metabolic pathologies in humans and other mammals” (Sieck, 2018: 85).

composed by a myriad of interacting complex systems, is by far larger than the amount of variety that any individual can handle. We humans can transform our environments to adapt them to our necessities, but there is still a certain amount of uncertainty when addressing the unpredictability of the external milieu (consider, for instance, hurricanes, earthquakes, or seaquakes). Social interactions are not a way to reduce demands by sharing that responsibility and controlling collectively the external environment, but another resource available to deal with them, and not necessarily better than any other, since it might rely strongly on the personal configuration of every individual. Regarding this last remark, and in relation to the pathological states of allostasis, Bruce McEwen did a specific research on the consequences of failure in adaptive systems responsible of this kind of sustained stressful situations.

7.3.3. Allostatic load

The allostatic load can be understood as a mean to know the cost of physiological adaptation. The allostatic load idea addresses the question of that ideal point present in the allostasis proposal, and fully develops the concept and explores the consequences of having a middle point of oscillation that is not an absolute anymore. The proposal of McEwen mostly consists to bound allostasis to the personal physiological and psychological configuration. In that sense, the quality of the responses to the external stressful situations that place the system into that regulatory arousal is "closely coupled to the psychological make-up of the individual" (McEwen, 1998: 37). McEwen switches the focus of pathological states from being referred to a medium point to the performance of those mechanisms that is, instead on focusing strongly on the system well-being, focuses in the response capacity of the mechanisms responsible of keeping the system stable when a challenging situation may supervene, adding another explanatory level to the allostasis proposal. The allostatic load, then, can be understood as the corrosion of body and brain when there is overreaction or no reaction at all to the stressful events of the environment that require some adaptation: "*Allostatic load is the wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge*" (McEwen, 1998: 37).

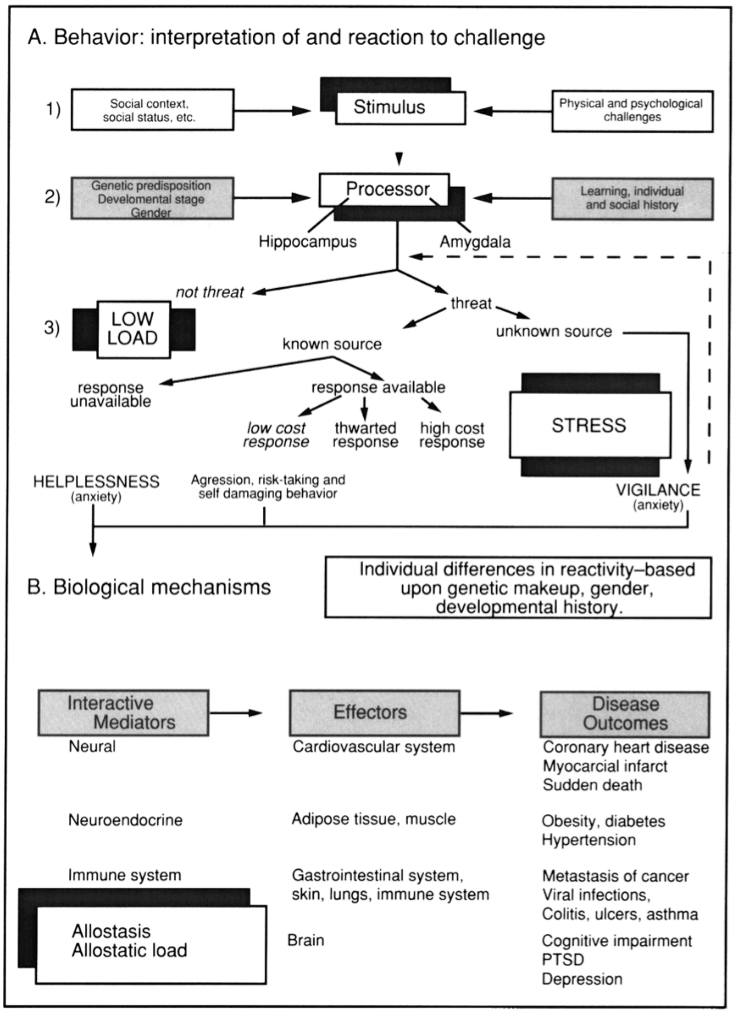

Figure 13 - How behavioural mechanisms affect biological mechanisms, explanation of allostatic load. Allostatic load (McEwen, 1998: 35)

There are three physiological responses that are mostly responsible for augmenting the allostatic load of an organism (McEwen, 1998: 38). One is being subject to stress rather frequently, which would provoke the constant activation of responses and alter their magnitude. The frequency and intensity of these responses increase the allostatic load of an organism by repetition. Another type of response that can increase the allostatic load is to maintain the regulatory arousal beyond necessary, or even make that altered regulation chronic. This usually happens when the response mechanisms fail to turn off and, for example, maintain a “persistently elevated blood pressure and glucocorticoids” that “accelerate obesity and Type II diabetes” (McEwen, 1998: 39). In addition, the last kind of response that can be blamed to raise the allostatic load is one that it is inappropriate to the challenge to face, either by overreacting or by underreacting. This, of course, leads to different kinds of allostatic charge, which can be observed in this graphic:

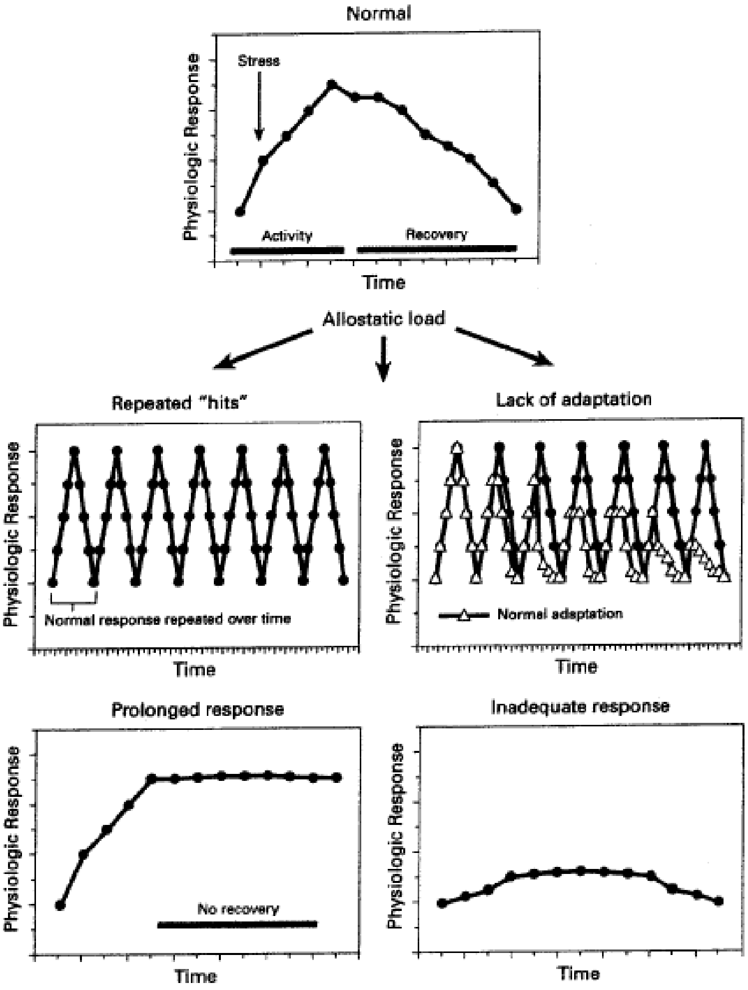

Figure 14 - Types of allostatic load. Four types of allostatic load are illustrated. The top panel illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The remaining panels illustrate four conditions that lead to allostatic load: 1) Repeated "hits" from multiple novel stressors; 2) Lack of adaptation; 3) Prolonged response due to delayed shut down; and 4) inadequate response that leads to compensatory hyperactivity of other mediators, e.g., inadequate secretion of glucocorticoid, resulting in increased levels of cytokines that are normally counter regulated by glucocorticoids). Figure drawn by Dr. Firdaus Dhabhar, Rockefeller University – McEwen (2000).

The allostatic load affects the immune system, since it might be activated in an early stage of stress, but chronic acute stress withdraws it: "What happens when stress is repeated? Preliminary data indicates that, whereas acute stress enhances the DTH response, chronic stress suppresses it, resulting in a lesser effect of acute stress as well" (McEwen, 1998: 40). Nevertheless, not every consequence of allostatic load is bad: the suppression of adverse inflammatory responses or even autoimmune responses are shut down too. Yet these last two are quite specific cases bounded to quite a peculiar configuration of individual, and it is also important to consider that the failure due to stress can also lead to quite contrary the case and provoke “an increased susceptibility to inflammatory and autoimmune processes” (McEwen, 1998: 41).

7.3.4. Rheostasis

It is difficult to tell apart allostasis and rheostasis. They were devised around the same time, and if we are to rely on literature, they are literally two years apart (Sterling and Eyer, 1988; and Mrosovsky, 1990). Both criticized the same aspects of homeostasis, namely the parameters considered, set points and oscillatory range together, as not fully reflecting organism dynamics. To this regard, rheostasis was conceived as an enhancement to homeostasis that accounted for *change*:

> *Rheostasis* refers to a condition or state in which, at any one instant, homeostatic defences are still present but over a span of time there is a change in the regulated level. Therefore, rheostasis includes a change in set-point, both when the term is used descriptively without specifying a mechanism (…) and when it is used to indicate a mechanism comprising negative feedback with a reference signal (Mrosovsky, 1990: 29).

This excerpt of text that holds rheostasis definition seems to be slightly in disagreement with a statement made a couple of lines after, where Mrosovsky mentions that it does not refer to an achievement of a stable state, but to change itself: “Rheostasis does not mean that new stable states are reached, only that there is a change in regulated levels” (ibid.). The best inference to make here might be to consider rheostasis as a notion aiming to quantify and describe physiological changes, which does not exclude the possibility that change may take some pauses as what we know as relatively stable states.

Changes can be progressive or abrupt, and rheostasis covers both, consequently. However, is there is no set points, where does change appear, or what can be regarded as a reference to be able to distinguish two different stages? Last cite mentioned that change happens in regulated levels, but there is no explicit description of what those levels should be. Later on, there is a reformulation of the term as descripted above, this time in relation with homeostasis, which clarification might be of some help: “*Rheostasis* is defined as a condition in which, at any one instant, homeostatic defences are present but over a span of time, there is a change in the level that is defended” (Mrosovsky, 1990: 31); or: [talking about the organizational and integrative aspects of physiological homeostatic functioning, and how for a full comprehension of it analysis should be done on different levels] “One appropriate level is that of organs systems and hormonal and neural signals between those systems” (Mrosovsky, 1990: 148).

Consequently, it seems legit to infer that rheostasis is the condition by which homeostatic change, that is, changes in regulatory mechanisms, happens. It seems to define a continuous process, instead of stable states or parameter limits shifting, as seems to be the case of allostasis. It may be more feasible to understand what rheostasis is if described in contrast with the very similar notion of allostasis[58]. One possible difference between them to start with is that rheostasis considers that set points are not hold for long periods of time, but they are rather rare. Allostasis, on the other hand, seems to stress on the continuity of resetting set points, as a series, and not as much as a completely random and rare feature.

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[58] Something funny happens with rheostasis and allostasis in literature: they avoid each other, meaning that I could find no text where both of them were mentioned, let alone used or explored, but for Schulkin (2004) who mentions nonchalantly rheostasis to quickly stick to allostasis for the rest of the text, this way reinforcing the idea that a clear distinction between them is rather troublesome.

	HOMEOSTASIS	HETEROSTASIS	ALLOSTASIS	RHEOSTASIS
Definition	Oscillation around a set point	Bouncing set points from normal to altered and back	The stability of organism through change	Regulation around shifting set points
Why is it needed	To explain the stability of the internal milieu and how is it maintained	To account for temporary, but harsh, homeostatic altered states	To account for the consequences of a sustained altered state in the body	To account for homeostatic changes when set points are rare
What criticizes	The *fixité* of the internal milieu	No critique, expansion of homeostasis to include extreme conditions	The lack of time perspective (homeostasis just considers the present of living systems) and homeostatic parameters	Set points and stable states
Major contribution/s	First analysis of maintenance control mechanisms within the body	Inclusion of extreme influences of the external milieu in the internal, therapeutic purposes	Ontogeny of organisms, inclusion of the influences of the higher control mechanism (brain), harmonization between the internal and the external milieu	Programmed rheostasis (accounts for easy adaptations of the body to fast changing circumstances; circadian changes)
When does it activate	Perturbation from the external milieu	Pathogen and/or stressor	Previous to perturbation, anticipation	Always activated, change is constant
What does it activate	Responses from the internal milieu, *agencies*	Response channels to return to previous stable state, even via meds	Anticipatory responses from the brain first	Changes happen on different regulatory levels

Table 4 - Some differences (often subtle) among different homeostatic notions

While allostasis is defined as “stability through change”, rheostasis puts on the table the idea that this change might not be linear, but cyclic, like the seasonal changes that affect our bodies (like to storage extra fat to get through winter; see McEwen, 2009: 558). One of the most important consequences of this concrete proposal is that rheostasis occurs in two ways: *reactive rheostasis* refers to the regulatory levels maintaining their stability through change, and *programmed rheostasis*, which can be regarded as the major contribution from rheostasis, accounts for the circadian changes an organism goes through, including changes in set points during ontogeny (both happen regardless of conditions). Also, while allostasis focuses on control mechanisms and how to coordinate each of them within the body, as in a hierarchy, rheostasis seems to hold a less quantitative more general perspective, on the behaviour and action of mechanisms involved in the regulation of a living system, rather like a constant and coordinated flow, which seems to be rheostasis case.

7.4. Homeodynamics and homeostatic dynamics

There seems to be an inherited dissatisfaction in physiology regarding how derived notions from homeostasis incorporate the dynamics of life. A salient critique from the different concepts of the homeostatic tradition comes from the perception that homeostasis describes how living system *are*, but not how do they came to be. This critique finds its echo in a tradition of biology (and related fields such as physiology or medicine) that considers living phenomena not as a thing, or a state, but as a process. To put it in another words, it points out to the necessity of including time as a constitutive dimension in the description of living beings, as a mean to include the changing operating characteristics of regulation, and to avoid that ideal middle point of Cannon that pushes argumentation towards some implicit, undefined, notion of *normality*.

To that respect, the notion of homeodynamics was proposed. A homeodynamic regulation still considers that there is a medium point but includes the changing ability of response of living beings, the learning as incorporation of variety. Within this proposal, the individual is the stable medium point and regulation happens around it, forming a structural unit. Dynamics refer to the ability to re-organize and adapt to changing and new situations. For instance, Austin and Marmodoro (2017) expose that the unit of an organism can be described in synchronic or in diachronic terms. The former refers to the observation of an organism's unity at some point in the existence of it, without any consideration for its origins, whether ontogenetic or phylogenetic. The latter is bounded to the history of the organism, as a mandatory requisite to fully understand how organisms work and how is it possible that they maintain themselves the same while constantly changing.

To answer this question, the Aristotelian conception of living beings is recovered, which conceived animals as complex structures with a specific kind of organization, that is, the kind that allows them to perform their peculiar activities, emphasizing the study of form over the analysis of its material components. They do not deny the unity of organisms that comes through homeostatic regulation, their proposal aims to point out that a regulation based on a revision of the kind of Aristotelian dynamics, enriches organism unity by attributing it a range of morphological variability that might as well account for their privileged situation in the ontological scale.

Another proposal for a less static understanding of organisms is the one by Waddington. He defined homeostasis as a kind of stability prone to a stationary or stable state, as opposed to his proposed term to refer to developing and evolving organisms, that is, *homeorhesis*. The problem with Waddington's proposal is that he did not develop it explicitly and specifically, even if he proposes it as the general principle of epigenetics (Waddington, 1957/2014: 54). He is constantly defining homeorhesis in contrast to homeostasis, in the sense that he conceives homeostasis as some sort of anabolic state, while "ensuring the continuation of a given type of change it is called *homeorhesis*, a word which means preserving a flow" (Waddington, 1977: 140). What can be deduced from the different fragments alluding to homeorhesis is that Waddington seemingly conceived living beings more like processes ongoing towards an invariant end state, and not attached to a determined state (Waddington, 1957/2014: 53). This invariant end state could be understood as some sort of goal, or fixed point, that may as well be taken as the foundation of their unity. The problem is that, unless sharply defined, to describe the unity of organisms as tending to a concrete end might leave living beings that are not to be consider agents aside from the living systems classification.

However, the physiological homeostatic tradition seems to constantly point to the imperious necessity to analyse and comprehend the complexity of life dynamics through its paradigmatic representative, that is, the organism and its constituent elements. A truthful analysis on the history of the study of living beings' organization would conclude that each idea rising within has contributed with its best to deepen the understanding of the complexity of living beings. That is why I totally endorse the idea that there is no need for a specific field in homeostasis analysing life dynamics, since the very same idea of homeostasis comprehends it (see Pezzulo, Rigoli and Friston, 2015), and the real contribution to this debate would be to distinguish between synchronous homeostasis, according to which every process happens at the same (reacting) time, and diachronic homeostasis, which allows for a hierarchy of processes, better depicting biological complexity (which is implicit in allostasis, but for an explicit insight see Torday, 2015).

7.5. What homeostasis is (Final remarks)

As stated modestly in the section of what homeostasis is not, one of the very first observations made when tracing back homeostasis is that it was devised within a specific way of looking at biological phenomena, which can be cleared up to the work of Aristotle at least: living beings' distinctiveness converge in their special kind of organization. Developing a better understanding of that kind of organization should be the goal, and so far, it has been done by focusing, mostly, at the level of organisms, understood for the most part as mammals. One important thing to consider in contemporary studies about living organization should be to widen the research to include a study on the mutual influences between living systems and how that shapes their behaviour, from the lowest to the highest, following the modern integrative stream of Systems Biology (SB).

This might seem a titanic task if following the reductionist approach aiming to find a holistic explanation by accumulating data of the constituent elements, which would force researchers to gather the biggest amount of data possible in order to understand the performance of any living system as a whole. That happened before, when the Human Genome Project was news. They gathered every bit of data available, they used it and made some astonishing breakthroughs in the knowledge about organisms are shaped. Soon they realized that the expectations of finding the "recipe" for living beings was way out of reach. Even if it has proven quite fruitful, focusing in the low-level constituents (bottom-up methodology) of a system reaches a limit when attempting to describe systems as unities, and it must be complemented with the kind of approach that looks at the whole picture (top-down methodology), apprehending the general state of affairs.

There has been a lot of misunderstanding regarding the homeostasis notion. It has been used and criticized thoughtlessly, to the extent to compare it to some similar state to death: "there is only homeostasis after the arrest of metabolism, that is to say the virtual death of the living being" (René Thom comments, in Waddington, 1968: 34). Now, hopefully this work has pointed out some of the misrepresentation of the idea of homeostasis that might have given away some hints about the definition is aimed here.

One of the first statements about homeostasis is to clarify that it includes some processes that fit the model of feedback, it must since some of the mechanisms present in nature behave in a way that totally follows the model. However, it is important to remember that not every single natural phenomenon follows that scheme, and homeostasis aim is to include the study of every single natural phenomenon. Parallel to SB critique about biology in need for a holistic approach that can offer a new perspective in the study of Nature, there is a critique for homeostasis to take back its holistic background and integrate it with its operational developments, pushing them together. The process to follow for the general biological formulations to achieve this integrative goal might be a good guidance for homeostasis to be revised and gain back its holistic character.

To regain its holistic approach, homeostasis must be understood as a notion to be referred to all living systems. These are distinguished by a specific kind of organization that allows them to harmonize their behaviour and functioning with their surrounding relevant environment, including every element of it, to achieve their internal optimal regulation. That *optimal* is relative to each individual's configuration of their biological organization. The possibilities to reach that level of performance depend not only on their peculiar make-up, but also on their environment, namely, every single rapport established with it and its constituent elements: everything that can be accountable to be part of their *context*.

In addition, an optimal regulation is not an ideal and abstract point, nor even absolute or static. Optimal regulation stands for an internal configuration where structure and functions are coordinated in a way that they get their best performance. For instance, when removing one of the kidneys of the human body, the regulation would readjust itself, helped as well and according to the most favourable interpretation, by a consciousness acquired of the need to reshape the intercourse with the environment (such as diet changes or a reformation of the social habits, for instance). Every single action and change have an echo in its surroundings, even if, of course, with different degrees of influence (for instance, how that change of diet could affect other organs or the general well-being of the individual). The amount of influence might be determined not only by proximity, but as well by individual configuration, considering that similarly shaped individuals would be more influenced that those that are not.

.8.

Discussion and conclusions

Contemporary modern biology is mainly focused on the perspective brought by Systems Biology, a discipline born from a necessary inclusion of other disciplines in order to manage the molecular data available. Furthermore, modern biology aims to complete the regular, reductionist approach to the study of living beings with a system-focused, holistic approach. This would provide, ideally, an explanation on the behaviour of living beings as wholes or unities, and not just as an assemblage of microelements.

In this work we explored the notion of homeostasis as a possible macro term that may help present biological research to unify all the collected micro data due to its holistic quality, like some scientists mentioned previously did before. Homeostasis was one of the ideas recovered from history, since it seemed a suitable term probably because it was formulated under a research program of biological organisation and stability founded on physiological grounds that aimed for the study of biological phenomena from a holistic perspective.

Homeostasis was born as a hypothesis to find an explanation about what makes organisms alive and stable. It is heir of a tradition that focused on the organisation of the living, as a characteristic exclusive to them. That is why Bernard is relevant in this context. He described the internal milieu as the main feature that distinguishes organisms as autonomous entities. According to his work, while the external milieu is chaotic and constant source of perturbations, the external milieu is organised to the extreme that it is extraordinarily delicate.

Bernard proposed a reason why it is really difficult to manipulate the internal milieu, as one of the main complications when studying the living entities. The internal enclosure of the living has a delicate stability, and any intervention or manipulation compromises its analysis and the gathering of information of existing processes while still active. His contributions to physiological research were the base for Cannon to create the notion of homeostasis. Bernard provided an explanation of what makes organisms clearly separated from their environment and a seminal proposal on how does the internal milieu work. Cannon deepened the studies on the subject by offering an explanation on how living beings maintain their stability.

Hence, the first definition of homeostasis was clearly offering an explanation on the organisation of the living, and Cannon (1963) offered several experimental results to sustain his argument. To sum it up, what Cannon considered to be characteristic of organisms was their capacity to maintain their stability, and that maintenance is possible since their bodies may oscillate when facing adversities around an ideal point. In this sense, Cannon sharpened Bernard's proposal by including in his definition a flexibility observable in living beings. They do not just resist the external influences, they exhibit some kind of resilience (notion that would appear some years later in some biological discussions and research).

Cybernetics followed the interest on the organisation of living beings. However, even if its contributions to this kind of research are undeniable, they altered the original proposal of homeostasis. By focusing on the description of the minimum mechanisms that may sustain a living entity stable, cyberneticists also brought some ambiguity to the term. This is so because homeostasis was supposed to be a term to refer to the system as a whole, that is, to the organisation of organisms, and focusing on the minimum mechanisms of living organisation shifted the focus slightly, but enough to alter the previous approach to this matter. Even if it might have not been the intention of cybernetics, homeostasis was now bounded theoretically to feedback loops, the fundamental mechanisms of self-maintenance.

Bertalanffy (1968, 1975, 1976) did not really helped in this sense, even if his perspective claimed to be holistic or, at least, systemic. He reinforced the idea of homeostasis as a basic self-maintenance mechanism, using the term as a simple and elegant way to describe interactions between systems, but did not fully unfold the holistic potential of homeostasis. This would have been closer to the original proposal of homeostasis, and it would also have contributed earlier to the expansion of the term in its most comprehensive form, meaning to include all kinds of internal and external interactions, in all their complexity, accountable for the stability of the organisms. In other words, what Bertalanffy could have proposed was a homeostatic perspective to analyse the complexity and variety of interactions that shape biological systems but, instead, he took homeostasis as a simplified model of them, reinforcing the cybernetics idea of homeostasis as a model for primary stability maintenance.

Further physiological and biological research followed this reductionist turn that homeostasis went through, referring to the studies on the minimum requirements of a living entity and how to model it, as mentioned earlier in this work. This may have been because a great part of scientific research works from bottom to the top, that is, from the most basic elements that belong to a system. This perspective has no negative connotations a priori, but when Bernard and Cannon were analysing the subject, they had another approach in mind and, if I may say, for a reason. As suggested here, a biological system cannot be described just as the sum of its material parts. It is also constituted by its interactions as Bertalanffy proposed, and not only their intra-, but their interrelationships are also to be considered to obtain a more exhaustive description of what a living being is and how it is organised.

This could have been the inspiration of the physiological developments of homeostasis brought by the middle of the 20st century, such as heterostasis or allostasis. These proposals try to understand systems as unities, like the minimum model perspective or General Systems Theory (GST), but instead on focusing on the components of the system, they rather stress the dynamics of the system and how they maintain stability. To say it differently, they are closer to the original proposal of homeostasis and the study of living beings since they do not isolate their components but rather analyse them within their context.

Heterostasis, allostasis, allostatic load, rheostasis and even homeorhesis (as proposed by Waddington - 1957) are concepts keen to the study of organisms from a holistic perspective, and we consider them to be an interesting approach to the current analysis of living beings. They study the changes and oscillations in the stability of organisms as a whole, instead on focusing the ultimate cause or the minimum component to be affected. This physiological approach allows a pragmatical use of the complete original proposal of homeostasis to fields of study such as medicine, just to name one.

This does not mean under any circumstance that the proposals in between did not contribute to the understanding of the matter and to the widening of our specific knowledge. Cybernetics contribution was really helpful to understand how metabolism works. Feedback loops are a useful model to understand how the body manages inputs and outputs, as well as their hierarchical interactions and how they support the body maintenance. Cybernetics also contributed by formalising Cannon's agencies and modelling the minimum processes required to maintain stability. Concretely, feedback loops are useful to understand how some natural cycles work, and Ashby's law of requisite variety (1956) helped by offering a method to calculate the capacity of a system to embrace perturbations, with a minimum margin of error.

Even so, the limits of the homeostatic oscillation are still difficult to picture, and this is a really interesting aspect to deepen the study of homeostasis. Systems and their resilience defined in terms of variety fail since homeostasis, or self-regulation, are supposed to be an arrangement of economy, and the more complex the system, the more variety it can embrace, but the more resources it needs. As a consequence, no theoretical limit can be foreseen.

Furthermore, cybernetics, by focusing on an old-mechanist approach to the study of living beings, are inattentive to the qualitative features of the system under analysis. Materials are revealing when understanding how a system is configured and how it works. But cybernetics approach makes impossible to know whether the system is biological or artificial, not even if the values obtained from that system are universally valid or if they are context dependent, or to what extent are dependent. It is hard to determine how the inclusion of the quality, condition and nature of materials could influence the calculation of the homeostatic oscillation range.

On another stream, deviations from the allowed oscillation are considered as a variety "competition" between the system and its environment, but cybernetics do not describe how those deviations are to be considered pathological or lethal to the body. This indeterminacy of the system is accountable of the loss of some of the most important features of homeostasis and, consequently, living beings.

Organisation is described in quantitative terms, and as stated before, the qualitative part of organisation plays a major role on how biological systems work. Because of this reductionist quantification, homeostasis lost or, in the best-case scenario, weakened its status as demarcation criterion of living beings. And second order cybernetics, even if widening the perspective on systems, it did so by adding up feedback loops, using them as building blocks as Beer said. Hence their proposal is useful, but to some extent, that is, the metabolic level, i.e., the most basic processes of self-maintenance of the body.

Bertalanffy criticised cybernetics in order to emphasize the differences between his proposal and theirs. One of the main contrasts between the one and the other is that GST maintains a holistic, or wholesome in the words of Bertalanffy, approach to the study of living beings, by focusing on the interactions between systems. Bertalanffy defends several times that the interactions and the components involved cannot be understood by focusing on the lower levels. Even so, the contributions to this matter are still biased by the cybernetics perspective and, even if widening it, it is still bounded to a mechanistic perspective of living systems.

Another contribution that distinguishes GST is its emphasis on the dynamics of systems, their interactions and, specifically, the system's exchange of matter and energy with its environment. Internal hierarchy is raised by the same interacting dynamics of the parts of the system, and they explain different levels of organisation, such as metabolic and regulatory, like cybernetics. However, and unlike cybernetics, GST defines organisation as a principle of organisms that fulfils an integrative function, positioning Bertalanffy's proposal closer to those ideas of Bernard and Cannon. Nevertheless, matter and energy exchange do not describe the full range of interactions living beings experience through their lives, and even if it might be enough explanation for simpler organisms, there are interactions missing when focusing on complex living beings, social interactions to name one.

This idea of system from Bertalanffy inspired Systems Biology depiction of organisms. The relevance of the organisation and the interactions within and between systems is central for both theories. Both approaches defend that the system is more than the sum of its parts, as well as the influence on the constituent parts by the whole. More importantly, those components are connected dynamically and are interdependent. This last remark, together with the idea of the parts not being knowable through the study of the system as a whole, inspired the specific methodology of systems biology: middle-out.

To overcome the difficulties to study the parts and the system and how they influence each other, systems biology came up with that methodology, which offers the opportunity to analyse those parts as belonging to a system by isolating the object or process of interest. This reflects the general interdisciplinary tendency of this academic area. Systems biology appealed to a collaboration between several disciplines in order to face the extraordinary amount of molecular data and conciliate the reductionist approach to the study of organisms and an organicist perspective. Maybe because this is a relatively new approach to the scientific analysis, it is still a secondary type of analysis, in the sense that the main core of systems biology still holds strongly to the analysis of minimum components of living entities, barely equilibrated by its top-down and middle-out counterparts.

Nowadays, some of the most relevant disciplines composing Systems Biology are bioinformatics, computer science, and engineering (that allow to manage molecular data and carry experiments in silico), physics, and of course biology. Philosophy is also included, which provides a theoretical framework and the analysis of different terms and methodologies and may as well offer possible developments of the study of living beings. These allow to unify the data gathered up until the last studies on biological systems, but they are still to offer a holistic approach that concludes and includes those components and the data available on them.

As mentioned earlier, O'Malley and Dupré (2005) discussed the relevance of including philosophy when analysing organisms while maintaining an organicist approach. Top-down methodology, that is, the investigation on the system as a whole and its properties and how it influences its constituent parts, may be regarded as the closest perspective to the organicist approach.

Organicism focuses on the organisation of living beings as unities and considers this organisation accountable for the specific features of living beings. It is complemented with a mechanist perspective, that focuses on the components of a system and their dynamics. These are not opposite approaches, since both aim to explain how organisms work, but they present some differences.

Organicism is closer to the notion of system inherited from Bertalanffy in Systems Biology. From this perspective, the parts that compose a system and their peculiar characteristics cannot be grasped from the holistic perspective, i.e., from the analysis of the system as a whole. Some distinction may need to be done between organicism, vitalism, reductionism, and mechanism.

Vitalism, scientifically defined, was the name given to the analysis on organisms that focused on their living properties, that is, what made them alive. The notion permeated into everyday use, and together with the limitations of experimenting, caused the concept to be misinterpreted later in time and to be accused of not being completely scientific and opening to metaphysic interpretations. It was confused with animism more often than not and it could be possible to think that, when religious instances started to influence a little less on political affairs, it changed the way science was approached. Even if analysing the connections between religion, politics, society and science is a really interesting subject of study, it is broad and complex enough to surpass the limits of the study of this work and deserves a specific analysis. To stress how important this is, even Cannon itself mentions some of the applications of the notion of homeostasis on such areas.

Mechanism can be understood as the approach to the study of living beings that emerged in response to the alleged limits of vitalism. That is a debatable perspective, but strictly defined, mechanism is the investigation on biological systems as a complex compound of several interacting parts that are, at least theoretically, divisible. The main issue with this perspective is addressed a few times in this work, and it is exclusively related to the difficulty of putting together all those components analysed in a manner that accounts for the behaviour and functioning of the systems as wholes, and how they interact within such perspective. Nevertheless, mechanism has provided the main impulse in scientific studies in the last centuries, and it has proven that the explanations on some mechanisms can help us understand the functioning of complex systems through its models.

For instance, biological minimum models, such as those described earlier in this work, proposed by Gánti, and Maturana and Varela, are useful inasmuch they offer a simplified and visual explanation on a highly complex process of maintenance and separation from the environment, respectively. However, both of them aim to make understandable the same kind of system. Also, both of them show some limitations when widening the application of the model to any other level of a biological system.

Concretely, following Diéguez (2013) and his proposed criteria on models, the aforementioned models do not completely fulfil two of the main basic features needed to consider a representative model to accomplish their explanatory function. The first one is the requisite of include relevant functional factors, i.e., constitutive behaviour of the modelled system.

In the case of the chemoton, the oversimplification of the model forbids the model to be applied to the behaviour of the system as a whole, since it does not include how the general behaviour of the system affects to the system's components and subsystems. And in the case of biological systems this might be regarded as one of the main features to take into consideration, in the line of Bertalanffy's proposal: the connections between and within organisms, and their environment.

The other requirement mentioned by Diéguez focuses on the gap between the model and the targeted system. Concretely, it refers to those idealisations that are so separated from the regular conditions a system embraces that even after several corrections it is challenging to figure how the system varies when manipulating it. Minimum life models presented here show some limitations when confronted to real life systems, namely, their complexity.

Gánti's model (2003) is built on an idealisation of what a minimum system would require to be considered alive. This idealisation is based on the observation of the minimum constituent of an organism, the cycle at metabolic level. This kind of feedback system is what Beer from second-order cybernetics called “building blocks”.

They are useful inasmuch the goal is to find an explanation on basic levels of self-maintenance, but they fall short when facing explanations of regulation. It also becomes difficult to explain how the interaction between this kind of systems can account for the behaviour of the system as a whole. Growth by threshold is also complicated to apply unless there is a more general system controlling it and avoiding the system to grow and divide indefinitely.

To understand reductionism, it is important to understand the perspective used by mechanism. Reductionism searches for the explanation of a phenomenon or an object by decomposing it into smaller parts or pieces and analysing it with the belief that it would provide an explanation for the phenomenon or the system under study as a whole. The main difference between mechanism and reductionism is that mechanism decomposes also a system or phenomenon into smaller bites, but the understanding of the system or phenomenon as a whole under a reductionist perspective holds that this understanding is to be obtained from bottom to top, that is, as mentioned earlier, from the components to the entire system, but not the other way around.

In other words, and to better define the difference, reduction can be understood as a widely used scientific methodology, specially by mechanism, and reductionism is an ideology that privileges reduction over any other scientific method. As mentioned above, reduction has some limits, and soon the scientific community started to propose alternatives that could enhance the development of scientific studies, specially in biology. Organicism is an alternative that allows the analysis of living beings under a different perspective.

Organicism conceives the living as organized systems. Moreover, it stresses the relevance of organization of life above any constituent parts. In that sense, it can be considered as a holistic perspective, and that is one of the main reasons some consider organicism to be the new vitalist perspective, as opposed to reductionism. This approach to the study of living beings considers that every living system is an organized system, from an ant to the entire ecosystem.

Under this perspective, not only the constituent parts are responsible for the behaviour of a system, but also the system influences the behaviour of the constituent parts that compose it. The influences between different levels of organization do not extinguish on top-down and bottom-up relationships. Within organicism, each relation between every component and subsystem inside has an impact on the rest, making them, as well as the complete system, adjust their performance to the different stimuli as they show. This is one of the main reasons that separates organicism from mechanism, since organicism considers the maximum possible of interactions, while mechanism includes a few, even if stacked up together as in Beer’s model and its building blocks. And also, what makes homeostasis so keen to modern organicism, and one of the reasons this work came to be on the first place.

The original formulation of homeostasis by Cannon (1929, 1963) already underlined the relevance of organization. Cannon defined homeostasis as a type of organization exclusive to living beings as complex organisms. As such, he establishes a correlation between living beings and other complex systems such as society. Nevertheless, the definition provided of homeostasis was devised with an idea of system clearly defined and separated, not isolated, from its surroundings. The systems conceived by Cannon had their stability and organization tuned until a perturbation from the external environment altered it, and even if he never excludes the possibility of positive influences, he dedicates most of his efforts to analyse the negative ones.

An altered state, for Cannon, has most commonly negative connotations, and considers an altered organic system to be at risk of severe illness and death. The range of oscillation of an organism around a set point is the range of that organism to have a healthy and full life experience. Selye (1973) proposed that an altered range of oscillation is not only possible, but probably the only way to guarantee the survival of a determined organism. Heterostasis is the notion he used to explain the effect of medication on an organism and why that prescription becomes necessary.

The seminal idea is that an organism, no matter how wide its oscillation range, is prone to face situations that could endanger its well-being and even its possibilities of survival. Selye widens the seminal definition of homeostasis by including a scenario where a living organism can access to an altered state of homeostasis in order to maintain its own regulation under control. Concretely, how can it become necessary to get a treatment that can alter the usual regulation of the body to an altered one for the purpose of keeping or, in this case, recuperating its original homeostatic regulation.

When an organism gets sick, their homeostasis will be altered. The regulation of the body, according to the main proposal, can get back to a healthy state by itself in most cases. But in those cases that the alteration is so extreme that the body needs to expend a great part of its resources to just maintain the system alive, it gets dangerous. The system might collapse by exhaustion, by burning all its resources in keeping the system alive, and in the worst-case scenario, it could succumb to the disease and die. Before reaching that dangerous point, medicine intervenes. Treatment would provide an alternative set point, which places the organism within a new oscillation range, that hopefully allows the organism to spend less resources in getting back to its original stable state.

This new oscillation range is provided by medicaments, and when the organism has fought its altered state provoked by external stimuli, treatment would be no longer necessary, and the organic system can recover its original range of oscillation. Heterostasis explains external influences that cannot really be considered positive or negative. Medication can be considered positive when needed, but that positive influence is brief and further beyond can be considered deleterious. In this sense, heterostasis can be understood as an aid for a healthy, regular homeostatic oscillation. But the differentiation is needed since it constitutes an altered, different regulatory regime than the regularly held by the living system.

On another completely different discourse, Sterling and Eyer (1988) came with the notion of allostasis. Their main inspiration to define it was the limits of the notion of homeostasis regarding the influence of perturbations in a biological system. Cannon focused in defining how a perturbation can alter an organism in present time. Sterling and Eyer thought about the learning process of an organism when confronted several times with perturbations, and defined allostasis as the stability of an organism through change.

In a sense, Sterling and Eyer complemented the seminal definition of homeostasis by Cannon. Noticing that most organisms alter they usual regulation to adapt to the external influences, and that not every single external perturbation has to be necessarily negative for the biological system, they proposed that living entities can anticipate to some of those disturbances before they actually affect them. Instead of burning resources and exhaust itself, an organism with an effective regulation has the ability or capacity to anticipate the stressful perturbation and get ready through changes in its biological performance, either physiological or psychological.

Allostasis is the notion referring to some past records of previous adaptations to the external environment based on the interactions between the organism and its context. They observed in their experiments that a biological system did not completely return to its previous regulatory regime after being altered. Hence, they concluded that an organism needs to modify its internal milieu, adapting to environmental requirements, for it to maintain its stability, since enduring perturbations and regaining its original state did not seem to be exactly the way that organisms maintain stability. By Sterling and Eyer's definition, there is not an organism enduring the external environment, but rather an adjustment of parameters from the internal environment to the external milieu.

In order to control these parameter adjustments, a higher control is needed. Sterling and Eyer, since they focus on the therapeutic implications of allostasis, propose the brain as the perfect candidate to coordinate and regulate the parameters of the internal milieu. The brain has the capacity to distribute the resources of the body, where they are best needed, and also to avoid sending them to areas that are not. This ability of buffering allows it to store all the information about the body and brain state and handle it to obtain the best performance possible.

This last ability also enables the brain to keep a historic record of past stable states or configurations of the regulation of the system. And this is the key feature that is responsible for allostasis to happen, since it is responsible for the capacity of the brain to anticipate needs and perturbations of the system and prepare the necessary adjustments beforehand. To rephrase it, the brain enables the fundament of allostasis that is historicity, or the capacity to keep records of past stress situations. Thanks to it, the system can prepare for imminent situations of stress since it has a record for previous circumstances and enhance the performance of the organism to resist them by saving and distributing the existing resources within.

The main difference with homeostasis is that the internal milieu does not react to a determined perturbation, but rather the system as a whole responds by creating a stable state closer to the altered state to come. Nevertheless, homeostasis and allostasis are not competing terms under the perspective of this work at least. Allostasis is defined within a framework of pathological states and the response of an organic system to them. Homeostasis is not preferable over allostasis since homeostasis is still a valid model for the general stability of the regulation of a system.

Homeostasis, as Cannon pointed in his work, is a model that can apply to complex organic systems even if not just biological. Society is one perfect example for this. And allostasis is completely centred in biological systems through their pathological and stable states. Homeostasis offers a model to analyse the momentary, concrete influence of a perturbation on a system, whilst allostasis can make that analysis more complicated since for Sterling and Eyer pathological states are often provoked by several causes. Most of the time, modern physiological therapeutics use the homeostatic model, since most common, primary treatments are focused on alleviate the symptoms of a disease or palliate a lack of resources of the body that leads to diseases, and usually the different causes that lead to a disease are difficult to find.

This can result in mistreatments or incompatible treatments if several symptoms develop at the same time. The allostatic model offers an alternative where those causes can be, ideally, tracked and discovered easier, but it requires to follow and record the condition of every patient, the earlier in their life the better. That is the main obstacle for a practical change in medicine and therapeutics, since this kind of practice should require, most likely, a lot of human and economic resources.

These are the main developments of the homeostasis proposal by Cannon. Of course, there is more vocabulary related to them, such as allostatic load, as explained in chapter six, as well as rheostasis. The difference between allostasis and rheostasis is so minuscule that it is complicated to separate them. Theoretically, rheostasis differs from allostasis in that rheostasis does not consider there are set points, but rather a constant change and adaptation to the environment, like seasonal changes and their influence on a biological system. Under the rheostasis perspective, what is rare is having a set point, not an external influence on the organism.

In a certain sense, it can be considered that rheostasis is some kind of allostasis extended. Not only the body learns and gets ready for the perturbation to come, but the body have learned to ride the waves of constant change and how to deal with the unexpected, to the extent of their resilience at least. Rheostasis is interesting since it takes into consideration the constant exchange and interaction between biological systems and, at the same time, highlights the difficulties of analysing these interactions to understand which ones and to what extent they influence a concrete, specific system.

On another stream, rheostasis makes even more complicated to clearly define a system due to this. The lack of set points and the constant exchange forces to study systems under an alternative perspective, as well as to find another explanation of their enclosure and how it works. They are not completely closed like Bernard suggested. They are not just being pushed by external perturbations and resisting all of the in order to survive. The tension between what an organism can handle, and their response or preparation time loses its relevance.

If the relationship between systems is so fluid, without set points or oscillation limits, and it is under constant change, maybe the only alternative we have is to define a system as what we have in front of us at every time. This would be a good approach to the personal configuration of every patient when considering the medical applications of homeostasis and its derived terms. But for a broader analysis of biological systems might not be the best perspective to adopt. This is why, when approaching the current scientific literature, the notion of homeostasis or allostasis, which are most used, does not seem to differ from biological regulation. And this has been the most challenging theoretical intent of this work.

To sum it up, when this research began, as mentioned somewhere else here, it started with the hope for homeostasis to be a profitable scientific perspective in the study of living beings, that is, useful to define what a biological system is, how it is delimited, and how it interacts with other biological systems at their same level (i.e. rabbit to rabbit) or with other interacting biological systems that are not necessarily considered to be at their same level (for instance, rabbit to forest). Guided by previous studies on Systems Biology, this research onset was to point to a possible alternative when analysing organisms that included, but was not limited to, their constitution as independent beings as well as their interactions and how those influence them.

While gaining more and more knowledge on the matter, it was clear soon enough that the difference between regulation as is commonly defined and homeostasis, used here as the broad concept comprising all the developed terms coined after, is not characterized enough to separate them clearly. Maybe one way to do this is to define regulation as internal, the processes involved in the stability of a system, and homeostasis or allostasis or rheostasis as the relationship between those different regulations.

What is beneficial to a plant is not necessarily to a bear, even if those quite different biological systems have some necessities in common, they use them so differently. Rain is directly beneficial to a plant, but indirectly beneficial to a bear. That difference between the use of resources, its comparison, and how do they relate, could be better understood under the homeostatic perspective, since it offers a broader point of view on the analysis of biological systems and how they influence each other. Regulation is more difficult to apply to this kind of interactions since a plant and a bear do not regulate each other, even if they influence their own survival while affecting their shared environment.

Homeostasis was a term coined to define the internal stabilization of living entities, but regulation take that place fairly early since it offered some useful and elegant models and widened our understanding of the internal operational system of organisms. Internal regulation is still developing, but it can be regarded as a rather defined term. Homeostasis and its related terms have been explored here, but yet need to be further investigated within biological interactions at least, and how they can be applied specifically to them.

Homeostasis includes regulation at least theoretically since it refers to the stability maintenance of systems, but regulation also includes homeostasis as a special, broader case. From the perspective of this work, both are complementary and necessary to fully define biological systems, their interactions and their delimitation. As defined here, allostasis and rheostasis specifically refer to the interaction between the internal and the external environment of biological systems and should be included closer to what homeostasis means, while heterostasis is more focused on the internal regulation of the body and the process it goes through towards regaining stability while externally treated.

To sum it up, if the term is focused on the internal processes of a system, it should be regarded as regulation or closer to it, while if it focuses on the interactions between systems and how they contribute to the harmonization of their own stability and enhancement of long-term survival with their interactions, it should be understood as a homeostatic perspective. This differentiation might not be the most decisive, but it could be used as a starting point in further research on the topic.

This distinction is based on the research carried in the last years in the biological and philosophical fields. Regulation was, and still is, the widespread used term to refer to the homeostatic maintenance of the stability within the body, including the materials, processes, and structure participating in that maintenance. However, internal regulation was deeply analysed and studied, hence the development of the knowledge on the subject has become quite specific and accurate. Changing the way we refer to the processes and elements involved in the internal regulation at this point is, to say the least, highly difficult and not really necessary.

Homeostasis can still be used as an umbrella term when referring to the internal regulation of living beings. Nevertheless, homeostasis can also account for the interactions between living systems, as well as their interactions with their niche, concretely, and their environment, in a wider sense. There are still potentialities and scenarios to be explored related to how do the changes in their environments affect organisms, and how the changes in an organism, or a group of organisms, can affect the relationships and exchanges they have with other living beings, even the shaping of their occupied external *milieux*.

For instance, within the filed of medicine, it would be interesting to use the idea of homeostasis to create an alternative doctor-patient relationship, as well as a holistic approach to the diagnosis of different diseases. In that sense, this alternative approach would help us understand better how different experiences can alter the patient's likelihood to develop a determined disease and how they can present immunity, or even more resistance, to certain conditions. Concretely, it might be interesting how mental health can affect to these parameters. This exceeds the aim of this work, but it is expected to be analysed in further investigations.

An idea that still stands at the end of this research is that regulation and homeostasis are not interchangeable terms, since they both relate to a biological phenomenon that is, even if closely related, different to each other. Furthermore, the notion of homeostasis, as mentioned earlier, is understood here as having clear applications to the field of medicine and our understanding of how diseases affect differently to distinct individuals that can be understood to be theoretically the same biological system. Because now medicine understands diseases as perturbations to the internal milieu of a biological system, but it could be interesting to include how the interactions of a concrete organism shape their specific regulatory system.

As it was alluded to in the above paragraph, the field of medicine could be enriched if it could consider the complete health history of a patient, as well as conditions that might not seem directly related to their present condition. In the above mentioned postulation it was explained that could be interesting to deepen our understanding on how mental conditions can affect the appearance of determined future diseases, for instance, how a childhood trauma could influence the body so that it develops cancer. This is just a hypothetical case, but still based in some early studies on the consequences of mental state in the stability of the body.

Since the notion of homeostasis includes everything that affects the stability of living beings, it would be sensible to use it to explore the relevant influences of the external milieu on the organism, since it is yet a field to be fully explored and understood. The field focused on the study of relations between different levels of organization could find of use this term and the holistic approach it provides, and obtain alternative outcomes in their research that can, ideally, keep us researchers more attentive to the inclusion of the methodologies available in biological studies, that is, top-down and middle-out methodologies.

To recapitulate, in this work homeostasis is defended to be still a useful term for some of the actual biological research. More specific analysis must be carried to determine concretely to what extent and how homeostasis may help current research in the organization of living beings or medicine. A certain amount of biological research uses the term homeostasis, but going through the literature published until this day it was noticeable a requirement for an extended analysis of the roots of homeostasis, since some notions seemed to be in the need of clarification.

In this work, the different terms derived from homeostasis and how they relate to regulation and organization have been explained as widely as the kind of project a PhD is allows to. Hopefully it could be useful for those that we are interested in this matter and would help to set fair foundations for further research.

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References

Ahn, A. C., Tewari, M., Poon, C. S., & Phillips, R. S. (July 2006). The clinical applications of a systems approach. *PLoS Medicine, 3*(7)

Ahn, A. C., Tewari, M., Poon, C. S., & Phillips, R. S. (June 2006). The limits of reductionism in medicine: Could systems biology offer an alternative? *PLoS Medicine, 3*(6)

Andersen, P. B. (2000). *Downward causation: Minds, bodies and matter*. Denmark: Aarhus University Press.

Arminjon, M. (2016). Birth of the allostatic model: From Cannon's biocracy to critical physiology. *Journal of the History of Biology, 49*(2), 397-423.

Ashby, W. R. (1954). *Design for a brain*. New York: John Wiley and sons.

Ashby, W. R. (1957). *Introduction to cybernetics*. London: Chapman and Hall LTD.

Ashby, W. R. (1964). *An introduction to cybernetics*. Michigan: Methuen & Co.

Ashby, W. R. (1965). *Design for a brain: The origin of adaptive behavior*. London: Chapman & Hall.

Ashby, W. R. (1972). *Introducción a la cibernética* (2a ed.). Buenos Aires: Nueva Visión.

Bailey, K. D. (1984). Equilibrium, entropy and homeostasis: A multidisciplinary legacy. *Systems Research and Behavioral Science, 1*(1), 25-43.

Bale, L. (1995). Bateson, G., Cybernetics, and the Social/behavioral sciences. *Cybernetics & Human Knowing, 3*(1), 27-45.

Barrett, L. F., & Simmons, W. K. (2015). Interoceptive predictions in the brain. *Nature Reviews Neuroscience, 16*(7), 419.

Bateson, G. (1972). Cybernetic explanation. In G. Bateson (Ed.), *Steps to and ecology of mind. Collected essays in anthropology, psychiatry, evolution, and epistemology* (pp. 405-431). San Francisco: Jason Aronson Inc.

Bechtel, W. (2007). Organization and biological mechanisms: Organized to maintain autonomy. In F. Boogerd, F. Bruggeman, J. -. Hofmeyr & H. Westerhoff (Eds.), *Systems biology: Philosophical foundations* (pp. 269-302). Manchester: Elsevier.

Bechtel, W., & Abrahamsen, A. (2005). Explanation: A mechanistic alternative. *Studies in History and Philosophy of Biological and Biomedical Sciences, 36*, 421-441.

Beer, S. (1972). *Brain of the firm: A development in management cybernetics*. New York: Herder and Herder.

Beer, S. (1984). The viable system model: Its provenance, development, methodology and pathology. *Journal of the Operational Research Society, 35*(1), 7-25.

Bernard, C. (1865). *An introduction to the study of experimental medicine* [Introduction à l'Étude de la Médecine Expérimental] (H. C. Greene Trans.). (1949th ed.). New York: Henry Schuman, Inc.

Bernard, C. (1872). L'expérimentation dans les sciences de la vie. In J.-B. Baillière (Ed.), *Leçons de pathologie expérimentale* (pp. 477). Paris: J.B. Baillière et fils Real Academia Nacional de Mèdicine.

Bernard, C. (1949). *An introduction to the study of experimental medicine*. New York: Henry Schuman, Inc.

Bernard, C., & Barona, J. L. (1989). *Bernard: Antología*. Barcelona: Península.

Bernard, C., & Pi Sunyer, J. (1976). *Introducción al estudio de la medicina experimental*. Barcelona: Fontanella.

Bernard, C. (1966). *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux*. Paris: J. Vrin.

Berntson, G. G., & Cacioppo, J. T. (2007). Integrative physiology: Homeostasis, allostasis, and the orchestration of systemic physiology. In J. T. Cacioppo, L. G. Tassinary & G. G. Berntson (Eds.), *The handbook of psychophysiology* (3rd ed., pp. 433-452). Cambridge: Cambridge University Press.

Boogerd, F. C. (2007). *Systems biology: Philosophical foundations*. Amsterdam: Elsevier.

Boorse, C. (1997). A rebuttal on health. In J. M. Humber, & R. F. Almeder (Eds.), *What is disease?* (pp. 3). New York: Springer Science+Business Media.

Boorse, C. (December 1977). Health as a theoretical concept. *Philosophy of Science, 44*(4), 542-573.

Boulopaep, E. L., & Boron, W. F. (2017). Foundations of physiology. In E. L. Boulopaep, & W. F. Boron (Eds.), *Medical physiology: A cellular and molecular approach* (2nd ed., pp. 3-6). Michigan: Saunders.

Breathnach, C. S. (2014). Claude Bernard and his revelations in physiology. *Irish Journal of Medical Science, 183*, 139-146.

Brigandt, I., & Love, A. (2017). *Reductionism in biology.* Retrieved May 3rd, 2017, from https://plato.stanford.edu/archives/spr2017/entries/reduction-biology/

Brown, W. M. (1985). On defining 'disease'. *The Journal of Medicine and Philosophy, 10*(4), 311-328.

Buchman, T. G. (2002). The community of the self. *Nature, 420*(6912), 246.

Buss, L. W. (1987). *The evolutionary of individuality*. Princeton: Princeton University Press.

Cacioppo, J. T., & Berntson, G. G. (2007). The brain, homeostasis, and health. Balancing demands of the internal and external milieu. In H. S. Friedman, & R. Cohen Silver (Eds.), *Foundations of health psychology* (pp. 73-91). Oxford: Oxford University Press.

Canguilhem, G. (1974). *Régulation (épistémologie),* 2018, from https://www.universalis.fr/encyclopedie/regulation-epistemologie/

Cannon, W. (1929). Organization for physiological homeostasis. *Physiological Reviews, 9*(3), 399-431. doi:10.1152/physrev.1929.9.3.399

Cannon, W. (1963). *The wisdom of the body*. New York: The Norton Library.

Caponi, G. (2001). Claude bernard y los límites de la fisiología experimental. *História, Ciências, Saúde-Manguinhos, VIII*(2), 375-406.

Caponi, G. (2015). Claude Bernard y el lugar de la fisiología en un mundo físicamente determinado. *Ludus Vitalis, XXIII*(44), 43-68.

Cariani, P. (2017). Open peer commentary: Beware false dichotomies. In A. Riegler, K. Müller & S. A. Umpleby (Eds.), *New horizons for second-order cybernetics* (pp. 59 - 61-404). Singapore: World Scientific Publishing Co. doi:doi:10.1142/10605

Collier, J. (2003). Organization in biological systems. In V. Arshinov, & C. Fuchs (Eds.), *Causality, emergence, self-organization* (pp. 287-302). Moscow: Nia-Piroda.

Cooper, S. J. (2008). From Claude Bernard to Walter Cannon. Emergence of the concept of homeostasis. *Appetite, 51*(3), 419-427. doi:http://dx.doi.org/10.1016/j.appet.2008.06.005

Cornish-Bowden, A. (1995). *Fundamentals of enzyme kinetics* (Rev ed.). Portland: Portland Press.

Craver, C., & Bechtel, W. (2006). Mechanism. In J. Pfeifer, & S. Sarkar (Eds.), *The philosophy of science: An encyclopedia* (pp. 469-478). Texas: Routledge.

Damasio, A. (1997). *El error de descartes* (2nd ed.). Barcelona: Andrés Bello.

Di Paolo, E. (2005). Autopoiesis, adaptivity, teleology, agency. *Phenomenology and the Cognitive Sciences, 4*, 429-452.

Diéguez, A. (2011). La filosofía de la biología como campo interdisciplinar. *Ludus Vitalis, XIX*(36), 261-265.

Diéguez, A. (2013). La función explicativa de los modelos en biología. *Contrastes. Revista Internacional De Filosofía, Suplemento 18*, 41-54.

Diéguez, A. (2013). Life as a homeostatic property cluster. *Biological Theory, 7*, 180-186.

Drack, M. (2009). Ludwig von Bertalanffy's early system approach. *Systems Research and Behavioral Science, 26*, 563-572.

Drack, M., Apfalter, W., & Pouvreau, D. (2007). On the making of a system theory of life: Paul A. Weiss and Ludwig von Bertalanffy's conceptual connection. *The Quarterly Review of Biology, 82*(4), 349-373.

Drack, M., & Pouvreau, D. (2015). On the history of Ludwig von Bertalanffy's "general systemology", and on its relationship to cybernetics - Part III: Convergences and divergences. *International Journal of General Systems, 44*(5), 523-571.

Dupré, J. (2009). It is not possible to reduce biological explanations to explanations in chemistry and/or physics. *Contemporary debates in philosophy of biology* (pp. 32-47). Oxford: Wiley-Blackwell. doi:10.1002/9781444314922.ch2

Dussault, A. C., & Gagné-Julien, A. -. (2015). Health, homeostasis, and the situation-specificity of normality. *Theoretical Medicine and Bioethics, 36*, 61-81.

Ehrenberg, M., Elf, J., Aurell, E., Sandberg, R., & Tegnér, J. (2003). Systems biology is taking off. *Genome Research, 13*, 2377-2380.

Etxeberria, A., & Bich, L. (2017). Auto-organización y autopoiesis. *Diccionario Interdisciplinar Austral,* Retrieved from http://dia.austral.edu.ar/Auto-organizaci%C3%B3n_y_autopoiesis

Etxeberria, A., & Umerez, J. (2006). Organismo y organización en la biología teórica: ¿Vuelta al organicismo? *Ludus Vitalis, 14*(26), 3-38.

Fell, D. (1996). *Understanding the control of metabolism*. London: Portland Press.

Fell, D. (1999). *Bases del control del metabolismo*. Barcelona: Omega.

Foucault, M. (1966). *Les mots et les choses: Une archéologie des sciences humaines: Une archéologie des sciences humaines*. Paris: Gallimard.

Fox Keller, E. (2007). The disappearance of function from 'self-organizing systems'. In F. Boogerd, F. Bruggeman, J. -. Hofmeyr & H. Westerhoff (Eds.), *Systems biology* (pp. 303-317). Amsterdam: Elsevier.

Fox Keller, E. (2008). Organisms, machines, and thunderstorms: A history of self-organization, part one. *Historical Studies in the Natural Sciences, 38*(1), 45-75.

Gánti, T. (2003). *The principles of life*. Oxford: Oxford University Press.

García Santesmases, J. (1980). In Real Academia de Ciencias Exactas, Físicas y Naturales (Ed.), *Cibernética: Aspectos y tendencias actuales*. Madrid: Paraninfo.

George, F. H. (1968). *Cibernética y biología* (1a ed.). Madrid: Alhambra.

Gilbert, S. F., & Sarkar, S. (2000). Embracing complexity: Organicism for the 21st century. *Developmental Dynamics, 219*, 1-9.

Glanville, R. (2002). Second order cybernetics. *Systems Science and Cybernetics, 3*, 59-85.

Goodfield, G. J. (1987). *El desarrollo de la fisiología científica: El método fisiológico y la controversia mecanicismo-vitalismo ilustrados por los problemas de la respiración y el calor animales*. Mexico D. F.: Universidad Nacional Autónoma de México.

Goudsmit, A. (1992). A one-sided boundary: On the limits of knowing organizational closure. In G. Van de Vijver (Ed.), *New perspectives on cybernetics* (pp. 175-205). Dordrecht: Springer. doi:https://doi.org/10.1007/978-94-015-8062-5_11

Green, S. (2017). Introduction to philosophy of systems biology. In S. Green (Ed.), *Philosophy of systems biology: Perspectives from scientists and philosophers* (pp. 1-23). Cham: Springer International Publishing. doi:10.1007/978-3-319-47000-9_1

Green, S. (accepted in 2017). Scale-dependency and downward causation in biology. *Philosophy of Science, Proceedings of the Biennal Meeting of the Philosophy of Science Association* Retrieved from https://www.researchgate.net/publication/320943921_Scale-dependency_and_Downward_Causation_in_Biology

Green, S., & Wolkenhauer, O. (2013). Tracing organizing principles: Learning from the history of Systems biology. *History and Philosophy of the Life Sciences, 35*, 553-576.

Greenhaff, P. L., & Hargreaves, M. (2011). 'Systems biology' in human exercise physiology: Is it something different from integrative physiology? *The Journal of Physiology, 589*(5), 1031-1036.

Grene, M., Grene, M. G., & Depew, D. (2004). *The philosophy of biology: An episodic history*. Cambridge: Cambridge University Press.

Griesemer, J., & Szathmáry, E. (2008). Gánti's chemoton model and life criteria. *Protocells - bridging nonliving and living matter*. London: The MIT Press.

Grocott, M. P. W. (2013). Integrative physiology and systems biology: Reductionism, emergence and causality. *Extreme Physiology & Medicine, 2*(9)

Gross, C. G. (1998). Claude Bernard and the constancy of the internal environment. *The Neuroscientist, 4*(5), 380-385.

Haller, J. S. (1981). *American medicine in transition, 1840-1910*. Champaign, Illinois: University of Illinois Press. Retrieved from: https://books.google.es/books?id=FeaucvGO41MC

Hardy, R. N. (1979). *Homeostasis*. Barcelona: Omega.

Heim, R., & Fondation Singer-Polignac. (1967). *Les concepts de Claude Bernard sur le milieu intérieur*. Paris: Masson et Cie.

Heylighen, F., & Joslyn, C. (2001). Cybernetics and second-order cybernetics. *Encyclopedia of Physical Science & Technology, 4*, 155-170.

Hofmeyr, J. , & Hofmeyr, J. (2007). An abstract cell model that describes the self-organization of cell function in living systems. *Journal of Theoretical Biology, 246*(3), 461-476.

Holling, C. S. (1987). Simplifying the complex: The paradigms of ecological function and structure. *European Journal of Operational Research, 30*(2), 139-146. doi:https://doi.org/10.1016/0377-2217(87)90091-9

Holling, C. S. (2001). Understanding the complexity of economic, ecological, and social systems. *Ecosystems, 4*(5), 390-405. doi:10.1007/s10021-001-0101-5

Jacob, F. (1970). *La logique du vivant*. Paris: Gallimard.

Jonas, H. (1982). *The phenomenon of life: Toward a philosophical biology*. Chicago: University of Chicago Press.

Joyner, M. J., & Pedersen, B. K. (2011). Ten questions about systems biology. *Journal of Physiology, 589*(5), 1017-1030.

Kant, I. (1892). *Critique of judgement*. New York: Macmillan and Company.

Kant, I. (2007). In García Norro J. J., Rovira R. and García Morente M. (Eds.), *Crítica del juicio*. Madrid: Tecnos.

Kauffman, L. H., & Umpleby, S. A. (2017). A brief history of (second-order) cybernetics. *New Horizons for Second-Order Cybernetics, 60*, 3.

Kauffman, S. (1969). Homeostasis and differentiation in random genetic control networks. *Nature, 224*, 177-178.

Kauffman, S. A. (2000). *Investigations*. Oxford: Oxford University Press.

King, L. S. (1954). What is disease? *Philosophy of Science, 21*(3), 193-203.

Kitano, H. (2002). Systems biology: A brief overview. *Science, 295*(5560), 1662-1664.

Kitano, H. (2010). Grand challenges in systems biology. *Frontiers in Physiology, 1*(Article 3), 1-3.

Krieger, N. (2005). Embodiment: A conceptual glossary for epidemiology. *Journal of Epidemiology and Community Health, 59*(5), 350-355. doi:10.1136/jech.2004.024562

Langley, L. L., & Miralles Vila, L. K. (1969). *Homeostasis*. Madrid: Alhambra.

Louie, A. H., Rosen, R., & Richardson, I. W. (1985). *Theoretical biology and complexity: Three essays on the natural philosophy of complex systems*. Orlando: Academic Press.

Martí, O. (1980). *Conocer Claude Bernard y su obra*. Barcelona: Dopesa.

Maturana, H. R., & Varela, F. J. (1980). *Autopoiesis and cognition: The realization of the living*. Dordrecht: D. Reidel.

Maturana, H. R., & Varela, F. J. (1996). *El árbol del conocimiento: Las bases biológicas del conocimiento humano* (1a ed.). Madrid: Debate.

Maturana, H. R., & Varela, F. J. (2004). *De máquinas y seres vivos. autopoiesis: La organización de lo vivo* (6a ed.). Buenos Aires; Santiago de Chile: Lumen; Editorial Universitaria.

Maturana, H. R., & Varela, F. J. (2004). *El árbol de la vida*. Buenos Aires: Lumen.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*(1), 33-44.

McEwen, B. S. (2004). Structural and functional plasticity in the hippocampal formation: Stress, adaptation, and disease. *Neurobiology of Mental Illness;* 558-583.

McEwen, B. S. (2010). Stress: Homeostasis, rheostasis, allostasis and allostatic load. *Stress Science: Neuroendocrinology;* 10-14.

McEwen, B. S. (2016). Central role of the brain in stress and adaptation: Allostasis, biological embedding, and cumulative change. *Stress: Concepts, cognition, emotion, and behavior* (pp. 39-55). Amsterdam: Elsevier.

McEwen, B. S., & Stellar, E. (1993). Stress and the individual: Mechanisms leading to disease. *Archives of Internal Medicine, 153*(18), 2093-2101.

McEwen, B. S. (2016). Chapter 5 - central role of the brain in stress and adaptation: Allostasis, biological embedding, and cumulative change. In G. Fink (Ed.), *Stress: Concepts, cognition, emotion, and behavior* (pp. 39-55). San Diego: Academic Press. doi:https://doi.org/10.1016/B978-0-12-800951-2.00005-4

Meltzer, S. J. (1907). The factors of safety in animal structure and animal economy. *Science, 25*(639), 481-498.

Ménuret de Chambaud, J. J. (1765). Œconomie animale (médecine). *Encyclopédie Ou Dictionnaire Raisonné Des Arts Et Des Métiers,* , 360-366.

Mesarovic, S., Sreenath, S., & Keene, J. (2004). Search for organising principles: Understanding in systems biology. *Systems Biology, 1*(1), 19-27.

Moreno, A., Etxeberria, A., & Umerez, J. (2008). The autonomy of biological individuals and artificial models. *Biosysems, 91*, 309-319.

Moreno, A., & Mossio, M. (2010). Organisational closure in biological organisms. *History and Philosophy of the Life Sciences, 32*, 269-288.

Moreno, A., & Mossio, M. (2015). Teleology, normativity and functionality. In A. Moreno, & M. Mossio (Eds.), *Biological autonomy. A philosophical and theoretical enquiry* (pp. 63-88). New York: Springer.

Mossio, M., Saborido, C., & Moreno, A. (2009). An organizational account of biological functions. *The British Journal for the Philosophy of Science, 8*, 1-29.

Mrosovsky, N. (1990). *Rheostasis: The physiology of change*. Oxford: Oxford University Press.

Newman, S. A. (2003). The fall and rise of systems biology. *Genewatch, 16*(4), 8-12.

Noble, D. (2008). Claude Bernard, the first system biologist, and the future of physiology. *Experimental Physiology, 93*(1), 16-26.

Nordenfelt, L. (1986). Health and disease: Two philosophical perspectives. *Journal of Epidemiology and Community Health, 40*(4), 281-284.

Nordenfelt, L. (1995). *On the nature of health: An action-theoretic approach*. New York: Springer Science & Business Media.

Nordenfelt, L. (2007). The concepts of health and illness revisited. *Medicine, Health Care and Philosophy, 10*(1), 5.

Normandin, S. (2007). Claude Bernard and an introduction to the study of experimental medicine: "physical vitalism", dialectic, and epistemology. *Journal of the History of Medicine and Allied Sciences, 62*(4), 495-528.

Northrop, R. B. (2000). *Endogenous and exogenous regulation and control of physiological systems*. London: Chapman & Hall.

O'Malley, M. A., & Dupré, J. (2005). Fundamental issues in systems biology. *Bioessays, 27*, 1270-1276.

Pask, G. (1975). *Conversation, cognition and learning: A cybernetic theory and methodology*. Amsterdam: Elsevier.

Pattee, H. H. (1973). Physical basis and origin of control. In H. H. Pattee (Ed.), *Hierarchy theory. The challenge of complex systems* (1st ed., pp. 73-108). New York: George Braziller. International Library of Systems Theory and Philosophy.

Pezzulo, G., Rigoli, F., & Friston, K. (2015). Active inference, homeostatic regulation and adaptive behavioural control. *Progress in Neurobiology, 134*, 17-35.

Pradeu, T. (2016). Organisms or biological individuals? Combining physiological and evolutionary individuality. *Biology and Philosophy, 31*(6), 797-817.

Ramaprasad, A. (1983). On the definition of feedback. *Behavioral Science, 28*(1), 4-13. doi:10.1002/bs.3830280103

Rosen, R. (1991). *Life itself: A comprehensive inquiry into the nature, origin, and fabrication of life*. New York: Columbia University Press.

Rosenblueth, A., Wiener, N., & Bigelow, J. (1943). Behavior, purpose and teleology. *Philosophy of Science, 10*(1), 18-24.

Rosslenbroich, B. (2014). The concept of biological autonomy. In B. Rosslenbroich (Ed.), *On the origin of autonomy: A new look at the major 19 transitions in evolution, history, philosophy and theory of the life sciences* (pp. 19-40). Amsterdam: Springer International Publishing.

Ruiz-Mirazo, K., & Moreno, A. (2004). Basic autonomy as a fundamental step in the synthesis of life. *Artificial Life, 10*, 235-259.

Schulkin, J. (2004). *Allostasis, homeostasis and the costs of physiological adaptation*. Cambridge: Cambridge University Press.

Scott, B. (2001). Gordon Pask's conversation theory: A domain independent constructivist model of human knowking. *Foundations of Science, Special Issue on " the Impact of Radical Constructivism of Science", 6*(4), 343-360.

Selye, H. (1973). Homeostasis and heterostasis. *Perspectives in Biology and Medicine, 16*(3), 441-445.

Sieck, G. (2015). Transforming medicine through physiology. *Physiology, 30*(3), 173-174. doi:10.1152/physiol.00013.2015

Sieck, G. (2017). Physiology in perspective: Homeostasis and evolution. *Physiology, 32*(2), 98-99. doi:10.1152/physiol.00002.2017

Sieck, G. (2018). Physiology in perspective: Homeostasis and survival. *Physiology, 33*(2), 84-85. doi:10.1152/physiol.00006.2018

Smith, J. M. (1987). *Los problemas de la biología*. Madrid: Cátedra.

Sober, E. (1999). The multiple realizability argument against reductionism. *Philosophy of Science,* , 542-564.

Staunton, J. (1978). *Primary metabolism: A mechanistic approach*. Oxford: Clarendon Press.

Sterling, P. (2012). Allostasis: A model of predictive regulation. *Physiology & Behavior, 106*(1), 5-15.

Sterling, P., & Eyer, J. (1988). Handbook of life stress. *Cognition and Health. J.Wiley Ltd,*

Strange, K. (2005). The end of "naïve reductionism": Rise of systems biology or renaissance of physiology? *American Journal of Physiology - Cell Physiology, 288*, c968-c974.

Torday, J. S. (2015). Homeostasis as the mechanism of evolution. *Biology, 4*(3), 573-590.

Van de Vijver, G., Van Speybroeck, L., & Vandevyvere, W. (2003). Reflecting on complexity of biological systems: Kant and beyond? *Acta Biotheoretica, 51*(2), 101-140.

von Bertalanffy, L. (1950). The theory of open systems in physics and biology. *Science, 111*(January 13), 23-29.

von Bertalanffy, L. (1968). *General system theory. Foundations, development, applications* (1975th ed.). New York: George Braziller.

von Bertalanffy, L. (1975). *Perspectivas en la teoría general de sistemas* (1986th ed.). Madrid: Alianza.

von Bertalanffy, L. (1976). *Teoría general de los sistemas: Fundamentos, desarrollo, aplicaciones* [General System Theory: Foundations, Development, Applications] (J. Almela Trans.). México D. F.: Fondo de Cultura Económica.

von Foerster, H. (1960). On self-organizing systems and their environments. *Understanding understanding* (2003rd ed., pp. 1-19). Amsterdam: Springer.

von Foerster, H. (1979). Cybernetics of cybernetics. *Understanding understanding* (2003rd ed., pp. 283-286). Amsterdam: Springer.

von Foerster, H., & Pakman, M. (1991). *Las semillas de la cibernética: Obras escogidas*. Barcelona: Gedisa.

Waddington, C. H. (1957). *The strategy of the genes*. London: George Allen and Unwin.

Wiener, N. (1961). *Cybernetics or control and communication in the animal and the machine*. London: MIT Press.

Wiener, N. (1985). *Cibernética o el control y comunicación en animales y máquinas*. Barcelona: Tusquets.

Wiener, N. (1998). *Cibernética o el control y comunicación en animales y máquinas* (2a ed.). Barcelona: Tusquets.

Wimsatt, W. C. (2007). *Re-engineering philosophy for limited beings: Piecewise approximations to reality*. Cambridge: Harvard University Press.

Wolfe, C. T. (2011). From substantival to functional vitalism and beyond: Animas, organisms and attitudes. *Eidos, 14*, 212-235.

Wolfe, C. T. (2017). Models of organic organization in Montpellier vitalism. *Early Science and Medicine, 22*(2-3), 229-252.

Wolfe, C. T., & Terada, M. (2008). The animal economy as object and program in Montpellier vitalism. *Science in Context, 21*(4), 537-579.