SUPPLEMENTARY METHODS

Normalized fold induction for response R1

In the case of an enhancer being brought to the promoter, the fold induction and maximum fold induction are $FI = \bar{\Gamma}_{\mathrm{R1}} / \Gamma_{\mathrm{ref}}$ and $FI_{\max} = 1 + (\Gamma_{\mathrm{t}} / \Gamma_{\mathrm{ref}})$, respectively, which lead to a normalized fold induction given by

$$NFI_{\mathrm{R1}} = P_{\mathrm{t}} .$$

Therefore, in the case of response R1, the normalized fold induction is determined by just the probability of the conformation with the tetramer bound to the two DNA sites.

Normalized fold induction for response R2

The case of a coactivator being recruited by an active RXR dimer is more involved because the self-assembly modulator, 9cRA, is also an agonist of RXR. The reason is that an RXR dimer has to bind at least one 9cRA molecule to recruit a coactivator. Therefore, the quantities Γ_c (see text) are themselves effective transcription rates given by $\Gamma_c = \Gamma_{\mathrm{ref}} P_{\mathrm{no\ ligand}} + \Gamma_{\mathrm{act}} (1 - P_{\mathrm{no\ ligand}})$, where $P_{\mathrm{no\ ligand}}$ is the probability that none of the dimers of the group of binding states c has a ligand bound. It is given by $P_{\mathrm{no\ ligand}} = 1/(1+[s]/K_{lig})^2$ for the groups of binding states with one dimer (od and do) and by $P_{\mathrm{no\ ligand}} = 1/(1+[s]/K_{lig})^4$ for the group of binding states with the two dimers (dd). The resulting effective transcription rates for the groups of binding states with dimers — $\Gamma_{\mathrm{od}} = \Gamma_{\mathrm{ref}} + (\Gamma_{\mathrm{act}} - \Gamma_{\mathrm{ref}})\left(1-(1+[s]/K_{lig})^{-2}\right)$, $\Gamma_{\mathrm{do}} = \Gamma_{\mathrm{ref}} + (\Gamma_{\mathrm{act}} - \Gamma_{\mathrm{ref}})\left(1-(1+[s]/K_{lig})^{-2}\right)$,

and $\Gamma_{\mathrm{dd}} = \Gamma_{\mathrm{ref}} + (\Gamma_{\mathrm{act}} - \Gamma_{\mathrm{ref}})\left(1-(1+[s]/K_{lig})^{-4}\right)$ — depend explicitly on the self-assembly modulator concentration and take into account that binding of at least one ligand to RXR activates the dimeric form in addition to modulating the oligomerization state. In the case of response R2, therefore, we have $FI = \overline{\Gamma}_{\mathrm{R2}} / \Gamma_{\mathrm{ref}}$ and $FI_{\max} = 1 + (\Gamma_{\mathrm{act}} / \Gamma_{\mathrm{ref}})$ and the resulting normalized fold induction is given by

$$NFI_{\mathrm{R2}} = \left(1-(1+[s]/K_{\mathrm{lig}})^{-2}\right)(P_{\mathrm{od}} + P_{\mathrm{do}}) + \left(1-(1+[s]/K_{\mathrm{lig}})^{-4}\right)P_{\mathrm{dd}}$$

for the whole-parameter space, and by

$$NFI_{\mathrm{R2}} \approx \left(1-(1+[s]/K_{\mathrm{lig}})^{-4}\right)(1-P_{\mathrm{t}})$$

in the functional regime.

Modulator function for RXR

The self-assembly modulator of RXR is the hormone 9-*cis*-retinoic acid (9cRA), a derivative of Vitamin A, which binds each RXR molecule independently of its oligomerization state and prevents dimers with their two subunits occupied from tetramerazing. Therefore, there are several types of tetramerizing dimers. We use the notation $[n_{0,0}]$ for the dimer concentration with no hormone bound; $[n_{0,1}]$ and $[n_{1,0}]$ for those with just one 9cRA molecule bound; and $[n_{1,1}]$ for those with two 9cRA molecules bound. Binding of 9cRA to RXR follows the usual mass action law: $[n_{1,0}] = [n_{0,0}][s]/K_{\mathrm{lig}}$, $[n_{0,1}] = [n_{0,0}][s]/K_{\mathrm{lig}}$, and $[n_{1,1}] = [n_{0,0}][s]^2/K_{\mathrm{lig}}^2$, where K_{lig} is the ligand-RXR dissociation constant. The concentrations of tetramerazing and non-tetramerazing dimers are therefore related to each other by

$$[n_2] = [n_{1,0}] + [n_{0,1}] + [n_{0,0}] = [n_{0,0}](2[s] / K_{\text{lig}} + 1)$$

$$[n_2^*] = [n_{1,1}] = [n_{0,0}][s]^2 / K_{\text{lig}}^2$$

from which we obtain the explicit form of the modulator function:

$$f([s]) = \frac{[n_2^*]}{[n_2]} = \frac{[s]^2}{K_{\text{lig}}^2 + 2K_{\text{lig}}[s]} .$$

This expression explicitly indicates how the ligand controls the relative concentrations of the different oligomerization states that shape the transcriptional response.

Computational approach for RXR in the whole-parameter space

The whole-parameter space needs to consider explicitly the total nuclear RXR concentration, $n_{\text{T}} = 4[n_4] + 2[n_2] + 2[n_2^*] + [n_1]$, which includes the contributions from monomer concentration $[n_1]$ in addition to those from the tetramer, dimer, and non-tetramerizing dimer. Dimerization is described by $[n_1]^2 / \left([n_2] + [n_2^*]\right) = K_{\text{dm}}$, where K_{dm} is dimer-monomer dissociation constant. For given values of the parameters, the concentrations of the four oligomerization states are obtained by solving numerically the equations for the total nuclear RXR concentration, dimerization, tetramerization, and modulator function for each ligand concentration. The resulting oligomeric concentrations are used to obtain the corresponding probabilities (Table 2), which in turn are substituted in the expressions $NFI_{\text{R1}} = P_{\text{t}}$ and $NFI_{\text{R2}} = \left(1 - (1 + [s] / K_{\text{lig}})^{-2}\right)(P_{\text{od}} + P_{\text{do}}) + \left(1 - (1 + [s] / K_{\text{lig}})^{-4}\right) P_{\text{dd}}$ to obtain the normalized fold induction for responses R1 and R2, respectively.