SUPPORTING MATERIAL:
Protein logic: a statistical mechanical study of function at the single-protein level

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SI. 1 Optimization details

Optimization parameters

In Table SI-1 we provide bounds for our optimization parameters K_i^j, ω_0 and $\omega_{ii'}$. In this section we provide experimental support for the chosen bounds.

- ω_0
  Two experimental studies report on explicit values of ω_0. In the quorum sensing bacterium *V. Harveyi* an ω_0 value is reported of $e^{-\Delta\epsilon/k_BT} = e^{3.2} \approx 24$ (1). Next, a conformational spread model for the motor proteins in *E. coli* reported for $\omega_0 = e^{-E_A/k_BT} = e^{-0.66} = 0.51$ (2). Moreover, two modeling studies have also suggested values for ω_0. In (3) a value of $\omega_0 = e^{-E_A/k_BT} = 0.36$, while in (4) a large range for ω_0 is suggested $\omega_0 \sim [e^{-10} - e^{10}]$.

- $\omega_{ii'}$
  For *E. coli* different experimental observations are reported, both for the motor proteins and the receptors. The receptor coupling energy has been reported to be around 0 k_BT, leading to $\omega_{ii'} = 1$ (5, 6). For the motor protein, a value for $\omega_{ii'} = e^{E_{ii'}/k_BT} = 62$ has been reported (2). In a modeling study of the protein N-WASP $\omega_{ii'} \sim 300$ has been used (7). In the EGFR receptor for monomers $K_D \sim 10^0$ [nM], while for dimers $K_D \sim 10^{-2}$ [nM], suggesting a positive coupling between two monomers ($\omega_{ii'} > 1$) (8). In the same modeling studies as cited above, estimates are $E_j = \ln \omega_{ii'} =$ 0-4 k_BT (3) and a large range $\omega_{ii'} \sim [e^{-10} - e^{15}]$ (4).

- K_i^j
  In *E. coli* dissociation constants for different ligands and activation states for the Tar and Tsr receptors have been measured which vary between $[10^{-2} - 10^6]$ [mM] (5, 6). Experimental work on the receptors of the quorum sensing machinery in *V. Harveyi* where single amino-acids are replaced have resulted in dissociation constant varying between $[10^0 - 10^5]$ [nM] (1). For EGFR different K_D's are reported for different dimer pairs, ranging from 10 [pM] to 500 [nM] (8, 9). Synthetic proteins are constructed with varying dissociation constants for different ligands, where the K_D ranges from $[1 - 1000]$ [μM] (10) or $[10^{-1} - 10^5]$ [μM] (11). A mathematical model based upon a three-state receptor with multiple ligands used K_D values from $[10^{-9} - 10^{-5}]$ [μM] for each ligand and state of the system (12).

Multiple receptors

In the case where M different receptors (e.g. $Q_{\mathrm{UV}}, Q_{\mathrm{WV}}, Q_{\mathrm{UW}}$) are combined to act in different combinations as unique logic gates, the optimization algorithm follows a specific order in the optimization. A straightforward extension of the model for a single receptor is the optimization of three (or four) gates simultaneously, and taking as fitness $\mathcal{F}$ the summed fitness of every gate F_m:

$$\mathcal{F} = \sum_{m=1}^{M} F_m. \tag{SI-1}$$

However, this optimization is not capable of optimizing all the gates independently. Instead, the algorithm optimizes either one (or two) gates, but then cannot optimize the third gate. To optimize the third gate, the already optimized gates decrease (temporarily) in fitness. This decrease is larger

Model input	**Range**
$[S_1], [S_2]$	$\left[10^{-2} - 10^{2}\right]$ μM
Model parameter	**Bounds**
$K_{i,k}^{j}$	$\left[10^{-3} - 10^{4}\right]$ μM
ω_0	$\left[10^{-3} - 10^{3}\right]$
$\omega_{ii'}$	$\left[10^{-2} - 10^{2}\right]$
Optimization parameter	**Value**
Δ	0.3
N	4
R	50000
Steps	1000

Table SI-1: Overview of parameters. During optimization, model parameters are initialized and constrained within the indicated bounds.

than the increase in fitness for the third gate and the algorithm finds suboptimal peaks in this rugged fitness landscape.

Instead of optimizing all gates simultaneously, we optimize gates in order. For the homodimer construction ($Q_{\mathrm{WW}}, Q_{\mathrm{UW}}, Q_{\mathrm{WV}}$), we first optimize Q_{WW}, then Q_{UW}, where we only change the parameters of U, and then Q_{WV}, only changing V. The achieved results greatly outperform the results where we optimize all three gates simultaneously.

For the heterodimer construction ($Q_{\mathrm{UW}}, Q_{\mathrm{WV}}, Q_{\mathrm{UV}}$), we again start by optimizing gate Q_{UW}, then the two gates Q_{UW} and Q_{WV} simultaneously, and finally Q_{UW}, Q_{WV}, and Q_{UV}. Again this procedure gives much better results than simultaneous optimization of all three gates.

For the construction with $Q_{\mathrm{WW}}, Q_{\mathrm{UW}}, Q_{\mathrm{UV}}$), we start by optimizing gate Q_{WW}, then the two gates Q_{WW} and Q_{UW} simultaneously, and finally Q_{WW}, Q_{UW}, and Q_{UV}.

SI. 2 Formal proof that receptor Q_{UW} can perform an `XOR` gate

The probability to be active $p^A\left([S_1], [S_2]\right)$ in an `XOR` gate is a nonmonotonic function of $[S_1]$ and $[S_2]$ simultaneously. More specifically, for constant $[S_2] = [S_2^c]$, $p^A\left([S_1], [S_2^c]\right)$ is either monotonically increasing or decreasing, depending on the value $[S_2^c]$: for small $[S_2^c]$, p^A is monotonically increasing, while for large $[S_2^c]$, p^A is monotonically decreasing.

A positive derivative $\partial p^A/\partial[S_2]$ reflects a monotonically increasing function, while a negative derivative reflects a monotonically decreasing function. Therefore, in an `XOR` gate, the derivative of the probability with respect to $[S_2]$ at constant $[S_1^c]$ should change sign as function of $[S_1^c]$. Again due to symmetry, the derivative of the probability with respect to $[S_1]$ at constant $[S_2^c]$ should change sign as function of $[S_2^c]$. We will prove that the `XOR` gate is possible for the Q_{UW} receptor even with $\omega_{11} = \omega_{21} = 1$. Recalling Eq. 1, the derivative can be written $\partial p^A/\partial[S_2] = f/(Z^A + Z^I)^2$, where the numerator

$$f\left([S_1^c], [S_2]\right) = \frac{\partial Z^A}{\partial [S_2]} Z^I - Z^A \frac{\partial Z^I}{\partial [S_2]} \tag{SI-2}$$

alone determines the sign. We therefore must show that f changes sign as function of $[S_1^c]$. Specifically, the `XOR` gate requires

$$f > 0 \text{ for } [S_1^c] < [S_1^c]^*, \tag{SI-3}$$
$$f < 0 \text{ for } [S_1^c] > [S_1^c]^*, \tag{SI-4}$$

for some $[S_1^c]^*$ and all $[S_2]$.

The partition functions Z^A and Z^I for the Q_{UW} receptor are given by Eqs. 9-10 in the main text. Performing the derivatives in Eq. SI-2 reveals that f is a third order polynomial in $[S_1^c]$ in which all dependence on $[S_2]$ drops out. Only one root is potentially positive:

$$[S_1^c]^* = \frac{K_{1,W}^I K_{1,W}^A \left(K_2^I - K_2^A\right)}{K_{1,W}^I K_2^A - K_{1,W}^A K_2^I}. \tag{SI-5}$$

To satisfy Eqs. SI-3-SI-4, we require that the zeroth order term (the intercept) is positive and that the leading order term is negative; enforcing these conditions yields

$$K_2^I - K_2^A > 0, \tag{SI-6}$$
$$K_{1,W}^I K_2^A - K_{1,W}^A K_2^I > 0, \tag{SI-7}$$

which are in fact the precise conditions that maintain positivity of the root (Eq. SI-5). Parameters that satisfy these conditions enable the sign of $\partial p^A / \partial [S_2]$ to depend on constant $[S_1^c]$, which is one of the two conditions necessary to perform the `XOR` gate. Notably, Eq. SI-6 directly shows that the binding of ligand 2 to the W monomer in Q_{UW} in the active state is less likely than binding in the inactive state.

The second requirement is that the sign of $\partial p^A / \partial [S_1]$ depends on constant $[S_2^c]$. Specifically, as in Eqs. SI-3-SI-4, the `XOR` gate requires that the numerator $g([S_1], [S_2^c])$ of the derivative satisfies

$$g > 0 \text{ for } [S_2^c] < [S_2^c]^*, \tag{SI-8}$$
$$g < 0 \text{ for } [S_2^c] > [S_2^c]^*. \tag{SI-9}$$

for some $[S_2^c]^*$ and all $[S_1]$. Performing the derivative reveals that g is a second order polynomial whose coefficients depend on $[S_1]$. To satisfy Eqs. SI-8-SI-9, we again require that the intercept is positive and that the leading order term is negative; enforcing these conditions yields

$$h\left([S_1], K_{1,U}^I, K_{1,U}^A, K_{1,W}^I, K_{1,W}^A\right) > 0, \tag{SI-10}$$
$$K_{1,U}^I - K_{1,U}^A < 0, \tag{SI-11}$$

where the function h results straightforwardly from the derivative but is unwieldy, such that we do not reproduce it here. The roots of the polynomial $[S_2^c]^*$ are similarly unwieldy, but noting positivity requirements ($[S_2^c]^* > 0$, $K_{1,W}^I > 0$, $K_{1,U}^I > 0$, $K_2^I > 0$), parameter regimes can be derived that satisfy both Eqs. SI-6-SI-7 and Eqs. SI-10-SI-11 simultaneously. As an example we

present one possible regime here:

$$\frac{K^A_{1,W}}{K^I_{1,W}} < \frac{K^A_2}{K^I_2} < 1, \tag{SI-12}$$

$$0 < \frac{K^A_{1,W}}{K^I_{1,W}} \leq \frac{K^I_{1,U}}{K^I_{1,U} + K^I_{1,W}}, \tag{SI-13}$$

$$K^A_{1,W} + K^A_{1,U} > K^I_{1,U} + K^I_{1,W}. \tag{SI-14}$$

Eq. SI-12 states that the W monomer is activated by $[S_1]$ and $[S_2]$, and that activation by $[S_1]$ is stronger than activation by $[S_2]$. Note that for small concentrations of either $[S_1]$ or $[S_2]$, W is inactive. The two more interesting constraints are in Eq. SI-13 and Eq. SI-14. Eq. SI-14 states that $[S_1]$ bound to monomer U deactivates the receptor ($K^A_{1,U} > K^I_{1,U}$), since, from Eq. SI-12, we have seen that $K^A_{1,W} < K^I_{1,W}$. More importantly the deactivation of U by binding $[S_1]$ is stronger than the activation of W by $[S_1]$, and following Eq. SI-12, it is thus also stronger than activation of W by $[S_2]$. This is precisely the interference interaction as described in the main text. The last constraint, Eq. SI-13, provides the required binding strength of $[S_1]$ to U and W to satisfy all constraints. In the main text we argue that W should preferably bind $[S_2]$, such that in the presence of both ligand $[S_2]$ binds to W and $[S_1]$ binds to U with as result that Q_{UW} is inactive.

Here we have shown that the Q_{UW} receptor is capable of the nonmonotonic derivatives required by the `XOR` gate. This capability is necessary but not sufficient to perform the gate, as an ideal logic gate requires that the output be maximally high and low at the appropriate input values. Our numerical results, however, indeed confirm that the Q_{UW} receptor can perform the `XOR` gate.

SI. 3 Parameter sensitivity

In this section we discuss the sensitivity to parameter variation of the results at the six parameter sets φ_k shown in Fig. 3. Robustness against parameter fluctuations generally is considered an important quality of biochemical systems, due to stochastic nature of intra- and extracellular processes. If the observed logic gates only function within a very narrow parameter regime, this could lead to unreliable functioning.

Parameters are varied according to

$$\varphi^z_{\mathrm{new}} = \varphi^z_{\mathrm{old}} \left(1 + n^z\right) \tag{SI-15}$$

where n^z is the zth component of a uniformly distributed random vector $\mathbf{n}$ with norm $|\mathbf{n}| = \eta$. Under this implementation, η sets the average (root mean square) factor by which each parameter changes via $\langle \delta\varphi^z/\varphi^z \rangle = \eta/\sqrt{Z}$, where Z is the number of parameters. We sample 10^6 different vectors $\mathbf{n}$.

Sensitivity is measured by computing the fraction of new parameter sets for which, for each individual gate m, the relative change in fitness is less than a factor λ:

$$\frac{\left|F^{\mathrm{new}}_m - F^{\mathrm{old}}_m\right|}{F^{\mathrm{old}}_m} < \lambda \quad \forall\, m. \tag{SI-16}$$

Figure SI-1 reveals that for all φ_k, most random perturbations in which each parameter changes by an average of $\langle \delta\varphi^z/\varphi^z \rangle \sim 20\%$ change the fitness of none of the three logic gates by more than $\lambda = 10\%$.

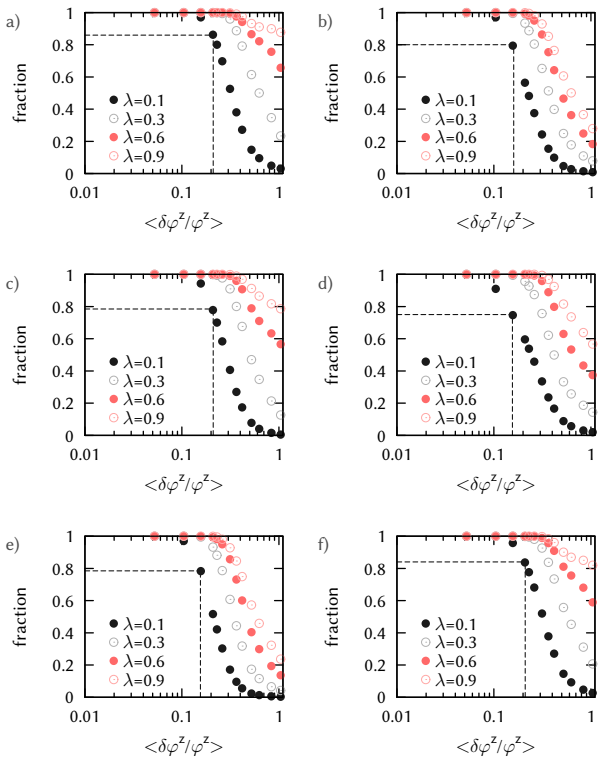

Figure SI-1: Robustness to parameter variation for the six parameter sets at which dimers can form three unique logic gates (Fig. 3): (a) φ_1, (b) φ_2, (c) φ_3, (d) φ_4, (e) φ_5, and (f) φ_6. An increase in $\langle \delta\varphi^z/\varphi^z \rangle$ reflects a larger range of parameter fluctuations and an increase in λ reflects a loosening of the robustness constraint. The dashed black lines indicate that a significant fraction of random perturbations in which each parameter changes by an average of $\langle \delta\varphi^z/\varphi^z \rangle \sim 20\%$ change the fitness of none of the three logic gates by more than $\lambda = 10\%$.

SI. 4 Further intuition behind functions accessible by recombination

In the main text, we provide the intuition behind how the first two groups of logic gates in Fig. 3 are performed by the corresponding receptors. Here, we provide similar intuition for the last four groups. Then, we argue why the six groups observed in Fig. 3 (and their counterparts obtained upon ligand exchange) are the *only* groups of three unique logic gates that one expects to observe under this model.

Parameter sets not discussed in the main text

Parameter set φ_3 (Fig. 3, third row) is similar to set φ_2 (see discussion of φ_2 in main text). In particular, receptor Q_{UW} performs the `XOR` gate in the same way. The difference between φ_3 and φ_2 is that ligand-bound V promotes activation instead of suppressing activation. Since ligand-bound W also promotes activation, this feature allows receptor Q_{WV} to perform the `OR` gate. However,

ligand-bound U suppresses activation more strongly than ligand-bound V promotes activation. This feature allows receptor Q_{UV} to perform the $\texttt{ANDN}_{S_1}$ gate, since only in the presence of ligand 2 and not 1 will activation be promoted via V and not suppressed via U.

Parameter set φ_4 (Fig. 3, fourth row) corresponds to a case where ligand-bound U and ligand-bound V both promote activation. This feature is sufficient for receptor Q_{UV} to perform the `OR` gate. Furthermore, ligand 2 binds more strongly to V than to W, and ligand-bound W suppresses activation more strongly than ligand-bound V promotes activation. These features allow receptor Q_{WV} to perform the $\texttt{ANDN}_{S_1}$ gate, since only in the presence of ligand 2 and not 1 will activation be promoted via V and not suppressed via W. Finally, (i) ligand 1 binds more strongly to W than to U, (ii) ligand 2 binds more strongly to W than ligand 1 does, and (iii) ligand-bound U promotes activation more strongly than ligand-bound W suppresses activation. These three features allow receptor Q_{UW} to perform the `AND` gate: when ligand 1 is present alone, feature (i) results in suppression via W; when ligand 2 is present alone, it only binds to W, resulting in suppression; and when both ligands are present, features (ii) and (iii) cause ligand 2 to bind to W, forcing ligand 1 to bind to U and thus activating the receptor.

Parameter set φ_5 (Fig. 3, fifth row) is once again similar to set φ_2. In particular, receptors Q_{WW} and Q_{UW} perform the `OR` gate and the `XOR` gate in the same way, respectively. Additionally, ligand 1 suppresses activation via U more strongly than ligand 2 promotes activation via V. This feature allows receptor Q_{UV} to perform the $\texttt{ANDN}_{S_1}$ gate, since only in the presence of ligand 2 and not 1 will the receptor be active.

Parameter set φ_6 (Fig. 3, sixth row) is similar to set φ_1 (see discussion of φ_1 in main text). In particular, receptors Q_{WW} and Q_{UW} perform the `AND` gate and the `OR` gate in the same way, respectively. Additionally, ligand 2 suppresses activation via V more strongly than ligand 1 promotes activation via U. This feature allows receptor Q_{UV} to perform the $\texttt{ANDN}_{S_2}$ gate, since only in the presence of ligand 1 and not 2 will the receptor be active.

Figure 3 is exhaustive

Here, we argue why the groups observed in Fig. 3 (and their counterparts obtained upon ligand exchange) are the only groups of three unique logic gates that one expects to observe under this model. The overall logic is presented first, with the arguments subsequently given in subsections.

There are 4 ways to choose a group of three from the four functional dimers Q_{WW}, Q_{UW}, Q_{WV}, and Q_{UV} to perform the three unique logic gates: $\{Q_{\mathrm{WW}}, Q_{\mathrm{UW}}, Q_{\mathrm{WV}}\}$, $\{Q_{\mathrm{UW}}, Q_{\mathrm{WV}}, Q_{\mathrm{UV}}\}$, $\{Q_{\mathrm{WW}}, Q_{\mathrm{UW}}, Q_{\mathrm{UV}}\}$, and $\{Q_{\mathrm{WW}}, Q_{\mathrm{WV}}, Q_{\mathrm{UV}}\}$. The last two groups are symmetric upon ligand exchange; we therefore consider only the first three groups.

The first group is $\{Q_{\mathrm{WW}}, Q_{\mathrm{UW}}, Q_{\mathrm{WV}}\}$. As shown in the main text, receptor Q_{WW} is capable of performing an `AND` gate, an `OR` gate, or an `ANDN` gate, but not an `XOR` gate (Fig. 2). If receptor Q_{WW} performs an `AND` gate, receptor Q_{UW} can perform an `ANDN` gate or an `OR` gate, but not an `XOR` gate (Argument 1). Receptor Q_{WV} then performs the `OR` gate or the `ANDN` gate, respectively (it also cannot perform an `XOR` gate by the same argument). These two possibilities are represented by parameter set φ_1 (Fig. 3) and its counterpart upon ligand exchange. If receptor Q_{WW} performs an `OR` gate, receptor Q_{UW} can perform an `ANDN` gate or an `XOR` gate, but not an `AND` gate (Argument 2). Receptor Q_{WV} then performs the `XOR` gate or the `ANDN` gate, respectively (it also cannot perform an `AND` gate by the same argument). These two possibilities are represented by parameter set φ_2 (Fig. 3) and its counterpart upon ligand exchange. If receptor Q_{WW} performs an `ANDN` gate, three

unique gates cannot be performed (Argument 3). Therefore, this group is exhaustively represented by φ_1 and φ_2.

The second group is $\{Q_{\mathrm{UW}}, Q_{\mathrm{WV}}, Q_{\mathrm{UV}}\}$. As shown in the main text, receptor Q_{UV} is capable of performing an `ANDN` gate, an `OR` gate, or an `AND` gate, but not an `XOR` gate (Fig. 2). If receptor Q_{UV} performs an `ANDN` gate, receptor Q_{UW} can perform an `XOR` gate or an `OR` gate, but not an `AND` gate (Argument 4). Receptor Q_{WV} then performs the `OR` gate or the `XOR` gate, respectively (it also cannot perform an `AND` gate by the same argument). These two possibilities are represented by parameter set φ_3 (Fig. 3) and its counterpart upon ligand exchange. If receptor Q_{UV} performs an `OR` gate, receptor Q_{UW} can perform an `AND` gate or an `ANDN` gate, but not an `XOR` gate (Argument 5). Receptor Q_{WV} then performs the `ANDN` gate or the `AND` gate, respectively (it also cannot perform an `XOR` gate by the same argument). These two possibilities are represented by parameter set φ_4 (Fig. 3) and its counterpart upon ligand exchange. If receptor Q_{UV} performs an `AND` gate, three unique gates cannot be performed (Argument 6). Therefore, this group is exhaustively represented by φ_3 and φ_4.

The third group is $\{Q_{\mathrm{WW}}, Q_{\mathrm{UW}}, Q_{\mathrm{UV}}\}$. We note that this group is different from the first two groups, since it does not contain the two receptors Q_{UW} and Q_{UV} which are symmetric upon ligand exchange. As shown in the main text, receptor Q_{WW} is capable of performing an `AND` gate, an `OR` gate, or an `ANDN` gate, but not an `XOR` gate (Fig. 2). If receptor Q_{WW} performs an `AND` gate, receptor Q_{UW} can perform an `ANDN` gate or an `OR` gate, but not an `XOR` gate (Argument 1). If receptor Q_{UW} performs an `ANDN` gate, receptor Q_{UV} cannot perform an `OR` gate (Argument 7); since receptor Q_{UV} also cannot perform an `XOR` gate (Fig. 2), three unique gates cannot be performed. Therefore, receptor Q_{UW} must perform an `OR` gate, leaving receptor Q_{UV} to perform an `ANDN` gate. This possibility is represented by parameter set φ_6 (Fig. 3). If receptor Q_{WW} performs an `OR` gate, receptor Q_{UW} can perform an `ANDN` gate or an `XOR` gate, but not an `AND` gate (Argument 2). If receptor Q_{UW} performs as an `ANDN` gate, receptor Q_{UV} cannot perform an `AND` gate (Argument 8); since receptor Q_{UV} also cannot perform an `XOR` gate, three unique gates cannot be performed. Therefore, receptor Q_{UW} must perform an `XOR` gate, leaving receptor Q_{UV} to perform an `ANDN` gate. This possibility is represented by parameter set φ_6 (Fig. 3). If receptor Q_{WW} performs as an `ANDN` gate, three unique gates can not be performed (Argument 9). Therefore, this group is exhaustively represented by φ_5 and φ_6.

This completes the logic arguing that the groups observed in Fig. 3 are exhaustive.

Argument 1

If receptor Q_{WW} performs an `AND` gate, ligand 2 alone does not promote activation when binding to monomer W. Therefore, because ligand 2 does not bind to monomer U, the receptor Q_{UW} is always inactive if ligand 2 is present alone. This behavior is inconsistent with the logic of the `XOR` gate.

Argument 2

If receptor Q_{WW} performs an `OR` gate, ligand 2 alone promotes activation when binding to monomer W. Therefore, because ligand 2 does not bind to monomer U, the receptor Q_{UW} is always active if ligand 2 is present alone. This behavior is inconsistent with the logic of the `AND` gate.

Argument 3

If receptor Q_{WW} performs an `ANDN` gate, receptors Q_{UW} and Q_{WV} can each perform neither an `XOR` gate nor an `AND` gate, thereby preventing the group $\{Q_{\mathrm{WW}}, Q_{\mathrm{UW}}, Q_{\mathrm{WV}}\}$ from performing three unique gates. The reason is straightforward: if receptor Q_{WW} performs an `ANDN` gate, one ligand must suppress activation via W while the other ligand promotes activation via W. This feature immediately excludes the `XOR` gate since, as described in the main text, an `XOR` gate requires both ligands to promote activation via W. This feature also excludes an `AND` gate since, as also described in the main text, an `AND` gate requires either that activation via W is promoted only weakly or that both ligands suppress activation via W. In the first case, activation of receptor Q_{UW} (or Q_{WV}) is only achieved cooperatively when both ligands are present. In the second case, activation is achieved with both ligands present via U (or V) due to an interference effect similar to that underlying the `XOR` gate (see discussion of parameter set φ_4 above).

Argument 4

If receptor Q_{UV} performs an $\texttt{ANDN}_{S_1}$ gate, Q_{UW} cannot function as an `AND` gate. To function as an `AND` gate (see Eq. 9), this requires that $\omega_0 K_{1,U}^A K_2^A \ll K_{1,U}^I K_2^I$, while $\omega_0 K_{1,U}^A \gg K_{1,U}^I$ and $\omega_0 K_2^A \gg K_2^I$. This conditions cannot be satisfied simultaneously.

Argument 5

If receptor Q_{UV} performs an `OR` gate, ligand 1 activates the receptor via U. However, for receptor Q_{UW} to perform the `XOR` gate, ligand 1 must suppress activation via U, as described in the main text.

Argument 6

If Q_{UV} functions as an `AND` gate U is activated by S_1 and V is activated by S_2, but both activation biases alone are insufficient to activate the receptor. This excludes the formation of a `XOR` gate for either the Q_{UW} or Q_{WV}. As we have discussed in the previous section, the `XOR` gate is obtained by the deactivation of U (V) by ligand S_1 (S_2). However, it is possible that Q_{UW} is a `OR` gate, while Q_{WV} is a `ANDN` gate. The Q_{UW}-`OR` gate requires that W is activated by S_2 and S_1, since monomer U is not active in the presence of S_1. The Q_{WV}-`ANDN` gate requires that W is strongly deactivated by S_1. These two conditions on W are mutually exclusive.

Argument 7

If receptors Q_{WW} and Q_{UW} perform an `AND` gate and an `ANDN` gate, respectively, the `ANDN` gate must be $\texttt{ANDN}_{S_1}$, not $\texttt{ANDN}_{S_2}$. The reason is that the `AND` gate requires ligand 2 to promote activation via W, while the $\texttt{ANDN}_{S_2}$ gate requires ligand 2 to suppress activation via W. Then, if Q_{UW} indeed performs the $\texttt{ANDN}_{S_1}$ gate, receptor Q_{UV} cannot perform an `OR` gate. The reason is that the `AND` and $\texttt{ANDN}_{S_1}$ gates require ligand 1 to suppress activation via U and not via W, while the `OR` gate requires ligand 1 to promote activation via U.

Argument 8

If receptors Q_{WW} and Q_{UW} perform an `OR` gate and an `ANDN` gate, respectively, the `ANDN` gate must be $\texttt{ANDN}_{S_1}$, not $\texttt{ANDN}_{S_2}$. The reason is that the `OR` gate requires ligand 2 to promote activation via W, while the $\texttt{ANDN}_{S_2}$ gate requires ligand 2 to suppress activation via W. Then, if Q_{UW} indeed performs the $\texttt{ANDN}_{S_1}$ gate, receptor Q_{UV} cannot perform an `AND` gate. The reason is that the `OR` and $\texttt{ANDN}_{S_1}$ gates require ligand 1 to suppress activation via U and not via W, while the `AND` gate requires ligand 1 to promote activation via U.

Argument 9

If receptor Q_{WW} performs an `ANDN` gate, receptor Q_{UW} cannot perform a `XOR` gate gate, since this requires that both ligands activate W. If receptor Q_{WW} performs an $\texttt{ANDN}_{S_1}$ gate, receptor Q_{UW} cannot perform an `AND` gate, since Q_{UW} is active if only ligand 2 is present. If receptor Q_{WW} performs an $\texttt{ANDN}_{S_1}$ gate, receptor Q_{UW} can perform an `OR` gate if ligand 1 activates U more strongly than it deactivates W. However, receptor Q_{UV} is then always active if ligand 1 is present, and this is inconsistent with the logic of the `AND` gate. If receptor Q_{WW} performs an $\texttt{ANDN}_{S_2}$ gate, receptor Q_{UW} cannot perform an `AND` gate, since Q_{UW} is active if only ligand 1 is present (ligand 1 activates U) or Q_{UW} is never active (ligand 1 deactivates U more strongly than it activates W). If receptor Q_{WW} performs an $\texttt{ANDN}_{S_2}$ gate, receptor Q_{UW} can perform an `OR` gate, if (i) ligand 1 activates U and (ii) in the presence of small ligand 1 and an abundance of ligand 2 the receptor Q_{UW} is active. However, receptor Q_{UV} is then always active if ligand 1 is present and this is inconsistent with the logic of the `AND` gate.

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