

Supporting Information

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SI Materials

Analysis of the Sensitivity and Error Functions. We now define the sensitivity function $S(c, \varepsilon_0)$, which summarizes the steepness of the slope of the activity curve as a function of c and ε_0 ,

$$S(c, \varepsilon_0) \triangleq N \frac{e^{-\varepsilon_0 \left(\frac{c}{K_A}\right)^N}}{\left(1 + e^{-\varepsilon_0 \left(\frac{c}{K_A}\right)^N}\right)^2}. \quad [\text{S1}]$$

Looking at the dynamics of activity with respect to ligand changing in time, we get the equation

$$\frac{da}{dt} = \frac{\partial a}{\partial c} \frac{dc}{dt} \approx S(c, \varepsilon_0) \frac{K_A}{c} \frac{d}{dt} \left(\frac{c}{K_A}\right) = S(c, \varepsilon_0) \frac{d}{dt} \left(\ln \frac{c}{K_A}\right). \quad [\text{S2}]$$

Here, we see the first requirements for a protein to give rise to logarithmic sensing: the rate of change of activity is naturally a function of the logarithm of the ligand concentration c . Eq. 5 is complicated by the sensitivity function $S(c, \varepsilon_0)$, which varies with c and is therefore not a simple proportional factor. An ideal logarithmic sensor requires that the activity function depends strictly on $\ln c$, as illustrated by the blue dashed line in Fig. 2B. To measure how well an MWC protein can act as a logarithmic sensor, let us quantify the extent to which $S(c, \varepsilon_0)$ varies as a function of c .

First, we note that an ideal logarithmic sensor coincides exactly with an MWC protein at the midpoint of the activity curve ($a = 1/2$, at the inflection point of a). This point also corresponds to the maximum of the sensitivity function $S_{\max} = \frac{N}{4}$ in Eq. 4 (i.e., the peak in Fig. 2C). Any variation in ligand which pushes activity away from the midpoint will lower the sensitivity and will do so in a nonlinear way. Our first task here is to define a regime of the sensitivity curve (the gray region in Fig. 2B–D) where the MWC protein can approximate a logarithmic sensor, and compute the corresponding error.

To parametrize variation from S_{\max} , we define the effective ligand concentration to be

$$\mathcal{L}(c, \varepsilon_0) = e^{-\varepsilon_0 \left(\frac{c}{K_A}\right)^N}. \quad [\text{S3}]$$

Deriving Eq. 4 in terms of \mathcal{L} , we obtain a natural representation of the sensitivity function,

$$S(\mathcal{L}) = \frac{da}{d\mathcal{L}} = \frac{\mathcal{L}}{(1 + \mathcal{L})^2}. \quad [\text{S4}]$$

In this representation, the sensitivity is now maximized at $\mathcal{L} = 1$. Next, we derive a lower limit on the sensitivity function. Let us define the parameter τ , such that for distance $\tau > 1$ from the midpoint of the activity curve, we have a minimum sensitivity,

$$S_{\min}(\tau) = \frac{\tau}{(1 + \tau)^2}. \quad [\text{S5}]$$

With these lower and upper limits on sensitivity, we now define the regime in the response curve over which the MWC protein approximates a logarithmic sensor as

$$S_{\min} < S(\mathcal{L}) < S_{\max}. \quad [\text{S6}]$$

Using Eq. S3, we can derive a corresponding lower limit on for the range of \mathcal{L} over which the bound holds, $\frac{1}{\tau} < \mathcal{L} < \tau$. These

limits give the ligand concentration range over which an MWC protein behaves as a logarithmic sensor,

$$\frac{\varepsilon_0 - \ln(\tau)}{N} < \ln\left(\frac{c}{K_A}\right) < \frac{\varepsilon_0 + \ln(\tau)}{N}. \quad [\text{S7}]$$

This range is shown in Fig. 2B and C, where the sensitivity regimes for different values of ε_0 are shaded in gray. We see that the range of ligand over which the MWC systems functions as a logarithmic sensor is set by a threshold for sensitivity S_{\min} . The error between the MWC activity curve and the idealized sensor is parametrized by τ . The range over which the MWC protein behaves as a logarithmic sensor depends on how much error the system can tolerate.

To derive the error, we first write the formal expression for an ideal logarithmic sensor,

$$a^*(\mathcal{L}) = \frac{1}{4} \ln \mathcal{L} + \frac{1}{2}. \quad [\text{S8}]$$

We will now use this expression to define an error function $r = 1 - \frac{a}{a^*}$ to quantify the deviation of the actual activity function a from the idealized one a^* . Combining Eq. 3 and Eq. S8, we have

$$r(\mathcal{L}) = 1 - \frac{a(\mathcal{L})}{a^*(\mathcal{L})} = 1 - \frac{2\mathcal{L}}{(1 + \mathcal{L})\left(1 + \frac{1}{2} \ln \mathcal{L}\right)}. \quad [\text{S9}]$$

At the midpoint of activity ($\mathcal{L} = 1$) the error function is minimized at $r(1) = 0$, because this is the point where MWC activity coincides exactly with the ideal logarithmic sensor. We observe that the error $r(\mathcal{L})$ increases as \mathcal{L} moves away from 1. Consequently, the error at the threshold τ , $r(\tau)$, corresponds to the worst case error in the sensitive regime. For example in Fig. 2E, where we set $\tau = 6$, we have $r(\tau) \approx 0.1$, so the MWC response differs by at most $\sim 10\%$ from the ideal logarithmic response in the sensitive regime. The threshold τ serves as a way to analyze how much the response of an MWC protein differs from an ideal logarithmic sensor as we expand the range of ligand concentration over which it is used. The maximum error $r(\tau)$ increases at an asymptotic rate of

$$\lim_{\tau \gg 1} r(\tau) = 1 - \frac{4}{\ln \tau}.$$

This limit shows that the error increases slowly with τ and that the MWC protein can approximate well an ideal logarithmic sensor over a wide range of the activity curve.

With the error function, we can now define the logarithmic regime of an MWC protein, as the ratio of the maximum and minimum ligand concentrations in the sensitive regime

$$c_S(\tau) = \frac{c_{\max}}{c_{\min}} = \frac{e^{\frac{\varepsilon_0 + \ln(\tau)}{N}}}{e^{\frac{\varepsilon_0 - \ln(\tau)}{N}}} = e^{\frac{2}{N} \ln(\tau)} = \tau^{\frac{2}{N}}. \quad [\text{S10}]$$

If we tolerate, for example, 10% error from the ideal logarithmic sensor (corresponding to $\tau \approx 6$), then an MWC protein with cooperativity $N = 4$ (as is the case, for example, with hemoglobin and PFK1), we have $c_S(\tau) = \sqrt{\tau} \approx 2.45$, so the protein can act as a logarithmic sensor over a 2.45 range of fold change in signal. If, for example, the protein of interest were a monomer (i.e., $N = 1$) that lacks cooperativity, we would have $c_S(\tau) = \tau^2 = 36$, so the

protein can act as a logarithmic sensor over a 36-fold range of signal. We see from these results that an MWC protein can approximate an ideal logarithmic sensor over a substantial range of ligand concentration. Reducing cooperativity effectively increases the regime over which an MWC protein responds logarithmically to ligand. Eq. S10 tells us that there is an intrinsic trade-off between sensitivity and signaling range. Because N corresponds to cooperativity and c_s corresponds to the width of the sensitivity regime, we see directly that increasing N for a given τ narrows the range over which the sensor can function.

Effects of the Allosteric Constant on the Sensitivity Function. We first analyze the effects of ε_0 on $S(c, \varepsilon_0)$ when c is in the range $K_A \ll c \ll K_I$ and then analyze the general case where c could be near saturation. In the former case, as we derive in the main text,

$$S(c, \varepsilon_0) \triangleq N \frac{e^{-\varepsilon_0 \left(\frac{c}{K_A}\right)^N}}{\left(1 + e^{-\varepsilon_0 \left(\frac{c}{K_A}\right)^N}\right)^2}.$$

Fig. S1 shows that $S(c, \varepsilon_0)$ shifts logarithmically as ε_0 is varied, in the same way as the activity curve $a(c, \varepsilon_0)$ does.

Next, we analyze the general case for all values of ligand concentration c . The general sensitivity function $S(c, \varepsilon_0)$ is defined in terms of the expression,

$$\frac{\partial a}{\partial t} = S(c, \varepsilon_0) \frac{d \log c}{dt}. \quad [\text{S11}]$$

For an MWC protein, we have from Eq. 2 that

$$\begin{aligned} \frac{\partial a}{\partial t} &= Na(1-a) \frac{K_A^{-1} - K_I^{-1}}{(1+c/K_A)(1+c/K_I)} \frac{dc}{dt} \\ &= Nca(1-a) \frac{K_A^{-1} - K_I^{-1}}{(1+c/K_A)(1+c/K_I)} \frac{d \log c}{dt} \end{aligned} \quad [\text{S12}]$$

$$\Rightarrow S(c, \varepsilon_0) = Nca(1-a) \frac{K_A^{-1} - K_I^{-1}}{(1+c/K_A)(1+c/K_I)} \quad [\text{S13}]$$

Next, assuming that $K_A \ll K_I$, we can rewrite the sensitivity function as

$$S(c, \varepsilon_0) = Na(1-a) \frac{c/K_A}{(1+c/K_A)(1+c/K_I)}. \quad [\text{S14}]$$

We see that, in the limit $K_A \ll c \ll K_I$ (i.e., $\frac{c}{K_A} \gg 1, \frac{c}{K_I} \ll 1$), Eq. S14 reduces to the sensitivity function we derive in the main text,

$$S(c, \varepsilon_0) = Na(1-a) = N \frac{e^{-\varepsilon_0 \left(\frac{c}{K_A}\right)^N}}{\left(1 + e^{-\varepsilon_0 \left(\frac{c}{K_A}\right)^N}\right)^2}.$$

Logarithmic tuning fails for very high or low values of ε_0 , when c is near saturation. To see why logarithmic tuning fails, we derive the limit of $S(c, \varepsilon_0)$ as $c \approx K_A$, corresponding to the ligand concentration being near the lower saturation limit. We can make the simplification $\frac{c}{K_I} \ll 1$, which yields

$$S_{lower}(c, \varepsilon_0) = Na(1-a) \frac{c/K_A}{1+c/K_A}. \quad [\text{S15}]$$

Fig. S2B shows the full sensitivity function (Eq. S14) as a solid black line and the approximation in Eq. S15 as a blue dotted line.

We see that, as c/K_A approaches 1, $S(c, \varepsilon_0)$ is scaled down by a factor of $\frac{c/K_A}{1+c/K_A}$ (shown as a dotted black line). This effect will become noticeable when ε_0 is small enough to push the center of the sensitivity function close to K_A .

At the upper limit, as $c \approx K_I$, which give the simplification $\frac{c}{K_A} \gg 1$, we can derive

$$S_{upper}(c, \varepsilon_0) = Na(1-a) \frac{1}{1+c/K_I}. \quad [\text{S16}]$$

Fig. S2C shows the Eq. S16 in red. As c approaches K_I , $S(c, \varepsilon_0)$ scales down by a factor of $\frac{1}{1+c/K_I}$. This effect will become noticeable when ε_0 is large enough to push the center of the sensitivity function close to K_I .

This analysis shows how c and ε_0 combine to determine the shape of the full sensitivity function and how logarithmic sensing breaks down as ligand concentration nears saturation.

Allosteric Activators and Inhibitors in the MWC Model. In their original model (21), Monod et al. did not express their ‘‘allosteric constant’’ in the general form e^{ε_0} but rather proposed a more detailed model where the binding of allosteric activators and inhibitors are explicitly accounted for, in much the same way as the primary ligand. In terms of our notation, their model can be expressed in the form

$$a(c, c_a, c_i) = \frac{\left(1 + \frac{c}{K_A}\right)^N}{\left(1 + \frac{c}{K_A}\right)^N + L \left(1 + \frac{c}{K_I}\right)^N}, \quad [\text{S17}]$$

where $L = e^{\varepsilon_0} \frac{\left(1 + \frac{c_i}{K_I}\right)^{n_i}}{\left(1 + \frac{c_a}{K_a}\right)^{n_a}}$. This version of the model assumes that the activator and inhibitor have n_a and n_i binding sites with dissociation constants K_a and K_i , respectively. Rewriting the expression for L , we get

$$L = \exp\left(\varepsilon_0 + n_i \ln\left(1 + \frac{c_i}{K_I}\right) - n_a \ln\left(1 + \frac{c_a}{K_a}\right)\right). \quad [\text{S18}]$$

If the allosteric effectors are far from saturation, then from the Taylor expansion of $\ln(1+x)$, we have

$$L \approx \exp\left(\varepsilon_0 + n_i \frac{c_i}{K_i} - n_a \frac{c_a}{K_a}\right). \quad [\text{S19}]$$

This approximation gives a mechanism for the linear dependence of free energy on the concentrations of allosteric regulators. Shimizu et al. found just such a dependence in experiments on receptor methylation in the bacterial chemotaxis pathway (28).

Logarithmic Tuning in the KNF Model. Shortly after Monod, Wyman, and Changeux published their MWC model of allostery via conformational selection, Koshland et al. put forth what is now called the induced fit or KNF model of allostery to explain hemoglobin binding kinetics (24). This model proposes that instead of undergoing spontaneous conformational change, individual binding events in one subunit could directly change the binding kinetics of another. This model has the advantage that it can both encapsulate positive cooperativity (like the MWC model) and negative cooperativity, where a given binding even could potentially inhibit the next. In the years after both models of hemoglobin were published, structural work by Perutz gave evidence that the MWC model was indeed more accurate. In reference to the work of Monod

et al., Perutz wrote, “These words ring prophetically if we look at the mechanism in terms of quaternary structure” (51).

Be that as it may, the concept of induced fit proved useful for describing other classes of allosteric systems, in particular, those in which negative cooperativity plays an important role (52). Here, we show under what conditions the KNF model can be logarithmically tuned. The KNF model differs from other models of binding typically discussed because the specific geometry of the protein plays an important role, we will use as an example the tetrahedral geometry discussed in the original paper by Koshland et al. (24), which results in the saturation function

$$Y(c, K_{BB}) = \frac{K_{AB}^3 \frac{c}{K_D} + 3K_{AB}^4 K_{BB} \left(\frac{c}{K_D}\right)^2 + 3K_{AB}^3 K_{BB}^3 \left(\frac{c}{K_D}\right)^3 + K_{BB}^6 \left(\frac{c}{K_D}\right)^4}{1 + 4K_{AB}^3 \frac{c}{K_D} + 6K_{AB}^4 K_{BB} \left(\frac{c}{K_D}\right)^2 + 4K_{AB}^3 K_{BB}^3 \left(\frac{c}{K_D}\right)^3 + K_{BB}^6 \left(\frac{c}{K_D}\right)^4}, \quad [\text{S20}]$$

where K_D is the ligand dissociation constant, and the subunit conformations are denoted A and B . By convention, A will be the low affinity inactive state and B will be the high-affinity active state. The interaction strengths K_{AB} and K_{BB} represent the relative strengths of interactions between the A and B conformations and the B conformation with itself, respectively. Here, we allow allosteric effects to enter through K_{BB} . The motivation for this assumption is the underlying model that the allosteric effectors alter the stability of the bonds between the active conformation.

The authors use $K_{AA} = 1$ as a reference interaction strength against which to measure the other two, so it does not have to be explicitly accounted for in Eq. S20. In this model, high cooperativity comes from high stability of the active state B (i.e., $K_{BB} \gg 1$ and $K_{AB} \approx K_{AA} = 1$). Under these conditions, the intermediate terms in the KNF model drop out the saturation function and we have the simplified expression

$$Y(c, K_{BB}) \approx \frac{K_{BB}^6 \left(\frac{c}{K_D}\right)^4}{1 + K_{BB}^6 \left(\frac{c}{K_D}\right)^4} = \frac{e^{\varepsilon_0} \left(\frac{c}{K_D}\right)^4}{1 + e^{\varepsilon_0} \left(\frac{c}{K_D}\right)^4}, \quad [\text{S21}]$$

where $\varepsilon_0 = 6 \ln(K_{BB})$. Here, we see that, in the limits of strong cooperativity, the KNF model satisfies the logarithmic tuning requirement in relationship 9. This observation is consistent with the data originally fitted by Koshland et al. (24), where they use $K_{AA} = K_{AB} = 1$ and, for the tetrahedral case, find $K_{BB} \in [1.8, 6.8]$. Even for the lower end of this range, we have $K_{BB}^6 \approx 34$, which is much greater than the next largest coefficient in Eq. S20, $K_{AB}^3 K_{BB}^3 \approx 5.8$.

Detailed Analysis of the GPCR Model. Here, we present a more detailed derivation of the activation function derived in Eq. 8. We begin again from the system of differential equations for GPCR activation:

$$\begin{aligned} \dot{R} &= k_1 c (1 - R) - k_2 R \\ \dot{T}_{GDP} &= k_3 \alpha_{GDP} - k_4 T_{GDP} R \\ \dot{T}_{GTP} &= k_4 T_{GDP} R - k_5 T_{GTP} \\ \dot{\alpha}_{GTP} &= k_5 T_{GTP} - k_6 \alpha_{GTP} \\ \dot{\alpha}_{GDP} &= k_6 \alpha_{GTP} - k_3 \alpha_{GDP}. \end{aligned}$$

From this system of equations, we will solve for $\hat{\alpha}_{GTP}$, the relative level α_{GTP} compared with the total level of G protein $T_{tot} = T_{GDP} + T_{GTP} + \alpha_{GDP} + \alpha_{GTP}$. Just by setting derivatives equal to zero, we get

$$\begin{aligned} \hat{\alpha}_{GTP} &= \frac{\alpha_{GTP}}{T_{tot}} = \frac{\alpha_{GTP}}{T_{GDP} + T_{GTP} + \alpha_{GDP} + \alpha_{GTP}} \\ &= \frac{\frac{k_5}{k_6} T_{GTP}}{T_{GDP} + T_{GTP} + \alpha_{GDP} + \frac{k_5}{k_6} T_{GTP}} \\ &= \frac{\frac{k_4}{k_6} T_{GDP} R}{T_{GDP} + \frac{k_4}{k_5} T_{GDP} R + \alpha_{GDP} + \frac{k_4}{k_6} T_{GDP} R} \\ &= \frac{\frac{k_4}{k_6} R}{1 + \frac{k_4}{k_5} R + \frac{k_4}{k_3} R + \frac{k_4}{k_6} R} \\ &= \frac{R}{\frac{k_6}{k_4} + R \left(\frac{k_6}{k_5} + \frac{k_6}{k_3} + 1 \right)}. \end{aligned}$$

We then use the fact steady-state relationship

$$R = \frac{c}{\frac{k_2}{k_1} + c}$$

to find

$$\begin{aligned} \hat{\alpha}_{GTP} &= \frac{\frac{c}{\frac{k_2}{k_1} + c}}{\frac{k_6}{k_4} + \frac{c}{\frac{k_2}{k_1} + c} \left(\frac{k_6}{k_5} + \frac{k_6}{k_3} + 1 \right)} \\ &= \frac{c}{\frac{k_6}{k_4} \left(\frac{k_2}{k_1} + c \right) + c \left(\frac{k_6}{k_5} + \frac{k_6}{k_3} + 1 \right)} \\ &= \frac{c}{\left(1 + \frac{k_6}{k_3} + \frac{k_6}{k_4} + \frac{k_6}{k_5} \right) c + \frac{k_6}{k_4} \frac{k_2}{k_1}}, \end{aligned}$$

just as in Eq. 8. Because $\frac{k_2}{k_1}$ is effectively a K_D for the receptors, it is taken as a fixed quantity. On the other hand, β -arrestin signaling alters the rate (k_4) at which T_{GDP} binds to active receptors. To this end, we will rewrite Eq. 8 to see whether it can be made to look like the form described in relationship 9, with the definition $K_D = \frac{k_2}{k_1}$,

$$\hat{\alpha}_{GTP} = \frac{c}{\left(1 + \frac{k_6}{k_3} + \frac{k_6}{k_4} + \frac{k_6}{k_5} \right) c + \frac{k_6}{k_4} \frac{k_2}{k_1}} = \frac{\frac{k_4}{k_6} \frac{c}{K_D}}{1 + \left(1 + \frac{k_6}{k_3} + \frac{k_6}{k_4} + \frac{k_6}{k_5} \right) \frac{k_4}{k_6} \frac{c}{K_D}}. \quad [\text{S22}]$$

Here, we see that, if we allow $\frac{k_4}{k_6}$ to play the role that e^{ε_0} plays in the MWC model, with variations in β -arrestin signaling effectively shifting the free energy ε , then the GPCR model almost fits the logarithmic tuning requirement in relationship 9. The confounding element is the factor of $\left(1 + \frac{k_6}{k_3} + \frac{k_6}{k_4} + \frac{k_6}{k_5} \right)$ that depends on k_4 and thus could potentially complicate things. Rearranging this term, we get

$$\left(1 + \frac{k_6}{k_3} + \frac{k_6}{k_4} + \frac{k_6}{k_5} \right) = \left(1 + k_6 \left(\frac{1}{k_3} + \frac{1}{k_4} + \frac{1}{k_5} \right) \right).$$

From this equation, we see that there dependence on k_4 will vanish so long as either $\frac{1}{k_4} \ll \frac{1}{k_3} + \frac{1}{k_5}$ or $k_6 \ll k_4$, and consequently under these conditions the system will behave as a logarithmic sensor. In terms of the biochemistry of the GPCR pathway, this means that β -arrestin binding is far from saturation so that T_{GDP} is always able to find active receptors, be it at an attenuated rate.

Fold-Change Detection Arises from Logarithmic Sensing and Negative Feedback. We present here simulations showing fold-change detection arising from a circuit containing allosteric regulation and negative feedback. We use as specific examples the Tar/Tsr receptor system (discussed in *Results*) and the GPCR system.

Tar/Tsr Receptor and Negative Feedback. We model the allosteric regulation of the receptor using the MWC model and the negative feedback as described in Shimizu et al. (28) and Pontius et al. (38). The negative feedback via methylation acts on a slower time scale than receptor activation, such that $a(c, \varepsilon_0)$ instantaneously responds to changes in ligand and allosteric effector concentrations. Furthermore, ε_0 and a are related by a linear feedback coupling, such that

$$a(c, \varepsilon_0) = \frac{\left(1 + \frac{c}{K_A}\right)^N}{\left(1 + \frac{c}{K_A}\right)^N + e^{\varepsilon_0} \left(1 + \frac{c}{K_I}\right)^N} \quad [\text{S23}]$$

$$\dot{\varepsilon}_0 = m(a - a_0),$$

where a_0 is the basal activation level to which the system adapts and m is a constant corresponding to the rate of adaptation. When $\varepsilon_0 = 0$, we have $a = a_0$, and the system will show precise adaptation, as expected. Fig. S4 shows the change in Tar/Tsr receptor activity (blue) in response to sequential threefold step increases in ligand concentration (orange). The system gives

identical responses for all three steps, performing fold-change detection.

GPCR and Negative Feedback. The dynamics of the GPCR system are described in the main text (Eq. 8). As described in the main text, allosteric regulation is implemented through k_4 , which characterizes the rate of receptor phosphorylation and β -arrestin binding. Although we could express feedback in terms of k_4 directly, we may run into problems because k_4 is a reaction rate and therefore must be nonnegative. To avoid running into negative values, we rewrite $k_4 = \beta e^{\varepsilon_0}$, for some constant β . The differential equations describing the GPCR system are now

$$\begin{aligned} \dot{R} &= k_1 c(1 - R) - k_2 R \\ \dot{T}_{GDP} &= k_3 \alpha_{GDP} - \beta e^{\varepsilon_0} T_{GDP} R \\ \dot{T}_{GTP} &= \beta e^{\varepsilon_0} T_{GDP} R - k_5 T_{GTP} \\ \dot{\alpha}_{GTP} &= k_5 T_{GTP} - k_6 \alpha_{GTP} \\ \dot{\alpha}_{GDP} &= k_6 \alpha_{GTP} - k_3 \alpha_{GDP} \\ \dot{\varepsilon}_0 &= m(a_0 - \hat{\alpha}_{GTP}), \end{aligned} \quad [\text{S24}]$$

where $\hat{\alpha}_{GTP} = \frac{\alpha_{GTP}}{T_{tot}}$. Fig. S5 shows the response of the GPCR system to sequential threefold step increase in signal. We see again that a logarithmic sensor coupled with negative feedback yields fold-change detection.

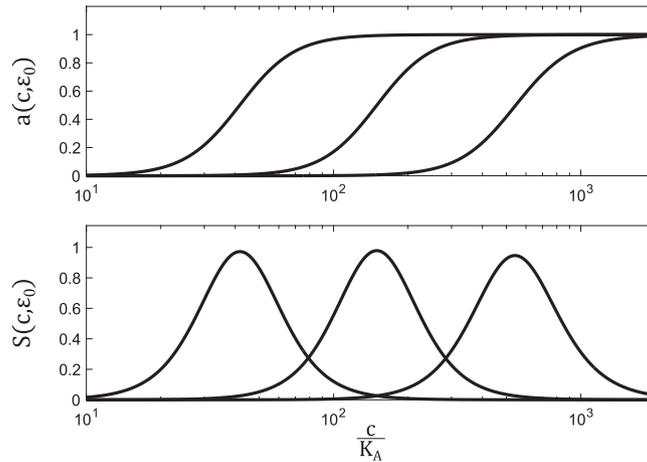


Fig. S1. Effects of ε_0 on the sensitivity function. (A) Activation curves for the MWC model in Eq. 1. The parameters used here are $K_A = 10^{-2}$, $K_I = 10^2$, $N = 4$, and $\varepsilon_0 \in [15, 25]$. (B) Sensitivity functions corresponding to the MWC activation curves in A.

