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Supporting Material

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1. Solution of the dual-transition-rates model

We consider the more general case where the relative diffusion constant of the receptor-ligand pair takes different values, D_a and D_i, while the receptor is in the active and inactive forms, respectively. The steady-state distribution functions satisfy the following reaction-diffusion equations

$$D_i\nabla^2\rho_i(r) - \omega_+\rho_i(r) + \omega_-\rho_a(r) = 0 \tag{1a}$$

$$D_a\nabla^2\rho_a(r) + \omega_+\rho_i(r) - \omega_-\rho_a(r) = 0 \tag{1b}$$

in the region $R < r < R_1$ and

$$D_i\nabla^2\rho_i(r) - \omega_{0+}\rho_i(r) + \omega_{0-}\rho_a(r) = 0 \tag{2a}$$

$$D_a\nabla^2\rho_a(r) + \omega_{0+}\rho_i(r) - \omega_{0-}\rho_a(r) = 0 \tag{2b}$$

in $r > R_1$. In the region $R < r < R_1$ the solution of Eq. (1) has the form

$$\rho_i(r) = A_1 D_a \exp(-\lambda r)/r + A_2 D_a \exp(\lambda r)/r + B_1\omega_-/r + B_2\omega_- \tag{3a}$$

$$\rho_a(r) = -A_1 D_i \exp(-\lambda r)/r - A_2 D_i \exp(\lambda r)/r + B_1\omega_+/r + B_2\omega_+ \tag{3b}$$

In the region $r > R_1$ the solution of Eq. (2) has the form

$$\rho_i(r) = AD_a \exp(-\lambda_0 r)/r + B_1\omega_{0-}/r + p_{0i} \tag{4a}$$

$$\rho_a(r) = -AD_i \exp(-\lambda_0 r)/r + B\omega_{0+}/r + p_{0a} \tag{4b}$$

which satisfies the boundary conditions $\rho_i(r) = 1 - p_{0a} \equiv p_{0i}$ and $\rho_a(r) = p_{0a}$ and at $r = \infty$. The two parameters in the exponential functions are

$$\lambda = [(\omega_+ D_a + \omega_- D_i)/D_a D_i]^{1/2} \tag{5a}$$

$$\lambda_0 = [(\omega_{0+} D_a + \omega_{0-} D_i)/D_a D_i]^{1/2} \tag{5b}$$

The six constants, A_1, A_2, B_1, B_2, A, and B, are determined by the continuity of $\rho_g(r)$ and $d\rho_g(r)/dr$, g = "i" and "a", at $r = R_1$ and the boundary conditions at $r = R$. For $\rho_i(r)$, the boundary $r = R$ is reflecting:

$$d\rho_i(r)/dr = 0 \text{ at } r = R \tag{6a}$$

On the other hand, the final complex can be formed from the active receptor when it is at the contact distance from the ligand. The complex formation is modeled by a partially reflecting boundary condition:

$$4\pi D_a R^2 d\rho_a(r)/dr = \kappa\rho_a(r) \equiv k_{on} \text{ at } r = R \tag{6b}$$

where κ is proportional to the rate at which the final complex is formed from the active receptor in the loosely bound state. The last identity of Eq. (6b) defines the binding rate constant. The final result is

$$\frac{k_{\rm on}}{\kappa} = \frac{(\alpha_+ + \alpha_-)p_{\rm a} - 2(p_{\rm a} - p_{0\rm a})(1+\lambda_0 R_{\rm l})D_{\rm i}\lambda / D_0\lambda_0}{\beta_+ + \beta_- - 2(p_{\rm a} - p_{0\rm a})\gamma\lambda R D_{\rm a} D_{\rm i} / D_0^{\,2}} \tag{7}$$

where

$$\alpha_\pm = (\lambda/\lambda_0 \pm 1)\exp(\pm\lambda\Delta)(1\pm\lambda R) \tag{8a}$$

$$\beta_\pm = (\lambda/\lambda_0 \pm 1)\exp(\pm\lambda\Delta)[(1\pm\lambda R+\gamma)D \pm p_{\rm a}\gamma\lambda R D_{\rm a}]/D_0 \tag{8b}$$

$$\gamma = \kappa / 4\pi D_{\rm a} R \tag{8c}$$

$$D_0 = p_{0\rm a} D_{\rm a} + p_{0\rm i} D_{\rm i} \tag{8d}$$

$$D = p_{\rm a} D_{\rm a} + p_{\rm i} D_{\rm i} \tag{8e}$$

In the last equation, $p_{\rm i} \equiv 1 - p_{\rm a}$. When both $D_{\rm a}$ and $D_{\rm i}$ are set to D, Eq. (7) reduces to Eq. (4) of the main text.

We note that $k_{\rm on0}$, the rate constant if the receptor stays in the active form, in the case considered here is given by

$$k_{\rm on0} = \frac{4\pi D_{\rm a} R\cdot\kappa}{4\pi D_{\rm a} R + \kappa} \tag{9}$$

2. Additional results for k_{on} when $D_a = D_i$

Some results for the binding rate constant when $D_{\rm i} = D_{\rm a}$ are displayed in Fig. 2 of the main text. These are calculated for a fixed equilibrium probability of the active form in the loosely bound state. They show that the operating range of the conformational-selection scenario expands as the active form becomes more favored in the unbound state. In Fig. S1, we display results for $k_{\rm on}$ at a fixed equilibrium probability of the active form in the unbound state. Now we find that the operating range of the induced-fit scenario expands as the active form becomes more favored in the loosely bound state.

3. Results for k_{on} when $D_a \neq D_i$

For the more general case where $D_{\rm a} \neq D_{\rm i}$, the rate constant in the fast conformational-transition limit is given by

$$k_{\rm on} = \frac{4\pi D_0 R\cdot p_{\rm a}\kappa}{4\pi D R + p_{\rm a}\kappa} = \frac{4\pi D_0 R\cdot (D_0/D)p_{\rm a}\kappa}{4\pi D_0 R + (D_0/D)p_{\rm a}\kappa} \tag{10a}$$

One may notice that this result has the same form as $k_{\rm on0}$ [see Eq. (9)], but with $D_{\rm a}$ replaced by D_0 and κ replaced by $(D_0/D)p_{\rm a}\kappa$. When $D_{\rm i} > D_{\rm a}$, we have $D_0 > D_{\rm a}$; that is, the diffusional approach of the receptor-ligand pair to the loosely bound state is faster than if the receptor stays in the active form. In addition, we have $D < D_0$; the smaller average diffusion constant D in the loosely bound state (compared to the counterpart D_0 in the unbound state) corresponds to a longer residence time in the loosely bound state and hence a higher chance to form the final complex. Consequently it is possible that the binding rate constant $k_{\rm on}$ becomes higher than $k_{\rm on0}$. Figure S2 shows the influence of $D_{\rm i}/D_{\rm a}$ on the binding rate constant. At

$D_i/D_a = 10$, as expected, k_{on} is greater than k_{on0} at the high end of the active-inactive transition rates. Conversely, at $D_i/D_a = 0.1$, the binding rate constant is lower than that for $D_i = D_a$ when the active-inactive transitions are fast. Note that the binding rate constant is independent of D_i in the slow conformational-transition limit. An example with $D_i/D_a > 1$ is provided by a protein receptor whose inactive form is a closed conformation and active form is an open conformation. Acetylcholine receptors, a ligand-gated ion channel, apparently have an active form that is more open than the inactive form when binding antagonists but an active form that is less open than the inactive form when binding agonists (1). The latter case, as illustrated in Fig. 1a of the main text, would have $D_i/D_a < 1$. Another example with $D_i/D_a < 1$ is provided by a protein that undergoes an unfolding-to-folding transition upon binding a ligand. Here the inactive form, corresponding to the unfolded protein, is more open and hence has a smaller diffusion constant than the active form, i.e., the folded protein.

REFERENCES

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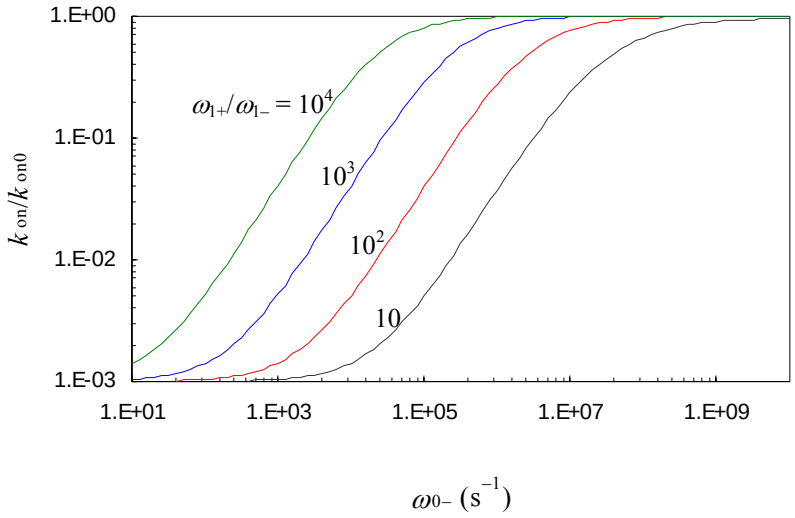

FIGURE S1 The binding rate constant at $D_i = D_a$. Results are shown for a range of ω_+/ω_-, when ω_{0+}/ω_{0-} is fixed at 10^{-3}. Other parameters are: $\gamma = 1$, $\Delta/R = 0.1$, $\omega_- = \omega_{0-}$, $D_a = 10$ Å^2/ns, and $R = 20$ Å.

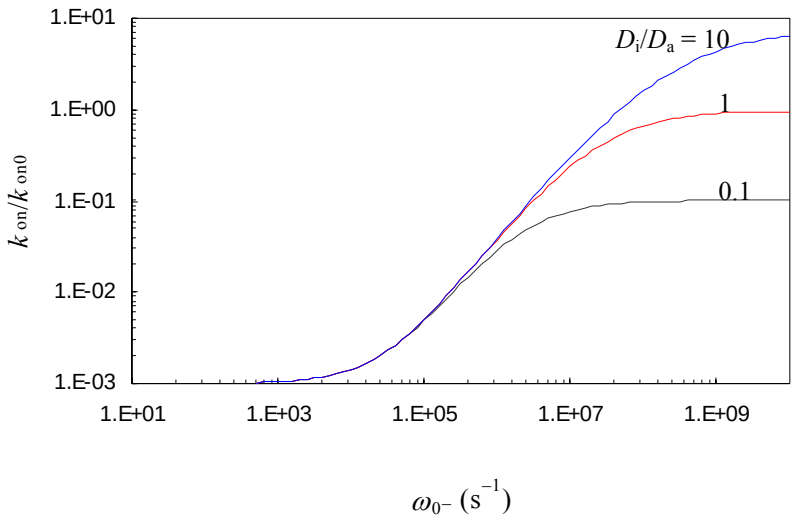

FIGURE S2 Influence of the disparity in relative diffusion constant between the active and inactive forms on k_{on}. The values of D_i/D_a are displayed. Other parameters are: $\gamma = 1$, $\Delta/R = 0.1$, $\omega_{0+}/\omega_{0-} = 10^{-3}$, $\omega_- = \omega_{0-}$, $\omega_+/\omega_- = 10$, $D_a = 10$ Å^2/ns, and $R = 20$ Å.