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Anomalous versus slowed-down Brownian diffusion in the ligand-binding equilibrium

Supporting Material

A. Space-dependent Brownian diffusion yields accumulation at equilibrium

Let us consider the 1d case for simplicity, and a constant-by-part dependence of the diffusion coefficient $D(x) = D_1$, $\forall x \in [a, b]$ and $D(x) = D_0$ outside the patch $[a, b]$. Let us then consider a single molecule and let $\pi(x, t)$ its probability to be located at position x at time t :

$$\pi(x, t + \Delta t) = \quad q(x)\pi(x, t) + \pi(x - \Delta x, t)\left(1 - q(x - \Delta x)\right)/2$$
$$+\pi(x + \Delta x, t)\left(1 - q(x + \Delta x)\right)/2 \tag{SI.1}$$

where $q(x)$ is the probability not to jump at each time step and is defined, using the jump probability $\beta(x) = 2\Delta t/(\Delta x)^2 D(x)$ (see Methods), as $q(x) = 1 - \beta(x)$. Noting $g(x, t) = (1 - q(x))\pi(x, t)/2$ and developing $g(x \pm \Delta x, t)$ in series of x, one obtains at order 2

$$\pi(x, t + \Delta t) \quad = q(x)\pi(x, t) + 2g(x) + (\Delta x)^2 \partial_{xx} g(x)$$
$$= \pi(x, t) + (\Delta x)^2 \partial_{xx} g(x, t) \tag{SI.2}$$

Dividing by Δt and taking the limit $\Delta t \to 0$, one gets

$$\partial_t \pi(x, t) = \partial_{xx}\left(D(x)\pi(x, t)\right) \tag{SI.3}$$

where we used the expression of $\beta(x)$ above to define $D(x)$. Noting $u(x, \infty)$ the density of molecules at x at equilibrium, one expects from eq. (SI.3)

$$D(x)u(x, \infty) = \mathcal{H}(D) \tag{SI.4}$$

where $\mathcal{H}(D)$ is the spatial harmonic mean of the (space-dependent) diffusion function

$$\mathcal{H}(D) = \left[\int D^{-1}(x)dx\right]^{-1} \tag{SI.5}$$

Now, using the constant-by-part function for $D(x)$ expressed above, this yields $u(x, \infty) = \mathcal{H}(D)/D_1$ $\forall x \in [a, b]$ and $u(x, \infty) = \mathcal{H}(D)/D_0$ outside. The equilibrium concentration inside the $[a, b]$ patch thus equals that found outside the patch multiplied by D_0/D_1. Hence the larger the slowdown of the Brownian motion inside the patch, the larger the accumulation inside it at equilibrium, explaining the simulation results of Fig.4B. In the present 2d case, the total number of molecules in the patch N_{inside} relates to total number N_{total}, the surface fraction of the patch ϕ, the total surface S and the diffusion coefficient according to :

$$N_{\text{inside}} = S\phi N_{\text{total}}\frac{\mathcal{H}(D)}{D_1} \ , \ \mathcal{H}(D) = \left[\frac{\phi}{D_1} + \frac{1 - \phi}{D_0}\right]^{-1} \tag{SI.6}$$

B. Optimum area for spatially restricted slowed-down Brownian motion

Let us consider a space domain of total area $S = w \times w$, in which molecules move by Brownian motion with diffusion coefficient $D(x) = D_1$ inside the central patch (of surface ϕS) and $D(x) = D_0$ in the outer region around this central patch (surface $(1 - \phi)S$). We denote numbers of molecules by lower-case letters to distinguish them from concentrations (denoted by capital letters) : x thus expresses the number of X molecules in the domain. Moreover, just like for the diffusion coefficient above, we use indices for each variable to indicate location, i.e. x_1 refers to the number of X molecules within the central patch while x_0 refers to its value outside the patch. Finally, in the following, all results will relate to equilibrium values, so that we drop the "eq" notation used above for readability.

Our major assumption in the following theoretical analysis is to consider that the reaction proceeds separately in each zone (inside or outside of the patch), independently of each other. Our goal then becomes to determine the value of ϕ that maximizes $c_0 + c_1 = c_T$, the total number of complexes. According to our space separation assumption, one has in each zone $i = \{0, 1\}$:

$$C_i = \frac{R_{i,T} L_{i,T}}{K_{Di} + L_{i,T}} \tag{SI.7}$$

where $R_{i,T} = R_i + C_i$ and $L_{i,T} = L_i + C_i$. In terms of molecule numbers, this translates into

$$c_0 = \frac{r_{0,T} l_{0,T}}{K_{D0}(1 - \phi)S + l_{0,T}} \quad \text{and} \quad c_1 = \frac{r_{1,T} l_{1,T}}{K_{D1}\phi S + l_{1,T}} \tag{SI.8}$$

Now, according to eq. (7) (main text), the relative amount of reactants in each zone is given by

$$\rho(x) = \frac{\mathcal{H}(D)}{D(x)} \tag{SI.9}$$

with $\mathcal{H}$ the (2D) spatial harmonic mean of the diffusion constant D

$$\mathcal{H}(D) = \left[\iint_S D^{-1}(x) dx \right]^{-1} = \left[S\frac{\phi}{D_1} + S\frac{(1 - \phi)}{D_0} \right]^{-1} \tag{SI.10}$$

The amount of reactant outside the central patch thus reads

$$r_{0,T} = r_T \int_{(1-\phi)S} \rho(u) du = \iint_{(1-\phi)S} \frac{\mathcal{H}(D)}{D(u)} du$$

so that

$$r_{0,T} = \frac{r_T (1 - \phi) S\mathcal{H}(D)}{D_0} \tag{SI.11}$$

Likewise, inside the patch :

$$r_{1,T} = r_T \int_{\phi S} \rho(u) du = \iint_{\phi S} \frac{\mathcal{H}(D)}{D(u)} du$$

yielding

$$r_{1,T} = \frac{r_T \phi S\mathcal{H}(D)}{D_1} \tag{SI.12}$$

Note that

$$(1 - \phi) S\mathcal{H}(D)/D_0 + \phi S\mathcal{H}(D)/D_1 = 1$$

and the above results stands for $l_{i,T}$ ($i = \{0, 1\}$) as well.

Therefore, noting

$$\alpha = (1 - \phi) S\mathcal{H}(D)/D_0 \tag{SI.13}$$

and

$$1 - \alpha = \phi S\mathcal{H}(D)/D_1 \tag{SI.14}$$

we obtain

$$c_T = c_0 + c_1 = r_T l_T \left(\frac{\alpha^2}{K_{D0}(1 - \phi)S + \alpha l_T} + \frac{(1 - \alpha)^2}{K_{D1}\phi S + (1 - \alpha)l_T} \right) \tag{SI.15}$$

In particular, in homogeneous conditions ($D_0 = D_1$ and $K_{D0} = K_{D1}$), one has $\mathcal{H}(D) = D_0/S$ and $\alpha = 1 - \phi$ so that eq.(SI.15) reduces to $c_T = r_T l_T/(K_{D0}S + l_T)$ $\forall \phi$, i.e. precisely the classical dose-response curve for homogeneous conditions. Note that except for homogeneous conditions, eq.(SI.15) does not generally display the classical parabolic shape, typical of the homogenous conditions ($y = cx/(d + x)$).

Now, the assumption of space separation between the two zones means that the movement is homogeneous (position-independent) Brownian motion for each zone. In this case we have found on Figure 3B1 (main text) that $K_{D1} \approx K_{D0}$ for all values of D_1 tested ($D_0 = 1$). We thus set $K_{D0} = K_{D1} \equiv K_D$ in the following. To find the extremum of eq.(SI.15), we search for the solutions of $dc_T/d\phi = 0$ and get :

$$\phi^\star = \frac{S + ad - \sqrt{d(S + ad)(a + Sd)}}{S(1 - d^2)} \tag{SI.16}$$

where we noted $d \equiv D_0/D_1$ and $a \equiv l_T/K_D$. We remark that in this expression, the value of the optimum area ϕ^* depends on the dose, i.e. the total concentration of ligand $L_T = L + R$. This is related to the fact that eq.(SI.15) generally has not a typical parabolic shape. However, eq.(SI.16) greatly simplifies when $S \gg ad$ (which is always valid in the simulations shown in the present article, given $S = 800^2$), to a very simple expression

$$\phi^\star \approx \frac{1 - \gamma}{2 - \gamma}, \quad S \gg ad \tag{SI.17}$$

with $\gamma = 1 - D_1/D_0$. It is remarkable that, in this limit, $\phi^\star$ does not depend on the dose a anymore, which in fact relates to the fact that the expression for c_T (eq.(SI.15)) in this case adopts a classical parabolic shape.

Taken together, this simple theoretical analysis predicts the existence of an optimal surface area $\phi^\star$ for the affinity, that depends on the value of D_1 relative to D_0. In the limit of large slowdowns $\gamma \to 1$, eq.(SI.17) gives $\phi^\star \to 0$: the larger the slowdown, the smaller the optimal patch area. This prediction is in general qualitative agreement with the simulation results of Figure5B that do not depend in a monotonous way on γ and ϕ but presents extrema along the ϕ-axis that shift leftward with increasing γ. In the limit of no-slowdown $\gamma \to 0$, eq.(SI.17) predicts $\phi^\star = 0.5$ but then, in this case, the value of c_T does not depend on ϕ anymore (see above for $D_0 = D_1$), so that no extremum are observed.