SI Appendix 1

Markov Model of Chemical Reaction: Derivation of the Stochastic Equations. The chemical reaction equations are derived by writing that the probability of formation of a new bond between times t and $t+\Delta t$ is $k_1\left(S_0-k+1\right)\Delta t+o(\Delta t)$, while the probability of breaking a bond is $k_{-1}\left(k+1\right)\Delta t+o(\Delta t)$. We get

$$\begin{aligned}\Pr\{SM(t+\Delta t)=k\} &= \Pr\{SM(t)=k+1\}\left[k_{-1}\Delta t\left(k+1\right)\right] \\ &+\Pr\{SM(t)=k-1\}\left[k_1\Delta t\left(S_0-k+1\right)\right] \\ &+\Pr\{SM(t)=k\}\left(1-kk_{-1}\Delta t-(S_0-k)k_1\Delta t\right)+o(\Delta t)\end{aligned}$$

for $S_0>k>1$.

Markov Model of a Generic Chemical Reaction. We develop now the general theory of a chemical reaction that involves only few species, such as

$$M+S\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}SM. \qquad \textbf{[38]}$$

We assume that M molecules are diffusing inside the domain Ω, and the substrate S consists of S_0 binding molecules of small size a, located on the boundary and are well separated (we assume for example that $S_0\geq M_0$). As before, the mean time for a diffusing molecule to unbind is $\frac{1}{k_{-1}}$, while k_1 represents the forward rate, which is given by the small window approximation as

$$k_1=\frac{4aD}{|\Omega|}.$$

Because a free substrate can now bind to only one M molecule at a time, the previous analysis has to be modified. To derive the master equation for the probability $p_k(t)=\Pr\{SM(t)=k\}$ that SM molecules are bound at time *t*, we consider the transition from *k* + 1 to *k* and from *k* - 1 to *k*. When *k* - 1 molecules are bound, the transition probability from k-1 to k bound molecules is proportional to the number of free sites equals to $S_0-(k-1)$ and to the number of free M_0-k+1 free molecule, we get $k_1(S_0-(k-1))(M_0-k+1)dt$. The transition probability from *k* + 1 to k reflects the fact that during the time interval dt, a M molecule is freed from a binding site, this probability is given by $k_{-1}(S_0-k-1))dt$. Finally, the probabilities $p_k(t)=\Pr\{SM(t)=k\}$ that there are exactly k SM molecules produced at time t satisfy the master equations

$$\begin{aligned}\dot{p}_k(t) &= -\left(k_{-1}k+k_1(S_0-k)(M_0-k)\right)p_k(t) \\ &+k_1(S_0-k+1)(M_0-k+1)\,p_{k-1}(t)+k_{-1}(k+1)\,p_{k+1}(t) \quad \text{for} \quad k\geq 1\end{aligned} \qquad \textbf{[39]}$$

$$\dot{p}_0(t) = -k_1 S_0 M_0 p_0(t) + k_{-1} p_1(t) \quad \text{for} \quad k = 0$$

$$\dot{p}_{S_0}(t) = -S_0 k_{-1} p_{S_0}(t) + k_1 (M_0 - S_0 + 1) p_{S_0 - 1}(t) \quad \text{for} \quad k = S_0.$$

The mean and the variance of p_k are defined, respectively, as

$$M(t) = \sum_{k=1}^{S_0} k p_k(t), \quad \sigma^2(t) = \sum_{k=1}^{S_0} k^2 p_k(t) - M^2(t).$$

For example, the steady state mean and variance are computed by solving directly the recurrence (Eq. **39**) with the normalization condition $\sum_{k=0}^{S_0} p_k = 1$. The steady state probabilities are

$$p_k = p_k(\infty) = \frac{(\frac{k_1}{k_{-1}})^k \frac{S_0(S_0-1)..(S_0-k+1)M_0(M_0-1)..(M_0-k+1)}{k!}}{\sum_{k=0}^{S_0} (\frac{k_1}{k_{-1}})^k \frac{S_0(S_0-1)..(S_0-k+1)M_0(M_0-1)..(M_0-k+1)}{k!}}. \qquad \textbf{[40]}$$

Contrary to the example given in the main text, there is no simple analytical expression of the moments (see SI Fig. 3).

Explicit Expression of the Dwell Time. An explicit expression of the Dwell time can be obtained in term of the geometry, by estimating asymptotically the probability $p_\delta(x)$ that a Brownian molecule starting at x exits before entering a binding disk of radius δ. The estimate was obtained so far when the binding domain is a disk of radius δ and the free diffusing space is an annulus A_δ of outer radius R. This estimate was obtained under the assumption that the ratio

$$\beta = \delta / R \ll \varepsilon,$$

where ε is the ratio of the small opening to the total length of the boundary. The other cases remain open. The results are

$$m_\delta = < p_\delta > = \frac{\int_{A(\delta)} p_\delta(r,\theta) r \, dr \, d\theta}{\int_{A(\delta)} r \, dr \, d\theta} = \frac{\ln \frac{1}{\beta}}{\ln \frac{1}{\beta} + 2 \ln \frac{1}{\varepsilon} + 2 \ln 2} + o(1).$$

Finally the dwell time formula is

$$E(\tau_D) = < \tau > + \frac{1 - m_\delta}{m_\delta} \left(< T > + \frac{1}{k_{-1}} \right) \qquad \textbf{[41]}$$

$$\approx \frac{R^2}{2D} \left(2 \log \frac{1}{\varepsilon} + 2 \log 2 + \frac{1}{2} - \frac{\log \frac{1}{\beta} + 2 \log \frac{1}{\varepsilon} + 2 \log 2)}{4(\log \frac{1}{\beta} - \frac{1}{2})} \right) + \left(\frac{2 \log \frac{1}{\varepsilon} + 2 \ln 2 + \frac{1}{2}}{\log \frac{1}{\beta} - \frac{1}{2}} \right) \frac{1}{k_{-1}} + o(1).$$

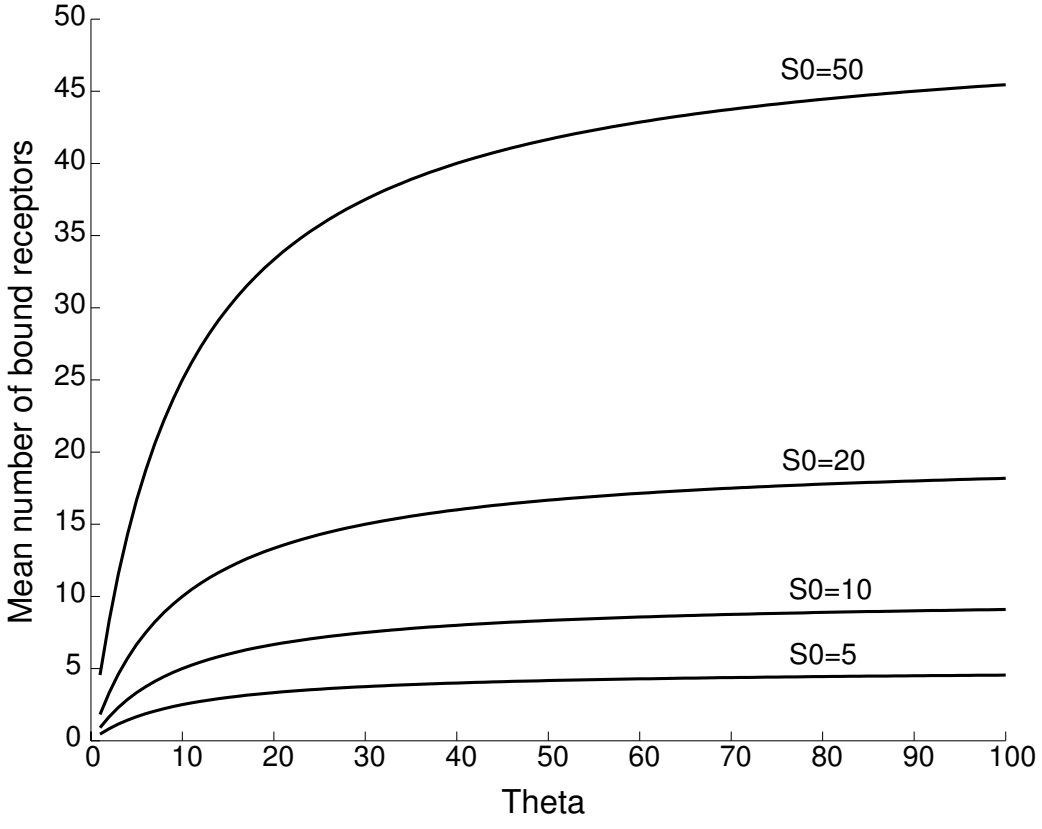
The mean $M_b = \frac{1 - m_\delta}{m_\delta}$ and the variance $V_b = \left(\frac{1 - m_\delta}{m_\delta^2} \right)$ of the number of bounds made by a single molecule before it exits Ω can be computed using the value of m_δ given by expression 6. We have

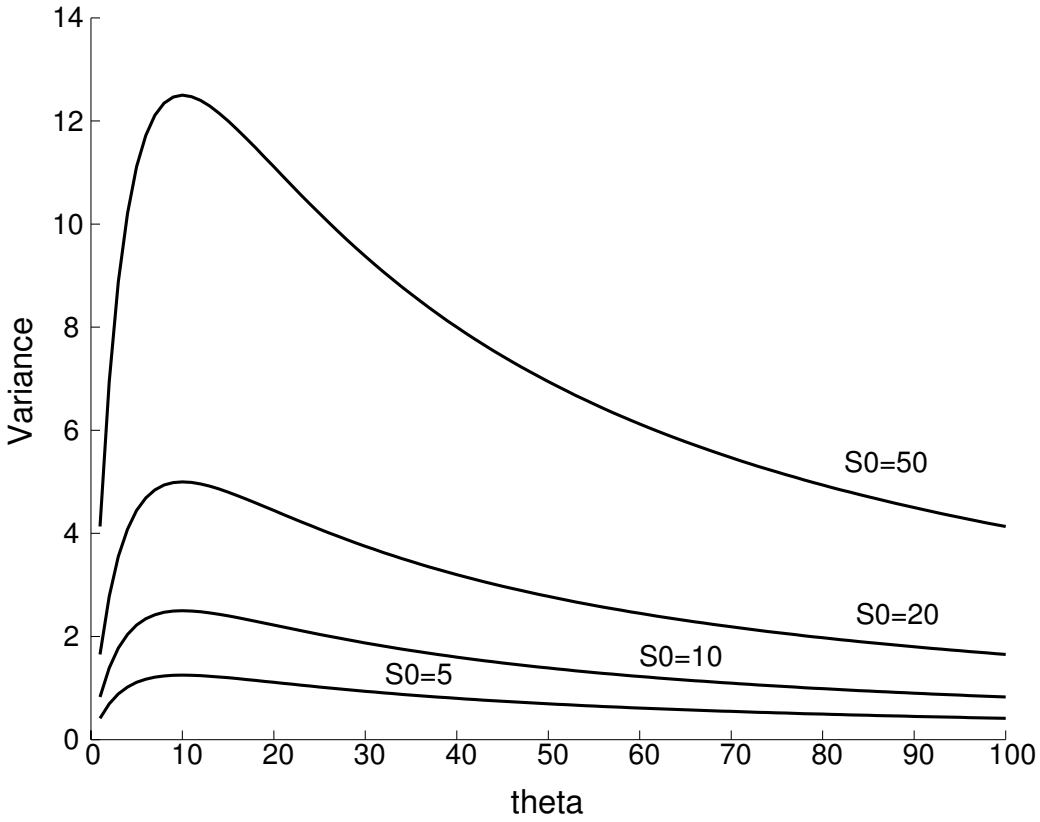
$$M_b = \frac{1-m_\delta}{m_\delta} = \frac{2\log\frac{1}{\varepsilon}}{\log\frac{1}{\beta}} + O(1) \qquad \textbf{[42]}$$

$$V_b = \left(\frac{1-m_\delta}{m_\delta^2}\right) \approx 2\ln\left(\frac{1}{\varepsilon}\right)\left(\frac{\ln\left(\frac{1}{\varepsilon}\right) + 2\ln 2 + 2\ln\left(\frac{1}{\beta}\right)}{\log^2\frac{1}{\beta}}\right) \qquad \textbf{[43]}$$

These expressions are valid for $\varepsilon << 1$ fixed but are uniformed for $\beta << 1$.

Fig. 3. The mean and variance of the number of bound receptors at a single synapse are plotted as a function of $\frac{k_2}{k_{-2}} < J_{in} > \tau_1$ for $S_0 = 5, 10, 20, 50$. When $\frac{k_2}{k_{-2}}$ is large, the variance vanishes and the mean converges to the total number of scaffolding molecules available. The unit of k_2 and k_{-2} are sec^{-1}. The rate k_2 has to be normalized by the concentration of scaffolding molecules.




14
12
10
8
6
4
2
0
Variance
0
10
20
30
40
50
60
70
80
90
100
theta
S0=50
S0=20
S0=10
S0=5