Microscopic model

Under the assumption of fast equlibration between the substrate and the enzyme, the probability of having N_{SE} complexes given m substrate molecules and N_E enzymes is given by equation **[3]** of the main text. To write the partition function explicitly, we define $u(x) = U(x, 1-m-N_E; -K)$, where U denotes the Confluent Hypergeometric function [1]. One can then write the partition sum as $Z_{m,N_E} = (-K)^{-N_E} u(-m)$. The turnover rate is then given by $w_m = \frac{k_2 N_E}{V}[-m\,u(1-m)]/[u(-m)]$, which can be approximated by Equation **[4]**.

Influx of metabolites

A metabolic reaction *in vivo* can be described as turnover of an incoming flux of substrate molecules, characterized by a Possion process with rate c, into an outgoing flux. To find the probability of having m substrate molecules we write down the Master equation,

$$\begin{aligned}\frac{d}{dt}\pi(m) &= [c(a-1) + (\hat{a}-1)w_m]\,\pi(m) \\ &= c[\pi(m-1) - \pi(m)] + [w_{m+1}\pi(m+1) - w_m\pi(m)]\,, \end{aligned} \quad \textbf{[S1]}$$

where we took the opportunity to define the lowering and raising operators a and $\hat{a}$, which – for any function $h(n)$ – satisfy $ah(n) = h(n-1)$, $ah(0) = 0$, and $\hat{a}h(n) = h(n+1)$. The first term in this equation is the influx, and the second is the biochemical reaction. The solution of this steady state equation is of the form $\pi(m) \sim c^m / \prod_{k=1}^m w_k$ (up to a normalization constant), as can be verified by plugging it into the equation,

$$\begin{aligned}&\left[c\left(\frac{\pi(m-1)}{\pi(m)} - 1\right) + \left(\frac{\pi(m+1)}{\pi(m)}w_{m+1} - w_m\right)\right] \\ &\qquad = c\left(\frac{w_m}{c} - 1\right) + \left(\frac{c}{w_{m+1}}w_{m+1} - w_m\right) = 0. \end{aligned} \quad \textbf{[S2]}$$

Using the approximate form of w_m, as given in **[4]**, the probability $\pi(m)$ takes the form,

$$\pi(m) = \binom{m + K + (N_E - 1)}{m}(1-z)^{K+N_E} z^m\,, \qquad \textbf{[S3]}$$

as given in equation **[5]** of the main text.

Directed linear pathway

We now derive our key results, equation **[8]** (The result has been derived previously in the context of queueing networks [2], and of mass-transport systems [3]). To this end we write the Master equation for the joint probability function $\pi \equiv \pi(m_1, m_2, \cdots, m_L)$,

$$\frac{d}{dt}\pi = \left[c(a_1 - 1) + \sum_{i=1}^{L-1}(\hat{a}_i a_{i+1} - 1)w_{m_i}^{(i)} + (\hat{a}_L - 1)w_{m_L}^{(L)}\right]\pi\,, \quad \textbf{[S4]}$$

which generalizes **[S1]**. As above, a_i and $\hat{a}_i$ are lowering and raising operators, acting on the number of S_i molecules. The first term in this equation is the incoming flux c of the substrate, and the last term is the flux of end product. Let us try to solve the steady-state equation by plugging a solution of the form $\pi(m_1, m_2, \cdots, m_L) = \prod g_i(m_i)$, yielding

$$\begin{aligned}c[\frac{g_i(m_1-1)}{g_1(m_1)} - 1] + \sum_{i=1}^{L-1}[w_{m_i+1}^{(i)}\frac{g_i(m_i+1)g_{i+1}(m_{i+1}-1)}{g_i(m_i)g_{i+1}(m_{i+1})} - w_{m_i}^{(i)}] \\ + [w_{m_L+1}^{(L)}\frac{g_L(m_L+1)}{g_L(m_L)} - w_{m_L}^{(L)}] = 0\,. \end{aligned} \quad \textbf{[S5]}$$

Motivated by the solution to **[S1]**, we try to satisfy this equation by choosing $g_i(m) = c^m / \prod_{k=1}^m w_k^{(i)}$. With this choice we have $g(m+1)/g(m) = c/w_{m+1}$ and $g(m-1)/g(m) = w_m/c$. It is now straightforward to verify that indeed

$$c\left(\frac{w_{m_1}^{(1)}}{c} - 1\right) + \sum_{i=1}^{L-1}\left(w_{m_{i+1}}^{(i+1)} - w_{m_i}^{(i)}\right) + \left(c - w_{m_L}^{(L)}\right) = 0\,. \quad \textbf{[S6]}$$

Finally, in our choice of $g_i(m)$ we replace $w_m^{(i)}$ by the MM- rate $v_i m_i/(m_i + K_i)$, and find that in fact $g_i(m) = \pi_i(m)$, namely

$$\pi(m_1, m_2, \ldots, m_L) = \prod_{i=1}^{L}\pi_i(m_i)\,, \qquad \textbf{[S7]}$$

as stated in **[8]**.

End-product inhibition

Equation **[13]** of the main text is a self-consistent equation for the steady- state flux c through a pathway regulated via end-product inhibition. Using considerations analogous to what led to the exact result on the product measure distribution for the cyclic pathways, we conjecture that even for the present case of end-product inhibition, the distribution function can still be approximated by the product measure **[S7]** with the form of the single node distributions given by **[S3]**. The flux c enters the calculation of the average on the right-hand side through the probability function $\pi(m)$. Solving this equation for c yields the steady state current, and consequently determines the mean occupancy and standard deviation of all intermediates.

To verify the validity of this conjecture, and to demonstrate its application, we consider the case $h = 1$. In this case one can carry the sum, and find

$$\begin{aligned}c &= \sum_{m_L=0}^{\infty} c_0\left[1 + (m_L/K_I)^h\right]^{-1}\pi_L(m_L) \\ &= c_0(1-z)^{K_L}\,{}_2F_1(K_I, K_L; K_I + 1; z)\end{aligned} \quad \textbf{[S8]}$$

with $z = c/v_L$ and ${}_2F_1$ the hypergeometric function [1]. This equation was solved numerically, and plotted in supporting figure 2(a) for some values of K_I and K_L. Note that predictions based on the

* To whom correspondence should be addressed. Email: elevine@ucsd.edu

product measure (lines) are in excellent agreement with the results of numerical simulation (circles) for the different sets of parameters tried.

Results obtained from equation **[S8]** can be used, for example, to compare the flux that flows through the noisy pathway with the mean-field flux $c_{\rm MF}$, obtained when one ignores fluctuations in m_L, i.e.,

$$c_{\rm MF} = \frac{c_0}{1+(s_L/K_I)^h} \ . \qquad \textbf{[S9]}$$

The fractional difference $\delta c = (c - c_{\rm MF})/c_{\rm MF}$ is plotted in supporting figure 2(b). The results show that number fluctuations in the end-product always *increase* the flux in the pathway since $\delta c > 0$ always. Quantitatively, this increase can easily be several percent. For large c_0, a simplifying expression can be derived by using an asymptotic expansion of the hypergeometric function [1]. For example, when $K_I < K_L$,

$$(1-z)^{K_L}\,{}_2F_1(K_I, K_L; K_I+1; z) \sim \frac{v_L K_L}{1+K_L-K_I} \ , \qquad \textbf{[S10]}$$

which yields

$$\frac{c - c_{\rm MF}}{c_{\rm MF}} \sim \frac{1}{K_I}\frac{v_L}{c_0} \ . \qquad \textbf{[S11]}$$

Thus the effect of end-product fluctuations on the current is enhanced by stronger binding of the inhibitor (smaller K_I), as one would expect. We note that obtaining these predictions from Monte-Carlo simulation is rather difficult, given the fact that one is interested here in sub-leading quantities.

1. M. Abramowitz, Handbook of Mathematical Functions (Dover, New York, 1972).

2. Taylor, H.M. & Karlin, S. (1998) An Introduction to Stochastic Modeling, 3rd edition (Academic Press); Ross, S.M. (1983) Stochastic Processes (John Wiley & Sons).

3. Levine, E. , Mukamel, D. & Schütz, G.M. (2005) *J. Stat. Phys.* **120**, 759.