Supporting Information

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SI Text

Cumulants of the Coarse-Grained Reaction. As described in the main text and *Materials and Methods*, the first 3 cumulants for the coarse-grained $S_B \to P$ reaction can be obtained by differentiating the corresponding CGF. This gives

$$c_1 = T\frac{1}{2k_1}\left[k_1(k_0+k_2)+q(k_2+k_{-1})-\sqrt{k_1^2(k_0-k_2)^2+2k_1q(k_0+k_2)(k_2+k_{-1})+q^2(k_2+k_{-1})^2}\right], \quad [S1]$$

$$c_2 = Fc_1, \quad [S2]$$

$$F = 1-\frac{q(2k_1k_0k_2+k_1(k_0+k_2)k_{-1}+qk_{-1}(k_2+k_{-1}))}{k_1^2(k_0-k_2)^2+2k_1q(k_0+k_2)(k_2+k_{-1})+q^2(k_2+k_{-1})^2}+\frac{qk_{-1}}{\sqrt{k_1^2(k_0-k_2)^2+2k_1q(k_0+k_2)(k_2+k_{-1})+q^2(k_2+k_{-1})^2}}. \quad [S3]$$

$$\begin{aligned} c_3 = -T\frac{\kappa}{\rho(-\kappa k_1+\rho^2)^5}\{&\kappa^5k_1^5-\rho^{10}+\kappa\rho^7[5k_1^2k_2+q(11k_1+6q)s]-\kappa^2k_0^2k_1^4\rho^2[5k_1^2k_2^2+6k_2(k_1-2q)qs+24q^2s^2] \\ &+2\kappa^2k_0k_1^2\rho^3[5k_1^3k_2^2+k_2q(14k_1^2-9k_1q-6q^2)s+6q^2(5k_1+3q)s^2]-2\kappa k_0k_1\rho^4[5k_1^4k_2^3+19k_1^3k_2^2qs+9k_1^2k_2q^2s^2 \\ &+6k_2q^4s^2+3k_1q^3s(-2k_2^2+8k_2s+s^2)]\}, \end{aligned} \quad [S4]$$

where

$$s = k_1\langle S_M\rangle + k_2 + k_{-1},\ \langle S_M\rangle = \frac{1}{2k_1q}\{k_0k_1-k_1k_2-k_2q-k_{-1}q+[4k_1k_0q(k_2+k_{-1})+(k_1k_2-k_1k_0+k_2q+k_{-1}q)^2]^{1/2}\}$$

is the average number of membrane-bound substrates, $k_0 = q_0S_B$, $\kappa = k_0k_1k_2$, $\rho = k_1k_2 + qs$, and, finally, T is the time step over which S_B changes by a relatively small amount, but many membrane reactions happen.

Simulating the Michaelis–Menten Enzyme. We consider a MM enzyme with $S_M = 140 = \text{const}$, $k_1 = 0.01$, $k_{-1} = 2.0$, $k_2 = 1.0$. We analyze the number of product molecules produced by this enzyme over time $\delta t = 35$, with the enzyme initially in the (stochastic) steady state. To strain both the Gillespie and our methods, we require a very high simulation accuracy, namely convergence of the fourth cumulant of the product flux distribution to 2 significant digits. For both methods, this means ≈10 million realizations of the same evolution.

In Table S1 we report the results of our simulations. We see that the analytical coarse-grained results differ from the exact Gillespie simulations by, at most, 2%, which is an expected deviation given the quality of the steady-state approximation. Further, the Langevin-like coarse-grained simulations, which accounted for the first 4 cumulants of the reaction events distribution, as in *Materials and Methods: Simulations with Near-Gaussian Distributions*, produce results nearly indistinguishable from the analytical expressions, and, at most 2% different from the Gillespie runs. Yet coarse-grained simulations require only 1/40th the time of their Gillespie analogue because the time step is large, $\delta t = 35$.

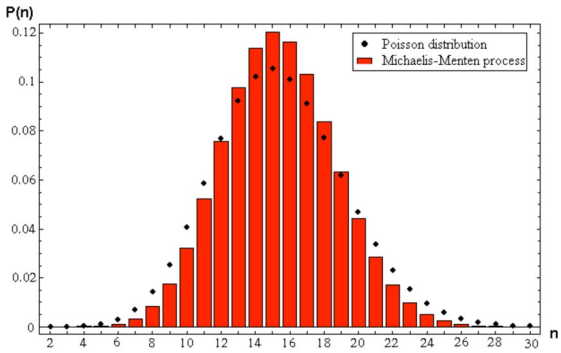

Fig. S1. Distribution of the number of MM reactions over a time $\delta t = 35$ with $S_M = 140$, $k_1 = 0.01$, $k_{-1} = 1$, and $k_2 = 1$ vs. the Poisson distribution with the same mean. The distribution for the MM process is obtained by using the Gram–Charlier expansion with 4 known cumulants, see *Materials and Methods* in the main text. The MM process is clearly non-Poissonian.

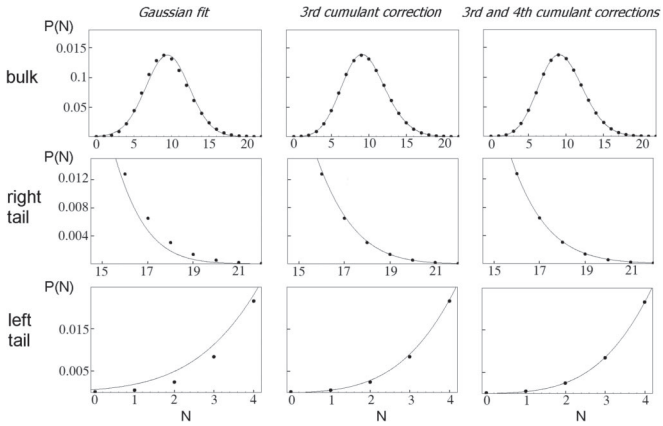

Fig. S2. Comparison of the exact discrete distribution of product molecules generated by the MM enzyme (points) with the continuous approximations by the GC series (lines). *Left* column compares the exact result to the Gaussian approximation. *Center* and *Right* columns show improvements due to inclusion of the third and the fourth cumulant corrections, respectively. We used $S_M = 140 = \text{const}$, $k_1 = 0.02$, $k_{-1} = 2$, $k_2 = 1$, $q = 0.01$, and $\delta t = 35$.

Table S1. Comparison of the Gillespie and the coarse-grained simulation algorithms

Cumulants	Gillespie	Coarse-grained	Analytics
c1	11.24 (1)	11.14 (1)	11.14
c2/*c1*	0.843 (1)	0.855 (1)	0.855
c3/*c1*	0.613 (4)	0.628 (4)	0.628
c4/*c1*	0.32 (2)	0.32 (2)	0.319
Time	8 min 45 s	12 s	N/A

The numbers are reported for 12 million realizations of the same evolution for each of the methods. To highlight deviations from the Poisson and the Gaussian statistics, we provide ratios of the higher-order cumulants to the mean of the product flux distribution. In the last column, we report analytical predictions obtained from the quasi-steady-state approximation to the CGF. Numbers in parentheses are the estimated errors of the last significant digits.