Note: Parameter-independent bounding of the stochastic Michaelis-Menten steady-state intrinsic noise variance

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The Michaelis-Menten approximation is commonly used for enzyme kinetics in computational modeling of biological systems. It approximates the enzyme-catalyzed conversion of a substrate S, to which the enzyme E reversibly binds, to product P via a catalytic reaction that produces P from the enzyme-substrate complex ES, freeing the enzyme E again. Together with input reaction and product decay, this corresponds to the reaction set:

with rate constants k_i for reactions R_i . In an ordinary differential equation (ODE) model, the reaction system (R1)–(R3) translates to the set of ODEs for the component concentrations $[X]$

$$\frac{d[S]}{dt} = k_0 - k_1[E][S] + k_2[ES], \quad (1a)$$

$$\frac{d[E]}{dt} = -k_1[E][S] + (k_2 + k_3)[ES], \quad (1b)$$

$$\frac{d[P]}{dt} = k_3[ES] - k_4[P], \quad (1c)$$

and the enzyme conservation relation $[ES] = [E]_T - [E]$, where $[E]_T$ is the total enzyme concentration. The initial conditions at $t = 0$ are given as follows: $[S](0) = [S]_0$, $[E](0) = [E]_0$, $[P](0) = [P]_0$, $[ES](0) = [E]_T - [E]_0$.

The deterministic Michaelis-Menten approximation reduces the three reactions (R2) into a single substrate-to-product conversion reaction

with rate

$$v_{MM} = v_{\max}/(K_M + [S]), \quad (2)$$

where $v_{\max} = k_3[E]_T$ and $K_M = (k_2 + k_3)/k_1$.

It is based on the deterministic quasi steady-state assumption (QSSA)¹ for the enzyme-substrate complex, i.e., $d[ES]/dt = 0$. If the steady-state substrate concentration $[S]^*$ exists, i.e., if $k_0 < v_{\max}$, it is the same by construction for both the full reaction set (R2) and the Michaelis-Menten reaction (R4), namely,

$$[S]^* = \frac{k_0 K_M}{v_{\max} - k_0}, \quad 0 \leq k_0 < v_{\max}. \quad (3)$$

The Michaelis-Menten reaction is non-elementary, with a non-constant reaction rate (2) that depends on the amount of substrate S present in the system. As such, it is *a priori* not clear whether its usage as a heuristic stochastic propensity is valid.² Sanft *et al.*² have shown that the mean system dynamics of the reaction system (R2) are approximated well by the stochastic Michaelis-Menten approximation under the same condition as in the deterministic regime, i.e., the Segel-Slemrod condition:³

$$[E]_T \ll [S]_0 + K_M. \quad (4)$$

We will now analyze the accuracy of the intrinsic noise variance of the substrate and product concentrations in the stochastic Michaelis-Menten approximation. We employ the linear noise approximation (LNA),⁴ which has received renewed validation,⁵ in conjunction with the slow-scale linear noise approximation (ssLNA),⁶ to derive the intrinsic noise variance of the full reaction set (R2) under the stochastic equivalent of the QSSA, and the stochastic Michaelis-Menten approximation with reaction (R4), assuming a system volume Ω in both cases.

Thomas *et al.* showed that, at steady-state with input reaction (R1), the variance $\sigma_{[S]^*,F}^2$ given by the ssLNA for the full system with reaction set (R2), and the variance $\sigma_{[S]^*,MM}^2$ given by the LNA for the Michaelis-Menten approximated system with reaction (R4), respectively, are the following:⁶

$$\sigma_{[S]^*,F}^2 = \frac{[S]^*}{\Omega} \left(1 + \frac{[S]^*}{K_M} \frac{k_2/k_1 + [S]^*}{K_M + [S]^*} \right), \quad (5)$$

$$\sigma_{[S]^*,MM}^2 = \frac{[S]^*}{\Omega} \left(1 + \frac{[S]^*}{K_M} \right). \quad (6)$$

They concluded that the stochastic Michaelis-Menten approximation *overestimates* the steady-state substrate variance of the full reaction system (R2). Here, we show that it is possible

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to derive an *analytical, parameter-independent lower and upper bound* from their results. We simultaneously derive this for the product variance, for which the respective equations are

$$\sigma_{[P]^*,F}^2 = \frac{[P]^*}{\Omega} \left(1 - \frac{[S]^* k_3 / k_1}{\Sigma([S]^* + [P]^*) K_M} \right), \quad (7)$$

$$\sigma_{[P]^*,MM}^2 = \frac{[P]^*}{\Omega} \text{ with } \Sigma = [S]^* + K_M. \quad (8)$$

Proposition. The ratios of the substrate and product variances (5) and (7) of the full system (R2) under the ssLNA and (6) and (8) of the Michaelis-Menten approximated system (R4) under the LNA, at steady-state, are bounded as follows:

$$\frac{3}{4} \leq \frac{\sigma_{[S]^*,F}^2}{\sigma_{[S]^*,MM}^2}, \frac{\sigma_{[P]^*,F}^2}{\sigma_{[P]^*,MM}^2} \leq 1. \quad (9)$$

Proof. Substituting Eq. (3) for $[S]^*$ into the ratios of ((5) and (6)) and ((7) and (8)), and defining $\alpha \in [0, 1)$ and $\beta, \epsilon \in \mathfrak{R}_{\geq 0}$ as

$$\alpha := k_0/v_{\max}, \quad \beta := k_2/k_3, \quad \epsilon := [P]^*/[S]^*$$

gives rise to the simpler variance ratio equations

$$\frac{\sigma_{[S]^*,F}^2}{\sigma_{[S]^*,MM}^2} = 1 - \frac{\alpha(1-\alpha)}{\beta+1}, \quad (10)$$

$$\frac{\sigma_{[P]^*,F}^2}{\sigma_{[P]^*,MM}^2} = 1 - \frac{\alpha(1-\alpha)}{\beta+1} \frac{1}{1+\epsilon(1-\alpha)}. \quad (11)$$

The right inequalities of proposition (9) hold because $\alpha \in [0, 1)$, $\beta, \epsilon \in \mathfrak{R}_{\geq 0}$. To prove the left inequalities, the minimum of the right-hand sides can easily be computed analytically:

$$\alpha = 1/2, \quad \beta = 0, \quad \epsilon = 0. \quad (12)$$

Now we can find the bound for the left inequalities in (9) by substituting (12) into (10) and (11). $\square$

This means that while the stochastic Michaelis-Menten approximation will overestimate the noise variance of reaction set (R2), it will only do so by a maximum of one-third at steady-state—given that the (ss)LNA holds. This maximum is reached at conditions (12), which are consistent with a previously published result.⁷ It is also apparent from Eq. (10) that introducing a backward reaction ($\beta > 0$) for the substrate-enzyme binding decreases the overestimation of the noise variance by the stochastic Michaelis-Menten approximation.

We can examine the applicability of the proposition by comparing with the variance ratio computed on a stochastic simulation algorithm (SSA) ensemble of, e.g., the previously

FIG. 1. (a) Stochastic Michaelis-Menten to full system substrate variance ratio (9), predicted by the LNA and ssLNA (solid lines), and calculated directly from exact simulations of (R1), (R2), (R3) and (R1), (R4), (R3) with Gillespie's SSA¹⁰ (pluses) for $\beta = 0$ (black), $\beta = 1$ (blue), $\beta = 5$ (orange), $\beta = 10$ (magenta). The black dashed lines indicate the predicted ratio extrema at 1 and 4/3. (b) Product variance ratio for $\beta = 0$ predicted with the (ss)LNA (surface), and calculated with Gillespie's SSA (magenta) with prediction errors (orange). Note that for very small values of ϵ the Michaelis-Menten approximation is more accurate than the prediction, as the assumption of P being a slow variable no longer holds. SSA ensembles were generated using StochKit2¹¹ v2.0.8 with $n = 1e6$, $\Omega = 1$ at $t = 5e3$.

employed² system $[S]_0 = 100$, $[E]_0 = [E]_T = 1$, $k_3 = 1$, $k_1 = 0.01$, where the Segel-Slemrod condition (4) clearly holds.²

Note that for $K_M \Omega \rightarrow 0$, the steady state concentration and variance computed using the reaction rate equations (RREs) and LNA are known to be inaccurate when the enzyme is operating close to saturation,^{8,9} i.e., $\alpha \rightarrow 1$. However, if the RRE and (ss)LNA describe the system at steady state accurately, then in cases where the Michaelis-Menten approximation can be expected to lead to a faster stochastic simulation (i.e., $\beta \gg 1$),² it should accurately describe the system variance (Figure 1).

Finally, we note that if uncompetitive or competitive inhibition is introduced into the reaction system, the left inequality of (9) still seems to hold when numerically optimizing the (ss)LNA ratio prediction. For the right inequality, however, one can easily construct a counterexample: For a fixed dissociation constant and both inhibitory constants approaching zero, the variance of the full system can be arbitrarily underestimated by the reduced one.

¹D. L. Nelson and M. M. Cox, *Lehninger Principles of Biochemistry*, 5th ed. (W. H. Freeman and Company, 2008).

²K. R. Sanft, D. T. Gillespie, and L. R. Petzold, *IET Syst. Biol.* **5**, 58 (2011).

³L. A. Segel, *Bull. Math. Biol.* **50**, 579 (1988).

⁴N. G. van Kampen, *Stochastic Processes in Physics and Chemistry*, 3rd ed. (Elsevier Science & Technology Books, 2007).

⁵E. W. J. Wallace, D. T. Gillespie, K. R. Sanft, and L. R. Petzold, *IET Syst. Biol.* **6**, 102 (2012).

⁶P. Thomas, A. V. Straube, and R. Grima, *BMC Syst. Biol.* **6**, 39 (2012).

⁷P. Thomas, A. V. Straube, and R. Grima, *J. Chem. Phys.* **135**, 181103 (2011).

⁸R. Grima, *Phys. Rev. Lett.* **102**, 218103 (2009).

⁹R. Grima, *J. Chem. Phys.* **136**, 154105 (2012).

¹⁰D. T. Gillespie, *J. Phys. Chem.* **81**, 2340 (1977).

¹¹K. R. Sanft, S. Wu, M. Roh, J. Fu, R. K. Lim, and L. R. Petzold, *Bioinformatics* **27**, 2457 (2011).