

The status of the QSSA approximation in stochastic simulations of reaction networks

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Abstract Stochastic models of chemical reactions are needed in many contexts in which the copy numbers of species are low, but only the simplest models can be treated analytically. However, direct simulation of computational models for systems with many components can be very time-consuming, and approximate methods are frequently used. One method that has been used in systems with multiple time scales is to approximate the fast dynamics, and in this note we study one such approach, in which the deterministic QSSH is used for the fast variables and the result used in the rate equations for the slow variables. We examine the classical Michaelis-Menten kinetics using this approach to determine when it is applicable.

1 Introduction

Since many key biological molecules are present in low copy numbers, stochastic effects can play an important role in diverse processes, including gene expression

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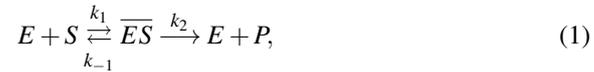
and spatial pattern formation in development [2, 3, 6, 22]. While stochastic effects may simply add noise to an otherwise deterministic system, in which case it may have no beneficial role, but in others, such as asymmetric cell division, their role may be essential [2, 22]. Thus understanding the time-dependent behaviour of a system of interacting species and how noise influences the outcome is important in many different contexts, including temporal gene expression profiles, signal transduction, and other biochemical processes. In the regime of large copy numbers for all species in the process of interest, a ‘law of large numbers’ argument shows that for finite times the stochastic formulation described later converges to the mass-action based deterministic description commonly used, at least in well-mixed systems [13].

In many reacting systems there is a wide separation of time scales between the fastest and slowest reactions, and in the deterministic (large number) limit this is well understood and widely exploited to simplify the description of time-dependent systems [15]. However the effects of large time scale separation is less well understood for stochastic systems. While there are established techniques for deriving reduced Markov models that govern the slow evolution of the system [10, 8, 9], such reductions do not use the reduced kinetic descriptions that result from the quasi steady-state approximation (QSSA) applied to the continuum description directly. However, in practice it is far simpler to change the propensities in the master equation by using the deterministic QSSA, and hence this approach is widely used in the literature. Here we investigate the validity of such direct applications of the deterministic QSSA rate laws to stochastic simulations.

2 The QSSA assumption in well-mixed stochastic systems

2.1 Background

The classical Michaelis-Menten deals with the reaction



where E is an enzyme, S is the substrate, \overline{ES} is the intermediate complex of E and S , and P is the product. The over-all effect of these reactions is to convert the substrate S to the product P , and we suppose that this follows mass-action kinetics. The governing equations are¹

¹ We use the same symbol for a species and its concentration.

$$\frac{dS}{dt} = -k_1 E \cdot S + k_{-1} \overline{ES} \quad (2)$$

$$\frac{dE}{dt} = -k_1 E \cdot S + (k_{-1} + k_2) \overline{ES} \quad (3)$$

$$\frac{d\overline{ES}}{dt} = k_1 E \cdot S - (k_{-1} + k_2) \overline{ES}, \quad (4)$$

with initial conditions $S(0) = S_0, E(0) = E_0, \overline{ES}(0) = \overline{ES}_0$. Since the enzyme is conserved in these reactions, $E(t) + \overline{ES}(t) = E_T$, and the equations can be reduced to

$$\frac{dS}{dt} = -k_1 E_T S + (k_1 S + k_{-1}) \overline{ES} \quad (5)$$

$$\frac{d\overline{ES}}{dt} = k_1 E_T S - (k_1 S + k_{-1} + k_2) \overline{ES}. \quad (6)$$

When \overline{ES} varies rapidly compared with S , a singular perturbation analysis shows that the outer solution to this system is defined by the QSSA relationship

$$\overline{ES} = \frac{k_1 E_T S}{k_1 S + k_{-1} + k_2} = E_T \frac{S}{K_m + S}, \quad (7)$$

where $K_m \equiv (k_{-1} + k_2)/k_1$ is the Michaelis constant. It is known that the timescale of the substrate evolution is much slower than that of the complex \overline{ES} provided that [18]

$$\varepsilon = \frac{E_T}{K_m + S_0} \ll 1. \quad (8)$$

This is a ratio of concentrations, not of time scales, which it should be for the singular perturbation reduction, but one can show that the slow and fast time scales are simply $(k_1 E_T)^{-1}$ and $(k_1 (K_m + S_0))^{-1}$, resp. [16]. When this applies S is the solution of

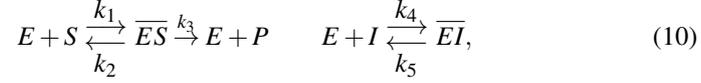
$$\frac{dS}{dt} = -k_2 \overline{ES} = -k_2 E_T \frac{S}{K_m + S}. \quad (9)$$

Clearly, this approximation leads to a kinetic equation that is not in a mass-action kinetics form.

However, it has not been established that this form of the rate law for the slow conversion for S to P is appropriate when the copy number of S is low. An algorithm for stochastic systems that does not use the continuum QSSA as a rate law, but involves a two-time-scale reduction of the full chemical master equation is developed in [9]. This leads to the slow-time-scale dynamics in terms of certain projections that involve the stationary distributions of the fast system, and under suitable conditions the generator of the reduced system is a Markov generator. In this approach the rates or propensities of the reduced system are modified rates of the slow reactions conditioned on the expectations of fast steps, which leads to a significant reduction

in the dimension of the evolution equation. As the following example shows, it is very accurate, even in the regime of low copy number of some species.

The set of reactions in the model are those in (1), with the addition of a competitive inhibition step



where E, S and P are as before, and I is the inhibitor. The evolution of the means and standard deviations of numbers of the product P , using the dimensionless parameter values $k_1 = k_2 = k_4 = k_5 = 10, k_3 = 0.1$, and the the initial condition $(E, S, ES, I, EI, P) = (5, 100, 0, 5, 0, 0)$, are shown in Figure 1. The full state space is $\mathcal{O}(10^8)$, while the evolution on the slow time scale is governed by a four-dimensional system of equations. The results shown in the figure are based on 5000 realizations of the stochastic processes. Details of the algorithm and computations are given in [9].

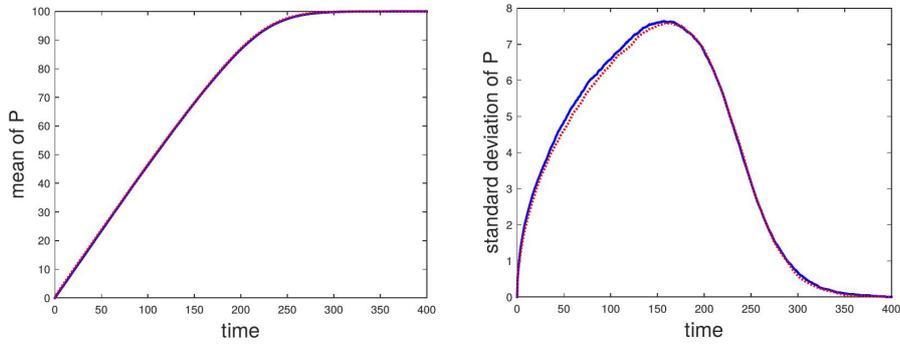


Fig. 1 Comparison of the results from the approximate stochastic simulation algorithm (red dotted line) with the results of the exact stochastic simulation algorithm (blue solid line). From [9] with permission.

Despite the fact that application of the deterministic QSSA for the conversion of S has not been established mathematically for stochastic systems, it is widely used, and differing claims have been made concerning its validity [5, 17, 4, 1, 11, 14, 12]. One example of the applications is the following model that involves negative feedback in a transcriptional network (Figure 2).

The governing equations are

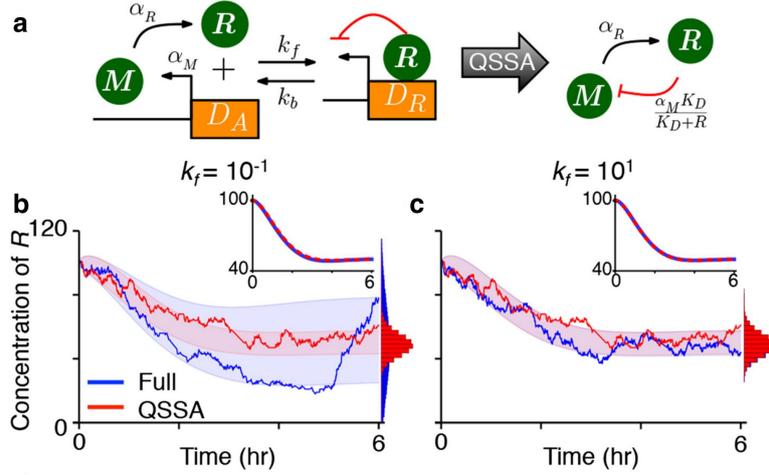


Fig. 2 The relationship between the accuracy of the deterministic and the stochastic QSSA. a The diagrams for the full model (Eqs. 11) and the reduced model (Eqs. 12). The deterministic QSSA is accurate when both $k_f = 10^{-1} \text{h}^{-1}$ and $k_f = 10^1 \text{h}^{-1}$ (the insets). However, the corresponding stochastic QSSA is accurate only when $k_f = 10$. The colored ranges and histograms represent a standard deviation of R from its mean and the distribution of R at steady state, respectively. Here, $K_D = 10$, $\alpha_M = 300 \text{h}^{-1}$, $\beta_M = \beta_R = 1 \text{h}^{-1}$. $M(0) = R(0) = 100$ and $D_A(0) = 0$. Since $K_D = k_b/k_f$ is fixed, $k_b = 10k_f$ throughout. From [12].

$$\begin{aligned}
 \frac{dM}{dt} &= \alpha_M D_A - \beta_M M \\
 \frac{dR}{dt} &= \alpha_R M - \beta_R R - k_f R D_A + k_b D_R \\
 \frac{dD_A}{dt} &= -k_f R D_A + k_b D_R
 \end{aligned} \tag{11}$$

where M, R, D_A and D_R are the concentrations of mRNA, repressor, active DNA, and repressed DNA, respectively. It is assumed only one copy of the gene is present, and therefore $D_A + D_R = 1$. Details of the parameter meaning and values can be found in [12].

The authors assumed that the active DNA, D_A , evolves much faster than M and R , which leads to the deterministic QSSA system:

$$\begin{aligned}
 \frac{dM}{dt} &= \alpha_M \frac{K_D}{K_D + R} - \beta_M M \\
 \frac{dR}{dt} &= \alpha_R M - \beta_R R
 \end{aligned} \tag{12}$$

where $K_D = k_b/k_f$. The authors then consider the stochastic version of these equations, using the right-hand sides of (12), to define the propensities. They observed

that the accuracy of the stochastic QSSA varied for different values of the forward rate k_f , of repressor binding to DNA, as can be seen in Figure 2 (b) and (c). However they showed that the accuracy of the deterministic QSSA was always valid while varying k_f . To quantify the difference between the two stochastic models, we focus on the stationary distribution of the repressor R and analyse the relative error in the variance between the full and reduced systems given by

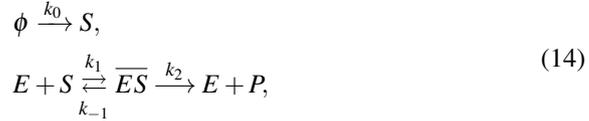
$$\varepsilon = \frac{\sigma_F - \sigma_R}{\sigma_F}, \quad (13)$$

where σ_F and σ_R are the variances of the stationary distribution of the repressor in the full and reduced system [20].

In Figure 3(a) we plot the mean and standard deviation of the stationary distribution of the repressor from the full and the reduced system as a function of k_f . Since K_D is fixed, the mean and variance of the reduced system are constant. The standard deviation of the full system is greater than the that of the reduced system for smaller values of k_f , but it approaches that of the reduced system for large k_f . This effect can be seen more clearly in Figure 3(b), where we plot the relative error in variance, ε , which is monotone decreasing as function of k_f . In effect, this quantifies the transition of the standard deviation from Figure 2(b) to Figure 2(c). The authors hypothesize that the stochastic QSSA is more accurate as k_f increases, because the deterministic QSSA is accurate over a larger range of initial conditions that includes the most probable fluctuations.

2.2 Analytical results for the errors of the stochastic QSSA

In this section we compare the stochastic description of the reactions at (1), with an input of substrate,



with the reduced system given by the following reactions, which uses the QSSA rate for the second step²



To better understand the effects of using the QSSA in a stochastic setting, we compare the stationary distribution of the full system with the stationary distribution of the reduced system. As before, we use ε as defined in (13) to quantify the differences. An analytical approximation to this based on the linear noise approximation

² Exmple 18 in [9] gives the rigorous derivation of the propensities for the slow dynamics in this example.

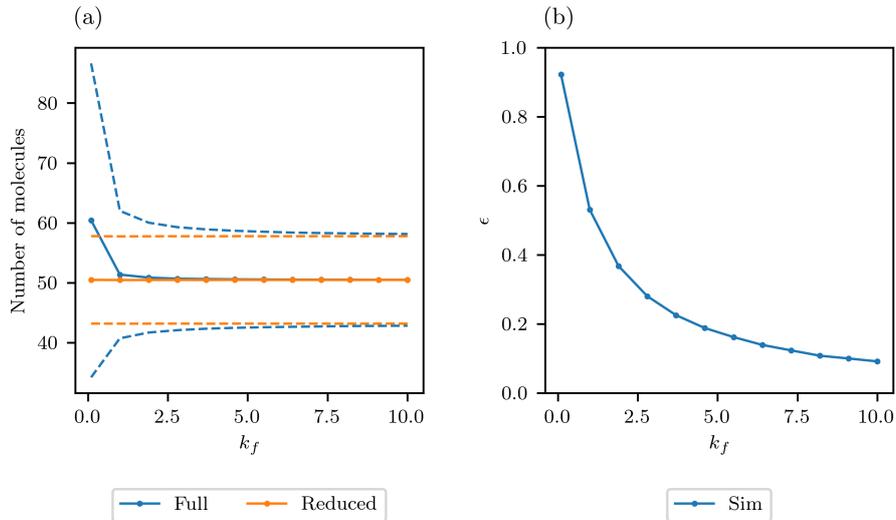


Fig. 3 Comparison of the full ((11)) and the reduced system ((12)) for the model shown in Figure 2. While varying k_f between 10^{-1} to 10^1 we plot (a) the mean and standard deviation of the stationary distribution of the repressor for both models and (b) the relative error in variance (Equation (13)) between the stationary distribution of the repressor for the two systems. The standard deviation is shown as a dashed line in the corresponding colour in (a). The discrepancy between the models is higher for smaller values of k_f . All other parameters have the same value as the ones considered in Figure 2.

is

$$\epsilon = \frac{-(1-\alpha)\alpha\beta}{1+\beta(1-\alpha(1-\alpha))}, \quad (16)$$

where $\alpha = k_0/(k_2E_T)$ and $\beta = k_2/k_{-1}$ [20]. We compare the variances of the stationary distributions of the full and reduced systems, using (13), and further, compare this prediction with the predicted value of ϵ using (16). Figure 4 shows the effect of varying the production rate k_0 of species S, and varying the dissociation rate k_{-1} of the complex \overline{ES} . We consider two regimes of the parameter space that lead to large number of molecules (Figure 4(a) and (c)) and small number of molecules (Figure 4(b) and (d)), corresponding to $k_0 = .03$ and $k_0 = 0.0003$, resp.

In both regimes the means of the stationary distributions of the full and reduced systems show good agreement, as seen in Figure 4(a) and (b). However, the variances of the stationary distributions show larger differences, particularly in the regime of large numbers, as shown in Figure 4(c). Large negative values of ϵ for small values of k_{-1} in Figure 4(c) indicate that the variance in the reduced system is larger than in the full system in this parameter regime. Increasing the value of k_{-1} in Figure 4(c) increases ϵ , which indicates that the variances of the stationary dis-

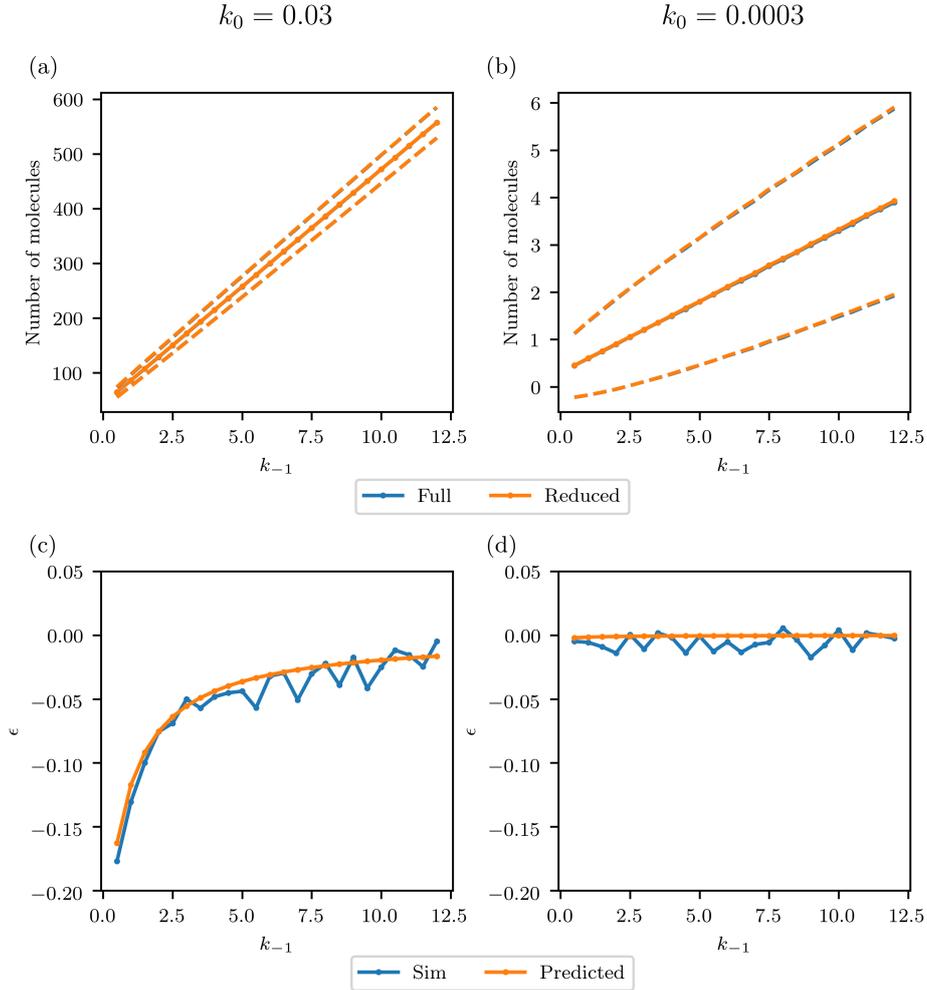


Fig. 4 Comparison of simulations for the full and reduced systems with $k_1 = 1.0, k_2 = 1.0$. We vary k_{-1} from 0 to 12, and display two cases for k_0 : 0.03 (left column) and 0.0003 (right column). The mean of the stationary distribution for both systems changes as we vary k_{-1} for $k_0 = 0.03$, shown in (a), and $k_0 = 0.0003$, shown in (b). In (c) and (d), we show how ϵ varies for the simulations and the predicted value in (16). In (c) we see that decreasing k_{-1} , increases the disagreement of the variances between the full and the reduced system with $k_0 = 0.03$, in both the simulations and the predictions, whereas (d) shows that when $k_0 = 0.0003$, there is little difference between the variances.

tributions agree better for large values of k_{-1} in the regime of large copy numbers. There is little difference between the two, either from the simulations or the theoretical prediction, when the copy numbers are small (Figure 4 (d)). When we compare

values of ε between systems with $k_0 = 0.03$ and with $k_0 = 0.0003$ (Figure 4(c) and Figure 4(d) respectively), we see that the reduced model captures the variance of the system better in the case $k_0 = 0.0003$, which may be due to the fact that it is in the low-copy number regime and as a result, the variance of the system is restricted to much smaller values than in the case of $k_0 = 0.03$. In all cases the difference between the ε computed from the simulations and that using (16) is relatively small.

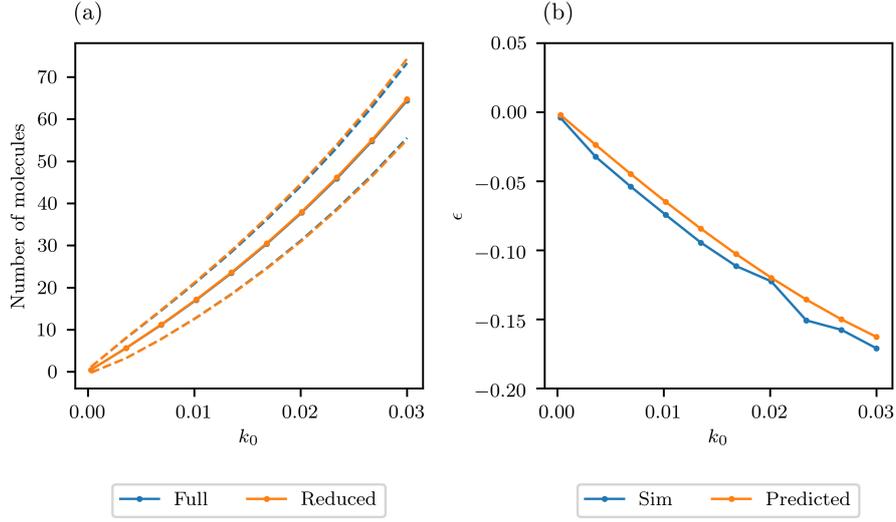


Fig. 5 Comparison of simulations for the full and reduced systems with $k_1 = 1.0$, $k_{-1} = 0.5$, $k_2 = 1.0$ and values of k_0 from 0 to 0.03. The mean of the stationary distribution for both systems increases as k_0 is increased, as shown in (a). In (b), we see that the difference in the variances between the full and the reduced systems increases as we increase k_0 .

To further study how the stationary distributions of the two systems differ in different parameter regimes, we studied how the means and variances of the stationary distributions change as the input rate k_0 is varied, while keeping the other parameters constant. Figure 5 shows how the means and the values of ε change. As expected, increasing the value of k_0 at fixed values of other reaction rates leads to an increase in the copy number of S (Figure 5(a)), and also in the difference between the variances in the stationary distributions, as shown in Figure 5(b). The latter agrees with the results shown in Figure 4, where increasing the value k_0 , especially for low values of k_{-1} , increases the difference between the variance of the stationary distributions.

3 Conclusions

Herein we have reviewed some of the previous works that analyse the suitability of applying the rate laws derived from the deterministic QSSA to stochastic systems. By analysing two specific chemical systems, we observed that the QSSA applied to stochastic systems does not have the same range of validity as when it is applied to deterministic systems. Specifically, the criterion ensuring the accuracy of the QSSA reduced rate equations, does not ensure the accuracy of the QSSA reduced master equations. In the first system we studied an example in which the reduced system underestimates the variance of the full system, and in the second system we observed the opposite behaviour. It has been shown that for those parameter regimes such that chemical systems are in rapid equilibrium and simultaneously the deterministic QSSA holds, the QSSA reduced master equation is in good agreement with the full master equation, at least for the case of small molecule number fluctuations [21, 19, 7]. While several works have been developed to analyse the suitability of the QSSA in the stochastic framework, universal conditions under which the QSSA approximation is applicable remain to be developed. In particular, currently there is no equivalent of Eq. (8) guaranteeing the validity of the QSSA reduced master equations for general chemical reaction networks. At present the best alternative to applying the QSSA is to apply the more rigorous approach developed in [9].

References

1. Agarwal, A., Adams, R., Castellani, G.C., Shouval, H.Z.: On the precision of quasi steady state assumptions in stochastic dynamics. *The Journal of Chemical Physics* **137**(4), 044,105 (2012). DOI 10.1063/1.4731754. URL <http://aip.scitation.org/doi/10.1063/1.4731754>
2. Balázsi, G., van Oudenaarden, A., Collins, J.J.: Cellular decision making and biological noise: from microbes to mammals. *Cell* **144**(6), 910–925 (2011)
3. Ball, P., Borley, N.R.: *The self-made tapestry: pattern formation in nature*, vol. 198. Oxford University Press Oxford (1999)
4. Barik, D., Paul, M.R., Baumann, W.T., Cao, Y., Tyson, J.J.: Stochastic simulation of enzyme-catalyzed reactions with disparate timescales. *Biophysical journal* **95**(8), 3563–74 (2008). DOI 10.1529/biophysj.108.129155. URL <http://www.ncbi.nlm.nih.gov/pubmed/18621809> <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2553150>
5. Darden, T.A.: Enzyme kinetics: stochastic vs. deterministic models. *Instabilities, bifurcations, and fluctuations in chemical systems* (Austin, Tex., 1980) pp. 248–272 (1982)
6. Elowitz, M.B., Levine, A.J., Siggia, E.D., Swain, P.S.: Stochastic gene expression in a single cell. *Science* **297**(5584), 1183–1186 (2002)
7. Gillespie, D., Sanft, K., Petzold, L.: Legitimacy of the stochastic MichaelisMenten approximation. *IET Systems Biology* (2011). DOI 10.1049/iet-syb.2009.0057
8. Goutsias, J.: Quasiequilibrium approximation of fast reaction kinetics in stochastic biochemical systems. *J. Chem. Phys.* **122**, 184,102– (2005)
9. Kan, X., Lee, C.H., Othmer, H.G.: A multi-time-scale analysis of chemical reaction networks: II. Stochastic systems. *Journal of Mathematical Biology* **73**(5), 1081–1129 (2016). DOI 10.1007/s00285-016-0980-x
10. Kang, H.W., Kurtz, T.G., et al.: Separation of time-scales and model reduction for stochastic reaction networks. *The Annals of Applied Probability* **23**(2), 529–583 (2013)

11. Kim, J.K., Josić, K., Bennett, M.R.: The Validity of Quasi-Steady-State Approximations in Discrete Stochastic Simulations. *Biophysical Journal* **107**(3), 783–793 (2014). DOI 10.1016/J.BPJ.2014.06.012. URL <https://www.sciencedirect.com/science/article/pii/S0006349514006183>
12. Kim, J.K., Josić, K., Bennett, M.R.: The relationship between stochastic and deterministic quasi-steady state approximations. *BMC systems biology* **9**(1), 87 (2015). DOI 10.1186/s12918-015-0218-3. URL <http://www.biomedcentral.com/1752-0509/9/87>
13. Kurtz, T.G.: The Relationship between Stochastic and Deterministic Models for Chemical Reactions. *The Journal of Chemical Physics* **57**(7), 2976–2978 (1972). DOI 10.1063/1.1678692. URL <http://aip.scitation.org/doi/10.1063/1.1678692>
14. Lawson, M.J., Petzold, L., Hellander, A.: Accuracy of the Michaelis-Menten approximation when analysing effects of molecular noise. *Journal of the Royal Society, Interface* **12**(106), 20150,054 (2015). DOI 10.1098/rsif.2015.0054. URL <http://www.ncbi.nlm.nih.gov/pubmed/25833240>
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4424680>
15. Lee, C.H., Othmer, H.G.: A multi-time-scale analysis of chemical reaction networks: I. Deterministic systems. *Journal of Mathematical Biology* **60**(3), 387–450 (2010). DOI 10.1007/s00285-009-0269-4
16. Othmer, H.G.: Analysis of complex reaction networks in signal transduction, gene control and metabolism (2006). Lecture Notes – University of Minnesota
17. Rao, C.V., Arkin, A.P.: Stochastic chemical kinetics and the quasi-steady-state assumption: Application to the Gillespie algorithm. *The Journal of Chemical Physics* **118**(11), 4999–5010 (2003). DOI 10.1063/1.1545446. URL <http://aip.scitation.org/doi/10.1063/1.1545446>
18. Segel, L.A., Slemrod, M.: The Quasi-Steady-State Assumption: A Case Study in Perturbation. *SIAM Review* (1989). DOI 10.1137/1031091
19. Thomas, P., Grima, R., Straube, A.V.: Rigorous elimination of fast stochastic variables from the linear noise approximation using projection operators. *Physical Review E* **86**(4), 41,110 (2012)
20. Thomas, P., Straube, A.V., Grima, R.: Communication: Limitations of the stochastic quasi-steady-state approximation in open biochemical reaction networks. *Journal of Chemical Physics* **135**(18), 1–7 (2011). DOI 10.1063/1.3661156
21. Thomas, P., Straube, A.V., Grima, R.: The slow-scale linear noise approximation: An accurate, reduced stochastic description of biochemical networks under timescale separation conditions. *BMC Systems Biology* **6** (2012). DOI 10.1186/1752-0509-6-39
22. Tsimring, L.S.: Noise in biology. *Reports on Progress in Physics* **77**(2), 026,601 (2014)