Product-form stationary distributions for deficiency zero networks with non-mass action kinetics: Errata in Example 1

David F. Anderson*†, Simon Cotter‡†

January 16, 2017

Abstract

Post-publication a small error was found in Example 1, a typo which also lead to comparing the QSSA and constrained approximations to the wrong distribution. Below we represent this material with the amendments highlighted in red, along with a corrected Figure 1. This didn't overly affect the presentation of the example, but did underplay the accuracy of the constrained approach for this example.

1 Examples

1.1 Example 1: Motivating Example

First we consider a motivating example arising from model reduction, through constrained averaging [2, 3, 4], of the following system:

$$2S_1 \underset{\kappa_2 x_2}{\overset{\kappa_1 x_1(x_1-1)}{\rightleftharpoons}} S_2, \quad \emptyset \xrightarrow{\kappa_3} S_2, \quad S_2 \xrightarrow{\kappa_4 x_1} \emptyset, \tag{1}$$

where the intensity functions are again placed next to the reaction arrows. Note that the intensities of all the reactions follow mass action kinetics. We consider this system in a parameter regime where the reversible dimerization reactions $2S_1 \rightleftharpoons S_2$ are occurring more frequently than the production and degradation of S_2. Both S_1 and S_2 are changed by the fast reactions, but the quantity $S = S_1 + 2S_2$ is invariant with respect to the fast reactions, and as such is the slow variable in this system. We wish

*Department of Mathematics, University of Wisconsin, Madison, USA. anderson@math.wisc.edu, grant support from NSF-DMS-1318832 and Army Research Office grant W911NF-14-1-0401.

†DFA and SLC would like to thank the Isaac Newton Institute for Mathematical Sciences, Cambridge, for support and hospitality during the program Stochastic Dynamical Systems in Biology: Numerical Methods and Applications, where work on this paper was undertaken. This work was supported by EPSRC grant no EP/K032208/1.

‡Department of Mathematics, University of Manchester, Manchester, UK. simon.cotter@manchester.ac.uk, grant support from EPSRC first grant EP/L023393/1.

to reduce the dynamics of this system to a model only concerned with the possible changes in S:

$$\emptyset \xrightarrow{\bar{\lambda}_3(s)} 2S, \quad S \xrightarrow{\bar{\lambda}_4(s)} \emptyset, \tag{2}$$

where $\bar{\lambda}_3(s)$ and $\bar{\lambda}_4(s)$ are the effective rates of the system.

Using the QE approximation (QEA), $\bar{\lambda}_3(s) = \kappa_3$ and $\bar{\lambda}_4(s) = \kappa_4 \mathbb{E}_{\pi_{\text{QEA}}(s)}[X_1]$, where $\pi_{\text{QEA}}(s)$ is the stationary distribution for the system

$$2S_1 \underset{\kappa_4 x_2}{\overset{\kappa_1 x_1(x_1-1)}{\rightleftharpoons}} S_2, \tag{3}$$

under the assumption that $X_1(0) + 2X_2(0) = s$. Since the system (3) satisfies the necessary conditions of the results of [1] (weak reversibility and deficiency of zero), the invariant distribution $\pi_{\text{QEA}}(s)$ is known exactly.

In comparison, the constrained approach requires us to find the invariant distribution π_{Con} of the following system:

$$2S_1 \underset{(\kappa_2+\kappa_4)x_2}{\overset{\kappa_1 x_1(x_1-1)+\kappa_3 \mathbb{1}_{\{x_1>1\}}}{\rightleftharpoons}} S_2, \tag{4}$$

subject to $X_1(0) + 2X_2(0) = s$. Readers interested in seeing how this is derived should refer to [2]. This network is weakly reversible, and has a deficiency of zero. However, the form of the rates in this system do not satisfy the conditions specified in [1]. In the context of constrained averaging, this lack of a closed form for the stationary distribution would result in the need for some form of approximation of the stationary distribution. There are two common methods utilized for performing this approximation. One possibility would be to perform exhaustive stochastic simulation of the system (4). Another option involves finding the distribution by finding the null space of the adjoint of the generator (see the discussion in and around (5)). However, as the state space of (4) will typically be huge, the latter method often involves truncating the state space and approximating the actual distribution with that of the stationary distribution of the truncated system [2]. Both approaches will lead to approximation errors and varying amounts of computational cost. However, note that the system (4) does satisfy Assumption 1, with $\alpha_1 = 2$ and $\alpha_2 = 1$. We denote the rate of dimerization by λ_D and its reverse by λ_{-D}. Therefore

$$\begin{aligned}
\lambda_D(x) &= k_1 x_1(x_1-1) + k_3 \mathbb{1}_{\{x_1>1\}}, \\
&= k_1 \left(x_1(x_1-1) + \frac{k_3}{k_1} \mathbb{1}_{\{x_1>1\}} \right), \\
&= k_1 \theta_1(x_1),
\end{aligned}$$

with θ_1 defined in the final equality. The form of the rate of the reverse reaction is much simpler, and is given by

$$\lambda_{-D}(x) = (k_2+k_4)x_2 = (k_2+k_4)\theta_2(x),$$

which defines θ_2.

By Theorem 2, we can write down the stationary distribution of this system. The complex balanced equilibrium of the associated deterministically modeled system with

$c_1 + 2c_2 = 1$, is given by $(c_1, c_2) = \left(\frac{\sqrt{(k_2+k_4)(k_2+8k_1+k_4)}-k_2-k_4}{4k_1}, \frac{1-c_1}{2} \right)$. Then by Theorem 2, and by recalling that all states (x_1, x_2) in the domain satisfy $s = x_1 + 2x_2$, the stationary distribution for S_2 is given by

$$\pi_{\text{Con}}(x_2) = \frac{1}{\Gamma_{\text{Con}}} \frac{c_1^{(s-2x_2)}}{\prod_{j=0}^{\lfloor (s-2x_2)/2 \rfloor - 1} \left((s-2x_2-2j)(s-2x_2-2j-1) + \frac{k_3}{k_1} \right)} \frac{c_2^{x_2}}{x_2!}, \tag{5}$$

where Γ_{Con} is a normalization constant and s is the conserved quantity. Note that the indicator function in θ_1 (in the denominator) has disappeared since it is always equal to one over the domain of the product.

We can compare (5) with the distribution of (3), which arises from the QEA, and also with the distribution of the full system (1) conditioned on $S_1 + 2S_2 = s$ (which can be approximated by finding the null space of the adjoint of the generator of the full system on the truncated domain). First we consider the QEA approximation. The invariant distribution of the fast subsystem (3) can be found using Theorem 1, and is given by

$$\pi_{\text{QEA}}(x) = \frac{1}{\Gamma_{\text{QEA}}} \frac{d_1^{s-2x_2}}{(s-2x_2)!} \frac{d_2^{x_2}}{x_2!}, \tag{6}$$

where $(d_1, d_2) = \left(\frac{\sqrt{k_4(8k_1+k_4)}-k_4}{4k_1}, \frac{1-d_1}{2} \right)$ is the complex balanced equilibrium for this system satisfying $d_1 + 2d_2 = 1$, and Γ_{QEA} is a normalizing constant.

Since the full system (1) does not have a deficiency of zero, we are not able to find its invariant distribution directly. However, by truncating the state space appropriately, we are able to approximate the full distribution by constructing the generator on this truncated state space and finding the null space of the adjoint.

Once we have approximated the null space of the truncated generator, we can find the approximation of $\mathbb{P}(X_2 = x_2 | X_1 + 2X_2 = s)$ by taking the probabilities of all states with $x_1 + 2x_2 = s$ and renormalizing. In what follows, we truncated the domain of the generator to $x \in \{0, 1, \ldots, 1000\} \times \{0, 1, \ldots, 500\}$.

We consider the system (1) with parameters given by:

$$k_1 = 1, \qquad k_2 = 100, \qquad k_3 = 1500, \qquad k_4 = 30. \tag{7}$$

Note that it is not obvious from these rates that the reactions with rates k_3 and k_4 are in fact the slow reactions in this system. The invariant density is largely concentrated in a small region centered close to the point $x = (99, 114)$. By using the approximation of the invariant density that we have computed on the truncated domain, we can compute the expected ratio between occurrences of the fast reactions with rates k_1 and k_2 with the slow reactions with rates k_3 and k_4. For this choice of parameters, the expected proportion of the total reactions which are fast reactions (dimerization/disassociation) is 82.68%. This indicates a difference in timescales between these reactions, but the difference is not particularly stark, and as such we would expect there to be significant error in any approximation relying on the QEA.

Figure 1 shows the three approximations of the distribution $\mathbb{P}(X_2 = x_2 | X_1 + 2X_2 = 300)$ for the system (1) with parameters given by (7). The constrained and QEA approximations are computed using (5) and (6) respectively, with the normalizing

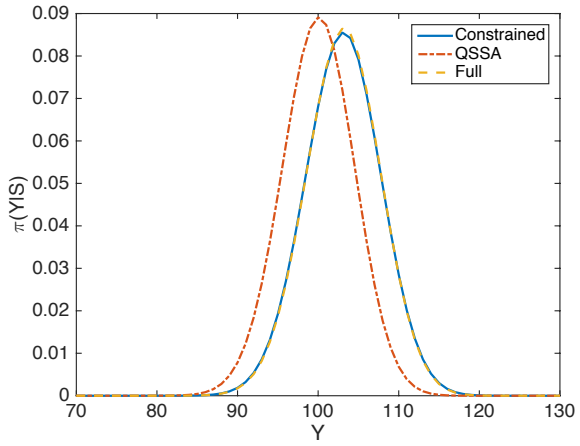

Figure 1: Approximations of the distribution $\mathbb{P}(X_2 = x_2 | X_1 + 2X_2 = 300)$ for the system (1) with parameters given by (7) using constrained averaging, QEA averaging, and through approximation of the invariant distribution of the full system on $x \in \{0, 1, \ldots, 1000\} \times \{0, 1, \ldots, 500\}$.

constants computed numerically. As would be expected in this parameter regime, the constrained approximation is far more accurate than the QEA.

We can quantify the accuracy of each of the approximations by computing the relative l^2 differences with the distribution computed using the full generator on the truncated domain. This relative difference was 4.760×10^{-1} for the QEA, in comparison with 1.0897×10^{-2} for the constrained approximation. The Kullback-Leibler divergences of these two approximations with respect to the true distribution were 2.2291×10^{-1} and $1.5304e \times 10^{-4}$ for the QEA and constrained approximations respectively. This demonstrates the improvement in approximation that can be achieved by using constrained averaging, and which motivates the need for results like Theorem 2 which take non-mass action kinetics into account.

References

[1] David F. Anderson, Gheorghe Craciun, and Thomas G. Kurtz. Product-form stationary distributions for deficiency zero chemical reaction networks. *Bull. Math. Biol.*, 72(8):1947–1970, 2010.

[2] Simon L. Cotter. Constrained approximation of effective generators for multiscale stochastic reaction networks and application to conditioned path sampling. *Journal of Computational Physics*, 323:265 – 282, 2016.

[3] Simon L. Cotter and Radek Erban. Error analysis of diffusion approximation methods for multiscale systems in reaction kinetics. *SIAM J. Sci. Comp.*, 38(1):144–163, 2016.

[4] Simon L. Cotter, Konstantinos C. Zygalakis, Ioannis G. Kevrekidis, and Radek Erban. A constrained approach to multiscale stochastic simulation of chemically reacting systems. *J. Chem. Phys.*, 135(9):094102, 2011.