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Maximum Entropy Prediction of Non-Equilibrium Stationary Distributions for Stochastic Reaction Networks with Oscillatory Dynamics.

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Abstract

Many chemical reaction networks in biological systems present complex oscillatory dynamics. In systems such as regulatory gene networks, cell cycle, and enzymatic processes, the number of molecules involved is often far from the thermodynamic limit. Although stochastic models based on the probabilistic approach of the Chemical Master Equation (CME) have been proposed, studies in the literature have been limited by the challenges of solving the CME and the lack of computational power to perform large-scale stochastic simulations.

In this paper, we show that the infinite set of stationary moment equations describing the stochastic Brusselator and Schnakenberg oscillatory reactions networks can be truncated and solved using maximization of the entropy of the distributions. The results from our numerical experiments compare with the distributions obtained from well-established kinetic Monte Carlo methods and suggest that the accuracy of the prediction increases exponentially with the closure order chosen for the system.

We conclude that maximum entropy models can be used as an efficient closure scheme alternative for moment equations to predict the non-equilibrium stationary distributions of stochastic chemical reactions with oscillatory dynamics. This prediction is accomplished without any prior knowledge of the system dynamics and without imposing any biased assumptions on the mathematical relations among species involved.

Keywords

Chemical Master Equation; Moment Closure; Oscillatory Reactions; Maximum Entropy

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1. Introduction

1.1. Biochemical Oscillators and Synthetic Biology

Ever since the Belousov-Zhabotinsky discovery (Belousov, 1959; Sagués and Epstein, 2003; Zhabotinsky, 1964), and with the molecular revolution in biology, an increasing number of experimental papers have been published on a variety of biological systems that exhibit oscillatory behavior (Novák and Tyson, 2008). In diverse contexts such as metabolism, signaling and cell development (Nelson et al., 2004; Tyson and Novák, 2010; Zatorsky et al., 2006), these oscillations control important features of cell physiology, including DNA synthesis, glycolysis (Higgins, 1964; Sel'kov, 1968), cyclic AMP production (Goldbeter, 1975), protein-interaction networks in the eukaryotic cell cycle (Ferrell et al., 2011; Kar et al., 2009; Pomerening and Kim, 2005), circadian rhythms (Goldbeter, 1995; Tyson et al., 1999), etc.

The mathematical modeling of synthetic biological systems through mapping of biomolecular interactions into small and well-characterized reaction networks is an important approach used to explain dynamical phenotypes (Adrianantoandro et al., 2006; Biliouris et al., 2012; Karen et al., 2003; Kaznessis, 2009; Salis and Kaznessis, 2005; Serrano, 2007; Smolke and Silver, 2011). The famous repressilator (Elowitz and Leibler, 2000), for instance, being the first synthetic gene network to exhibit sustained oscillations in engineered bacteria was a major achievement of synthetic biology.

According to classical thermodynamics, systems without heat and mass exchange with surroundings will naturally tend towards an equilibrium state. However, using Onsager's relations and detailed balance, Prigogine (1967) proved that even if the system is open (given isothermal conditions) and operating close to equilibrium it will approach a stable steady state. Therefore, it is currently recognized that some necessary conditions for sustained oscillations are that the system is nonlinear, open and far from equilibrium (Hearon, 1953; Prigogine, 1967; Shear, 1967).

1.2. Brusselator and Schnakenberg Models

The Brusselator (Herschkowitz-Kaufman and Nicolis, 1972; Lavenda and Nicolis 1971; Lefever, 1968; Lefever and Nicolis, 1971; Prigogine and Lefever, 1967, 1968; Nicolis, 1971; Nicolis and Portnow, 1973; Tyson, 1973) and the Schnakenberg (1979; Edelstein-Keshet, 2004) models are hypothetical sets of chemical reactions (Table 1.1) that can produce limit cycle oscillations and provide a qualitative description of biochemical oscillators. Since input reactants A and B are assumed to be chemical reservoirs, their concentration is lumped together with their respective rate constants. Hence, both models represent open systems and are constrained to be far from their equilibrium states.

One important feature of these oscillatory systems is the feedback nature provided by the autocatalytic step of the intermediate X (Novák and Tyson, 2008). For two-component systems, this step necessarily involves a trimolecular reaction, which makes them unrealistic (Tyson, 1973; Schnakenberg, 1979; Edelstein-Keshet, 2004). However, it also makes the system satisfy the mathematical requirements of the Poincaré-Bendixson theorem (Strogatz, 2015), which is sufficient to prove the existence of a closed orbit in the phase plane.

Considering the reaction steps as elementary and applying the law of mass action for each species, a set of coupled ODEs is derived (Table 1.1) that can be numerically solved (Figure 1). It is possible to transition—through what is called a Hopf bifurcation—from a stable solution (Figures 1a, 1d) to sustained oscillations (Figures 1b, 1e) by varying the kinetic parameters (Strogatz, 2015). As a result, a limit cycle is formed in the phase plane (Figures 1c, 1f). Although for each system there is only one steady state solution, the stability of the solution changes because the pair of eigenvalues of the Jacobian matrix of the system crosses the imaginary axis (Murray, 2002).

2. Theoretical Background

The design principles of deterministic biochemical oscillators are well-established in the literature (Novák and Tyson, 2008). However, in many biological applications the number of molecules involved is too small (e.g., in transcription there may be a single copy of a DNA molecule) for one to neglect fluctuations. Therefore, the internal noise or the inherent stochasticity for such systems has to be taken into account (Gillespie, 2007). The probabilistic model proposed by Oppenheim (1965) and McQuarrie (1967) that generated the famously known Chemical Master Equation (CME) is more appropriate (Gillespie, 1992; Van Kampen, 2004).

2.1. Chemical Master Equation

The Chemical Master Equation governs the probability distribution $\mathcal{P}_{\mu_i}$ of the molecular populations over time. It can be viewed as a balance equation between arriving and leaving each state $\mathbf{X}(t)$ of the system based on the concept of conservation of probability (Kaznessis, 2012). Define a state-change matrix $\mathbf{v} (N \times M)$, whose elements v_{ij} represent the stoichiometric coefficients of species i in reaction j for an isothermal chemical reaction network with N species and M reactions at constant volume. The Chemical Master Equation is given by:

$$\frac{\partial \mathcal{P}(\mathbf{X}, t)}{\partial t} = \sum_{j=1}^M \left[a_j(\mathbf{X} - \mathbf{v}_j) \mathcal{P}(\mathbf{X} - \mathbf{v}_j, t) - a_j(\mathbf{X}) \mathcal{P}(\mathbf{X}, t) \right] \quad (1)$$

where the propensity function $a_j(\mathbf{X})$ expresses the probability density that reaction j will occur in the next infinitesimal time interval. Its form depends on the reaction order, the rate constants and the number of possible combinations among reacting molecules (Gillespie, 2007).

2.1.1. Chemical Master Equation for the Brusselator Model—The CME for the Brusselator will be explicitly stated in this subsection to illustrate the use of Equation (1), while the Schnakenberg CME can be found in the Supplementary Material A. First, we define the state vector as $\mathbf{X} = [X \ Y]^T$ and from Table 1.1 its stoichiometric matrix is given by:

$$v = \begin{bmatrix} 1 & 1 & -1 & -1 \\ 0 & -1 & 1 & 0 \end{bmatrix} \quad (2)$$

The propensity function for each reaction channel is determined by the kinetic constants and the number of possible combinations for reactants to collide, according to the rate law equations. Hence:

$$a_1 = k'_1 A = k_1 \quad (3)$$

$$a_2 = k_2 X(X-1)Y \quad (4)$$

$$a_3 = k'_3 BX = k_3 X \quad (5)$$

$$a_4 = k_4 X \quad (6)$$

Therefore, plugging Equations (3)-(6) into Equation (1), we obtain the Chemical Master Equation for the Brusselator model:

$$\begin{aligned} \frac{\partial \mathcal{P}(X, Y, t)}{\partial t} = & k_1 \mathcal{P}(X-1, Y, t) + k_2 (X-1)(X-2)(Y+1) \mathcal{P}(X-1, Y+1, t) \\ & + k_3 (X+1) \mathcal{P}(X+1, Y-1, t) + k_4 (X+1) \mathcal{P}(X+1, Y, t) \\ & - [k_1 + k_2 X(X-1)Y + k_3 X + k_4 X] \mathcal{P}(X, Y, t) \end{aligned} \quad (7)$$

Observe that Equation (7) is in fact not a single equation but an infinite set of coupled equations; it is an implicit function of the probability distribution evaluated at other points of the phase space. As a result, the CME is analytically unsolvable for the Brusselator and the Schnakenberg models.

2.2. Moment Equations

An alternative approach through a series of mathematical transformations is to rewrite the CME in terms of probability moments. By definition, moments are expectation (or mean) values of functions of random variables. Therefore, it is a common method in probability theory and statistics to employ moment generating functions instead of working directly with probability distributions. The mathematical details behind this transformation will be omitted for simplicity, but they can be found in other references (Smadbeck and Kaznessis, 2012; Sotiropoulos and Kaznessis, 2010).

The main concept, however, is that the moments can be obtained from derivatives of these generating functions with respect to some introduced variable. Therefore, multiplying the chemical master equation (Eq. 1) by a multivariate moment generating function and summing over all states of the phase space leads to the dynamical equations of the moments describing the distribution itself. The final result takes the following canonical form of a set of differential equations evolving such moments:

$$\frac{d\boldsymbol{\mu}}{dt} = \boldsymbol{\mu}_0 + A\boldsymbol{\mu} + A'\boldsymbol{\mu}' \quad (8)$$

where $\boldsymbol{\mu}$ and $\boldsymbol{\mu}'$ are the vectors of lower and higher order moments, respectively, with A and A' being their coefficient matrices and $\boldsymbol{\mu}_0$ a constant vector. Since the dynamics of the lower order moments explicitly depends on the higher ones, this set of moment equations is underspecified. This infinite system needs to be truncated and closed in order to be solved.

2.2.1. Moment Equations for the Brusselator Model—Because both the Brusselator and the Schnakenberg models are two-component systems, the vector $\boldsymbol{\mu}$ up to the second order polynomial moments, for instance, is defined as:

$$\boldsymbol{\mu} = \begin{bmatrix} E(X) \\ E[Y] \\ E[X^2] \\ E[XY] \\ E[Y^2] \end{bmatrix} \quad (9)$$

After applying the transformation to the master equation of the Brusselator, Equation (7), the following system of ODEs for the lower order moments in Equation (9) can be found:

$$\frac{dE[X]}{dt} = k_1 - (k_3 + k_4)E[X] - k_2E[XY] + k_2E[X^2Y] \quad (10)$$

$$\frac{dE[Y]}{dt} = k_3E[X] + k_2E[XY] - k_2E[X^2Y] \quad (11)$$

$$\begin{aligned} \frac{dE[X^2]}{dt} = & k_1 + (2k_1 + k_3 + k_4)E[X] - 2(k_3 + k_4)E[X^2] - 5k_2E[XY] \\ & + 3k_2E[X^2Y] + 2k_2E[X^3Y] \end{aligned} \quad (12)$$

$$\begin{aligned} \frac{dE[XY]}{dt} = & -k_3 E[X] + k_1 E[Y] + k_3 E[X^2] + (3k_2 + k_3 - k_4)E[XY] - 2k_2 E[X^2Y] \\ & -k_2 E[XY^2] - k_2 E[X^3Y] + k_2 E[X^2Y^2] \end{aligned} \quad (13)$$

$$\frac{dE[Y^2]}{dt} = -k_3 E[X] + (2k_3 - k_2)E[XY] + k_2 E[X^2Y] + 2k_2 E[XY^2] - 2k_2 E[X^2Y^2] \quad (14)$$

However, note that many other higher order moments are needed to solve the system for first and second order dynamics, namely:

$$\boldsymbol{\mu}' = \begin{bmatrix} E[X^3] \\ E[X^2Y] \\ E[XY^2] \\ E[Y^3] \\ E[X^4] \\ E[X^3Y] \\ E[X^2Y^2] \end{bmatrix} \quad (15)$$

Hence, if we set the ODE system in Equations (10)-(14) into vector form, it becomes clear that the constant vector shown in Equation (8) for the Brusselator is given by:

$$\boldsymbol{\mu}_0 = \begin{bmatrix} k_1 \\ 0 \\ k_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (16)$$

While the square matrix A of constant coefficients for lower order moments becomes:

$$A = \begin{bmatrix} -(k_3 + k_4) & 0 & 0 & -k_2 & 0 \\ k_3 & 0 & 0 & k_2 & 0 \\ (2k_1 + k_3 + k_4) & 0 & -2(k_3 + k_4) & -5k_2 & 0 \\ -k_3 & k_1 & k_3 & (3k_2 - k_3 - k_4) & 0 \\ k_3 & 0 & 0 & (2k_3 - k_2) & 0 \end{bmatrix} \quad (17)$$

And finally the matrix A' of coefficients for higher order moments of the Brusselator is found to be:

$$A' = \begin{bmatrix} 0 & k_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 3k_2 & 0 & 0 & 0 & 2k_2 & 0 \\ 0 & -2k_2 & -k_2 & 0 & 0 & -k_2 & k_2 \\ 0 & k_2 & 2k_2 & 0 & 0 & 0 & -2k_2 \end{bmatrix} \quad (18)$$

Smadbeck and Kaznessis (2012) have developed efficient algorithms to generate these moment matrices for arbitrary networks (See Suppl. Mat. B for the Schnakenberg moment equations).

2.3. Zero-Information Closure Scheme

Most of the moment closure techniques currently found in the literature are based on the idea of assuming a specific functional form of the probability distribution. In this manner, the higher order moments are explicitly expressed only as functions of the lower order moments. Examples of probability distribution forms that are commonly assumed are normal, lognormal, binomial and Poisson (Gillespie, 2009; Singh and Hespanha, 2011).

Recently, our group proposed a closure scheme for the moment equations called Zero-Information, or ZI-closure (Smadbeck and Kaznessis, 2013). The method is based on the maximization of the entropy of the unknown probability distribution constrained to its lower order moments, so that higher order ones may be calculated.

According to the Maximum Entropy Principle (MEP), if some features of a probability distribution are known *a priori*, then one should look for the distribution with maximum uncertainty to get a full estimate that also satisfies the given knowledge (unbiased estimate) (Jaynes, 1957, 2003). Contrary to our common use of the word ‘information’, in the field of Information Theory more knowledge or certainty means less information (Gleick, 2011). Therefore, we can say that lower order moments contribute zero information, in the sense that they are fully determined by the closed set of moment equations, while higher order moments represent all the uncertainty and contain all the unknown features of the distribution.

Using the definition of information entropy (represented as H) introduced by Shannon (1948) as a measure of uncertainty or unexpectedness, it can be shown (Kapur, 1989; Sobczyk and Trebicki, 1999) that the resulting maximum information entropy distribution $p_H(X, Y)$ for a discrete bivariate system is given by:

$$p_H(X, Y) = \frac{\exp\left(-\sum_{i=1}^N \lambda_i f_{\mu i}(X, Y)\right)}{\sum_{\Omega} \exp\left(-\sum_{i=1}^N \lambda_i f_{\mu i}(X, Y)\right)} \quad (19)$$

where N_m is the number of lower-order moments, λ_i and f_{μ_i} are the Lagrange multiplier and the functional form of the i -th lower moment, respectively, and Ω corresponds to the bidimensional state space of all possible values for (X, Y) . The higher-order moments calculated from the most unbiased estimate of the distribution are:

$$\mu'_{H_i} = \sum_{\Omega} f_{\mu'_i}(X, Y) \mathcal{P}_H(X, Y) \quad (20)$$

where $f_{\mu'_i}$ now represents the functional form of the i -th higher-order moment. Replacing the unknown higher moments in equation (8) with the ones estimated from maximum uncertainty, the closed system of moment equations becomes:

$$\frac{d\mu}{dt} = \mu_0 + A\mu + A'\mu'_H \quad (21)$$

Although the approach has been validated for small networks of nonlinear chemical reactions with simple dynamics (Constantino et al., 2016; Smadbeck and Kaznessis, 2013), we present in this paper the first results for oscillatory systems.

3. Computational Method

Ensembles of kinetic Monte Carlo simulations were performed using different kinetic parameters to predict the stochastic behavior of the two models presented. In all experiments, 10^6 reaction trajectories were simulated in Hy3S (Salis et al., 2006) at the Minnesota Supercomputing Institute for Advanced Computational Research (MSI). From this sampling of the phase space, we calculated the frequency of the system visiting each state so that the probability distribution could be constructed. Even though each individual reaction trajectory for these systems in the oscillatory region is unstable and never settles to a steady state (Figure 2), the ensemble averages (i.e., moments) reach a stable stationary behavior. This is mainly because besides amplitude fluctuations across trajectories there are also phase fluctuations that eventually cancel each other out (Baras, 1997; Feistel and Ebeling, 1978). We could confirm whether the system had reached steady state by tracking these ensemble averages. For each system, stationary time points were defined as those where first and second order moment fluctuations were within 2% of their mean values.

The Brusselator SSA simulations were run using 400 processors and 2500 MB of used memory. The wall clock time ranged from 5 to 136 hours, while the total CPU time ranges from 35 hours to 45 days; all reaction trajectories were run in parallel at Itasca/MSI: an HP Linux cluster with nodes using Intel Xeon 5560 Nehalem EP processors. The Schnakenberg SSA simulations used 216 processors and 2500 MB memory. Wall clock time ranged from 3 minutes to 1 hour; total CPU time ranges from 1.2 to 5 hours; reaction trajectories run at Mesabi/MSI: an HP Linux cluster with nodes using Haswell E5-2680v3 processors.

The most important computational advantage of the ZI closure method is its ability to determine stationary solutions without supercomputing and without solving all previous dynamics. This particular feature drastically reduces the total computational cost of the method compared to SSA.

Setting the LHS of Equation (21) to zero and expressing both lower and higher moments in terms of the maximum entropy distribution generates a system of N_m nonlinear algebraic equations with N_m unknown Lagrange multipliers. The algorithm initially proposed by Smadbeck and Kaznessis (2013) used the null space of the augmented matrix $[A|A']$ in Equation (21) to find the set of Lagrange multipliers that satisfy the stationary distribution. The lower order moments plus the zeroth order moment constituted the independent vector basis of this null space. However, the matrix A for the Brusselator and Schnakenberg has the peculiar characteristic that one of its columns is zero, meaning that one of the lower order moments does not appear in any equation of the system of ODEs (see Suppl. Mat. B). Final results with ZI-closure were obtained for both systems by reframing the problem with the constraint that the sum of probabilities should add to one and using a direct Newton-Raphson method to calculate the multipliers—instead of computing the null space matrix. These iterations were implemented and performed off-line in MATLAB (Release 2015b, The MathWorks Inc., Natick, MA, United States).

For both the Brusselator and the Schnakenberg models the moment closure was performed from first to the twentieth order. The number of moments corresponding to a certain closure order increases in a combinatorial fashion. Therefore, in a two-component system, while the first order closure corresponds to two moments, the twentieth order yields 230 moments—because of all possible combinations of cross-moments. Resulting matrices from closure orders higher than 20 became ill-conditioned and were affected by the introduction of round-off errors.

A residual vector was defined whose elements corresponded to the difference between available data points from Gillespie's Stochastic Simulations Algorithm (SSA) and the theoretical model in Equation (19) in order to generate initial guesses for the Newton-Raphson iterations. A Linear Least Squares method was then used to obtain the optimal set of Lagrange multipliers that fits the distribution for different closure orders by minimizing the squares of the residuals of each SSA data point (Suppl. Mat. C).

The range of total computational time for LSQ estimation for initial guess of Lagrange multipliers plus ZI closure moment equations generation and NR iterations in CPU time is of 30 seconds to about 24 min, depending mostly on the size of the phase space for the systems presented in this paper. Further computational details of the methods are also available in Salis et al (2006) as well as in Smadbeck and Kaznessis (2012a, 2013).

4. Results and Discussion

Figure 3A indicates that the norm of the residual vector between SSA and the ZI-closure method decreases as the closure order increases for the Brusselator. The best fit for the data was selected on the basis of the coefficient of determination (R-squared) closest to unity.

This decay is observed for both dynamical regions of the model, but the rate is faster in the non-oscillatory region. Interestingly, the exponential decay is not initially evident in the oscillatory region. However, both trend lines after the fifth order closure—which were included for visualization—approach similar lower residues. From 3B we observe that the maximum entropy functional form fits better the distribution as we increase the closure order for the Schnakenberg model as well. Nonetheless, one difference from Figure 3A can be perceived. The trend curve for data points in the oscillatory region (orange) fails to reach the same level of low residues as in the non-oscillatory region within these 20 first closure orders.

Both plots in Figure 3 suggest that increasing the number of moments improves the quality of the description of the distribution regardless the parametric region of the dynamical system. Inductively, an infinite number of moments could perfectly describe the stationary distribution, but the gain of adding more moments becomes insubstantial.

For more quantitative comparison, Figure 4 records the 20 first moments (up to fifth order) of the distributions with the lowest residual norm in each dynamical region. The range of error for the Brusselator non-oscillatory region goes from 0.04% to 5.45% with an average value of 0.67% relative to SSA results. The error for the oscillatory distribution ranges from 0.09% to 4.76% with a slightly worse average performance of 2.51%. For the Schnakenberg model, the range of error for the non-oscillatory region goes from 0.13% to 2.46% with an average value of 1.12% relative to SSA results. The error for the Schnakenberg oscillatory distribution ranges from 0.68% to 12.09% with an average performance of 7.36%.

Figures 5 and 6 present the stationary probability distributions for Brusselator and Schnakenberg, respectively, using the closure orders with the lowest residual norm for the two different parametric regions: non-oscillatory (5A-C, 6A-C), and oscillatory regimes (5D-F, 6D-F). Before the bifurcation point, in the non-oscillatory region, the stationary probability distribution takes a 2-D Gaussian-like shape, as shown in Figure 5A and Figure 6A. Depending on the size of the system—how far or near from thermodynamic limit—this bell shape might be sharper (Figure 5A) or broader (Figure 6A). The peaks of these Gaussian distributions lie close to the stable deterministic solutions so that as the system size goes to infinity the Gaussian should become a delta function at the stable fixed points, according to the theory (Lemarchand, 1980).

From a quantitative perspective, the maximum entropy distribution is able to describe the non-oscillatory phenomena for the Brusselator reasonably well with as low as fifth order closure (Figure 3A). However, the accuracy can be improved with a 17th order closure, as shown in Figure 5(B, C). The necessity of 170 moments to neatly fit the distribution indicates that the distribution is not exactly Gaussian shaped, although we could have been misled by a superficial inspection of SSA results. For the Schnakenberg model, Figure 6(B, C) also confirms that the ZI closure prediction accurately matches the SSA distribution in the non-oscillatory region. We needed to go up to the 14th order to have the lowest residual (Figure 3B).

As the systems are shifted to their transition regions, the distributions begin to flatten against the X and Y axes as other local maxima appear. When oscillations are present at the individual trajectories level, the stationary distributions become topologically complex (Figure 5D and 6D) and develop craters of near zero probabilities. The distinct distribution peaks tell us that some of the states in the limit cycle are more likely to be visited than others, hence the trajectories spend more time in those states. This results from the fact that the periods of oscillations present different time scales—the oscillations do not have constant velocity—and hence each system travels faster along the diagonal leg of the limit cycle than along the axes (Gillespie, 1977; Lumsden, 1984). Nonetheless, Figure 5(E) and Figure 6(E) demonstrate that the simple product of exponentials of the moments—assumed by the Maximum Entropy Principle—is able to capture all the nuances of the distribution shape, however geometrically challenging they might be.

The oscillatory Schnakenberg system with the lowest residual was the one closed at the 15th order as shown in Figure 3B. Confirming the residual gap from the non-oscillatory results observed in Figure 3B, some noticeable error is present in Figure 6F and hence the fitted model fails to perfectly match the SSA distribution. However, it is remarkable that the product of exponentials of the distribution moments is able to take such complex shapes in the 3-dimensional space. All the qualitative features that are needed for the description are verified in the figure, namely the topological crater and the squeezing against the origin corner, just as in the deterministic limit cycle. Furthermore, we emphasize that the moments for this closure in the oscillatory region were quantitatively accurate (Figure 4B)

Our results indicate that for these two systems, the numerical performance of ZI-closure is generally lower in the oscillatory region, and then for the Schnakenberg more than for the Brusselator. We suggest that this issue is mainly related to the size of the phase space. The number of available SSA data points (i.e., visited states in the phase space) is larger for the oscillatory region than for the non-oscillatory region and specifically for the Schnakenberg model. Given that SSA simulations performed in all experiments included exactly a million trajectories, an increase in the number of data points means that our confidence in their probabilities is reduced (law of large numbers and uncertainty). A way to mitigate this error propagation to the calculation of moments would be to perform better sampling—e.g., taking averages not only across trajectories but also over stationary time intervals. On the other hand, the larger the size of the phase space, the more data points we have to fit into a model, and the more it gets intrinsically difficult to maintain low residual norms. Hence, the larger residuals and discrepancies for the oscillatory region and for the Schnakenberg models can be explained by a combination of such factors: larger size of the phase space and larger errors from SSA sampling.

The method, as presented in this paper, has a few theoretical and numerical limitations. The Chemical Master Equation approach, for instance, implicitly assumes that the reaction process is Markovian and that the time scale for reaction is much slower than the time scale for molecular collisions. By imposing the restriction that the system is well-stirred and most collisions are nonreactive, it becomes unnecessary to describe molecular positions and velocities. However, the model also loses its spatial dependence and the possibility of describing heterogeneous phenomena with diffusional symmetry breaking, which is very

characteristic of oscillatory reaction networks (e.g., Turing patterns). Therefore, it is our goal in the future to extend this moment closure scheme to include the implementation of reaction-diffusion problems. Even more challenging, perhaps, would be the implementation of reaction systems with 3 or more components in which there is a possibility of chaotic behavior due to the nonlinearity of the rate laws (Epstein and Showalter, 1996).

The two major numerical limitations of the current implementation are the high sensitivity to the initial guess and to the choice of size of the state-space for numerical convergence. ZI closure uses Newton-Raphson iterations to find the set of Lagrange multipliers that solves the nonlinear algebraic system of stationary moment equations. As with all Newton-Raphson implementations, the algorithm is guaranteed to have quadratic convergence to the solution, provided that the initial guess is sufficiently close to the same. Moreover, if the state-space defined is irreducible, then the stationary solution is unique (i.e., globally attracting). Therefore, choosing the smallest possible state space for each system and having a good initial guess for multipliers will speed up the computation, guarantee convergence to the correct solution and minimize numerical errors from ill-conditioning. However, the way we currently select the initial guess and the size of the space-state is by exploring the SSA solution first. Ideally, we would like to make both methods completely independent of each other.

Furthermore, the algorithm currently used for ZI-closure can only handle reactions with elementary kinetics, which greatly limits the range of application for simulations of more realistic systems. Because of many different challenges—such as lack of knowledge about reaction mechanisms or lack of experimental data of reliable kinetic constants for all reaction steps—not a few biochemical networks are modeled with Hill-type kinetics (e.g., Michaelis-Menten enzyme kinetics). These hyperbolic models already include approximations, such as quasi-steady state or near equilibrium assumptions, which simplify the mechanism of many gene regulatory systems exhibiting oscillatory behavior (Smadbeck and Kaznessis, 2012b). Therefore, it is of great interest to expand the implementation of ZI-closure algorithms to these types of reaction networks so that it can be directly applied to real systems.

Other numerical and practical limitations involve the ill-conditioning with increase in number of components and closure order; the current lack of dynamical results from ZI closure, with convergence only for stationary distributions; the scarcity of experimental kinetic constants and elementary reaction steps in the literature, which creates the need for an implementation of Hill-type kinetics for the simulations of more realistic biochemical reaction models;

5. Conclusion

Using mathematical models as an essential tool for understanding, designing and engineering new biological phenotypes, synthetic biologists can employ computational simulations and thereby generate hypotheses that may be tested experimentally. Even though it is a well-known fact that many natural phenomena in biological systems involve oscillatory chemical reaction networks, modeling such dynamical systems can be a

demanding task. This is mainly because biochemical reactions away from the thermodynamic limit are intrinsically stochastic.

We have established in this paper that the maximum entropy distribution is mathematically capable of describing the phenomenological bifurcations that distinctly characterize stochastic networks with oscillatory dynamics—namely going from Gaussian-like shapes to limit cycle crater developments. There exists a set of Lagrange multipliers capable of describing distributions with complex topography even such as oscillatory systems. More sophisticated optimization methods and other numerical developments can be employed to improve the estimation and minimize residual errors. However, that would be beyond the scope of this paper and shall be performed as future work. We conclude that the Maximum Entropy Principle works accurately as moment closure criterion for nonlinear stochastic biochemical reaction networks with oscillatory behavior.

In closing, we would like to briefly note that the field of Stochastic Thermodynamics has rapidly grown into a solid theoretical extension of the work of Onsager and Prigogine (Van den Broeck, 2013). New and profound reformulations of the second law based on an irreversible Markovian description of small systems have allowed the treatment of dissipative systems far from equilibrium (Esposito and Van den Broeck, 2010; Van den Broeck and Esposito, 2015). Even more interestingly for the field of biochemical engineering, Polettini et al. (2015) and Rao and Esposito (2016) have extended such theoretical developments to describe open and complex balanced chemical reaction networks, including oscillatory systems. Since this Stochastic Thermodynamics approach is built upon the Master Equation formulation, we also conclude that the results shown in this paper provide further confirming evidence for their theory. Conversely, the choice of maximum entropy as closure criteria for moment equations can hence be theoretically justified from a thermodynamics perspective.

Furthermore, the potential to derive analytical expressions for the stability analysis of nonlinear stochastic systems using this closure scheme is intriguing. We believe that such analysis will prove helpful in guiding the design of synthetic biological systems, which in turn will shed light on our understanding of natural phenomena.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Adrianantoandro E, Basu S, Karig DK, Weiss R, 2006, Synthetic biology: new engineering rules for an emerging discipline. *Mol. Syst. Biol.* 2, 28–42; DOI: [0.1038/msb4100073](https://doi.org/10.1038/msb4100073)
- Baras Florence, 1997, Stochastic analysis of limit cycle behavior *Stochastic Dynamics, Lecture Notes in Physics*, Springer Berlin Heidelberg, Volume 484, p. 167–178.
- Belousov BP, 1959, An oscillating reaction and its mechanism *Sb. Ref. Radiats. Med Medgiz*, Moscow, 145
- Biliouris K, Babson D, Schmidt-Dannert C, Kaznessis YN, 2012, Stochastic simulations of a synthetic bacteria-yeast ecosystem. *BMC systems biology* 6 (1), 58; DOI: 10.1186/1752-0509-6-58 [PubMed: 22672814]
- Constantino PH, Vlysidis M, Smadbeck P, Kaznessis YN, 2016, Modeling stochasticity in biochemical reaction networks. *J. Phys. D: Appl. Phys* 49 093001; DOI: 10.1088/0022-3727/49/9/093001
- Edelstein-Keshet L, 2004, *Mathematical Models in Biology Classics in Applied Mathematics*, University of British Columbia, Vancouver, Canada, pp. 311–380
- Elowitz MB, Leibler S, 2000, A synthetic oscillatory network of transcriptional regulators. *Nature*, 403, 335–338; DOI: 10.1038/35002125 [PubMed: 10659856]
- Epstein IR, Showalter K, 1996, Nonlinear chemical dynamics: oscillations, patterns and chaos, *J. Phys. Chem*, 100, 13132–13147; DOI: 10.1021/jp953547m
- Esposito M, Van den Broeck C, 2010, The three faces of the second law: I. Master equation formulation, *Phys. Rev. E* 82, 011143; DOI: 10.1103/PhysRevE.82.011143
- Feistel R, Ebeling W, 1978, Deterministic and stochastic theory of sustained oscillations in autocatalytic reaction systems. *Physica A* 93, 114–137; DOI: 10.1016/0378-4371(78)90213-3
- Ferrell JE, Jr., Tsai TY, Yang Q, 2011, Modeling the Cell Cycle: Why do Certain Circuits Oscillate? *Cell* 144, 874–885; DOI: 10.1016/j.cell.2011.03.006 [PubMed: 21414480]
- Gillespie DT, 1992, A rigorous derivation of the chemical master equation, *Physica A* 188: 404–425; DOI: 10.1016/0378-4371(92)90283-V
- Gillespie DT, 2007, Stochastic Simulation of Chemical Kinetics, *Ann. Rev. Phys. Chem* 58:35–55; DOI: 10.1146/annurev.physchem.58.032806.104637 [PubMed: 17037977]
- Gillespie CS, 2009, Moment-closure approximations for mass-action models. *IET Syst. Biol* 3, 52–58; DOI: 10.1049/iet-syb:20070031 [PubMed: 19154084]
- Gleick J, 2011, *The information: a history, a theory, a flood*; First ed. Vintage, New York.
- Goldbeter A, 1995, A model for circadian oscillations in the *Drosophila* period protein (PER). *Proc. Biol. Sci* 261, 319–324; DOI: 10.1098/rspb.1995.0153 [PubMed: 8587874]
- Goldbeter A, 1975, Mechanism for oscillatory synthesis of cyclic AMP in *Dictyostelium discoideum*. *Nature* 253, 540–542; DOI: 10.1038/253540a0 [PubMed: 163974]
- Hearon JZ, 1953, The kinetics of linear systems with special reference to periodic reactions. *Bull. Math. Biophys*, 15, 121–141; DOI: 10.1007/BF02476377
- Herschkowitz-Kaufman M, Nicolis G, 1972, Localized spatial structures and nonlinear chemical waves in dissipative systems. *J. Chem. Phys.* 56, 1890–1895; DOI: 10.1063/1.1677471
- Higgins J, 1964, A chemical mechanism for oscillation of glycolytic intermediates in yeast cells. *Proc. Natl Acad. Sci, USA* 51, 989–994 [PubMed: 14215656]
- Jaynes ET, 1957, Information theory and statistical mechanics, *Phys. Reviews* 106, 620–630. 108, 171–197; DOI: 10.1103/PhysRev.106.620
- Jaynes ET, 2003, *Probability Theory: The Logic of Science*. Ed Bretthorst GL Cambridge University press, Cambridge, UK, chap. 11.
- Kapur JN, 1989, *Maximum-Entropy Models in Science and Engineering*, first ed. New Age International Publishers, Delhi.
- Kar S, Baumann WT, Paul MR, Tyson JJ, 2009, Exploring the roles of noise in the eukaryotic cell cycle. *Proc. Natl. Acad. USA* 16, 6471–6476; DOI: [0.1073/pnas.0810034106](https://doi.org/10.1073/pnas.0810034106)
- Karen M, Blake WJ, Collins JJ, 2003, The engineering of gene regulatory networks. *Annu. Rev. Biomed. Eng.* 5, 179–206; DOI: 10.1146/annurev.bioeng.5.040202.121553 [PubMed: 14527313]

- Kaznessis YN, 2012, Statistical Thermodynamics and Stochastic Kinetics: An Introduction for Engineers, first ed. Cambridge University Press, Cambridge.
- Kaznessis YN, 2009, Computational methods in synthetic biology. *Biotechnol. J.* 4, 1392–1405; DOI: 10.1002/biot.200900163 [PubMed: 19830714]
- Lavenda B, Nicolis G, Herschkowitz-Kaufman M, 1971, Chemical instabilities and relaxation oscillations. *J. Theor. Biol.* 32, 283–292; DOI: 10.1016/0022-5193(71)90166-4 [PubMed: 5566787]
- Lefever R, 1968, Dissipative structures in chemical systems. *J. Chem. Phys.* 49, 4977–4978; DOI: 10.1063/1.1669986
- Lefever R, Nicolis G, 1971, Chemical instabilities and sustained oscillations. *J. Theor. Biol.* 30, 267–284; DOI: 10.1016/0022-5193(71)90054-3 [PubMed: 5548027]
- Lemarchand H (1980) Asymptotic solution of the master equation near a nonequilibrium transition: The stationary solutions. *Physica A*, 101, 518; DOI: 10.1016/0378-4371(80)90192-2
- McQuarrie DA, 1967, Stochastic approach to chemical kinetics. *J. Appl. Prob.* 4 413–478; DOI: 10.1017/S002190020002547X
- Murray JD, 2002, Mathematical biology I: An introduction, third ed. Springer, New York
- Nelson DE, Ihekweaba AEC, Elliott M et al., 2004, Oscillations in NF- κ B Control the Dynamics of Gene Expression. *Science*, 306, 704–708; DOI: 10.1126/science.1099962 [PubMed: 15499023]
- Nicolis G, 1971, Stability and Dissipative Structures in Open Systems far from Equilibrium. *Adv. Chem. Phys.* 19, 209–324; DOI: 10.1002/9780470143674.ch4
- Nicolis G, Portnow J, 1973, Chemical Oscillations. *Chem. Rev.* 73, 365–384; DOI: 10.1021/cr60284a003
- Novák B, Tyson JJ, 2008, Design Principles of Biochemical Oscillators. *Nature Reviews Molecular Cell Biology*, 9, 981–991; DOI: 10.1038/nrm2530 [PubMed: 18971947]
- Polettini M, Wachtel A, Esposito M, 2015, Dissipation in noisy chemical networks: The role of deficiency, *The Journal of Chemical Physics*, 143, 184103; DOI: 10.1063/1.4935064 [PubMed: 26567642]
- Pomerening JR, Kim SY, 2005, Systems-Level Dissection of the Cell-Cycle Oscillator: Bypassing Positive Feedback Produces Damped Oscillations. *Cell* 122, 565–578; DOI: [0.1016/j.cell.2005.06.016](https://doi.org/10.1016/j.cell.2005.06.016) [PubMed: 16122424]
- Prigogine I, 1967, Introduction to Thermodynamics of Irreversible Processes, third ed. Wiley-Interscience, New York.
- Prigogine I, Lefever R, 1967, On symmetry-breaking instabilities in dissipative systems. *J. Chem. Phys.* 46, 3542–3550; DOI: 10.1063/1.1841255
- Prigogine I, Lefever R, 1968, Symmetry-breaking instabilities in dissipative systems II. *J. Chem. Phys.* 48, 1695–1700; DOI: 10.1063/1.1668896
- Rao R, Esposito M, 2016, Nonequilibrium thermodynamics of chemical reaction networks: wisdom from stochastic thermodynamics, *Phys. Rev. X* 6, 041064; DOI: 10.1103/PhysRevX.6.041064
- Sagués F, Epstein IR, 2003, Nonlinear Chemical Dynamics. *J. Chem. Soc. Dalton Trans* 1201–1217; DOI: 10.1039/B210932H
- Salis H, Kaznessis YN, 2005, Numerical simulation of stochastic gene circuits, *Comp. Chem. Engin* 29 (3), 577–588, DOI: 10.1016/j.compchemeng.2004.08.017
- Salis H, Sotiropoulos V, and Kaznessis YN, 2006, Multiscale Hy3S: hybrid stochastic simulations for supercomputers *BMC Bioinf* 7 93; DOI: 10.1186/1471-2105-7-93
- Schnakenberg J, 1979, Simple chemical reaction systems with limit cycle behaviour. *J. Theor. Biol.* 81, 389–400 [PubMed: 537379]
- Sel'kov EE, 1968, Self-oscillation in glycolysis. 1. A simple kinetic model. *Eur. J. Biochem* 4, 79–86 ; DOI: 10.1111/j.1432-1033.1968.tb00175.x [PubMed: 4230812]
- Serrano L, 2007, Synthetic biology: promises and challenges. *Mol. Syst. Biol.* 3, 158; DOI: 10.1038/msb4100202 [PubMed: 18091727]
- Shannon CE, 1948, A mathematical theory of communication, *Bell System Tech J.*, 27, 379–423, 623–659; DOI: 10.1002/j.1538-7305.1948.tb01338.x

- Shear D, 1967, An analog of the Boltzmann H-theorem (a Liapunov function) for systems of coupled chemical reactions. *J. Theor. Biol.*, 16, 212–228; DOI: 10.1016/0022-5193(67)90005-7 [PubMed: 6048540]
- Singh A, Hespanha JP, 2011, Approximate moment dynamics for chemically reacting systems *IEEE Trans. Autom. Control*, 56, 414–418; DOI: 10.1109/TAC.2010.2088631
- Smadbeck P, Kaznessis YN, 2012, Efficient moment matrix generation for arbitrary chemical networks. *Chem Eng. Sci.*, 84, 612–618; DOI: 10.1016/j.ces.2012.08.031 [PubMed: 23175571]
- Smadbeck P., Kaznessis P, 2012b, Stochastic model reduction using a modified Hill-type kinetic rate law. *J. Chem. Phys* 137, 234109; DOI: 10.1063/1.4770273 [PubMed: 23267473]
- Smadbeck P, Kaznessis YN, 2013, A closure scheme for chemical master equations. *PNAS*, 110, 35:14261–65; DOI: 10.1073/pnas.1306481110 [PubMed: 23940327]
- Smolke CD, Silver PA, 2011, Informing Biological Design by Integration of Systems and Synthetic Biology. *Cell* 144, 855–859; DOI: 10.1016/j.cell.2011.02.020 [PubMed: 21414477]
- Sobczyk K, Trebicki J, 1999, Approximate probability distributions for stochastic systems: maximum entropy method. *Comput. Methods Appl. Mech. Engrg.*, 168, 91–111
- Sotiropoulos V, Kaznessis YN, 2010, Analytical derivation of moment equations in stochastic chemical kinetics. *Chem. Eng. Sci.*, 66, 268–277; DOI: 10.1016/j.ces.2010.10.024
- Strogatz SS, 2015, *Nonlinear Dynamics and Chaos*, second ed. Westview Press, Boulder, CO.
- Tyson JJ, 1973, Some further studies of nonlinear oscillations in chemical systems. *J. Chem. Phys.*, 58, 3919–3930; DOI: 10.1063/1.1679748
- Tyson JJ, Hong CI, Thron CD, Novák B, 1999, A simple model of circadian rhythms based on dimerization and proteolysis of PER and TIM. *Biophys. J* 77, 2411–2417; DOI: 10.1016/S0006-3495(99)77078-5 [PubMed: 20540926]
- Tyson JJ, Novák B, 2010, Functional Motifs in Biochemical Reaction Networks. *Ann. Rev. Phys. Chem.*, 61, 219–240; DOI: 10.1146/annurev.physchem.012809.103457.
- Van den Broeck C, 2013, Stochastic thermodynamics: a brief introduction. *Physics of Complex Colloids*, 184, pp.155–193; DOI: 10.3254/978-1-61499-278-3-155
- Van den Broeck C, Esposito M, 2015, Ensemble and trajectory thermodynamics: A brief introduction, *Physica A: Statistical Mechanics and its Applications*, 418, 6–16; DOI: 10.1016/j.physa.2014.04.035
- Van Kampen NG, 2004, *Stochastic processes in physics and chemistry*, Revised and enlarged edition, Elsevier, San Diego, CA.
- Zatorsky NG, Rosenfeld Net al, 2006, Oscillations and variability in the p53 system. *Molecular Systems Biology*, 2:n/a. DOI: 10.1038/msb4100068
- Zhabotinsky AM, 1964, Periodic process of the oxidation of malonic acid in solution. *Biofizika*, 9, 306–311 [PubMed: 14206238]

Highlights

- Maximum entropy is used as closure criterion for stochastic oscillatory reactions.
- Distributions are estimated without any prior knowledge of the system dynamics.
- No biased assumptions on the mathematical relations among species are imposed.
- Numerical results compare with more computationally costly Monte Carlo methods.
- Prediction accuracy increases exponentially with closure order.

Figure 1 |. Deterministic Brusselator (a-c) and Schnakenberg (d-f) models.

Concentration of intermediates X (solid line) and Y (dashed line). Plots (a-c). $k_1 = 625$, $k_3 = 50$, $k_4 = 5$. Plots (d-f). $k_1 = 0.55$, $k_2 = 3.1 \times 10^{-2}$, $k_3 = 5.0 \times 10^{-2}$, $k_4 = 3.1 \times 10^{-5}$. Initial conditions (X_0, Y_0) and stable steady states (X_{ss}, Y_{ss}) also pictured in phase planes (c) and (f).

Figure 2 |.
Sample reaction trajectories from kinetic Monte Carlo SSA for Brusselator (a, b) and Schnakenberg (c, d) models in non-oscillatory (a, c) and oscillatory (b, d) regions. Kinetic parameters presented in Figure 1.

Figure 3 |. Residual Norm and Closure Order.

Norm of the residual vector between SSA and ZI-closure moments with different closure orders for (A) the Brusselator and (B) the Schnakenberg models in the non-oscillatory (◆) and oscillatory (■) parametric regions. Exponential trend lines added to guide the eye. Kinetic parameters presented in Figure 1.

Figure 4 I. Numerical Comparison of Stationary Moments.

Magnitude of the first 20 moments of the stationary distributions obtained from SSA (points) and ZI-closure (lines) for (A) the Brusselator and (B) the Schnakenberg models. Lines were used to represent the ZI-closure results for better visualization. Kinetic parameters presented in Figure 1. Closure orders presented in Figures 5 and 6.

Figure 5 I. Brusselator Stationary Distributions.

(A-C) distribution for kinetic parameters in the non-oscillatory region; (D-E) in the oscillatory region. (A, D) SSA results; (B, E) ZI-closure at 17th and 19th orders, respectively, and initial Lagrange multipliers estimated from SSA distribution; (C, F) the absolute difference of each point of the phase space between SSA and ZI. Same color map is used for plots (A-C) and (D-F). Kinetic parameters presented in Figure 1.

Figure 6 | Schnakenberg Stationary Distributions.

(A-C) distribution for kinetic parameters in the non-oscillatory region; (D-E) in the oscillatory region. (A, D) SSA results; (B, E) ZI-closure at 14th and 15th orders, respectively, and Lagrange multipliers estimated from SSA distribution; (C, F) the absolute difference of each point of the phase space between SSA and ZI. Same color map is used for plots (A-C) and (D-F). Kinetic parameters presented in Figure 1.

Table 1.1 |

Brusselator and Schnakenberg models.

	Brusselator	Schnakenberg
<i>Reaction Network</i>	$A \xrightarrow{k_1} X$	$A \xrightarrow{k_1} B$
	$2X + Y \xrightarrow{k_2} 3X$	$X \xrightarrow{k_2} B$
	$B + X \xrightarrow{k_3} Y + C$	$B \xrightarrow{k_3} X$
	$X \xrightarrow{k_4} D$	$2X + Y \xrightarrow{k_4} 3X$
		$3X \xrightarrow{k_5} 2X + Y$
<i>Rate Law Equations</i>	$\frac{dX}{dt} = k_1 - (k_3 + k_4)X + k_2X^2Y$	$\frac{dX}{dt} = k_3 - k_2X + k_4X^2Y - k_5X^3$
	$\frac{dY}{dt} = k_3X - k_2X^2Y$	$\frac{dY}{dt} = k_1 - k_4X^2Y + k_5X^3$