



Short communication

A linearization method for probability moment equations

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ABSTRACT

We present a new method for calculating the time-transient behavior of stochastic reaction networks. We first derive the set of equations for the moments of the master probability distribution. We then linearize these equations calculating the Jacobian matrix around the stationary probability distribution. In order to demonstrate the method, we present examples of stochastic reaction networks and compute their dynamic behavior. We find that the calculations are accurate and significantly more efficient than stochastic simulation algorithms based on Gillespie's algorithms.

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1. Introduction

Linearization techniques have been developed for over six decades to solve non-linear initial value problems in chemical kinetics (Aris and Amundson, 1958; Bilous and Amundson, 1955; Schmitz and Amundson, 1963). Such techniques have also been applied to a plethora of other fields besides reaction kinetics (Kumar and Sridhar, 1964; Schei, 1997; Taylor, 1982; Wittwer et al., 2004; Yudovich, 1989).

Linearization of non-linear reaction rate equations requires knowledge of their steady-state solution. Using this information and an initial condition, linearized equations can be solved to compute time-dependent behaviors (Bequette, 1991; Bilous and Amundson, 1956).

In chemical engineering processes involving reacting systems, the canonical choice involves a continuous-deterministic modeling formalism, thereupon reaction kinetics of homogeneous systems are modeled with ordinary differential equations; the concentration of molecular species is a continuous variable, and reactions are events occurring with a certain frequency per unit time, per unit volume (Fogler, 2006).

An important hypothesis underlying the choice of a continuous-deterministic model is that the studied system is at the thermodynamic limit. At this limit the size of the system and the number of molecules of chemical species in the system are large enough

for the concentration to be accurately represented with a continuously changing variable (although the number of molecules is always discrete), and for the ensemble of individual reaction events to average out to the deterministic reaction rate (although each reaction event is a probabilistic one).

More recently stochastic reaction models have been the focus of numerous studies because they describe important aspects of biological processes more accurately than deterministic reaction kinetic models (Gillespie, 1992; Grima, 2012; Kampen, 2004). In biomolecular systems, the number of molecules of reacting species is often very small. Stochasticity then impacts the observed cellular phenotypes, requiring modeling formalisms that consider the inherent variability in biological systems (McQuarrie, 1967). For example, there may only exist a few copies of a mRNA molecule inside a cell that will react with the ribosome and produce protein. Modeling these translation events with ordinary differential equations may be distinctly false.

The prevalent techniques to model stochastic reaction networks have largely relied on Gillespie's stochastic simulation algorithms (Ale et al., 2013; Cao et al., 2004; Gillespie, 1976; 1992; Salis and Kaznessis, 2005a; 2005b). The SSA is an established modeling formalism that accurately captures the discrete and probabilistic nature of biomolecular interactions. However, the SSA and its numerous variants suffer from significant computational inefficiencies, principally because each reaction event is explicitly accounted for in the model. The computational challenge becomes insurmountable when there are system reactions with multiple, disparate time scales. The SSA will then spend inordinate amounts of computer

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time, simulating fast reaction events, in order to properly sample slower reaction events (Salis and Kaznessis, 2005a).

We and others have developed alternative methods for modeling stochastic reaction networks that rely on the moments of the probability distribution of these networks (Singh and Hespanha, 2006; Smadbeck and Kaznessis, 2012; Sotiropoulos and Kaznessis, 2011). Assuming the entropy of the network is maximum, we developed a closure scheme for probability moment equations. We have shown that this scheme can be employed to quickly and accurately compute the steady state of non-linear reaction networks (Constantino and Kaznessis, 2017; Constantino et al., 2016; Smadbeck and Kaznessis, 2013; 2015).

Based on this moment closure steady state approach, herein we propose a linearization method for probability moment equations to calculate the time-transient behavior of stochastic reaction networks close to steady state. We propose that this new method can be used to model reaction networks away from the thermodynamic limit, including biomolecular and metabolic reaction networks in biological systems.

In the following section, we present the theoretical underpinnings of the linearization method, first describing the derivation of moment equations.

2. Theory

A complete model for describing the time evolution of the probability distribution of a system with chemical reactions is the Chemical Master Equation (CME) (Gillespie, 1992; McQuarrie, 1967). For all its elegance, the CME is not often used in modeling reaction systems because it is not tractable for any but the simplest of reacting systems (Singh and Hespanha, 2006).

2.1. Moment equations

An alternative method for computing probability distributions relies on calculating probability moments. There exist different types of moments, such as central, factorial, or polynomial ones, all equally valid for describing the probability distribution (Gillespie, 2009; Kampen, 2004; Smadbeck and Kaznessis, 2012). The derivations in this document apply to any kind of probability moments.

Let us consider a chemical reaction network with N reactants and products. The state of the network is described by the N -dimensional vector $\mathbf{X} = (\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_N)$ that contains the number of molecules of each component (all reactants and products). If the functional form of the moment μ_i is denoted as f_{μ_i} (e.g. $f_{\mu_1} = X_1$, for the first moment of a single-dimensional system) then the moment itself is defined as follows:

$$\mu_i = \sum_{\mathbf{X}} f_{\mu_i}(\mathbf{X}) \cdot \mathbf{P}(\mathbf{X}; t) \quad (1)$$

where, $\mathbf{P}(\mathbf{X}; t)$ is the probability for the system to be at state \mathbf{X} at time t .

With no loss of information, CMEs can be transformed into moment equations through a Z-transform (Smadbeck and Kaznessis, 2012). The resulting moment equations are a set of coupled differential equations. The most general form for a system with elementary reaction rates is:

$$\frac{d\boldsymbol{\mu}}{dt} = \mathbf{A} \cdot \boldsymbol{\mu} + \mathbf{A}' \cdot \boldsymbol{\mu}' + \boldsymbol{\mu}_c \quad (2)$$

where $\boldsymbol{\mu}$ is the lower-order moment vector (not including the zero-order moment, which is always equal to 1), $\boldsymbol{\mu}'$ is the higher-order moment vector, $\boldsymbol{\mu}_c$ is a vector of constants, and t represents time.

In most cases, vectors $\boldsymbol{\mu}$ and $\boldsymbol{\mu}'$ have different dimensions (Gillespie, 2009). For nonlinear reaction networks, the $\boldsymbol{\mu}'$ vector

is nonempty. It is then apparent that the lower-order moments depend on the higher-order ones, and the set of equations cannot be closed (Smadbeck and Kaznessis, 2012). In 2012, we described a closure scheme that relies on the assumption that the entropy of a reacting system is maximum. The interested reader is referred to recent descriptions of the ZI-closure scheme where closure scheme algorithms are detailed (Constantino and Kaznessis, 2017; Constantino et al., 2016).

3. Calculation/linearization

Moment equations can be linearized around the stationary probability distribution by computing the steady state Jacobian (J_{ss}). By carrying out a Taylor expansion of the right side of Eq. (2) around the steady state, we can use the following approximation:

$$\frac{\partial \boldsymbol{\mu}}{\partial t} \approx \left. \frac{\partial \boldsymbol{\mu}}{\partial t} \right|_{ss} + J_{ss}(\boldsymbol{\mu} - \boldsymbol{\mu}_{ss}) \quad (3)$$

where the subscript ss stands for steady state, i.e. $\boldsymbol{\mu}_{ss}$ denotes the stationary probability moments. When evaluated at steady state the time derivative is zero ($\left. \frac{\partial \boldsymbol{\mu}}{\partial t} \right|_{ss} = \mathbf{0}$). As a result, Eq. (3) is simplified to

$$\frac{\partial \bar{\boldsymbol{\mu}}}{\partial t} = J_{ss} \bar{\boldsymbol{\mu}} \quad (4)$$

with $\bar{\boldsymbol{\mu}} = (\boldsymbol{\mu} - \boldsymbol{\mu}_{ss})$.

Section 3.1 provides details on the calculation of steady state Jacobians, based on the knowledge of stationary probability moments.

Eq. (4) has a known analytical solution (Gillespie, 1992), based on the eigenvalues (λ_e) and eigenvectors (\mathbf{v}) of the Jacobian matrix J_{ss} . Through an eigenvalue analysis (Davis and Thomson, 2000; Gillespie, 1992), Eq. (4) can be transformed into

$$\boldsymbol{\mu}(t) = \mathbf{v} \exp(\lambda_e t) \mathbf{v}^{-1} [\boldsymbol{\mu}(\mathbf{0}) - \boldsymbol{\mu}_{ss}] + \boldsymbol{\mu}_{ss} \quad (5)$$

where t is the time that the moment vector $\boldsymbol{\mu}$ is evaluated and \mathbf{v}^{-1} is the inverse of the eigenvector matrix \mathbf{v} .

With this method, one can calculate probability moments at any time, with only the knowledge of the stationary solution (i.e. the Jacobian matrix around the steady state) and an initial condition ($\boldsymbol{\mu}(\mathbf{0})$) of the moments.

3.1. Steady state Jacobian matrix

By definition, the Jacobian matrix is given by:

$$J_{ss} = \left. \frac{\partial \left[\frac{\partial \boldsymbol{\mu}}{\partial t} \right]}{\partial \boldsymbol{\mu}} \right|_{ss} = \mathbf{A} + \mathbf{A}' \left. \frac{\partial \boldsymbol{\mu}'}{\partial \boldsymbol{\mu}} \right|_{ss} \quad (6)$$

Smadbeck and Kaznessis (2013) developed ZI-closure scheme method to connect lower and higher order moments with the Lagrange multipliers (λ_m) of the maximum entropy distribution. Thus, with the use of the chain rule for partial derivatives the following stands

$$\left. \frac{\partial \boldsymbol{\mu}'}{\partial \boldsymbol{\mu}} \right|_{ss} = \left. \frac{\partial \boldsymbol{\mu}'}{\partial \lambda_m} \right|_{ss} \left. \frac{\partial \lambda_m}{\partial \boldsymbol{\mu}} \right|_{ss} = \left. \frac{\partial \boldsymbol{\mu}'}{\partial \lambda_m} \right|_{ss} \left(\left. \frac{\partial \boldsymbol{\mu}}{\partial \lambda_m} \right|_{ss} \right)^{-1} \quad (7)$$

The Jacobian matrix can be then expressed (Smadbeck and Kaznessis, 2015) as

$$J_{ss} = \mathbf{A} + \mathbf{A}' \left. \frac{\partial \boldsymbol{\mu}'}{\partial \lambda_m} \right|_{ss} \left(\left. \frac{\partial \boldsymbol{\mu}}{\partial \lambda_m} \right|_{ss} \right)^{-1} \quad (8)$$

In order to calculate the steady state Jacobian one needs to calculate matrices $\left. \frac{\partial \boldsymbol{\mu}'}{\partial \lambda_m} \right|_{ss}$ and $\left. \frac{\partial \boldsymbol{\mu}}{\partial \lambda_m} \right|_{ss}$.

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