18th World IMACS / MODSIM Congress, Cairns, Australia 13-17 July 2009
http://mssanz.org.au/modsim09

The Chemical Master Equation With Respect To Reaction Counts

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Abstract

It is well known that many realistic mathematical models of biological and chemical systems, such as enzyme cascades and gene regulatory networks, need to include stochasticity. These systems can be described as Markov processes and are modeled using the Chemical Master Equation (CME). The CME is a differential-difference equation (continuous in time and discrete in the state space) for the probability of certain state at a given time. The state space is the population count of species in the system. However we can also consider the CME with the state space given by the counts of the number of reactions occurring in the system. This form of CME is not frequently used in the literature. This paper, through new results, gives motivation towards considering computing the CME over the reaction counts rather than species counts.

Keywords: Chemical Master Equation, Systems Biology.

1 Introduction

Realistic mathematical models of biological and chemical systems need to include stochasticity, especially systems where single molecular events may dramatically affect the outcome of the system. When dealing with systems with small species counts, the deterministic models fail to capture the inherent randomness needed in the modeling of the system. A mathematical model which can be used to include stochasticity is the Chemical Master Equation(CME). This model is a differential-difference equation (continuous in time and discrete in the state space), which describes the probability of the system at a particular state at a given time. The CME is used to model systems such as enzyme cascades [LP07] and gene regulatory networks [HBS$^+$07]. Large systems can be solved using the CME [MBBS08]. We find that the CME has a unique solution, however the computation of the solution has the 'curse of dimensionality'. There exists a rich literature on methods of solving the CME, such as the Stochastic Simulation Algorithm(SSA) [Gil76] [Gil77], Finite State Projection Algorithm (FSPA) [KM06], Wavelet approximation [JG08] and Sparse grid methods [HHL08]. We shall describe some of these methods in more detail in the following sections. Our focus within this paper is not to write a new solver but to see the CME in a new light. We shall study a pre-existing formulation of the CME and highlight structure which has been overlooked before. We shall begin with the definition of the CME, followed by the formulation for the CME with respect to the reaction counts, instead of population counts. Once we have formulated the CME in this way, we shall present some new results and conclude with discussion regarding possible further research.

1.1 Mathematical Background

Let us consider a system of M distinct reacting species in a solution which has fixed temperature, is well-mixed and has fixed volume, where N independent reactions can occur. The CME that describes such a system is :

$$\frac{\partial P(\mathbf{x};t)}{\partial t} = \sum_{k=1}^{N} a_k(\mathbf{x}-\mathbf{v}_k)P(\mathbf{x}-\mathbf{v}_k;t) - \sum_{k=1}^{N} a_k(\mathbf{x})P(\mathbf{x};t), \tag{1}$$

where $P(\mathbf{x};t)$ is the probability of being at a state $\mathbf{x} \in \Omega \subset \mathbb{N}_0^M$ for a time t. Given a reaction $R_k : \Omega \to \Omega$, for $k \in \{1, \ldots, N\}$, the non negative *propensity function* of R_k is $a_k : \Omega \to \mathbb{R}^+$ and the *stoichiometric transition vector* of R_k is $\mathbf{v}_k := R_k(\mathbf{x}) - \mathbf{x}$. A more rigorous definition of a_k can be found in [Gil76]. For the purpose of this paper, the definition above is sufficient.

There is a very simple physical interpretation of the CME given in (1). The CME states that the flow of the probability of being at a state $\mathbf{x} \in \Omega$ at time t is equal to the probability of arriving at $\mathbf{x}$ using R_k, given by $a_k(\mathbf{x}-\mathbf{v}_k)P(\mathbf{x}-\mathbf{v}_k)$, minus the probability of leaving $\mathbf{x}$ by R_k, given by $a_k(\mathbf{x})P(\mathbf{x};t)$. Considering this over all possible reactions gives us (1).

Solving for $P(\mathbf{x},t)$ in (1) for $\mathbf{x} \in \Omega$, involves solving (1) simultaneously over all Ω. Hence solving the CME resolves to solving the following first order differential equation;

$$\frac{d\mathcal{P}(t)}{dt} = \mathbf{A}_s \mathcal{P}(t), \tag{2}$$

which is a coupled linear differential equation, where $\mathcal{P}(t)$ is a vector with components $P(\cdot,t)$. Even though we know the solution for (2) is $\mathcal{P}(t) = e^{\mathbf{A}_s t}\mathcal{P}(0)$, in many cases the systems we are interested in solving will have $|\Omega|$ infinite and $\mathbf{A}_s$ being singular, which invoke the difficulty of solving the CME. Techniques have been developed to deal with systems with high dimensional state spaces, two of which are FSPA and the State Space Aggregation method. The FSPA [KM06] numerically solves (2) by truncating the state space, making $\mathbf{A}_s$ finite dimensional and then computing $e^{\mathbf{A}_s t}\mathcal{P}(t)$. By truncating the state space we are inferring that the states outside the truncation have probability zero, therefore computing $P(\cdot,t)$ using the FSPA leads to an approximation of $P(\cdot,t)$. This can be a good assumption if we have the stationary points inside our truncated space, or if probabilities outside the truncated space die away to zero. Another method which deals with controlling the size state space is the State Space Aggregation method [HHL08]. In this method we aggregate the space, solve the aggregated CME and then disaggregate.

Let us consider the CME for the following example: We have a species S_1, undergoing decay over time. Let the initial population of S_1 be x_0, and the reaction rate at which the decay occurs be $c > 0$. We denote this in the following way: $S_1 \xrightarrow{c} *$.

Example 1. *Reaction:* $S_1 \xrightarrow{c} *$, *with initial population of* $x_0 \in \mathbb{N}$ *at* $t = 0$. *For this reaction we have* $a_1(x) = xc$, $x \in \mathbb{N}_0$. *The CME for this system is given by:*

$$\begin{aligned} \frac{dP(x_0;t)}{dt} &= -a_1(x_0)P(x_0;t) \\ &= -x_0 c P(x_0;t), \;\; t > 0 \\ \frac{dP(x;t)}{dt} &= a_1(x+1)P(x+1;t) - a_1(x)P(x;t) \\ &= (x+1)cP(x+1;t) - xcP(x;t), \;\; x \in 0, \ldots, (x_0-1), t > 0. \end{aligned}$$

The analytic solution for $x \in 0, \ldots, x_0$ *is given by,*

$$P(x;t) = \frac{x_0!}{x!(x_0-x)!} e^{-cxt}(1-e^{-ct})^{x_0-x}. \tag{3}$$

This particular solution is called the binomial process. The result is stated in [JG08] and [Gil77].

2 CME with Respect to Reaction Counts

The CME with respect to reaction counts was initially investigated as a method for solving systems with multiple time scaled reactions [HR05] [VR97]. It was not considered as a method for solving general systems. One of the possible reasons is that the system based on reaction counts needs to be truncated in order to be solved in practice, whereas the species based CME does not. We shall see this in detail below. We believe however that solving the CME with respect to reaction counts is simpler than solving with respect to species counts. This is based on a simpler structure found in the CME with respect to reaction counts, which is not available in general for the species based CME. We shall begin by stating the CME with respect to the reaction counts, following which we shall state the major results of this paper.

Given a system, we define the following two spaces; $\Omega \subset \mathbb{N}_0^M$ and $\Lambda \subset \mathbb{N}_0^N$, where M is the number of species and N the number of reactions. We define $\mathbb{V} = [\mathbf{v}_1, \ldots, \mathbf{v}_N]^T \in \mathbb{M}_{N\times M}$ to be the *stoichiometric matrix*, where $\mathbf{v}_i$ are the stoichiometric vectors defined in (1). Using the stoichiometric matrix we define an affine map $\Gamma : \Lambda \to \Omega$, by $\Gamma(\mathbf{r}) = x_0 + \mathbb{V}^T\mathbf{r}$ for $\mathbf{r} \in \Lambda$. Furthermore, let $\{\Gamma_{\mathbf{x}} = \Gamma^{-1}(\mathbf{x}) : \mathbf{x} \in \Omega\}$ be the set of equivalence classes defined by the mapping Γ.

By a standard application of the push forward measure, we attain;

$$P(\mathbf{x}; t) = \sum_{\mathbf{r}\in\Gamma_{\mathbf{x}}} \bar{P}(\mathbf{r}; t). \tag{4}$$

Using (1) and (4) we can derive the probability of a system being at $\mathbf{r} \in \Lambda$ at time t by the following version of the CME;

$$\frac{\partial \bar{P}(\mathbf{r}; t)}{\partial t} = \sum_{j=1}^{N} a_j(\mathbf{x}_0 + \mathbb{V}^T(\mathbf{r} - \mathbf{I}_j))\bar{P}(\mathbf{r} - \mathbf{I}_j; t) - \sum_{j=1}^{N} a_j(\mathbf{x}_0 + \mathbb{V}^T\mathbf{r})\bar{P}(\mathbf{r}; t), \tag{5}$$

where N is the number of reactions in the system and M is the number of species. Also a_j is defined as in (1), I_j is the unit vector in the jth coordinate and $\mathbb{V}$ is the stochiometric matrix of the system. Computing the CME with respect to reaction counts given in (4), is the same as the original CME given in (1). However we find it easier to solve (4) rather than (1). Similar to (2), we find the solution to (5) by solving the the following linear differential equation;

$$\frac{d\mathcal{P}(t)}{dt} = \mathbf{A}_r\mathcal{P}(t), \tag{6}$$

where $\mathcal{P}(t)$ is the vector in $[0, 1]^{|\Lambda|}$ with coordinates $\bar{P}(\mathbf{r}, t)$, $\mathbf{r} \in \Lambda$. In this formulation the $\mathbf{A}_r$ has a simpler structure than $\mathbf{A}_s$ given in (2). The following results given for $\mathbf{A}_r$ cannot be applied to $\mathbf{A}_s$ for all systems.

Remark 1. *If* Γ *is bijective, then solving the CME with respect to reaction counts is the same as solving the original CME. We can expect* Γ *to be bijective when* $\mathbb{V}^T$ *is invertible. If* $\mathbb{V}^T$ *is rectangular or not invertible, we can see from linear algebra that* $|\Gamma_{\boldsymbol{x}}|$ *will be infinite for all* $\boldsymbol{x} \in \Omega$.

Theorem 2. *Given a system with* M *species and* N *reactions with* $\mathbb{V}$ *as the stoichiometric matrix, if* $\Lambda \neq \emptyset$*, then the matrix* $\boldsymbol{A}_r$*, (c.f. (6)), can be arranged to be lower triangular such that the eigenvalues of* $\boldsymbol{A}_r$ *are given by* $\{\sum_{j=1}^{N} a_j(\boldsymbol{x}_0 + \mathbb{V}^T\boldsymbol{r}) \ : \ \boldsymbol{r} \in \Lambda\}$.

Proof. For a fixed $\mathbf{r} \in \Lambda$, from (5) we can deduce that $\bar{P}(\mathbf{r}; t)$ is only dependent on $\bar{P}(\mathbf{r}_1; t)$ where $\mathbf{r}_1 \in \Lambda$ with $|\mathbf{r}_1| < |\mathbf{r}|$. Here $|\cdot|$ is the l^1 norm. Hence we can arrange the elements of $\mathcal{P}$ in such a way that we will get $\mathbf{A}_r$ to be lower triangular. Since $\mathbf{A}_r$ is lower triangular, its eigenvalues are the diagonal elements. We know from (5) that the diagonal is given by the following set, $\{\sum_{j=1}^{N} a_j(\mathbf{x}_0 + \mathbb{V}^T\mathbf{r}) \ : \ \mathbf{r} \in \Lambda\}$. $\square$

Corollary 3. *If there exist distinct* $\boldsymbol{r}_1, \boldsymbol{r}_2 \in \Lambda$ *such that* $\boldsymbol{r}_1, \boldsymbol{r}_2 \in \Gamma_{\boldsymbol{x}}$ *for any* $x \in \Omega$*, then* $\boldsymbol{A}_r$ *has non unique eigenvalues.*

Proof. If there exists an $x \in \Omega$ such that $|\Gamma_{\mathbf{x}}| \geq 2$, then for any $\mathbf{r}_1, \mathbf{r}_2 \in \Gamma_{\mathbf{x}} \subset \Lambda$, $\sum_{j=1}^{N} a_j(\mathbf{x}_0 + \mathbb{V}^T\mathbf{r}_1) = \sum_{j=1}^{N} a_j(\mathbf{x}_0 + \mathbb{V}^T\mathbf{r}_2)$. Hence the two eigenvalues corresponding with $\mathbf{r}_1$ and $\mathbf{r}_2$ given in Theorem 2 are the same. $\square$

When $\mathbb{V}$ has lower rank, then by Corollary 3 we know that $\mathbf{A}_s$ has non-distinct eigenvalues.

Proposition 4. *Given a system with M species and N reactions with stoichiometric matrix $\mathbb{V}$, if $\Lambda \neq \emptyset$ and $\bar{P}(\cdot, 0) = \delta_{\mathbf{0}}(\cdot)$, then the solution for* (5) *is given by:*

$$\bar{P}(\mathbf{0}; t) = e^{-(\sum_{j=1}^{n} a_j(\mathbf{x}_0))t}, t > 0, \tag{7}$$

and

$$\bar{P}(\mathbf{r}; t) = \sum_{j=1}^{N} \left(a_j(\mathbf{x}_0 + \mathbb{V}^T(\mathbf{r} - \mathbf{I}_j)) \int_0^t e^{-(\sum_{j=1}^{n} a_j(\mathbf{x}_0 + \mathbb{V}^T\mathbf{r}))(t-s)} \bar{P}(\mathbf{r} - \mathbf{I}_j; s) ds \right), \tag{8}$$

for $\mathbf{r} \in \Lambda \backslash \{\mathbf{0}\}$ and $t > 0$.

Proof. Case 1: Let $\mathbf{r} = \mathbf{0}$, then (5) reduces to;

$$\frac{\partial \bar{P}(\mathbf{0}; t)}{\partial t} = \sum_{j=1}^{N} a_j(\mathbf{x}_0) \bar{P}(\mathbf{0}; t).$$

We know this solves analytically to (7).

Case 2: Fix $\mathbf{r} \in \Lambda \backslash \mathbf{0}$. Let $g(t) := \sum_{j=1}^{N} a_j(\mathbf{x}_0 + \mathbb{V}^T(\mathbf{r} - \mathbf{I}_j))\bar{P}(\mathbf{r} - \mathbf{I}_j; t)$ and $\beta = \sum_{j=1}^{N} a_j(\mathbf{x}_0 + \mathbb{V}^T\mathbf{r})$. Then we can rewrite (5) as;

$$\frac{\partial \bar{P}(\mathbf{r}; t)}{\partial t} = g(t) - \beta \bar{P}(\mathbf{r}; t). \tag{9}$$

We take the Laplace transform of (9) with $\bar{\mathbf{P}} = \mathcal{L}(\bar{P})$ and $\mathbf{G} = \mathcal{L}(g)$;

$$s\bar{\mathbf{P}} - \bar{P}(\mathbf{r}, 0) = \mathbf{G}(s) - \beta \bar{\mathbf{P}}.$$

Since $\bar{P}(\mathbf{r}, 0) = 0$ by the initial condition, $\bar{P}(\cdot, 0) = \delta_{\mathbf{0}}(\cdot)$,

$$\bar{\mathbf{P}} = \frac{1}{s + \beta} G(s). \tag{10}$$

By taking the inverse Laplace transform we find;

$$\bar{P}(\mathbf{r}; t) = \int_0^t e^{-\beta(t-s)} g(s) ds.$$

After substituting $g(t)$ and β, we obtain (8). □

Remark 5. *If we consider a FSPA type solver for $\boldsymbol{A}_r$, we can apply the results above to show the problem is very simple to solve. If we truncate Λ to Λ' and solve* (5)*, we find that the solution for $\bar{P}(\boldsymbol{r}; t)$, $\boldsymbol{r} \in \Lambda'$, is not an approximation but an analytic solution. If for some $\boldsymbol{r} \in \Lambda'$, if the eigenvalue is zero, then we can simply remove the row and column and solve for $\bar{P}(\boldsymbol{r}; t)$ using Proposition 4, after we have solved over the rest of the domain. Note that without any zeros in the diagonal of $\boldsymbol{A}'_r$, this matrix will be negative definite.*

We can see that Proposition 4 can be used to explicitly solve (5) over any finite dimensional state space Λ. Another way to solve (5) over Λ would be to solve (6), using the the algorithm given in [GVL96, Theorem 11.1.3], by computing the matrix exponential for upper triangular matrix. These two methods are analogous.

3 Discussion

The purpose of this paper is to give motivation into the study of the CME with respect to reaction counts. We have given results which show that when solving over the reaction counts, we can find all the eigenvalues of $\mathbf{A}_r$ and also the solutions for the truncated $\mathbf{A}_r$ are analytic. If we do consider a FSPA solver of (5), then it is clearly easier to solve over reaction counts rather than species counts. However being easier to solve does not imply that the solution for (5) is close to (1). This is another important consideration which requires further research. We need to investigate the following question: how many $\mathbf{r} \in \Gamma_{\mathbf{x}}$ do we need to solve such that $\sum_{\mathbf{r}\in\Gamma'_{\mathbf{x}}} \bar{P}(\mathbf{r};t)$ is a good approximation of $P(\mathbf{x};t)$, for $\mathbf{x} \in \Omega$. If we find that $\sum_{\mathbf{r}\in\Gamma'_{\mathbf{x}}} P(\mathbf{r};t)$ converges to $P(\mathbf{x};t)$ quickly, then computing over the reaction counts will be computationally advantageous. We are expecting the convergence to be dependent on t.

Acknowledgements

This work would not have been completed without the continuous support of my supervisor Markus Hegland. Also many thanks to my family and friends who helped create a fantastic environment for me to live and work in.

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