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Solving a system of Master Equations for parallel chemical interactions

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Abstract

The stochastic kinetics of a well-stirred mixture of molecular species interacting through different biochemical reactions can be modelled by the chemical master equation. Till now the scientific computing community has focussed mostly on the development of numerical techniques to approximate the solution of the chemical master equation many realizations of the associated Markov jump process. Consequently, the domain of exact algorithms for directly solving a chemical master equation is still an open research area.

In this work we present a method to solve analytically a chemical master equation to describe a reversible molecular reaction and we propose a method to solve a system of such equations. In this method molecular populations are considered as time-dependent, integer-valued random variables. Moreover, we developed mathematical procedures for solving a system of chemical master equations referred to a set of parallel and interdependent biochemical interactions. The causal dependence between reactions is modeled on the time scale in the following way: a reaction starts when its antecedent has produced a sufficient quantity of reactants.

1 Background

The master equation is a differential form of the Chapman-Kolmogorov equation

$$p_{\rightarrow}(x_1, t_1 | x_3, t_3) = \int p_{\rightarrow}(x_1, t_1 | x_2, t_2) p_{\rightarrow}(x_2, t_2 | x_3, t_3) dx_2 \quad (1)$$

The terminology differs between different authors. Sometimes the term master equation is used only for jump processes. Jump processes are characterized by discontinuous motion, that is there is a bounded and non-vanishing transition probability per unit time

$$w(x|y, t) = \lim_{\Delta t \rightarrow 0} \frac{p_{\rightarrow}(x, t + \Delta t | y, t)}{\Delta t}$$

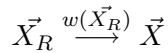
for some y such that $|x - y| > \epsilon$. Here, the function $w(x|y; t) = w(x|y)$. The master equation for jump processes can be written

$$\frac{\partial p(x, t)}{\partial t} = \int (w(x|x')p(x', t) - w(x'|x)p(x, t)) dx' \quad (2)$$

The master equation has a very intuitive interpretation. The first part of the integral is the *gain of probability* from the state x' and the second part is the *loss of probability* to x' . The solution is a probability distribution for the state space. Analytical solutions of the master equation are possible to calculate only for simple special cases.

1.1 The chemical master equation

A reaction R is defined as a jump to the state \vec{X} to a state \vec{X}_R , where $\vec{X}, \vec{X}_R \in \mathbb{Z}_+^N$. The propensity $w(\vec{X}_R) = \tilde{v}(\vec{X})$ is the probability for transition from \vec{X}_R to \vec{X} per unit time. A reaction can be written as



The difference in molecules numbers $\vec{n}_R = \vec{X}_R - \vec{X}$ is used to write the master equation (2) for a system with M reactions

$$\frac{dp(\vec{X}, t)}{dt} = \sum_{i=1}^M w(\vec{X} + \vec{n}_i) p(\vec{X} + \vec{n}_i, t) - \sum_{i=1}^M w(\vec{X}) p(\vec{X}, t) \quad (3)$$

This special case of master equations is called the *chemical master equation* (CME). It is fairly easy to write: however, solving it is quite another matter. The number of problems for which the CME can be solved analytically is even fewer than the number of problems for which the deterministic reaction-rate equations can be solved analytically. Attempts to use master equation

No.	Reaction	Rate equation	Type
1	$\emptyset \xrightarrow{v_1([A])} A$	$v_1([A]) = \frac{k_1}{1+[A]K_1}$	synthesis
2	$A \xrightarrow{v_2([A])} \emptyset$	$v_2([A]) = \mu[A]$	degradation
3	$\emptyset \xleftarrow{v_3([B])} B$	$v_3([B]) = \frac{k_2}{1+[B]/K_2}$	synthesis
4	$B \xrightarrow{v_4([B])} \emptyset$	$v_4([B]) = \mu[B]$	degradation
5	$A + B \xrightarrow{v_5([A],[B])} \emptyset$	$v_5([A],[B]) = k_3[A][B]$	bimolecular reaction

Table 1: Reactions of the chemical model displayed in Fig. 1. No. corresponds to the number in the figure.

to construct tractable time-evolution equations are also usually unsuccessful, unless all the reaction in the system are simple monomolecular reactions. Let consider for instance a deterministic model of two metabolites coupled by a bimolecular reaction, as shown in Fig. 1. The set of differential equation describing the dynamic of this model is given in Table 1, where the $[A]$ and $[B]$ are the concentrations of metabolite A and metabolite B , while k , K , and μ determine the maximal rate of synthesis, the strength of the feedback, and the rate of degradation, respectively.

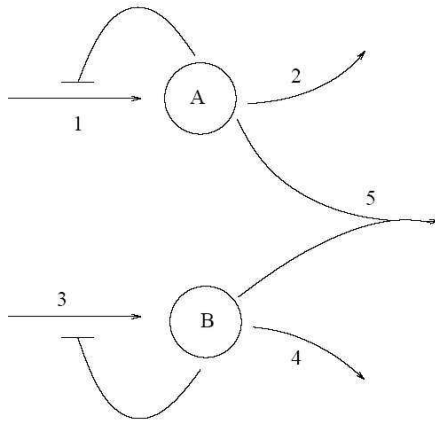


Figure 1: Two metabolites A and B coupled by a bimolecular reactions.

In the formalism of the Markov process, the reactions in Table 1 are written as in Table 2. The CME equation for the system of two metabolites of Fig. 1 looks fairly complex as in Table 3.

No.	Reaction	$w(\vec{x})$	\vec{n}_R^T
1	$\emptyset \xrightarrow{w_1(a)} A$	$w_1(a) = Vk_1/(1 + a/VK_1)$	$(-1, 0)$
2	$A \xrightarrow{w_2(a)} \emptyset$	$w_2(a) = \mu a$	$(1, 0)$
3	$\emptyset \xrightarrow{w_3(b)} B$	$w_3(b) = VK_2/(1 + b/(VK_2))$	$(0, -1)$
4	$B \xrightarrow{w_4(b)} \emptyset$	$w_4(b) = \mu b$	$(0, 1)$
5	$A + B \xrightarrow{w_5(a,b)} \emptyset$	$w_5(a, b) = k_2 ab/V$	$(1, 1)$

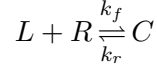
Table 2: Reactions of the chemical model depicted in Fig. 1, their propensity and corresponding "jump" of state vector \vec{n}_R^T . V is the volumes in which the reactions occur.

$$\begin{aligned}
\frac{\partial p(0, 0, t)}{\partial t} &= \mu p(1, 0, t) + \mu p(0, 1, t) + \frac{k_3}{V} p(1, 1, t) - V(k_1 + k_2)p(0, 0, t) \\
\frac{\partial p(0, b, t)}{\partial t} &= V \frac{k_2}{1 + \frac{b-1}{VK_2}} p(0, b-1, t) + \\
&\quad + \mu p(1, b, t) + \mu(b+1)p(0, b+1, t) + \frac{k_3}{V}(b+1)p(1, b+1, t) - \\
&\quad - \left(V \left(k_1 + \frac{k_2}{1 + \frac{b}{VK_2}} \right) + \mu b \right) p(0, b, t) \\
\frac{\partial p(a, 0, t)}{\partial t} &= V \frac{k_1}{1 + \frac{a-1}{VK_1}} p(a-1, 0, t) + \\
&\quad + \mu(a+1)p(a+1, 0, t) + \mu p(a, 1, t) + \\
&\quad + \frac{k_3}{V}(a+1)p(a+1, 1, t) - \\
&\quad - \left(V \left(\frac{k_1}{1 + \frac{a}{VK_1}} + k_2 \right) + \mu a \right) p(a, 0, t) \\
\frac{\partial p(a, b, t)}{\partial t} &= V \frac{k_1}{1 + \frac{a-1}{VK_1}} p(a-1, b, t) + V \frac{k_2}{1 + \frac{b-1}{VK_2}} p(a, b-1, t) + \\
&\quad + \mu(a+1)p(a+1, b, t) + \mu(b+1)p(a, b+1, t) + \\
&\quad + \frac{k_3}{V}(a+1)(b+1)p(a+1, b+1, t) - \\
&\quad - \left(V \left(\frac{k_1}{1 + \frac{a}{VK_1}} + \frac{k_2}{1 + \frac{b}{VK_2}} \right) + \mu(a+b) + \frac{k_3}{V} ab \right) p(a, b, t)
\end{aligned}$$

Table 3: Set of chemical master equations describing the metabolites interaction showed in Fig. 1.

2 Stochastic master equations to describe reversible molecular reactions

Let suppose to have a set of reversible molecular reactions of the type



where L , R and C represent ligands, receptors and complexes, respectively. Integer-valued random variables $L(t)$, $R(t)$ and $C(t)$ give the populations of the three species of molecules in a closed, small and well mixed volume initially containing λ , ρ and γ molecules of L , R and C .

In each of the four phases, the probability $P(l, r, c, t)$ that $L(t)$, $R(t)$ and $C(t)$ have values l , r and c , respectively is determined by a stochastic master equation, which can be written as

$$\begin{aligned} P(l, r, c, t + \Delta t) &= k_f(l+1)(r+1)\Delta t P(l+1, r+1, c-1, t) + \\ &+ k_r(c+1)\Delta t P(l-1, r-1, c+1, t) + \\ &+ (1 - k_f l r \Delta t - k_r c \Delta t) P(l, r, c, t) + \\ &+ O(\Delta t), \end{aligned} \quad (4)$$

where k_f and k_r are the forward reaction rate and the reverse reaction rate, respectively.

When $\Delta t \rightarrow 0$, we obtain the following:

$$\begin{aligned} \frac{dP(l, r, c, t)}{dt} &= k_f(l+1)(r+1)P(l+1, r+1, c-1, t) - \\ &- k_f l r P(l, r, c, t) + k_r(c+1)P(l-1, r-1, c+1, t) - \\ &- k_r c P(l, r, c, t). \end{aligned} \quad (5)$$

Looking at the stoichiometry of the chemical reaction and relating l , r and c as $\gamma + \lambda - l = \gamma + \rho - r = c$, the probability $P(l, r, c, t)$ can be expressed as a function of just one species population (let's say $L(t)$):

$$\begin{aligned} \frac{dP_l(\tau)}{dt} &= (l+1)(\rho - \lambda + l + 1)P_{l+1}(\tau) - \\ &- [l(\rho - \lambda + l) + K(\gamma + \lambda - l)] P_l(\tau) + \\ &+ K(\gamma + \lambda - l + 1)P_{l-1}(\tau), \end{aligned} \quad (6)$$

where $\tau = k_f t$ and $K = k_r/k_f$.

Laplace transformation of these equations yields to the linear system

$$pV = MV + \hat{P}, \quad (7)$$

where V and P are the $(\gamma + \lambda + 1)$ -dimensional vectors

$$V = \begin{pmatrix} V_0(p) \\ V_1(p) \\ \vdots \\ V_{\gamma+\lambda}(p) \end{pmatrix}, \quad \text{where} \quad V_l(p) = \int_0^\infty e^{-p\tau} P_l(\tau) d\tau \quad (8)$$

and

$$\hat{P} = \begin{pmatrix} P_0(t=0) \\ P_1(t=0) \\ \vdots \\ P_{\gamma+\lambda}(t=0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 1 \end{pmatrix}. \quad (9)$$

The $(\gamma + \lambda + 1) \times (\gamma + \lambda + 1)$ matrix M is defined as follows:

$$M = \begin{bmatrix} -u_0 & h_1 & 0 & 0 & \cdots & 0 \\ u_0 & -(h_1 + u_1) & h_2 & 0 & \cdots & 0 \\ 0 & u_1 & -(h_2 + u_2) & h_3 & \cdots & 0 \\ 0 & 0 & u_2 & -(h_3 + u_3) & \ddots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & h_{\gamma+\lambda} \\ 0 & 0 & 0 & \cdots & u_{\gamma+\lambda-1} & -(h_{\gamma+\lambda} + u_{\gamma+\lambda}) \end{bmatrix} \quad (10)$$

where $h_l = l(\rho - \lambda + l)$ and $u_l = K(\lambda - l + \gamma)$.

Solving the system (7) for V and using the definition of the inverse matrix in terms of the adjoint and the determinant of the matrix, we obtain

$$V = [pI - M]^{-1} \hat{P} = \frac{\text{adj}(pI - M)}{\det(pI - M)}. \quad (11)$$

Moreover, we can write V only in terms of the cofactors of the last row of $[pI - M]$, obtaining a simple way to calculate $V_l(p)$ [1]

$$V_l(p) = \frac{\lambda! \rho!}{\rho - \lambda + l} \frac{D_l(p)}{D_{\lambda+\gamma+1}(p)}, \quad (12)$$

where $D_l(p)$ is the determinant of the submatrix of $[pI - M]$ composed of its first l rows and column, that is to say that $D_l(p)$ is the characteristic polynomial of an $l \times l$ matrix ($l \in [0, \gamma + \lambda]$).

Since eq. (12) is the exact solution of eq. (6), we only have to find the polynomials $D_l(p)$. Once we have found these polynomials, we obtain the probability distribution $P_l(\tau)$ as

$$P_l(\tau) = \frac{1}{(\rho - \lambda + l)!} \frac{\lambda! \rho!}{(\rho - \lambda)!} \times \sum_{j=0}^{\lambda+\gamma} \frac{D_l(\mu_j)}{\partial_p D_{\lambda+\gamma+1}(\mu_j)} e^{\mu_j \tau}, \quad (13)$$

where

$$\partial_p D_{\lambda+\gamma+1}(\mu_j) = \left(\frac{\partial D_{\lambda+\gamma+1}(p)}{\partial p} \right)_{p=\mu_j} \quad (14)$$

and μ_j are the eigenvalues of the matrix M .

2.1 Uniqueness of the solution of the system

$$pV = MV + \hat{P}$$

Numerical computations for systems which have more than one solution usually yield meaningless results and numerical computations for systems which have no solutions are always meaningless. This is the reason why we are interested to find the conditions which assure us that the system $pV = MV + \hat{P}$ has a unique solution.

For this purpose we can use the following [3]

Theorem 2.1 *Let*

$$Ax = b \quad (15)$$

be a general linear algebraic system of n equations in n unknowns; it has one and only one solution if and only if the determinant of A is different from zero.

Instead of directly evaluating the determinant, some properties of the coefficient matrix of the system may be useful to assure that it is different from zero.

Definition 2.1 *System (15) is said to be diagonally dominant if and only if*

$$|a_{i,i}| \geq \sum_{\substack{j=1 \\ j \neq i}}^n |a_{i,j}| \quad i = 1, 2, \dots, n \quad (16)$$

with strict inequality valid for at least one value of i .

Definition 2.2 *System (15) is said to be tridiagonal if and only if all elements of A are zero except $a_{i,i}$, $a_{j,j+1}$, $a_{j+1,j}$, $i = 1, 2, \dots, n$; $j = 1, 2, \dots, n-1$, and none of these is zero.*

Using these definitions, we can prove that $\det(M) \neq 0$ applying the following

Theorem 2.2 *Let the system $Ax = b$ be tridiagonal, diagonally dominant, and satisfy*

$$\begin{aligned} a_{i,i} &< 0 & i &= 1, 2, \dots, n \\ a_{j,j+1} &> 0 & j &= 1, 2, \dots, n-1 \\ a_{j+1,j} &> 0 & j &= 1, 2, \dots, n-1 \end{aligned}$$

Then the solution of the system exists and is unique.

Since a matrix and its transpose matrix have the same determinant because of their similarity, we can prove that $\det(M^t) \neq 0$ obtaining the non-singularity of M .

The matrix M^t

$$M^t = \begin{bmatrix} -u_0 & u_0 & 0 & 0 & \cdots & 0 \\ h_1 & -(h_1 + u_1) & u_1 & 0 & \cdots & 0 \\ 0 & h_2 & -(h_2 + u_2) & u_2 & \cdots & 0 \\ 0 & 0 & h_3 & -(h_3 + u_3) & \ddots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & u_{\gamma+\lambda-1} \\ 0 & 0 & 0 & \cdots & h_{\gamma+\lambda} & -(h_{\gamma+\lambda} + u_{\gamma+\lambda}) \end{bmatrix} \quad (17)$$

shows a tridiagonal form; if $u_l > 0$ and $h_l > 0 \quad \forall \quad l \in [0, \gamma + \lambda]$ the coefficients of M^t verify the conditions of Theorem 2.2.

Moreover we have that the coefficients of M^t verify condition 16, thus the matrix M^t verify all the conditions of Theorem 2.2. Therefore $\det(M) = \det(M^t) \neq 0$, that is to say that if $u_l > 0$ and $h_l > 0 \quad \forall \quad l \in [0, \gamma + \lambda]$ the system (7) has one and only one solution.

2.2 How to find polynomials $D_l(p)$

The polynomial $D_l(p)$ ($l \in [0, \lambda + \gamma]$) is a characteristic polynomial, defined as $\det[pI - M]$ where $[pI - M]$ is a $l \times l$ matrix obtained considering the first l rows and columns of $[pI - M]$; being characteristic, $D_l(p)$ is a monic l th order polynomial of p .

The matrix $[pI - M]$ has a tridiagonal form, so its determinant can be evaluated using a recursion relation. Let's consider A, a tridiagonal $m \times m$ matrix

$$A = \begin{bmatrix} a_1 & b_1 & 0 & 0 & \cdots & 0 \\ c_1 & a_2 & b_2 & 0 & \cdots & 0 \\ 0 & c_2 & a_3 & b_3 & \cdots & 0 \\ 0 & 0 & c_3 & a_4 & \ddots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & b_{m-1} \\ 0 & 0 & 0 & \cdots & c_{m-1} & a_m \end{bmatrix}; \quad (18)$$

by reducing it to an upper-triangular form, the following recursion relation for its determinant can be obtained:

$$D_m(p) = a_m D_{m-1} - c_{m-1} b_{m-1} D_{m-2} \quad (19)$$

$$D_0(p) = 1 \quad (20)$$

$$D_1(p) = a_1 \quad (21)$$

where D_{n-j} are the determinants of the submatrixes of A obtained removing the last j columns and rows.

Since $[pI - M]$ takes the following tridiagonal form

$$\begin{bmatrix} p+u_0 & h_1 & 0 & 0 & \cdots & 0 \\ u_0 & p+h_1+u_1 & h_2 & 0 & \cdots & 0 \\ 0 & u_1 & p+h_2+u_2 & h_3 & \cdots & 0 \\ 0 & 0 & u_2 & p+h_3+u_3 & \ddots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & h_{\gamma+\lambda} \\ 0 & 0 & 0 & \cdots & u_{\gamma+\lambda-1} & p+h_{\gamma+\lambda}+u_{\gamma+\lambda} \end{bmatrix}, \quad (22)$$

it is possible to apply equations (19)-(21) with $a_l = p+u_{l-1}+h_{l-1}$, $b_l = -h_l$ and $c_l = -u_{l-1}$ so as to obtain

$$D_l(p) = (p+u_{l-1}+h_{l-1})D_{l-1} + u_{l-2}h_{l-1}D_{l-2} \quad (23)$$

$$D_0(p) = 1 \quad (24)$$

$$D_1(p) = p+u_0+h_0 = p+u_0, \quad \text{since } h_0 = 0. \quad (25)$$

Given (23), it is possible to compute the coefficients of D_l by a recursive method [2]:

$$d_{l,j} = d_{l-1,j-1} + (u_{l-1}+h_{l-1})d_{l-1,j} - u_{l-2}h_{l-1}d_{l-2,j} \quad (26)$$

$$\begin{aligned} d_{0,0} &= d_{1,1} = 1 \\ d_{1,0} &= u_0 \\ d_{1,-1} &= d_{1,2} = d_{0,-1} = d_{0,1} = 0 \\ d_{-1,0} &= d_{-1,-1} = 0 \end{aligned} \quad (27)$$

The main idea to solve a system of causally related chemical interactions is that each reaction depends on the previous one, that is to say that a reaction starts when the previous one has produced a sufficient quantity of complex; thus we propose to make master equations interact on the time scale, by choosing as initial time of each reaction the one at which the number of complexes produced by the previous one becomes stable and use the method presented here to solve each equation.

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