

Problems of high dimension in molecular biology

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Abstract

The deterministic reaction rate equations are not an accurate description of many systems in molecular biology where the number of molecules of each species often is small. The master equation of chemical reactions is a more accurate stochastic description suitable for small molecular numbers. A computational difficulty is the high dimensionality of the equation. We describe how it can be solved by first approximating it by the Fokker-Planck equation. Then this equation is discretized by in space and time by a finite difference method. The method is compared to a Monte Carlo method by Gillespie. The method is applied to a four-dimensional problem of interest in the regulation of cell processes.

Introduction

There has been a technological breakthrough in molecular biology during the last decade, which has made it possible to test hypothesis from quantitative models in living cells [1], [5], [9], [11], [18], [21], [28]. This development will contribute greatly to understanding of molecular biology [16], [30]. For instance, we can now ask questions about how the chemical control circuits in a cell respond to changes in the environment and reach a deep understanding by combining experimental answers with theory from systems engineering [4]. When put in an evolutionary context we can also understand why the control systems are the designed as they are [6], [8], [31].

The vast majority of quantitative models in cell and molecular biology are formulated in terms of ordinary differential equations for the time evolution of concentrations of molecular species [17]. Assuming that the diffusion in the cell is high enough to make the spatial distribution of molecules homogenous, these equations describe systems with many participating molecules of each kind. This approach is inspired by macroscopic descriptions developed for near equilibrium kinetics in test tubes, containing 10^{12} molecules or more. However, these conditions are not fulfilled by biological cells where the copy numbers of molecules often are less than a hundred [14] or where the system dynamics are driven towards critical points by dissipation of energy [3], [7]. Under such circumstances it is important to consider the inherent stochastic nature of chemical reactions for realistic modeling [2], [22], [23] [24].

The master equation [19] is a scalar, time-dependent difference-differential equation for the probability distribution of the number of molecules of the participating molecular species. If there are N different species, then the equation is N -dimensional. When N is large the problem suffers from the "curse of dimensionality". With a standard discretization of the master equation the computational work and memory requirements grow exponentially with the number of species. As an

example, engineering problems are nowadays solved in three dimensions and time, often with great computational effort.

A Monte Carlo method is suitable for problems of many dimensions in particular for the steady state solution of the probability distribution. In Gillespie's algorithm [12] the reactions in the system are simulated by means of random numbers. By sampling the number of molecules of each species as time progresses, an approximation of the probability distribution is obtained.

Our approach to reduce the work is to approximate the master equation by the Fokker-Planck equation [19]. This is a scalar, linear, time-dependent partial differential equation (PDE) with convection and diffusion terms. The solution is the probability density and the equation is discretized by a finite difference stencil. The advantage compared to the master equation is that fewer grid points are needed in each dimension, but the problem with exponential growth of the work still remains. When N is large there is no other alternative than a Monte Carlo method.

In the following sections the reaction rate equations, the master equation, and the Fokker-Planck equation are presented and written explicitly for a system with two reacting components. The Gillespie algorithm is discussed and compared to numerical solution of the master or Fokker-Planck equations. The Fokker-Planck equation is discretized in space by a second order method and in time by a second order implicit backward differentiation method. An example of a biological system in a cell is the control of two metabolites by two enzymes, see Fig. 1. The synthesis of the metabolites A and B is catalyzed by the enzymes E_A and E_B respectively. The synthesis is feedback inhibited and the expression of enzymes are under transcriptional control. The consumption of the metabolites is catalyzed by an unsaturated two-substrate enzyme.

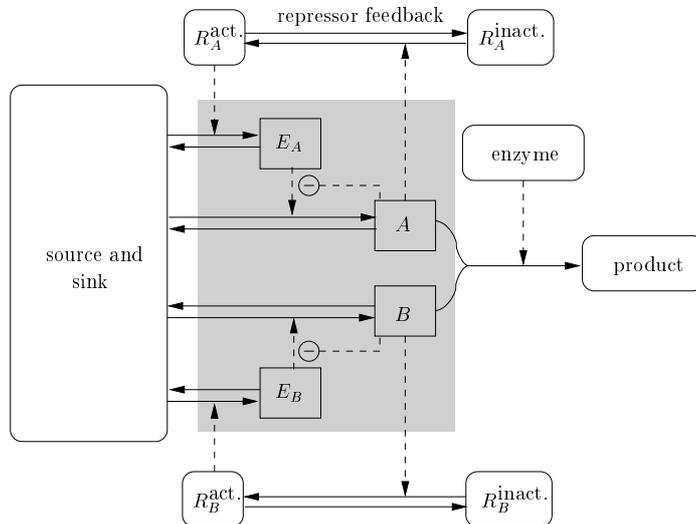


Figure 1: The synthesis of two metabolites A and B by two enzymes E_A and E_B .

The time evolution of this system is computed in the last section. The solution is obtained by a numerical approximation of the Fokker-Planck equation in four dimensions.

1 Equations

The deterministic and the stochastic descriptions of chemical reaction models in a cell are given in this section. On a macroscale, the concentrations of the species satisfy a system of ODEs. On a mesoscale, the probability distribution for the copy numbers of the participating molecules satisfies a master equation. The solution of the master equation can be approximated by the solution of a scalar PDE, the Fokker-Planck equation.

1.1 Deterministic equations

Assume that we have N chemically active molecular species and that the mixture is spatially homogeneous to avoid dependence in space. Then the reaction rate equations are a macroscopic description, valid for a system far from chemical instability and with a large number of molecules for each species [7]. The time evolution of the average concentrations are governed by a system of N coupled nonlinear ODEs. It is convenient to use average numbers of molecules instead of average concentrations, which is equivalent. We assume a constant reaction volume.

As an example, suppose that we have two species A and B. Let their copy numbers be denoted by a and b and their average numbers be denoted by $\langle a \rangle$ and $\langle b \rangle$. The species are created with the intensities $k_A e_A^*$ and $k_B e_B^*$, they are annihilated with the intensities μa and μb , and they react with each other with the intensity $k_2 ab$. Then the chemical reactions can be expressed in the following way:



The corresponding system of ODEs is

$$\begin{aligned}
 \frac{d\langle a \rangle}{dt} &= k_A e_A^* - \mu \langle a \rangle - k_2 \langle a \rangle \langle b \rangle, \\
 \frac{d\langle b \rangle}{dt} &= k_B e_B^* - \mu \langle b \rangle - k_2 \langle a \rangle \langle b \rangle.
 \end{aligned} \tag{2}$$

As an example, the coefficients in the system can be

$$k_A e_A^* = k_B e_B^* = 1s^{-1}, \quad k_2 = 0.001s^{-1}, \quad \mu = 0.002s^{-1}. \tag{3}$$

The system (2) may be stiff depending on the size of the coefficients μ and k_2 .

When the synthesis of A and B are under competitive feedback inhibition by A and B respectively



The ODE system is now

$$\begin{aligned}
 \frac{d\langle a \rangle}{dt} &= \frac{k_A e_A^*}{1 + \frac{\langle a \rangle}{K_I}} - \mu \langle a \rangle - k_2 \langle a \rangle \langle b \rangle, \\
 \frac{d\langle b \rangle}{dt} &= \frac{k_B e_B^*}{1 + \frac{\langle b \rangle}{K_I}} - \mu \langle b \rangle - k_2 \langle a \rangle \langle b \rangle.
 \end{aligned} \tag{5}$$

Reasonable coefficients in this case are

$$k_A e_A^* = k_B e_B^* = 600s^{-1}, \quad k_2 = 0.001s^{-1}, \quad \mu = 0.0002s^{-1}, \quad K_I = 1 \cdot 10^6. \quad (6)$$

1.2 The master equation

The master equation is an equation for the probability distribution p that a certain number of molecules of each species is present at time t [19]. Let a state $\mathbf{x} \in \mathbb{S}^N$ where N is the number of molecular species or the dimension of the problem and $\mathbb{S} = \mathbb{Z}^+$, the non-negative integer numbers. An elementary chemical reaction is a transition from state \mathbf{x}_r to state \mathbf{x} . Each reaction can be described by a step \mathbf{n}_r in \mathbb{S}^N . The probability for transition from \mathbf{x}_r to \mathbf{x} per unit time, or the reaction propensity, is $w_r(\mathbf{x}_r)$ and $w : \mathbb{S}^N \rightarrow \mathbb{R}$. One reaction can be written



The master equation for $p(\mathbf{x}, t)$ and R reactions is

$$\frac{\partial p(\mathbf{x}, t)}{\partial t} = \sum_{\substack{r=1 \\ (\mathbf{x} + \mathbf{n}_r) \in \mathbb{S}^N}}^{r=R} w_r(\mathbf{x} + \mathbf{n}_r) p(\mathbf{x} + \mathbf{n}_r, t) - \sum_{\substack{r=1 \\ (\mathbf{x} - \mathbf{n}_r) \in \mathbb{S}^N}}^{r=R} w_r(\mathbf{x}) p(\mathbf{x}, t). \quad (8)$$

The computational difficulty with this equation is that the number of dimensions of the problem grows with the number of species N in the chemical reactions.

Let x_A and x_B denote the number of A and B molecules and introduce the shift operator \mathbb{E}_A in x_A as follows

$$\mathbb{E}_A f(x_A, x_B, t) = f(x_A + 1, x_B, t).$$

The shift \mathbb{E}_B is defined in the same manner. Then the master equation of the reactions in (2) can be written

$$\begin{aligned} \frac{\partial p(x_A, x_B, t)}{\partial t} &= k_A e_A^* (\mathbb{E}_A^{-1} - 1) p(x_A, x_B, t) \\ &\quad + k_B e_B^* (\mathbb{E}_B^{-1} - 1) p(x_A, x_B, t) \\ &\quad + \mu (\mathbb{E}_A - 1) (x_A p(x_A, x_B, t)) + \mu (\mathbb{E}_B - 1) (x_B p(x_A, x_B, t)) \\ &\quad + k_2 (\mathbb{E}_A \mathbb{E}_B - 1) (x_A x_B p(x_A, x_B, t)). \end{aligned} \quad (9)$$

1.3 The Fokker-Planck equation

By truncating the Taylor expansion of the master equation after the second order term we arrive at the Fokker-Planck equation [19]. Let \mathcal{H} denote the Hessian matrix of second derivatives with respect to $\mathbf{x} \in (\mathbb{R}^+)^N$. Then the equation is

$$\begin{aligned} \frac{\partial p(\mathbf{x}, t)}{\partial t} &= \sum_{r=1}^R \mathbf{n}_r \cdot \nabla_{\mathbf{x}} (w_r(\mathbf{x}) p(\mathbf{x}, t)) + 0.5 \mathbf{n}_r \cdot \mathcal{H} (w_r(\mathbf{x}) p(\mathbf{x}, t)) \mathbf{n}_r \\ &= \sum_{r=1}^R \left\{ \sum_{i=1}^d n_{ri} \frac{\partial (w_r(\mathbf{x}) p(\mathbf{x}, t))}{\partial x_i} + \sum_{i=1}^d \sum_{j=1}^d \frac{n_{ri} n_{rj}}{2} \frac{\partial^2 (w_r(\mathbf{x}) p(\mathbf{x}, t))}{\partial x_i \partial x_j} \right\}. \end{aligned} \quad (10)$$

The Fokker-Planck equation of the chemical system (1) is after Taylor expansion of (9)

$$\begin{aligned} \frac{\partial p(x, y, t)}{\partial t} &= k_A e_A^* (-p_x + 0.5 p_{xx}) + k_B e_B^* (-p_y + 0.5 p_{yy}) \\ &+ \mu((xp)_x + 0.5(xp)_{xx}) + \mu((yp)_y + 0.5(yp)_{yy}) \\ &+ k_2((xyp)_x + (xyp)_y + 0.5(xyp)_{xx} + (xyp)_{xy} + 0.5(xyp)_{yy}), \end{aligned} \quad (11)$$

where $x = x_A$ and $y = x_B$. The boundary conditions at the lower boundaries are by assumption $p(\mathbf{x}, t) = 0$, $\mathbf{x}_i = 0$, $i = 1 \dots N$.

It is shown in [19] that for large systems with many molecules the solution can be expanded in a small parameter where the zero-order term is the solution to the deterministic reaction rate equations and the first perturbation term is the solution of a Fokker-Planck equation.

2 Methods for numerical solution

We have three different models for the time evolution of the chemical reactions in a cell. The numerical solution of the system of ODEs is straightforward [15]. The master equation is discrete in space and can be discretized in time by a suitable method for stiff ODE problems. The Fokker-Planck equation has straight boundaries at $\mathbf{x}_i = 0$, $i = 1 \dots N$, and is easily discretized in space by a finite difference method. An artificial boundary condition $p(\mathbf{x}, t) = 0$ is added at $\mathbf{x}_i = x_{max}$ for a sufficiently large $x_{max} > 0$ to obtain a finite computational domain. For comparison we first discuss the Gillespie algorithm, which is equivalent to solving the master equation.

2.1 Gillespie's method

A Monte Carlo method was invented in 1976 by Gillespie [12] for stochastic simulation of trajectories in time of the behavior of chemical reactions. Assume that there are M different reactions and that $\tilde{p}(\tau, \lambda)$, $\lambda = 1, \dots, M$, is a probability distribution. The probability at time t that the next reaction in the system will be reaction λ and will occur in the interval $(t + \tau, t + \tau + \delta t)$ is $\tilde{p}(\tau, \lambda) \delta t$. The expression for \tilde{p} is

$$\tilde{p}(\tau, \lambda) = h_\lambda c_\lambda \exp\left(-\sum_{\nu=1}^M h_\nu c_\nu \tau\right),$$

where h_ν is a polynomial in \mathbf{x}_i depending on the reaction ν and c_ν is a reaction constant (cf. k_2 and μ in (3)). The algorithm for advancing the system in time is:

1. Initialize N variables \mathbf{x}_i and M quantities $h_\nu(\mathbf{x})c_\nu$
2. Generate τ and λ from random numbers with probability density $\tilde{p}(\tau, \lambda)$
3. Change \mathbf{x}_i according to reaction λ , update h_ν , take time step τ
4. Store \mathbf{x}_i , check for termination, otherwise goto 2

The time steps are τ . For stiff problems with at least one large $h_\nu(\mathbf{x})c_\nu$, the expected value of τ is small and the progress is slow, similar to what it is for an explicit, deterministic ODE integrator. One way of circumventing these problems is found in [25].

2.2 Solving the master equation

The master equation (8) is solved on a grid in an N -dimensional cube with $\mathbf{x}_i = 0, 1, 2 \dots x_{max}$, and step size $\Delta x_i = 1$. The total number of grid points is $\prod_{i=1}^N (x_{max} + 1) = (x_{max} + 1)^N$. The time derivative is approximated by an implicit backward differentiation method of second order accuracy (BDF-2) [15]. The time step is chosen to be constant and a system of linear equations is solved in each time step.

2.3 Solving the Fokker-Planck equation

The computational domain for the Fokker-Planck equation (10) is an N -dimensional cube as above but with $\Delta x_i \geq 1$. Suppose that the j :th step in the i :th dimension is Δx_{ij} and that $\sum_{j=1}^{q_i} \Delta x_{ij} = x_{max}$. Then the total number of grid points is $\prod_{i=1}^N (q_i + 1) < (x_{max} + 1)^N$. The time integrator is BDF-2 with constant time step Δt . The space derivatives of $f_r(\mathbf{x}) = w_r(\mathbf{x})p(\mathbf{x})$ are replaced by centered finite difference approximations of second order of the first and second derivatives with respect to \mathbf{x}_i . One can show that with certain approximations and a step $\Delta x_i = 1$ there we obtain the master equation. It is known from analysis of a one-dimensional problem that for stability in space there is a constraint on the size of Δx_i [20].

If \mathbf{f}_r^n is the vector of $f_r(\mathbf{x})$ at the grid points at time t_n , then $\mathbf{A}_r \mathbf{f}_r^n$ approximates the space derivatives and \mathbf{A}_r is a constant matrix. It is generated directly from a state representation of chemical reactions and stored in a standard sparse format [26]. Let \mathbf{p}^n be the vector of probabilities at the grid points. With the matrix \mathbf{B} defined such that $\mathbf{B}\mathbf{p}^n = \sum_r \mathbf{A}_r \mathbf{f}_r^n$ the time stepping scheme is

$$\left(\frac{3}{2}I - \Delta t \mathbf{B}\right)\mathbf{p}^n = 2\mathbf{p}^{n-1} - \frac{1}{2}\mathbf{p}^{n-2}. \quad (12)$$

The system of linear equations is solved in each time step by BiCGSTAB after preconditioning by Incomplete LU factorization (ILU), see [13]. The same factorization is used in every time step. Since \mathbf{B} is singular, there is a steady state solution $\mathbf{p}^\infty \neq 0$ such that $\mathbf{B}\mathbf{p}^\infty = 0$.

The advantage with the Fokker-Planck equation compared to the master equation is that with $\Delta x_i > 1$ instead of $\Delta x_i = 1$ the number of grid points is reduced considerably making four-dimensional problems tractable. On the other hand, the Fokker-Planck equation only approximates the master equation, but one can show that error in this approximation is of the same order as in the numerical approximation of the Fokker-Planck equation [27].

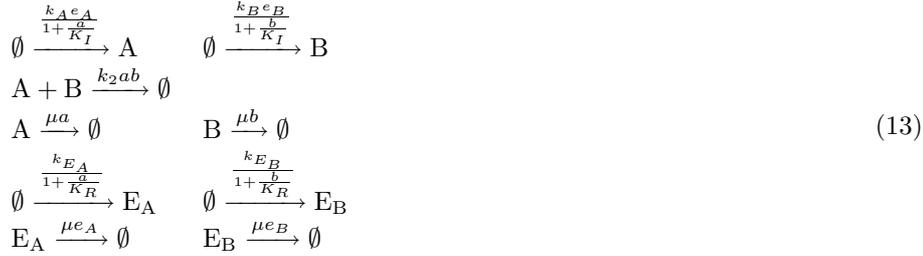
2.4 Comparison of the methods

Compared to the Monte Carlo method in section 2.1 smooth solutions $p(\mathbf{x}, t)$ are easily obtained with the Fokker-Planck equation also for time dependent problems. Many trajectories with Gillespie's method are needed for an accurate estimate of the time dependent probability. A steady state problem can be solved with a time-stepping procedure as in (12) or directly with an iterative method as the solution of $\mathbf{B}\mathbf{p} = 0$. A termination criterion is then based on the residual $\mathbf{r} = \mathbf{B}\mathbf{p}$. It is more difficult to decide when to stop the Monte Carlo simulation. The main advantage of Gillespie's algorithm is its ability to treat systems with large N and M . It needs only $N + 2M$ memory locations for a simulation whereas numerical solution of the Fokker-Planck equation with a traditional grid based method is limited to $N = 5$ or perhaps 6. When N is small it is, however, very competitive. In an example in [27] with $N = 2$ the steady state solution is obtained with the solver of the Fokker-Planck equation 330 times faster than with Gillespie's algorithm [27]. If

the statistics is collected for p with the Monte Carlo method and there are x_{max} molecules of each species, then also that method needs x_{max}^N storage.

3 Numerical results

The time evolution of the four-dimensional example in Fig. 1 with two metabolites A and B and the enzymes E_A and E_B is simulated with the Fokker-Planck equation in this section. The copy numbers of the E_A and $E_{t\text{extrm}B}$ are denoted by e_A and e_B . The reactions are:



The reaction constants have the following values

$$\begin{aligned}
 k_A = k_B = 0.3s^{-1}, k_2 = 0.001s^{-1}, K_I = 60, \mu = 0.002s^{-1}, \\
 k_{E_A} = k_{E_B} = 0.02s^{-1}, K_R = 30.
 \end{aligned}$$

The average copy numbers are denoted by $\langle e_A \rangle$ and $\langle e_B \rangle$. Then the deterministic equations are

$$\begin{aligned}
 \frac{d\langle a \rangle}{dt} &= \frac{k_A \langle e_A \rangle}{1 + \frac{\langle a \rangle}{K_I}} - \mu \langle a \rangle - k_2 \langle a \rangle \langle b \rangle, \\
 \frac{d\langle b \rangle}{dt} &= \frac{k_B \langle e_B \rangle}{1 + \frac{\langle b \rangle}{K_I}} - \mu \langle b \rangle - k_2 \langle a \rangle \langle b \rangle, \\
 \frac{d\langle e_A \rangle}{dt} &= \frac{k_{E_A}}{1 + \frac{\langle a \rangle}{K_R}} - \mu \langle e_A \rangle, \\
 \frac{d\langle e_B \rangle}{dt} &= \frac{k_{E_B}}{1 + \frac{\langle b \rangle}{K_R}} - \mu \langle e_B \rangle.
 \end{aligned} \tag{14}$$

The solution is computed with the Fokker-Planck equation and then plotted in two-dimensional projections in Fig. 2. The number of molecules of each species is found on the axis. The simulation starts at $t = 0$ and at $t = 1500$ the steady state solution is approximately reached.

4 Conclusions

A stochastic simulation of chemical reactions is necessary in certain models in molecular biology. The master equation governs the time evolution of the probability distribution of molecule numbers in a spatially homogenous system. N molecular species imply an N dimensional master equation. The standard approach to solve

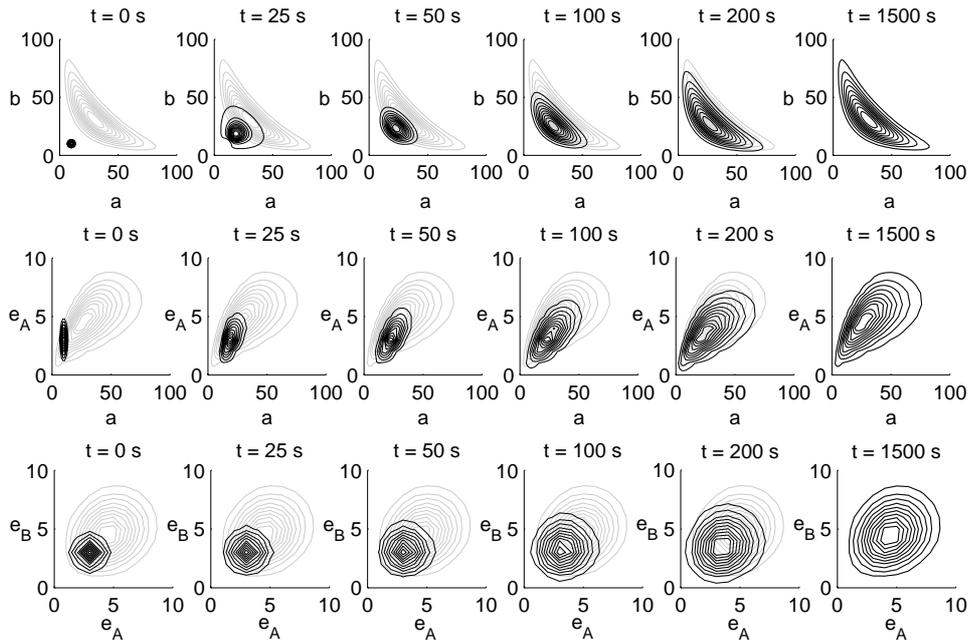


Figure 2: The isolines of $p(\mathbf{x}, t)$ (black) and the isolines of the steady state solution $p(\mathbf{x}, \infty)$ (grey) are displayed for different combinations of molecular species.

the master equation numerically is Gillespie's Monte Carlo method. The Fokker-Planck approximation of the master equation is an alternative for a limited number of molecular species with savings in computing time.

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