



Computing the moments of high dimensional solutions of the master equation

Stefan Engblom¹

Division of Scientific Computing, Department of Information Technology, Uppsala University, SE-75105 Uppsala, Sweden

Abstract

Derived from the Markov character only, the master equation of chemical reactions is an accurate stochastic description of quite general systems in chemistry. Exact solutions of this equation are rare and the most frequently used approximative solution method is to write down the corresponding set of *reaction rate* equations. In many cases this approximation is not valid, or only partially so, as stochastic effects caused by the natural noise present in the full description of the problem are poorly captured. In this paper it is shown how a certain set of higher order equations can be derived. It is shown by theory and example that stochastic effects are better captured using this technique while still maintaining the computational advantages of the reaction rate approach.

© 2006 Elsevier Inc. All rights reserved.

Keywords: Master equation; Reaction rate equations; Moment equations; Circadian clock

1. Introduction

Under fairly mild assumptions on the character of chemical reactions, all reacting systems obey the *master equation*. For D reacting species this is a differential-difference equation in D dimensions governing the behavior of the probability distribution of the systems different states. This equation suffers from the well-known “curse of dimensionality”—each species adds one dimension to the problem leading to a computational complexity that grows exponentially. As is to be expected, this equation is only rarely analytically solvable and numerical methods for solving it are of interest both in research and practice.

One classical approach to simulate chemical reactions is to derive, under suitable assumptions, *deterministic* or *reaction rate* equations which is a set of D ODEs governing some kind of average value of the unknowns, e.g. the expected value of the total number of molecules of the various species present in the system.

This typically works well when the number of molecules is large or when the system considered is in a state reasonably well separated from the critical points in phase-space. These conditions are typically always met in test-tubes containing large samples of, say, 10^{12} molecules, especially when the system is driven towards near equilibrium positions or even to steady-state.

¹ Financial support has been obtained from the Swedish National Graduate School in Mathematics and Computing.
E-mail address: stefane@it.uu.se

The situation is clearly different when biological systems inside living cells are considered. Here, the number of molecules is frequently less than 10^2 [8] and the system is often driven towards critical points for biological reasons. It is intuitively clear that under such circumstances the inherent stochasticity of the system plays a vital role. Close to a critical point, for instance, the inherent small fluctuation present in one variable produces a loss of mass in a direction that clearly can affect the rest of the system (and in some cases rather drastically so).

A *second* classical approach is to simulate the system by a stochastic method of some kind. Gillespie's method [7], or versions of it [6], are the methods in most frequent usage. Such methods share in common that they are *exact* (in a statistical sense) and that simulating one trajectory is performed at a relatively low computational cost. However, such methods still have a drawback for systems near unstable points or for large reaction rate constants since small time-steps are taken [3] and since many trajectories need to be simulated in order to compute statistical parameters accurately.

A *third* approach is to represent the full probability space in some way and “perform all possible reactions” in the same time. This approach must clearly always exhibit an exponential complexity growth, no matter the details. For a sufficiently low number of dimensions, however, carefully tuned variants may be quite effective [5].

There exist other approaches still, *van Kampen's* Ω -expansion [9] being the theoretically most well-founded method. While being accurate and effective, this method has the drawbacks that information about the system to be solved is required a priori and that analytical work needs to be done for each new system.

In this paper we will examine a generalization of the deterministic equation which we shall refer to as the *method of moments*. That is, we shall formulate and analyze equations for the central moments of order n for any chemical system. The main advantage of such an approach is efficiency: in general, the equations of order n can be solved in D^n time, where D is the number of reacting species. By only solving for the statistical parameters that one really is interested in, problems of rather high dimensionality can be solved.

The rest of the paper is organized as follows: in Section 2 we review the master equation and present some model problems. The equations for the various moments are given and analyzed to a certain extent providing us with some insight into how the method can be expected to work. In Section 3 we look at two quite different numerical examples and discuss some additional analysis of a somewhat more heuristic character. One example models the production of two metabolites controlled by two enzymes and the other example models a circadian clock where the stochastic noise is important for the clock to be periodic. We conclude by a short discussion on the various aspects of the method.

2. Equations and analysis

In this section we start by defining the master equation for a chemical system consisting of D reacting species along with a discussion of some simple model problems. By approximating the probability distribution of the system with a point-mass we recover the *deterministic equation*, a set of D ODEs governing the expected value of each species. The traditional approach of reaction rate equations can be motivated in the same way, but using concentrations instead of number of molecules as our unknowns. It is seen by an analysis of a model problem that this approximation can be expected to work well when the reaction rate constant is small in a certain sense, but that the approximation deteriorates when this condition is violated. We then examine the possibility of deriving equations governing the *covariance matrix* of the system, that is, a set of “second order” equations is derived and analyzed. These equations consist of an additional set of $D \times (D + 1)/2$ ODEs for the new unknowns. It is found that the problem with large reaction rate constants still persists but that the impact on the quality of the solution is somewhat relaxed when using these equations instead. We finally consider the generalization of this approach and give a general set of equations for central moments of arbitrary order. The section is closed by a discussion of the quality of the solution obtained using this approach.

2.1. The master equation

We consider a chemical system of D different species along with R prescribed reactions. Let $p(x, t)$ describe the probability distribution of the states $x \in \mathbf{Z}^{D+} = \{0, 1, 2, \dots\}^D$ at time t . That is, p simply describes the probability that a certain number of molecules is present at each time.

The reactions are specified as “moves” defined over the states x according to the *reaction propensities* $w_r: \mathbf{Z}^{D^+} \rightarrow \mathbf{R}$. These describe the probability for moving from the state x_r to x per unit time,

$$x_r = x + n_r \xrightarrow{w_r(x_r)} x, \tag{2.1}$$

where $n_r \in \mathbf{Z}^D$ describe the transition step.

The *master equation* [9] is then given by

$$\frac{\partial p(x, t)}{\partial t} = \sum_{\substack{r=1 \\ x+n_r^- \geq 0}}^R w_r(x+n_r)p(x+n_r, t) - \sum_{\substack{r=1 \\ x-n_r^+ \geq 0}}^R w_r(x)p(x, t) =: \mathcal{M}p, \tag{2.2}$$

where the transition steps are decomposed into positive and negative parts as $n_r = n_r^+ + n_r^-$.

As indicated, the summations are to be performed over *feasible* reactions only. In what follows, we shall only consider what we call “proper” formulations where $w_r(x) = 0$ whenever $x \not\geq n_r^+$ (note that $x \not\geq n_r^+$ is not the same thing as $x < n_r^+$ since the variables are vectors). This is reasonable since otherwise the propensity defines a loss of mass for a state where no such loss can occur. A convenient formulation for the master equation under this assumption is

$$\mathcal{M}p = \sum_{r=1}^R [x \geq -n_r^-] w_r(x+n_r)p(x+n_r, t) - w_r(x)p(x, t), \tag{2.3}$$

where the notation $[f]$ with f being a logical expression is used according to $[f] \equiv 1$ if f and $\equiv 0$ otherwise.

In the following sections we let $X = [X_1, \dots, X_D]$ be the D -dimensional stochastic variable for which p is the probability density function. We think of p and X as being two representations of the same thing and we will formulate the results using the representation that seems the most appropriate.

As a very simple example in one dimension only, consider the reactions



that is, x -molecules are created at constant rate and simultaneously destroyed at a rate proportional to the total number of molecules. In the previously used notation we have $n_1 = -1$ with $w_1(x) = k$ and $n_2 = 1$ with $w_2(x) = \mu x$ (so that the formulation indeed is proper thanks to the single zero of w_2 at $x = 0$). The master equation for this system thus becomes

$$\frac{\partial p(x, t)}{\partial t} = [x \geq 1]kp(x-1, t) - kp(x, t) + \mu(x+1)p(x+1, t) - \mu xp(x, t). \tag{2.5}$$

If initial data is given in the form of a Poisson distribution of expectation a_0 ,

$$p(x, 0) = \frac{a_0^x}{x!} e^{-a_0}, \tag{2.6}$$

then it can readily be verified that the full dynamic solution is given by

$$p(x, t) = \frac{a(t)^x}{x!} e^{-a(t)}, \tag{2.7}$$

where $a(t) = a_0 \exp(-\mu t) + k/\mu \times (1 - \exp(-\mu t))$. Independently of the initial solution, p approaches a Poisson distribution of expectation k/μ . By linearity, an initial distribution which is a superposition of Poisson distributions can be treated along the same lines.

As we shall see later (cf. Proposition 2.10), the example (2.4) above is essentially too simple for doing any convincing analysis of a numerical method and is therefore not a good model problem. A better set of reactions is



that is, an interacting problem in two dimensions. However, the complications of the analysis due to the two dimensions seem unnecessary. Under the *symmetric* assumption, $k_1 = k_2$ and $p(x, y, 0) = p(y, x, 0)$, the reactions (2.8) are *almost* the same as



We say *almost* since the formulation (2.9) is proper; the final propensity has zeros at $x \in \{0, 1\}$ —this may be thought of as a reflection of the fact that no molecule can react with itself. Simplifying even further, we drop the proportional loss of mass and consider only the reactions



with the corresponding master equation

$$\frac{\partial p(x, t)}{\partial t} = [x \geq 1]kp(x-1, t) - kp(x, t) + v(x+2)(x+1)p(x+2, t) - vx(x-1)p(x, t). \quad (2.11)$$

The usual way of solving equations like (2.11) is to introduce the probability generating function F ,

$$F(z, t) = \sum_{x \geq 0} z^x p(x, t). \quad (2.12)$$

After multiplying (2.11) by z^x and summing over $x \geq 0$ one is left with the partial differential equation (PDE)

$$\frac{\partial F}{\partial t} = -k(1-z)F + v(1-z^2)F'', \quad (2.13)$$

with the boundary conditions $F(1, t) = 1$ and that $F(\epsilon, t)$ stays bounded for small ϵ . Apparently, the time-dependent PDE (2.13) has no simple solution, but the corresponding steady-state problem can be solved ([9, X.2]). The solution is

$$F(z, \infty) = C^{-1}(1+z)^{1/2}I_1(2a(1+z)^{1/2}), \quad (2.14)$$

where $a = \sqrt{k/v}$, $C = \sqrt{2}I_1(2\sqrt{2}a)$ and where I_1 denotes a modified Bessel function. From this one can deduce that

$$p(x, \infty) = C^{-1} \frac{a^x}{x!} I_{x-1}(2a) \quad (2.15)$$

is the exact stationary solution to (2.10). We are interested in finding the first few moments of this distribution. The expectation value m can be computed according to the formula $m(t) = F'(1, t)$ and there are similar rules for the variance v and the third central moment (temporarily named s). By using some standard asymptotics [1] we get

$$m(\infty) = \frac{1}{4} + \frac{2\sqrt{2}a}{4} \frac{I_1'}{I_1}(2\sqrt{2}a) \sim \sqrt{\frac{k}{2v}} + \frac{1}{8} + \frac{3}{2^7 \sqrt{\frac{k}{2v}}} + \mathcal{O}(v/k), \tag{2.16}$$

$$v(\infty) = \frac{k}{2v} - m(\infty)^2 + m(\infty) \sim \frac{3}{4} \sqrt{\frac{k}{2v}} + \frac{1}{16} + \frac{3}{2^9 \sqrt{\frac{k}{2v}}} + \mathcal{O}((v/k)^{3/2}), \tag{2.17}$$

$$s(\infty) \sim \frac{7}{16} \sqrt{\frac{k}{2v}} - \frac{15}{2^{11} \sqrt{\frac{k}{2v}}} + \mathcal{O}(v/k), \tag{2.18}$$

where we keep one term below $\mathcal{O}(1)$ as an estimate of the error. In most applications we have that $v \ll k$ but we are interested in the cases when $v \lesssim k$ as well. Nevertheless, the asymptotic formulas above remain valid with an error of about 5% even when $v = k$ and we shall therefore continue to use them for these cases as well. Since $v \approx 3/4 \times m$, we note that this time the steady-state distribution is somewhat narrower than a Poisson distribution.

2.2. Equations for the expectation

In order to derive equations for the time derivative of the various moments, we shall frequently need the following lemma.

Lemma 2.1. *Let p satisfy a proper formulation of the master equation (2.2). Then as long as both sides make sense,*

$$\sum_{x \geq 0} T(x) \frac{\partial p(x, t)}{\partial t} = \sum_{r=1}^R E[(T(X - n_r) - T(X))w_r(X)], \tag{2.19}$$

where $T: \mathbf{Z}^{D^+} \rightarrow \mathbf{R}$ is any suitable test-function (see below).

Proof. Multiply both sides of (2.2) by $T(x)$ and sum over all $x \geq 0$ (that is, over all $x \in \mathbf{Z}^{D^+}$). One readily gets

$$\sum_{x \geq 0} T(x) \frac{\partial p(x, t)}{\partial t} = \sum_{r=1}^R \sum_{x \geq 0} [x \geq -n_r^-] T(x) w_r(x + n_r) p(x + n_r, t) - \sum_{r=1}^R \sum_{x \geq 0} T(x) w_r(x) p(x, t).$$

Substituting $y = x + n_r$ in the left sum produces

$$\sum_{r=1}^R \sum_{y \geq n_r^+} [y \geq n_r^+] T(y - n_r) w_r(y) p(y, t) - \sum_{r=1}^R \sum_{x \geq 0} T(x) w_r(x) p(x, t).$$

Now, write the first sum as a sum over $y \geq 0$ by inserting the factor $[y \geq n_r]$. In total we get the product $[y \geq n_r] \cdot [y \geq n_r^+]$ which equals $[y \geq n_r^+]$ by inspection. Since the formulation is assumed to be proper, we have that $w_r(y) = 0$ whenever $[y \not\geq n_r^+]$ and (2.19) follows. \square

The manipulations performed on infinite sums are justified under absolute convergence and since we shall only use Lemma 2.1 with $T(x)$ a polynomial, this is the case as long as sufficiently many moments of p exists.

We now need the following notation; let $m_i = E[X_i]$ denote the expected value of X_i and let n_r^i be the i th element of n_r . By taking $T(x) = x_i$ as our test-function we immediately recover the following result from Lemma 2.1.

Proposition 2.2

$$\frac{dm_i}{dt} = - \sum_{r=1}^R n_r^i E[w_r(X)]. \tag{2.20}$$

Note that (2.20) is an exact result valid as long as the corresponding master equation is properly formulated. Due to the presence of an unknown expectation, however, Proposition 2.2 can clearly not be used in general. For linear propensities one easily sees that the unknown expectation $E[w_r(X)]$ can be expressed in terms of the expectation m but this is not true in general. Assuming that the dimensions involved with nonlinear propensities can be approximated by a point-mass with vanishing higher moments evidently produces the following result.

Proposition 2.3. *Divide the integers $\{1, \dots, R\}$ into two disjoint sets R_1 and R_2 such that $\forall r \in R_1$: w_r is linear and $\forall r \in R_2$: w_r depends on dimensions with vanishing higher moments. Then*

$$\frac{dm_i}{dt} = - \sum_{r=1}^R n_r^i w_r(m). \quad (2.21)$$

Clearly, the set R_2 cannot in general be guaranteed to exist and we must then regard (2.21) as an approximation rather than an exact identity. We refer to this approximation as the *deterministic equation* which is just about the same thing as the customary reaction rate equations. The only difference is that what we call the deterministic equation is written with the unknowns being the number of molecules instead of concentrations.

As an example we apply the deterministic equation (2.21) to the model problem (2.10). This results in the ODE

$$\frac{d\tilde{m}}{dt} = k - 2v\tilde{m}(\tilde{m} - 1), \quad (2.22)$$

which is separable. The solution is given by

$$\tilde{m}(t) = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{k}{2v}} \times \frac{1 + \exp(-\sqrt{4v^2 + 8kvt})C}{1 - \exp(-\sqrt{4v^2 + 8kvt})C}, \quad (2.23)$$

where C is to be determined from the initial value of m . In order to analyze the quality of this solution, we note that the exact ODE (2.20) becomes

$$\frac{dm}{dt} = k - 2vE[X(X - 1)] = k - 2vm(m - 1) - 2vv. \quad (2.24)$$

Put $\tilde{m}(\infty) = m(\infty) + \delta$, where $\tilde{m}(\infty)$ is the steady-state of (2.22), $m(\infty)$ the exact steady-state of (2.24) and where δ is the error. Expanding (2.22) around $m(\infty)$ yields, since $m(\infty)$ satisfies (2.24),

$$0 = -2v(2m(\infty) - 1)\delta + 2vv(\infty) + \mathcal{O}(\delta^2), \quad (2.25)$$

so that $\delta = v(\infty)/(2m(\infty) - 1) \sim 3/8$ to first order. Since the exact solution is available this can also be seen directly by comparing (2.23) with (2.16) but the current approach works also when higher order equations are analyzed. We now let $\tilde{m}(t) = \tilde{m}(\infty) + \tilde{\epsilon}(t)$ and $m(t) = m(\infty) + \epsilon(t)$. Expanding (2.22) and (2.24) produces

$$\frac{d\tilde{\epsilon}}{dt} = -2v(2\tilde{m}(\infty) - 1)\tilde{\epsilon} + \mathcal{O}(\tilde{\epsilon}^2), \quad (2.26)$$

$$\frac{d\epsilon}{dt} = -2v(2m(\infty) - 1)\epsilon + \mathcal{O}(\epsilon^2), \quad (2.27)$$

that is, both solutions decay exponentially but at slightly different speed. Close to the steady-state solution the difference in the exponents is about $-2v(2\tilde{m}(\infty) - 2m(\infty)) \sim -3v/2$. We note that this last part of the analysis is only an approximation; we have assumed that the expectation value m is perturbed, but the *induced* perturbation on the variance v has been neglected.

To summarize, we have shown that the approximative equation (2.22) yields a slightly larger steady-state solution than the exact equation (2.24) and that the speed with which the steady-state is approached is slightly higher. For $v \ll k$ it is fair to say that (2.23) will produce a reasonably accurate value of the expectation value and we shall later see that this holds true also when higher moments are used. However, one also sees that for the cases when v approaches k , the approximation (2.22) deteriorates. This effect will be seen to improve to a certain extent when higher order moments are used.

2.3. Equations for the covariance

Since the approximation in Proposition 2.3 does not capture the effects of higher order moments, a natural idea is to try to formulate equations for those as well. In this section we therefore give equations for the time-derivative of the covariance matrix $C_{ij} = E[(X_i - m_i)(X_j - m_j)]$.

As before, there is an exact result that we now state and for this purpose we will use the notation $n_r^{[i,j]} = n_r^i n_r^j$.

Proposition 2.4

$$\frac{dC_{ij}}{dt} = - \sum_{r=1}^R (n_r^i E[(X_j - m_j)w_r(X)] + n_r^j E[(X_i - m_i)w_r(X)]) + \sum_{r=1}^R n_r^{[i,j]} E[w_r(X)]. \quad (2.28)$$

Proof. This is found by taking $T(x) = (x_i - m_i)(x_j - m_j)$ in Lemma 2.1. In Section 2.4 a general proof is given. \square

Again, we are interested in an approximative version of (2.28). Assume that all propensities are at most quadratic so that the Taylor series of w_r around the expected value $x = m$ becomes an identity,

$$w_r(x) = w_r(m) + \sum_k \frac{\partial w_r(m)}{\partial x_k} (x_k - m_k) + \sum_{k,l} \frac{\partial^2 w_r(m)}{\partial x_k \partial x_l} \frac{(x_k - m_k)(x_l - m_l)}{2!}, \quad (2.29)$$

where the sums run through all D dimensions independently. Comparing the unknown expectations in (2.28) with the series representation (2.29) it is clearly straightforward to evaluate the former. Note, however, that this will produce a *third order* central moment which is unaccounted for and we therefore do not formulate our next result in a fashion similar to Proposition 2.3, that is, there is no point in dividing the integers $\{1, \dots, R\}$ according to whether the corresponding propensities are at most quadratic or depend on dimensions with vanishing higher moments.

Proposition 2.5. *If all propensities w_r are at most quadratic and if the third central moments may be neglected, then*

$$\frac{dm_i}{dt} = - \sum_{r=1}^R n_r^i \left(w_r(m) + \sum_{k,l} \frac{\partial^2 w_r(m)}{\partial x_k \partial x_l} \frac{C_{kl}}{2!} \right), \quad (2.30)$$

$$\frac{dC_{ij}}{dt} = - \sum_{r=1}^R \left(n_r^i \sum_k \frac{\partial w_r(m)}{\partial x_k} \frac{C_{kj}}{1!} + n_r^j \sum_l \frac{\partial w_r(m)}{\partial x_l} \frac{C_{il}}{1!} \right) + \sum_{r=1}^R n_r^{[i,j]} \left(w_r(m) + \sum_{k,l} \frac{\partial^2 w_r(m)}{\partial x_k \partial x_l} \frac{C_{kl}}{2!} \right). \quad (2.31)$$

Again, we consider the model problem (2.10). The exact equations corresponding to Proposition 2.4 becomes

$$\frac{dm}{dt} = k - 2vm(m - 1) - 2vv, \quad (2.32)$$

$$\frac{dv}{dt} = k + 4vm(m - 1) + 4vv - 4v(2m - 1) - 4vs, \quad (2.33)$$

where s denotes the third central moment. The approximative version is obtained by setting $s = 0$ and we now attempt to analyze the error induced by this truncation. We use the linearization technique from the previous section and set $\tilde{m}(\infty) = m(\infty) + \delta_1$ and $\tilde{v}(\infty) = v(\infty) + \delta_2$, where as before $m(\infty)$ and $v(\infty)$ denote the exact steady-state moments and where the tilded versions are their corresponding approximations. By linearizing we find

$$0 = -2v(2m - 1)\delta_1 - 2v\delta_2, \quad (2.34)$$

$$0 = 4v(2m - 1)\delta_1 + 4v\delta_2 - 8vv\delta_1 - 4v(2m - 1)\delta_2 + 4vs, \quad (2.35)$$

where for brevity we dropped the argument ∞ . The solution to this linear system is

$$\delta_1 = \frac{s(\infty)}{2v(\infty) - (2m(\infty) - 1)^2} \sim -\frac{7}{64\sqrt{\frac{k}{2v}}}, \tag{2.36}$$

$$\delta_2 = -(2m(\infty) - 1)\delta_1 \sim -\frac{7}{32}, \tag{2.37}$$

where the asymptotical behavior for $k \gg v$ has been indicated. We thus see that for sufficiently large reaction rate ratio k/v , this new approximation is indeed “one order more accurate” than the previous approximation (2.22). Interestingly, there is also the possibility that the Jacobian is singular suggesting that very large errors may occur. This happens when $2v(\infty) = (2m(\infty) - 1)^2$, or approximately when $k/v = 1.8862$ and can be observed in practice; either as an ill-posed nonlinear steady-state problem or as a dynamic solution which diverges to infinity for no physical reasons.

As before, it is possible to approximately analyze the dynamic behavior close to $t = \infty$ by studying the effect of a small perturbation added to the steady-state solution. This is somewhat involved and will not be performed in detail here although we note that it still remains true that, close to the steady-state, the time-dependent difference between the approximative and the true solution depends on the error in the steady-state solution itself—which is now one order more accurate in the region away from the point $k \sim v$ where the approximation deteriorates.

2.4. Higher order approximations

We now turn our attention to the obvious generalization of the results found in the two previous sections. Since the master equation is an equation in D dimensions and since higher order moments in general are tensors we shall need to make use of a multi-index notation which we therefore first review.

An I -index is written using the capitals I, J, K and so on. If $I = [i_1, \dots, i_n]$ we put $|I| = n$ and write

$$x^I = x_{i_1} \cdots x_{i_n}, \tag{2.38}$$

where the empty product is $\equiv 1$. Permuting these multi-indices does not affect the operation defined above so that $x^{PI} = x^I$ for all permutations P .

An α -index is written using small Greek letters α, β, γ and so on. If $\alpha = [\alpha_1, \dots, \alpha_n]$ we define $|\alpha| = \sum_i \alpha_i$ along with the following products:

$$x^\alpha = x_1^{\alpha_1} \cdots x_n^{\alpha_n}, \tag{2.39}$$

$$\alpha! = \alpha_1! \cdots \alpha_n!. \tag{2.40}$$

Inequalities on α -index are defined element-wise so that, for example, $\alpha \leq \beta$ is true iff $\forall i: \alpha_i \leq \beta_i$. Note that $\not\leq$ and \geq are not equivalent; only the trivial implication $\neg(\alpha < \beta) \Leftrightarrow \alpha \geq \beta$ is true.

We define the map $\#$ as the unique α -index corresponding to a certain I -index. If $\alpha = \#I$, then clearly α_j is the number of elements in the set $\{i; I_i = j\}$ and we note that this mapping conserves the norm, $|I| = |\#I|$.

As before, we let X be the stochastic variable in D dimensions corresponding to the probability density function p that satisfies the master equation (2.2), and we assume the formulation to be proper so that Lemma 2.1 is applicable. We have already used the notation $m = E[X]$ for the expectation value of X and we shall use the following notation for the higher order central moments:

$$M_I^{|I|} = E[(X - m)^I] = \sum_{x \geq 0} (x - m)^I p(x), \tag{2.41}$$

where $|I| \geq 2$. For example, $M^2 = C$, the covariance matrix and in addition we set $M^1 = m$. For brevity we keep only the exponent whenever the index of the moment is irrelevant.

Proposition 2.6. For $|I| > 2$,

$$\frac{dM_I^{|I|}}{dt} = \sum_{x \geq 0} (x - m)^I \frac{\partial p(x, t)}{\partial t} - \sum_{j=1}^{|I|} m_{I_j}'(t) M_{I - \{I_j\}}^{|I|-1}. \tag{2.42}$$

Proof. Take the time derivative of (2.41),

$$\frac{dM_I^{|I|}}{dt} = \frac{d}{dt} \sum_{x \geq 0} (x - m)^I p(x, t) = \sum_{x \geq 0} (x - m)^I \frac{\partial p(x, t)}{\partial t} - \sum_{j=1}^{|I|} m_{I_j}'(t) \sum_{x \geq 0} (x - m)^{I - \{I_j\}} p(x, t),$$

where we note that the last term vanishes for $|I| = 2$. \square

At this point we need to introduce some further notation. Define the combination set \mathcal{Q}_k^n as the set of all combinations of k objects taken without respect to order from a collection of n objects. Obviously, we have that the number of such combinations is given by $|\mathcal{Q}_k^n| = \binom{n}{k}$. If $|I| = n$ it makes sense to apply any combination $Q \in \mathcal{Q}_k^n$ and we write $J = QI$ for this operation. Of course, the length of this new index is given by $|J| = k$. For a fixed combination $Q \in \mathcal{Q}_k^n$ we define the adjoint combination $Q^* \in \mathcal{Q}_{n-k}^n$ as the unique combination that makes $[Q, Q^*]$ a permutation. As an example of this notation, consider the case $n = 3$ and $k = 2$. We evidently have that

$$\mathcal{Q}_2^3 = [[1, 2], [2, 3], [1, 3]],$$

and the ordered set of adjoint combinations becomes

$$(\mathcal{Q}_2^3)^* = [[3], [1], [2]].$$

As another example we note that (2.42) can be written

$$\frac{dM_I^{|I|}}{dt} = \sum_{x \geq 0} (x - m)^I \frac{\partial p(x, t)}{\partial t} - \sum_{Q \in \mathcal{Q}_1^{|I|}} \frac{dM_{QI}^1}{dt} M_{Q^*I}^{|I|-1}. \tag{2.43}$$

The following Lemma will allow us to switch notation from α -index to I -index.

Lemma 2.7. *The inequality $\#J \leq \#I$ has the solutions*

$$J = QI \quad \text{with} \quad Q \in \mathcal{Q}_{|J|}^{|I|}. \tag{2.44}$$

There are no other solutions. Furthermore, there are exactly $\binom{\#I}{\#J}$ different $Q \in \mathcal{Q}_{|J|}^{|I|}$ that all produce the same solution J .

Proof. A solution J can be constructed from I by taking combinations in the following way: if $|J| = j$ is chosen beforehand then one solution is given by taking j different indices from I . By construction such a solution is given by QI for some $Q \in \mathcal{Q}_{|J|}^{|I|}$. A solution J' that cannot be constructed in this way must consist of at least one index from I taken more than once which clearly violates the given inequality $\#J \leq \#I$. To show the last part, define $\alpha = \#I$ and $\beta = \#J$, where J is any solution. By construction, there are α_1 ones in I , so β will result iff β_1 of those are taken. This can be done in $\binom{\alpha_1}{\beta_1}$ different ways. Continuing this reasoning we find that in total there are $\binom{\alpha}{\beta}$ different combinations Q that all produce the same J . \square

To state our major result we let E_r^I be a convenient shorthand for $E[(X - m)^I w_r(X)]$.

Lemma 2.8. *Let the master operator \mathcal{M} be defined by (2.3). Then, provided the indicated moments exist,*

$$\sum_{x \geq 0} (x - m)^I \mathcal{M}p(x, t) = \sum_{j=1}^{|I|} (-1)^j \sum_{r=1}^R \sum_{Q \in \mathcal{Q}_j^{|I|}} n_r^{QI} E_r^{Q^*I}. \tag{2.45}$$

Proof. From Lemma 2.1 with $T(x) = (x - m)^\alpha$ we get

$$\sum_{x \geq 0} (x - m)^\alpha \mathcal{M}p(x, t) = \sum_{r=1}^R E[(x - m - n_r)^\alpha - (x - m)^\alpha] w_r(x).$$

By the binomial theorem in D dimensions we get using the notation mentioned above

$$= \sum_{r=1}^R \sum_{0 < \beta \leq \alpha} (-1)^{|\beta|} n_r^\beta \binom{\alpha}{\beta} E_r^{\alpha-\beta}.$$

We now wish to switch back to I -index using Lemma 2.7. The inequality $\beta \leq \alpha$ is thus understood as $J = QI$ with $Q \in \mathcal{Q}_{|J|}^{|I|}$, where $\alpha = \#I$ and $\beta = \#J$. The remaining factor $\binom{\alpha}{\beta}$ is absorbed according to the final part of Lemma 2.7 and we are left with

$$= \sum_{r=1}^R \sum_{j=1}^{|I|} (-1)^j \sum_{Q \in \mathcal{Q}_j^{|I|}} n_r^{QI} E_r^{Q^*I},$$

where one realizes that $\alpha - \beta = Q^*I$. \square

Theorem 2.9. *Under the assumptions stated above,*

$$\frac{dM_I^{|I|}}{dt} = \sum_{j=1}^{|I|} (-1)^j \sum_{r=1}^R \sum_{Q \in \mathcal{Q}_j^{|I|}} n_r^{QI} E_r^{Q^*I} - [|I| \geq 3] \times \sum_{Q \in \mathcal{Q}_1^{|I|}} \frac{dM_{QI}^1}{dt} M_{QI}^{|I|-1}, \tag{2.46}$$

Proof. This follows from Propositions 2.2, 2.4, 2.6 and Lemma 2.8. \square

This is the general exact formula for the time derivative of the central moments. As before, we have the following result for linear propensities.

Proposition 2.10. *If all propensities are linear, then Theorem 2.9 can be written as a closed system of ODEs for the central moments. This set of ODEs is exact.*

Proof. Since w_r is linear we see (in the notation of (2.46)) that

$$E_r^{Q^*I} = E[(X - m)^{Q^*I} w_r(X)]$$

can be written as a combination of the moments M^n with $n \leq |Q^*I| + 1 \leq |I| - j + 1 \leq |I|$. Since no moment of higher order than $|I|$ enters, the system of ODEs is indeed closed. \square

Theorem 2.9 cannot be directly applied to the model problem (2.10) due to the quadratic propensity but a truncated version can as before easily be formed. It is awkward to fully analyze the behavior of this approximation although the effects can easily be found experimentally. In Table 2.1 the errors in the first two moments for the steady-state solution are given for different order of the highest moment ($n = \max|I|$ in the notation of Theorem 2.9).

In the left part of the table the parameters are $[k, v] = [1, 10^{-3}]$ and apparently, the result converges quite rapidly with increasing order of the highest order moment. Evidently, there is a kind of “pairwise conver-

Table 2.1
Absolute errors in the steady-state moments m and v

n	δm	δv	δm	δv
1	3.80×10^{-1}	–	3.89×10^{-1}	–
2	5.15×10^{-3}	2.26×10^{-1}	1.84×10^{-2}	2.46×10^{-1}
3	1.00×10^{-2}	4.41×10^{-1}	3.58×10^{-2}	4.82×10^{-1}
4	4.49×10^{-4}	1.97×10^{-2}	5.55×10^{-3}	7.43×10^{-2}
5	4.65×10^{-4}	2.05×10^{-2}	6.65×10^{-3}	8.91×10^{-2}
6	4.37×10^{-5}	1.92×10^{-3}	2.15×10^{-3}	2.88×10^{-2}
7	3.22×10^{-5}	1.42×10^{-3}	2.11×10^{-3}	2.82×10^{-2}
8	5.09×10^{-6}	2.24×10^{-4}	1.12×10^{-3}	1.50×10^{-2}
9	3.09×10^{-6}	1.36×10^{-4}	1.07×10^{-3}	1.43×10^{-2}

The parameters are $k = 1$ and $v = 10^{-3}$ ($v = 10^{-2}$) for the left (right) part of the table.

gence” in the sense that, for example, the 4th and the 5th order equations yield an error of about the same magnitude. That is, the error seems to decrease by some factor for every new set of even order equations. This behavior is visible also in the right part of the table where the parameters are $[k, v] = [1, 10^{-2}]$ although the rate of convergence clearly slows down towards the end.

To motivate, although not rigorously prove this observation we reason as follows. From the exact solution (2.14) one can find empirically using a computer algebra system that the n th central moment behaves asymptotically as $(k/v)^{\lfloor n/2 \rfloor / 2}$ (except when $n = 1$, the expectation value). If the highest order moment used is *even*, this means that the next *odd* order central moment is neglected and an error of the order of the n th central moment itself times the reaction rate constant v is introduced in the *last* equation. This error pollutes the rest of the equations via the couplings, but for every coupling to a lower order moment *the error is multiplied by the reaction rate constant v* . Thus, in effect, the impact on the lowest order moment is reduced by this factor for every equation. The same reasoning for an *odd* order version explains why the error is not reduced this time; here the error from the last equation is simply one order higher which equate the effect of the multiplication by the reaction rate constant.

As noted before, there is still the possibility of introducing unphysical instability due to the truncation. For the first nine central moments as tested above, this happens approximately when $k/v \sim 20$ or when the expectation value at steady-state is less than about 5.

Although obviously far from being a complete analysis of the method developed thus far, the discussion above suggests that one can *either* expect close to geometric convergence in the moments *or* that the convergence deteriorates when sufficiently high order moments are used. The analysis clearly does not reveal anything of what can happen when systems without a unique steady-state solution is solved, nor have higher order propensities been discussed although the quadratic case is theoretically quite important. As for the quality of the dynamic solution obtained this clearly depends on the dynamics of the system itself. In the model problem discussed above one expects the dynamic solution to be roughly as good as the steady-state solution is but this is no longer to be expected for systems with different dynamical properties.

3. Numerical experiments

In this section we present two numerical experiments. They differ from the model problem we have analyzed so far in two different ways; the first example investigates the behavior of the method of moments when used in problems with strongly nonlinear propensities. These have to be approximated by a polynomial in order for the method to apply and we give a simple suggestion of how to predict the behavior of this approximation. The second example treats an example of a system which exhibits periodic behavior and demonstrates how the method of moments may reproduce a solution driven by stochastic noise.

3.1. Enzyme-control of metabolites

This example is taken from [4] and simulates the synthesis of two metabolites x and y by two enzymes e_1 and e_2 . The reactions are



where the parameters are $k_1 = k_2 = 0.3$, $k_3 = k_4 = 0.02$, $k = 10^{-3}$, $\mu = 2 \times 10^{-3}$, $k_i = 60$ and $k_r = 30$. We are interested in understanding how the method of moments can be applied and if it can be expected to converge.

It is straightforward to write down the exact equations according to [Theorem 2.9](#) for this system. However, due to the nonlinear propensities, this produces expectation values that cannot be directly evaluated. As a concrete example we consider the lowest order equation which will contain the term

$$E\left[\frac{k_1 E_1}{1 + X/k_i}\right],$$

which cannot be directly evaluated. Here X and E_1 are the stochastic variables corresponding to x and e_1 respectively. The easiest way to get an approximation of this quantity has already been discussed in Section 2.3 and amounts to forming the Taylor series around the expectation values $m_x = E[X]$ and $m_{e_1} = E[E_1]$,

$$\frac{k_1 E_1}{1 + X/k_i} \approx k_1 E_1 \left[(1 + m_x/k_i)^{-1} - (1 + m_x/k_i)^{-2} (X - m_x)/k_i + \dots \right], \quad (3.2)$$

where the trivial shift in E_1 has been suppressed. In this way any expectation value may be approximated by a series containing central moments of the variables.

To be more general, suppose that $f: \mathbf{R}^D \rightarrow \mathbf{R}^D$ is well approximated by a polynomial around $m = E[X]$ (in multi-index),

$$f(x) \approx \sum_{|J|=0}^K a_J (x - m)^J, \quad (3.3)$$

then,

$$E[f(X)] \approx a_0 + \sum_{|J|=2}^K a_J M_J^{|J|}, \quad (3.4)$$

and the higher order versions present in Theorem 2.9 becomes

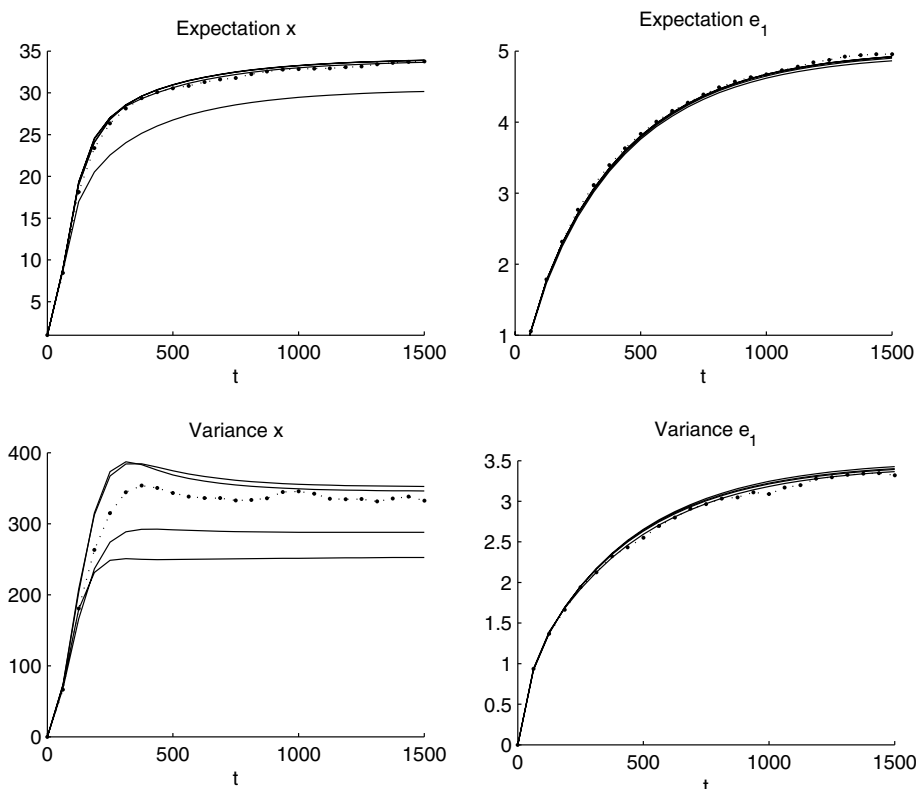


Fig. 3.1. Dynamics of (3.1). The simulation starts at $t = 0$ with one x and one y molecule. At $t = 1500$ the steady-state is approximately reached. Due to symmetry, the solutions of x (e_1) and y (e_2) are identical. Top/bottom left: the expectation and variance of x , top/bottom right: the expectation and variance of e_1 . Dotted: the result from 10000 Gillespie simulations. The number of moments used in the computations can be found in Fig. 3.2.

$$E[(X - m)^i f(x)] \approx \sum_{|J|=1}^K a_J M_{[i,J]}^{1+|J|}, \tag{3.5}$$

$$E[(X - m)^J f(x)] \approx \sum_{|J|=0}^K a_J M_{[J,J]}^{|J|+|J|}, \tag{3.6}$$

where $|i| = 1$ and $|J| \geq 2$. This is the key to assembling [Theorem 2.9](#) for *any* set of propensities w_r and, provided that moments with a degree higher than the number of equations are removed, produces a closed set of ODEs for the first n central moments. It is difficult to analyze the behavior of this approximation a priori but we shall discuss the possibility of an analysis a posteriori later.

Table 3.1
Steady-state solutions of (3.1) for different order n of the highest moment

n	m_x	v_x	m_{e_1}	v_{e_1}
1	30.44	–	4.96	–
2	34.15	288.23	5.00	3.50
3	33.91	253.16	5.02	3.44
4	34.16	351.60	5.02	3.48
5	34.14	345.29	5.02	3.47

With the exception of v_x all values have stagnated to within less than one percent at $n = 5$.

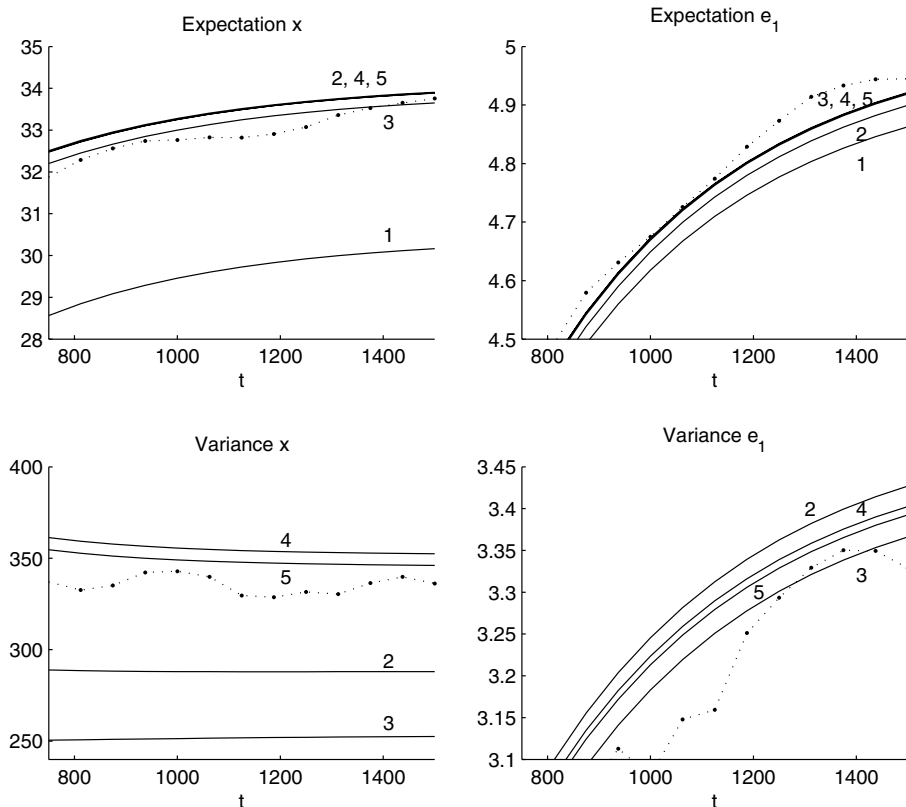


Fig. 3.2. A close-up of the situation in [Fig. 3.1](#). The numbers in the figures indicate the number of moments used for producing each curve. Comparing the results with the Gillespie simulation, it is seen that the higher order versions all produce better results than the lower order versions. Note in particular the poor results in the variable x obtained from the deterministic equation.

With this setup we performed experiments on the reactions (3.1). In Fig. 3.1 the results are displayed and it is seen that the procedure seems to converge with increasing order of the highest moment although the variance of x behaves somewhat nervously. This observation is confirmed in Table 3.1 where the steady-state solutions for the two first moments are given. All moments have settled to within less than one percent except for the variance in x which still differ by about 2% (Fig. 3.2).

Analyzing these results consists of two parts. Firstly, under the assumption that the propensities *can* be approximated by polynomials, we must show that the introduced “artificial reaction rate constants” are small. If this is the case, the error committed when setting certain moments to zero in the higher order equations is repeatedly filtered through these constants. Secondly, we must show that the approximation by a polynomial can be expected to perform well.

Recall again the series expansion (3.2). The term corresponding to a quadratic interaction is $k_1/k_i \cdot (1 + m_x/k_i)^{-2} \cdot e_1 x$, or, at steady-state about $2 \times 10^{-3} e_1 x$. From our experience with the model problem

Table 3.2
Parameters of the circadian clock (3.10)

α_a	50	β_a	50	γ_a	1	δ_{ma}	10	θ_a	50
α'_a	500	β_r	5	γ_r	1	δ_{mr}	0.5	θ_r	100
α_r	0.01			γ_c	2	δ_a	1		
α'_r	50					δ_r	–		

The parameter δ_r is varied in the experiments.

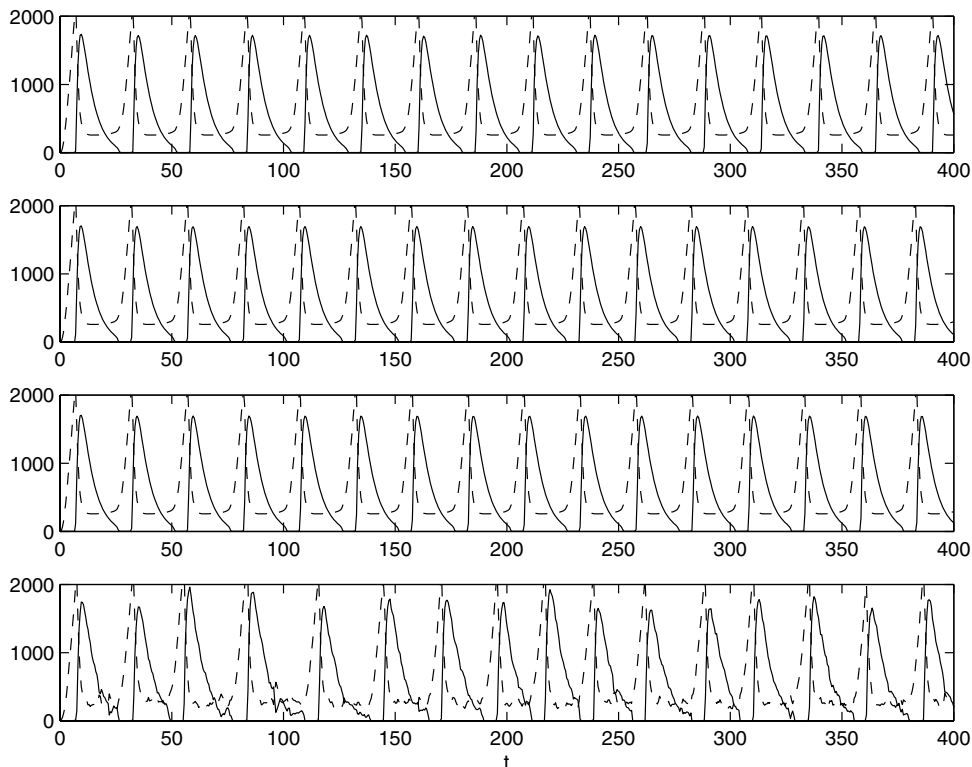


Fig. 3.3. Results from the experiments with the parameter δ_r set to 0.2. The first three graphs shows the method of moments for the first, the second and the third order central moments. Below is a comparison with a Gillespie simulation. Solid: the number of R molecules, dashed: the number of C molecules. With this choice of parameters all methods produce comparable results although the deterministic equation seem to be slightly out of phase by the end of the simulation.

(cf. Table 2.1) we expect this term to be sufficiently small that the method converges with increasing order moments. The other nonlinear propensities can be investigated in the same manner and turns out to be associated with quadratic terms of even smaller magnitude. We also note that the coefficients in front of higher order terms will be smaller yet so that these should not present problems either.

Turn now to the question of analyzing the validity of a series expansion like (3.2). The geometric series around $X = m_x$ converges provided $|X - m_x| < m_x + k_i$ but only rapidly so, say, when $|X - m_x| < (m_x + k_i)/2$. Recall the *Chebyshev inequality* [1],

$$P[|X - m_x| \geq t\sqrt{v_x}] \leq \frac{1}{t^2}, \quad (3.7)$$

where $\sqrt{v_x}$ is the standard deviation. At steady-state, the probability for slow convergence is therefore bounded by

$$P[|X - m_x| \geq (m_x + k_i)/2] \leq \frac{4v_x}{(m_x + k_i)^2} \approx 15.6\%, \quad (3.8)$$

and the probability for divergence by

$$P[|X - m_x| \geq (m_x + k_i)] \leq \frac{v_x}{(m_x + k_i)^2} \approx 3.9\%. \quad (3.9)$$

Since (3.7) is pessimistic for probability distributions with a tail decaying faster than an algebraic expression (which is to be expected), (3.8) and (3.9) indicate that a series expansion will indeed produce an accurate approximation. The other nonlinear propensity can be analyzed in the same way and, although the percentage

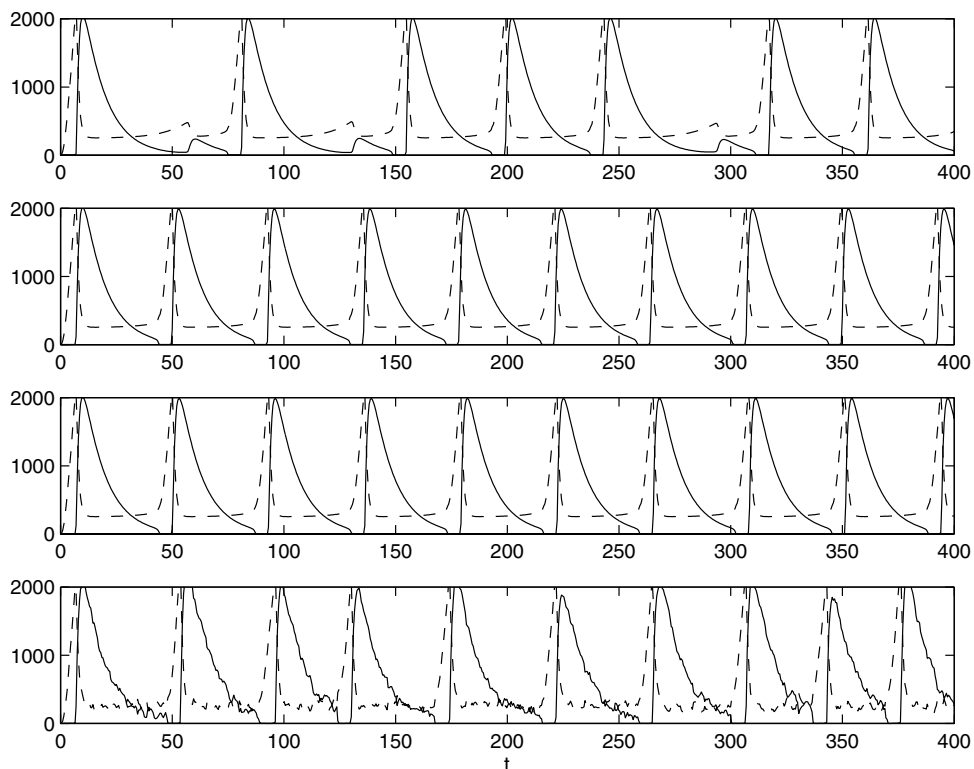
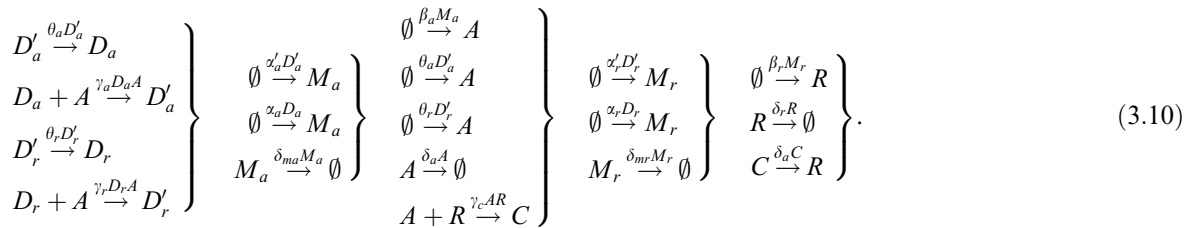


Fig. 3.4. The parameter δ , is set to 0.1 and the deterministic equation shows a somewhat different behavior with periods varying irregularly that is not present in the second and the third order methods. Comparing with the Gillespie simulation reveals that this behavior is incorrect.

bounds become slightly larger, the result also indicates that a series expansion will behave well for the largest part of the probability mass.

3.2. A circadian clock

In [2], a model for a *circadian clock* is given. A circadian clock is a set of species reacting in such a way that the resulting system produces reliable oscillations and may be used by an organism to e.g. keep track of time. This model is quite large and involves 9 species with 18 different reactions. Using slightly altered parameter names, the proposed model is



The values of the various parameters are given in Table 3.2 where, as indicated, the parameter δ_r will be varied with the experiment.

The reactions (3.10) can be solved by the method of moments in the usual way; all reactions but three are linear and will thus be captured exactly. In comparison with the rest of the parameters, the reaction constants associated with the quadratic reactions are quite small and so one may hope that the method of moment will perform reasonably well with increasing order. A difficulty with the system of ODEs produced by the method is that it is quite *stiff* and so an implicit ODE-solver is preferable—we used MATLABs `ode15s`.

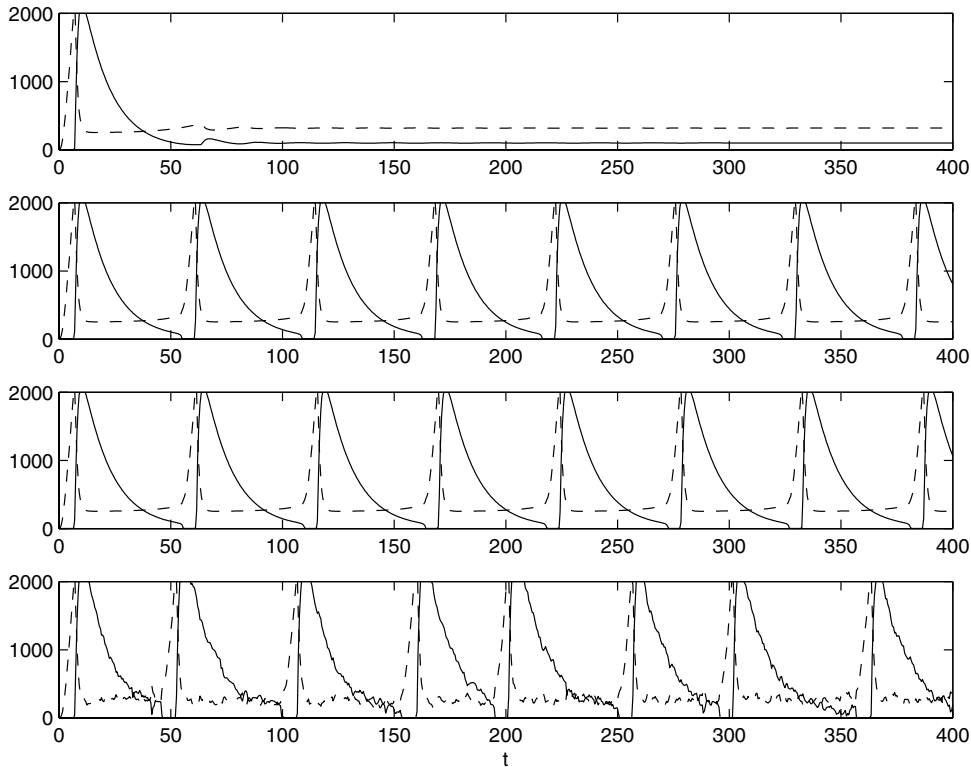


Fig. 3.5. Same as before but the parameter δ_r is now set to 0.08. The deterministic solution rapidly falls off to steady-state while the second and third order methods produce oscillations similar to what the Gillespie simulation does.

An interesting reduced version of the circadian clock is presented in [10]; by introducing various steady-state assumptions the model is reduced to 2 species only, coupled by a highly nonlinear reaction. The authors show that this simple model produces very similar behavior as the full 9 dimensional setup does while being much more easy to analyze. Certain choices of the parameters are shown to produce oscillating behavior using a *stochastic* method such as Gillespie's method, while the *deterministic* equation rapidly reaches a steady-state solution. The inherent stochastic fluctuations in a biological system thus *stabilizes* the clock and makes it resistant to changes in the surroundings.

In Fig. 3.3, results from four different methods are plotted over time. The methods are the deterministic equation, the second and the third order method of moments as well as one sample Gillespie trajectory. With the parameter $\delta_r = 0.2$, all methods produce comparable results.

We now lower the parameter δ_r and use the value 0.1 instead. This produces the behavior shown in Fig. 3.4 where one clearly sees that the deterministic equation produces an incorrect result; the periodic pattern becomes irregular and does not seem to match the results from the stochastic method.

As a final example we used the value $\delta_r = 0.08$. This produces the plot in Fig. 3.5 where the deterministic solution rapidly reaches steady-state after completing one period only. On the contrary, the second and third order method produces reliable periodic oscillations which seem to match those produced by the stochastic method fairly well. Note that, in all experiments, we used *one* sample trajectory from the stochastic method only—gathering enough samples to produce a smooth looking average path is a very expensive computation indeed, since different samples easily lose phase with respect to each other.

4. Conclusions

We have seen that the method of moments applied to the master equation can be a useful approach to compute and analyze chemical reactions. The main advantages of the method are that it is fairly easy to program, has low computational complexity (polynomial in the number of species D) and frequently produces the output that one is really interested in. In many applications the precise form of the probability distribution is irrelevant while on the other hand a few Gillespie trajectories are not sufficient to accurately compute a suitable average path. A general code for *any* given set of propensities has been developed by the author and is available through email communication. Yet another advantage of the method that has not been discussed is the simplicity with which *time dependent* propensities are treated; stochastic simulations are usually quite difficult to adapt for such situations.

On the other hand, the disadvantages of the method are that it is difficult to analyze a priori and that the produced system of ODEs can become very stiff as higher order moments enter the computation. The former issue can sometimes be solved by comparing the solutions obtained using an increasing number of moments but this procedure is obviously quite difficult to justify on theoretical grounds.

We also mention two possible improvements over the method as presented this far. Most importantly, when encountering 'problematic' dimensions a good idea could be to use a different and usually more expensive method over these dimensions. This method can then be coupled with the method of moments in order to reduce the complexity of the overall method. A second improvement is to interpolate missing moments instead of merely truncating them. The easiest way is probably to fit a normal distribution to the two first moments and then derive the missing higher order moments from this model. Evidently, this improvement is difficult to analyze but, on the other hand, it is hard to imagine that such an approach could be worse than simply setting the missing moments to zero.

In conclusion, we like to think of the method as a very useful complement to the reaction rate/deterministic approach—the deterministic equation alone is frequently used without much justification at all. Thanks to the simplicity of the method of moments, trying a few more moments is an effective and very useful improvement.

Acknowledgements

Many discussions with Per Lötstedt and Paul Sjöberg have influenced the contents of this paper. The author would also like to acknowledge the various inputs from Måns Ehrenberg and Johan Elf. Finally, Olof Runborg donated time and patience during a long and valuable discussion.

References

- [1] M. Abramovitz, I.A. Stegun, Handbook of Mathematical Functions, Dover, 1970.
- [2] N. Barkai, S. Leibler, Circadian clocks limited by noise, *Nature* 403 (2000) 267–268.
- [3] Y. Cao, D. Gillespie, L. Petzold, Multiscale stochastic simulation algorithm with stochastic partial equilibrium assumption for chemically reacting systems, *J. Comput. Phys.* 206 (2005) 395–411.
- [4] J. Elf, P. Lötstedt, P. Sjöberg, Problems of high dimension in molecular biology, in: W. Hackbusch, (Ed.), Proceedings of the 19th GAMM-Seminar in Leipzig High dimensional problems—Numerical Treatment and Applications, 2003, pp. 21–30.
- [5] L. Ferm, P. Lötstedt, P. Sjöberg, Adaptive, conservative solution of the Fokker–Planck equation in molecular biology, Technical Report 2004-054, Department of Information Technology, Uppsala University, Uppsala, Sweden, 2004.
- [6] M.A. Gibson, J. Bruck, Efficient exact stochastic simulation of chemical systems with many species and many channels, *J. Phys. Chem.* 104 (2000) 1876–1889.
- [7] D.T. Gillespie, A general method for numerically simulating the stochastic time evolution of coupled chemical reactions, *J. Comput. Phys.* 22 (1976) 403–434.
- [8] P. Guptasarama, Does replication-induced transcription regulate synthesis of the myriad low copy number proteins of *Escherichia coli*? *Bioessays* 17 (1995) 987–997.
- [9] N.G. vanKampen, Stochastic Processes in Physics and Chemistry, second ed., Elsevier, 2004.
- [10] J.M.G. Vilar, H.Y. Kueh, N. Barkai, S. Leibler, Mechanism of noise-resistance in genetic oscillators, *Proc. Natl. Acad. Sci.* 99 (2002) 5988–5992.