Numerical Solution Methods for the Master Equation

Stefan Engblom
Division of Scientific Computing
Department of Information Technology
Uppsala University

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Overview

- The master equation of chemical reactions: a difference-differential equation in $D$ dimensions
- The “weak” master equation
- Reduced information: the reaction-rate equations, equations of moments
- Case-study in 9-D: a circadian clock
- Detailed information: a discrete, adaptive spectral method based on Charlier’s polynomials
- Case-study in 2-D: a bistable problem
- Conclusions
Chemical systems

$x \in \mathbb{Z}_+^D$ defines the state of a chemical system consisting of $D$ different species ($x_i$ is # of molecules of species number $i$).

A reaction is a transition from state $x_r$ to state $x$:

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

(1)

where $n_r$ is the transition step and where $w_r : \mathbb{Z}_+^D \rightarrow \mathbb{R}$ is the probability for transition from step $x_r$ to $x$ per unit time.

- $R$ different reactions $(w_r, n_r)$, $r = 1 \ldots R$

- Unknown $p(x, t)$ is the probability that the system is in state $x$ at time $t$
The master equation

...is then given by

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

\[=: \mathcal{M}p,\]

(2)

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

-A difference-differential equation in \(D\) dimensions

The master equation...
Multiple scales

- Macroscopic scale: deterministic equations for concentrations of molecules
- Mesoscopic scale: stochastic equations for number of molecules of different species or deterministic equations for probability densities
- Microscopic scale: deterministic molecular dynamics; equations for a few molecules
A 2-D example

\[
\begin{align*}
\emptyset & \xrightarrow{k_1} x \\
x & \xrightarrow{\mu x} \emptyset \\
\emptyset & \xrightarrow{k_2} y \\
y & \xrightarrow{\mu y} \emptyset \\
x + y & \xrightarrow{k_{xy}} \emptyset
\end{align*}
\]
Solution at times $t = 0, 100$ and $400$
Solution methods

- Analytical expansions
- Reaction-rate equations for average values (average concentrations)
- Stochastic methods for sampling a trajectory from the correct probability distribution (Gillespie’s method)
- Approximation of the probability distribution: Fokker-Planck, linear noise, ...
The “weak” master equation

- Let $X$ be the stochastic variable corresponding to the probability distribution $p$
- Let $T : \mathbb{Z}_+^D \rightarrow \mathbb{R}$ be a suitable test-function, independent of time

Then,

$$
\frac{d}{dt} E[T(X)] = \sum_{r=1}^{R} E \left[ (T(X - n_r) - T(X)) w_r(X) \right].
$$

(4)
An immediate application

Let \( T(x) = x_i \). Then

\[
\frac{d}{dt} E[X_i] = - \sum_{r=1}^{R} n^i_r E[w_r(X)] \approx - \sum_{r=1}^{R} n^i_r w_r(E[X])
\]  \( (5) \)

The reaction-rate equations (expressed in number of molecules)

- A set of \( D \) ODEs (low complexity!), efficient and direct description

- Usually a good approximation when the number of molecules is large, when the reaction constants are small, ...

- Approximation deteriorates when the stochastic noise makes a difference, critical points, few molecules, ...

- Reduced information: knowledge of expectation values are not sufficient for all systems
**Obvious generalization**

Derive exact equations for the first few central moments, e.g. for the *Covariance* matrix,

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

(6)

-Must approximate \( w_r \) by (say) a polynomial

-Must *also* neglect the coupling to higher order moments
Pros and cons

+ A set of $O(D^n)$ ODEs where $n$ is the highest order moment
+ Usually a good approximation even when the number of molecules is quite small
+ Can be checked against itself

- Difficult to analyze, even for very simple systems
- Reduced information: for some systems, the exact shape of the probability distribution is highly relevant
Circadian clock

9 species, 18 reactions;

\[
\begin{align*}
D'_a & \xrightarrow{\theta_a D'_a} D_a \\
D_a + A & \xrightarrow{\gamma_a D_a A} D'_a \\
D'_r & \xrightarrow{\theta_r D'_r} D_r \\
D_r + A & \xrightarrow{\gamma_r D_r A} D'_r \\
\emptyset & \xrightarrow{\beta_a M_a} A \\
\emptyset & \xrightarrow{\theta_a D'_a} A \\
\emptyset & \xrightarrow{\theta_r D'_r} A \\
A & \xrightarrow{\delta_a A} \emptyset \\
A + R & \xrightarrow{\gamma_c AR} C \\
\emptyset & \xrightarrow{\alpha'_a D'_a} M_a \\
\emptyset & \xrightarrow{\alpha_a D_a} M_a \\
M_a & \xrightarrow{\delta_{ma} M_a} \emptyset \\
\emptyset & \xrightarrow{\beta_r M_r} R \\
\emptyset & \xrightarrow{\alpha'_r D'_r} M_r \\
\emptyset & \xrightarrow{\alpha_r D_r} M_r \\
R & \xrightarrow{\delta_r R} \emptyset \\
R & \xrightarrow{\delta_{mr} M_r} \emptyset \\
C & \xrightarrow{\delta_a C} R
\end{align*}
\]
| \( \alpha_a \)  | 50 | \( \beta_a \)  | 50 | \( \gamma_a \)  | 1 | \( \delta_{ma} \)  | 10 | \( \theta_a \)  | 50 |
| \( \alpha_a' \) | 500 | \( \beta_r \)  | 5  | \( \gamma_r \)  | 1 | \( \delta_{mr} \)  | 0.5 | \( \theta_r \)  | 100 |
| \( \alpha_r \)  | 0.01 | \( \gamma_c \)  | 2  | \( \delta_a \)  | 1 | \( \delta_r \)  | -   |
| \( \alpha_r' \) | 50  |                |    | \( \delta_r \)  | - |                |     |

Table 1: Parameters of the circadian clock. The parameter \( \delta_r \) is varied in the experiments.
Results

-Solved using the equations for the first, the second and the third order moments
-Implicit time integration
-Comparison with a stochastic simulation
Figure 1: $\delta_r = 0.2$. Solid: the number of $R$ molecules, dashed: the number of $C$ molecules.
Figure 2: $\delta_r = 0.1$
Figure 3: $\delta_r = 0.08$
A motivating example

$$\begin{array}{ccl}
\emptyset & \xrightarrow{k} & x \\
\phantom{\emptyset} & \xrightarrow{\mu x} & \emptyset
\end{array} \right\} \quad (8)$$

If initial data is given as

$$p(x, 0) = \frac{a_0^x}{x!} e^{-a_0}, \quad (9)$$

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

$$p(x, t) = \frac{a(t)^x}{x!} e^{-a(t)}, \quad (10)$$

where $a(t) = a_0 \exp(-\mu t) + k/\mu \cdot (1 - \exp(-\mu t))$. 
Charlier’s polynomials $C_n^a(x)$

Orthogonal w.r.t. the discrete scalar product

$$\langle f, g \rangle \equiv \sum_{x \geq 0} f(x)g(x) \frac{a^x}{x!} e^{-a}$$  \hspace{1cm} (11)

for a parameter $a \geq 0$.

Hence the Charlier functions $\hat{C}_n^a(x) := C_n^a(x) \cdot \sqrt{a^x/x! \cdot \exp(-a)}$ are orthogonal under

$$\langle f, g \rangle \equiv \sum_{x \geq 0} f(x)g(x).$$  \hspace{1cm} (12)
A Galerkin spectral method with the Charlier functions as a basis is possible (no continuous approximation)

Convergence is expected in the discrete $l^2$-norm

*Discrete* Gauss-Charlier quadratures must be used for evaluating the resulting rhs:

$$
\sum_{x \geq 0} f(x) \frac{a^x}{x!} e^{-a} = \sum_{j=1}^{n} f(x_j) w_j + R_n
$$  \hspace{1cm} (13)

Interestingly, the parameter $a$ can be moved along with the solution, providing for an “automatic adaptivity”
Bistable problem

\[
\begin{align*}
\emptyset & \xrightarrow{a/(b+y^2)} x \\
x & \xrightarrow{\mu x} \emptyset \\
\emptyset & \xrightarrow{c/(d+x^2)} y \\
y & \xrightarrow{\mu y} \emptyset \\
\end{align*}
\]

(14)

One unstable and two stable critical points

\[\implies\] Expectation value or higher order moments are not a suitable representation
• The master equation is an accurate stochastic model of chemical reactions in general

• In many cases, the reaction-rate equations produce useful results, avoiding the curse of dimension

• Problems with reaction-rate equations can be cured to a certain extent by solving for higher order moments, still avoiding the curse of dimension

• When detailed information about the underlying probability distribution is critical we have presented an effective and adaptive spectral method

• Future aim: couple the methods!