Numerical Solution Methods for the Master Equation

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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

$x \in \mathbf{Z}_+^D$ 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:

$$x_r = x + n_r \xrightarrow{w_r(x_r)} x, \tag{1}$$

where n_r is the transition step and where $w_r : \mathbf{Z}_+^D \longrightarrow \mathbf{R}$ 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

$$\frac{\partial p(x,t)}{\partial t} = \sum_{\substack{r=1 \\ x+n_r^- \geq 0}}^{R} w_r(x+n_r)p(x+n_r,t) - \sum_{\substack{r=1 \\ x-n_r^+ \geq 0}}^{R} w_r(x)p(x,t)$$
$$=: \mathcal{M}p, \tag{2}$$

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

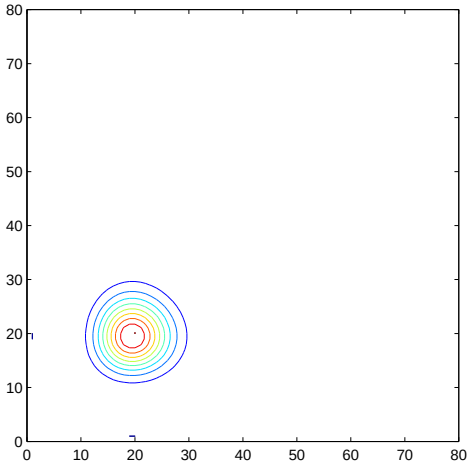
Multiple scales

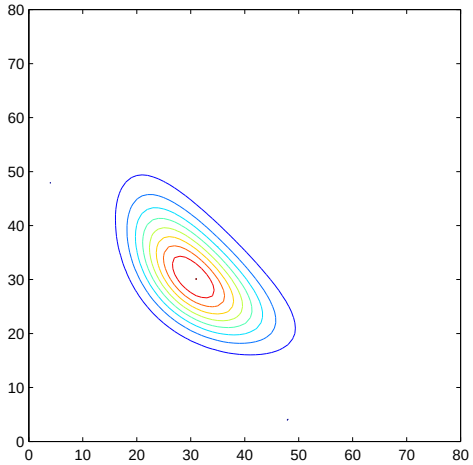
- Macroscopic scale: deterministic equations for concentrations of molecules
- Mesoscopic scale: stochastic equations for number of molecules of different species or deterministic equations for probability densities
- Microscopic scale: deterministic molecular dynamics; equations for a few molecules

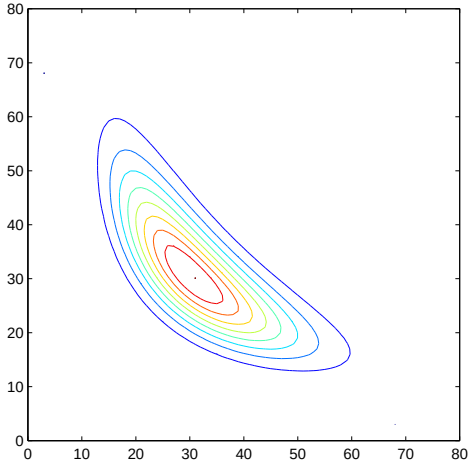
A 2-D example

$$\left.\begin{array}{rcl} \emptyset & \xrightarrow{k_1} & x \\ x & \xrightarrow{\mu x} & \emptyset \\ \emptyset & \xrightarrow{k_2} & y \\ y & \xrightarrow{\mu y} & \emptyset \\ x+y & \xrightarrow{kxy} & \emptyset \end{array}\right\} \qquad (3)$$

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 $T : \mathbf{Z}_+^D \longrightarrow \mathbf{R}$ be a suitable test-function, independent of time

Then,

$$\frac{d}{dt}E[T(X)] = \sum_{r=1}^{R} E\left[\left(T(X - n_r) - T(X)\right) w_r(X)\right]. \qquad (4)$$

An immediate application

Let $T(x) = x_i$. Then

$$\frac{d}{dt}E[X_i] = -\sum_{r=1}^{R} n_r^i E\left[w_r(X)\right] \approx -\sum_{r=1}^{R} n_r^i w_r\left(E[X]\right) \qquad (5)$$

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,

$$\frac{dC_{ij}}{dt} = -\sum_{r=1}^{R} \left(n_r^i E[(X_j - m_j) w_r(X)] + n_r^j E[(X_i - m_i) w_r(X)] \right) + \\ + \sum_{r=1}^{R} n_r^i n_r^j E[w_r(X)]. \tag{6}$$

-Must approximate w_r by (say) a polynomial

-Must *also* neglect the coupling to higher order moments

Pros and cons

+ A set of $\mathcal{O}\left(D^n\right)$ 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;

$$\left.\begin{aligned} D'_a &\xrightarrow{\theta_a D'_a} D_a \\ D_a + A &\xrightarrow{\gamma_a D_a A} D'_a \\ D'_r &\xrightarrow{\theta_r D'_r} D_r \\ D_r + A &\xrightarrow{\gamma_r D_r A} D'_r \end{aligned}\right\} \quad \left\{\begin{aligned} \emptyset &\xrightarrow{\alpha'_a D'_a} M_a \\ \emptyset &\xrightarrow{\alpha_a D_a} M_a \\ M_a &\xrightarrow{\delta_{ma} M_a} \emptyset \end{aligned}\right\} \tag{7}$$

$$\left.\begin{aligned} \emptyset &\xrightarrow{\beta_a M_a} A \\ \emptyset &\xrightarrow{\theta_a D'_a} A \\ \emptyset &\xrightarrow{\theta_r D'_r} A \\ A &\xrightarrow{\delta_a A} \emptyset \\ A + R &\xrightarrow{\gamma_c A R} C \end{aligned}\right\} \quad \left\{\begin{aligned} \emptyset &\xrightarrow{\alpha'_r D'_r} M_r \\ \emptyset &\xrightarrow{\alpha_r D_r} M_r \\ M_r &\xrightarrow{\delta_{mr} M_r} \emptyset \end{aligned}\right\} \quad \left\{\begin{aligned} \emptyset &\xrightarrow{\beta_r M_r} R \\ R &\xrightarrow{\delta_r R} \emptyset \\ C &\xrightarrow{\delta_a C} R \end{aligned}\right\}.$$

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	-		

Table 1: Parameters of the circadian clock. The parameter δ_r is varied in the experiments.

Results

-Solved using the equations for the first, the second and the third order moments

-Implicit time integration

-Comparision with a stochastic simulation

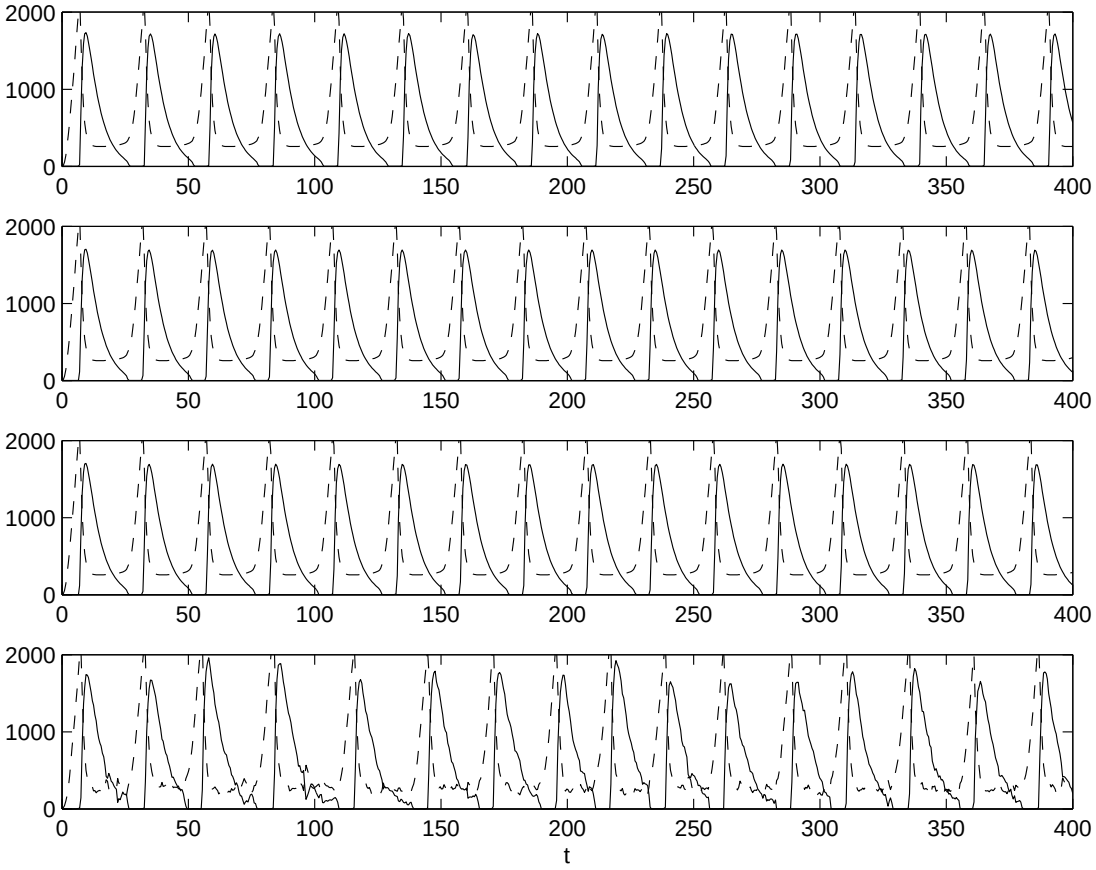


Figure 1: $\delta_r = 0.2$. Solid: the number of R molecules, dashed: the number of C molecules.

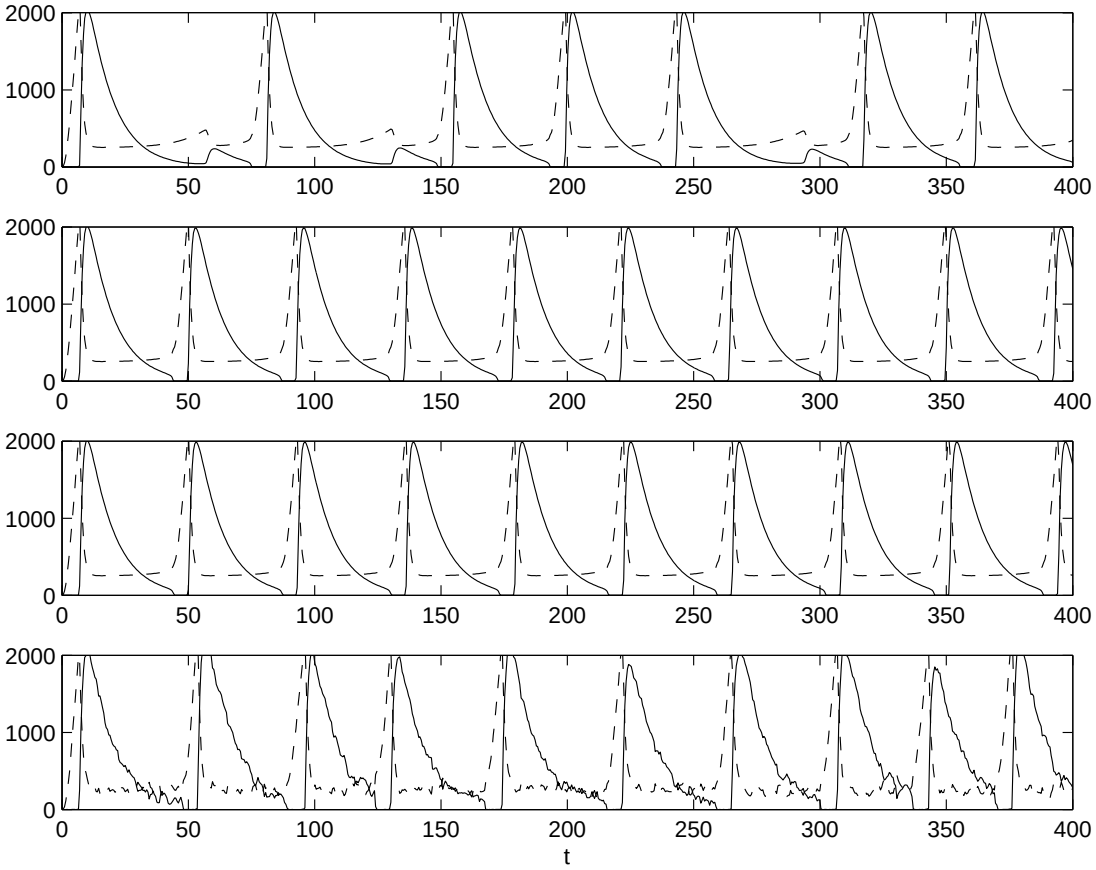


Figure 2: $\delta_r = 0.1$

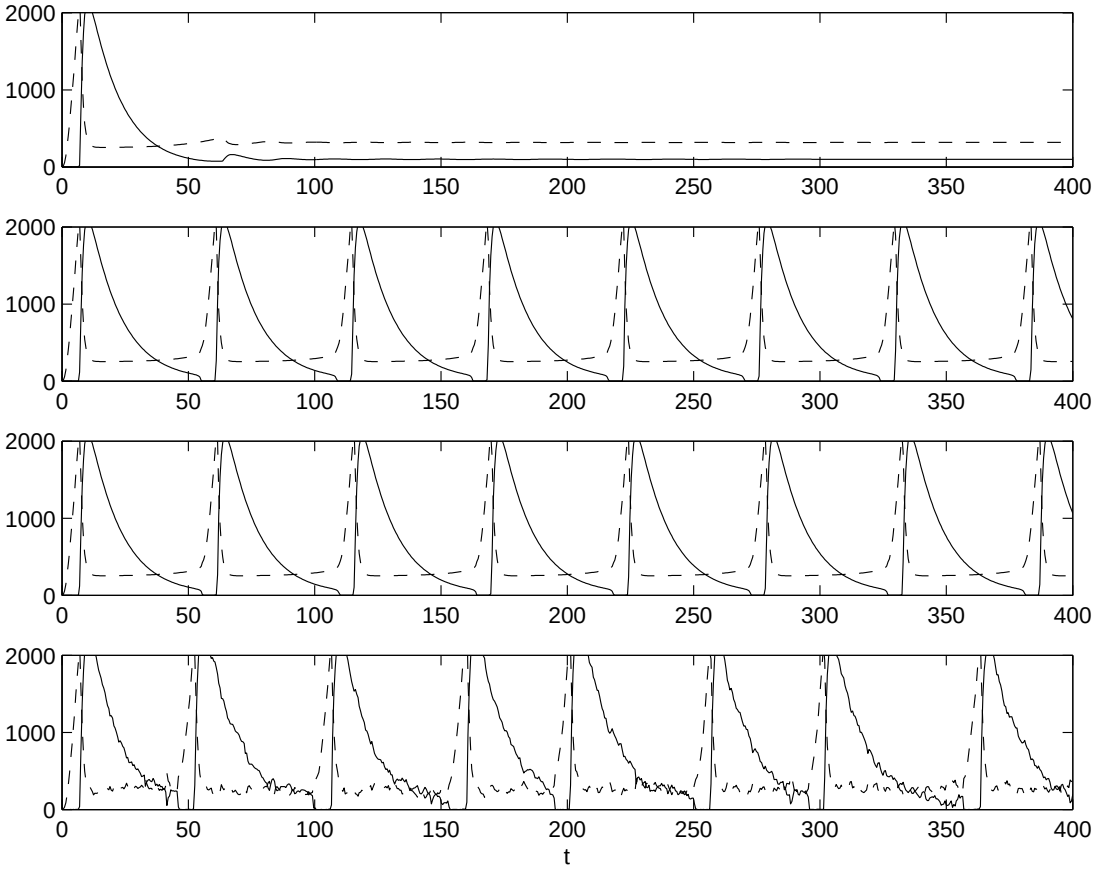


Figure 3: $\delta_r = 0.08$

A motivating example

$$\left.\begin{array}{lcl} \emptyset & \xrightarrow{k} & x \\ x & \xrightarrow{\mu x} & \emptyset \end{array}\right\} \tag{8}$$

If initial data is given as

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

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

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

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

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

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

$$(f, g) \equiv \sum_{x \geq 0} f(x) g(x). \tag{12}$$

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:

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

Interestingly, the parameter a can be moved along with the solution, providing for an "automatic adaptivity"

Bistable problem

$$\left.\begin{array}{lcl} \emptyset & \xrightarrow{a/(b+y^2)} & x \\ x & \xrightarrow{\mu x} & \emptyset \\ \emptyset & \xrightarrow{c/(d+x^2)} & y \\ y & \xrightarrow{\mu y} & \emptyset \end{array}\right\} \tag{14}$$

One unstable and two stable critical points

$\Longrightarrow$ 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!