Simulation of stochastic reaction-diffusion processes on unstructured meshes

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Joint work with

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• Motivation for stochastic chemical kinetics
• Well-stirred chemical kinetics
• Spatially inhomogeneous kinetics
• Unstructured meshes
• Examples
• Conclusions
### Modelling chemical reactions

<table>
<thead>
<tr>
<th>System size $\Omega$ (# molecules)</th>
<th>Model</th>
<th>Idea</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 10^2$</td>
<td>Micro</td>
<td>Movement of individual atoms/molecules</td>
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<td></td>
<td></td>
<td>Collisions $\rightarrow$ (Possible) reactions</td>
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<tr>
<td>$\sim 10^1 - 10^6$</td>
<td>Meso</td>
<td>Non-individual, assuming well-stirred mixture</td>
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<td></td>
<td></td>
<td>A <em>stochastic model</em> is used for reactions</td>
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<tr>
<td>$\geq 10^6$</td>
<td>Macro</td>
<td>“Average”; in the limit of many molecules</td>
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- With a mesoscopic stochastic model, an accurate but still manageable *non-individual* model is possible thanks to randomness (both the micro- and the macroscopic models are deterministic).
**Well-stirred**

**Assumption #1:** the chance of finding a molecule is equal throughout the volume (*homogeneous*).

**Assumption #2:** the energy of a molecule does not depend on its position in the volume (*thermal equilibrium*).

- Under these assumptions there is a favourable stochastic model of chemical kinetics — a *continuous-time Markov chain*.
- Actual behaviour often easier to capture: multi-stability, resonance and focusing effects.
**Well-stirred kinetics** (*Gillespie ’76, ’92, Gardiner, van Kampen*)

- Let the state vector \( x \in \mathbb{Z}_+^D \) count the number of molecules of each of \( D \) species.

- Let \( R \) specified reactions be defined as *transitions* between the states,

\[
x \xrightarrow{w_r(x)} x - N_r, \quad N \in \mathbb{Z}^{D \times R} \text{ (stoichiometric matrix)}
\]

where each transition intensity or *propensity* \( w_r : \mathbb{Z}_+^D \to \mathbb{R}_+ \) is the probability of reacting per unit of time. *This probability can be shown to exist provided that the system is well-stirred!*
The chemical master equation is given by

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

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

-A gain-loss discrete PDE in \(D\) dimensions for the probability density.

-Several exact Monte Carlo-type simulation algorithms exist ("SSA", "NRM", ...); determine what event and when.
**Not well-stirred:**

- When the molecular movement (diffusion) is slow compared to the reaction intensity, large *local* concentrations may easily build up.
- When some reactions are *localised* — e.g. depend on an enzyme molecule situated at a precise position.

These conditions are not unusual for reactions taking place inside living cells!
Mesoscopic spatial kinetics

- Not well-stirred in the whole volume, but if the domain $\Omega$ is subdivided into smaller computational cells $\Omega_j$ such that their individual volume $|\Omega_j|$ is small, then diffusion suffices to make each cell well-stirred.

![Diagram of a mesh]

Figure 1: Primal mesh (solid), dual mesh (dashed). The nodal dofs are the # of molecules in each dual cell.
• $D$ chemically active species $X_{ij}$ for $i = 1, \ldots, D$ but now counted separately in $K$ cells, $j = 1, \ldots, K$.

• The state of the system is an array $x$ with $D \times K$ elements.

• This state is changed by chemical reactions occurring between the molecules in the same cell (vertically in $x$) and by diffusion where molecules move to adjacent cells (horizontally in $x$).
Reactions

By assumption, each cell is well-stirred and consequently the master equation is valid as a description of reactions,

\[
\frac{\partial p(x, t)}{\partial t} = M p(x, t) := \sum_{j=1}^{K} \sum_{r=1}^{R} w_r(x_j + N_r) p(x_1, \ldots, x_j + N_r, \ldots, x_K, t) - \sum_{j=1}^{K} \sum_{r=1}^{R} w_r(x_j) p(x, t).
\]
**Diffusion**

A natural model of diffusion from one cell $\Omega_k$ to another cell $\Omega_j$ is

$$X_{ik} \xrightarrow{q_{kj} x_{ik}} X_{ij},$$

where $q_{kj}$ is non-zero only for connected cells.

*Ideally*, $q_{kj}$ should be taken as the inverse of the mean first exit time for a single molecule of species $i$ from cell $\Omega_k$ to $\Omega_j$. $\implies q_{kj} \propto \sigma^2/h^2$, where $\sigma^2/2$ is the macroscopic diffusion, $h$ the local length.

The diffusion master equation can therefore be written

$$\frac{\partial p(x, t)}{\partial t} = \sum_{i=1}^{D} \sum_{k=1}^{K} \sum_{j=1}^{K} q_{kj}(x_{ik} + M_{kj,k})p(x_1, \ldots, x_i + M_{kj}, \ldots, x_D, t) - q_{kj}x_{ik}p(x, t) =: \mathcal{D}p(x, t).$$

The transition vector $M_{kj}$ is zero except for $M_{kj,k} = -M_{kj,j} = 1.$
The reaction-diffusion master equation \( (Gardiner, \text{ van Kampen}) \)

\[
\frac{\partial p(x, t)}{\partial t} = (\mathcal{M} + \mathcal{D})p(x, t).
\]

- An approximation! Valid when

\[
\rho^2 \ll h^2 \ll \sigma^2 \tau_\Delta,
\]

\( \rho \) the molecular radius, \( \tau_\Delta \) average molecular survival time.

- Once formulated, any well-stirred algorithm can simulate the RDME. For a spatially resolved model, most of the simulation time is spent on diffusion events.
Formulation and consistency

-Mean first exit time only known for very simple geometries (e.g. circles).

-A solution in the Cartesian case: ensure that the expected value limits to the macroscopic diffusion equation.

Define $\varphi_{ij} = E\Omega_j^{-1}x_{ij}$. By linearity of the diffusion intensities, the diffusion master equation implies

$$\frac{d\varphi_{ij}}{dt} = \sum_{k=1}^{K} \frac{\Omega_k}{\Omega_j} q_{kj} \varphi_{ik} - \left( \sum_{k=1}^{K} q_{jk} \right) \varphi_{ij},$$

or simply

$$\frac{d\varphi_i^T}{dt} = Q\varphi_i^T.$$
-FEM applied to the macroscopic equation $u_t = \sigma^2 / 2 \Delta u$ with piecewise linear basis functions and lumped mass-matrix yields

$$\frac{du}{dt} = \frac{\sigma^2}{2} Du.$$  

With a good triangulation we have point-wise convergence FEM $\rightarrow$ diffusion PDE and the consistency of this interpretation ensures convergence in distribution to Brownian motion as $h \rightarrow 0$. 
**Bistable double-negative feedback system** (Elf/Ehrenberg)

\[
\begin{align*}
E_A & \xrightarrow{k_1} E_A + A & E_B & \xrightarrow{k_1} E_B + B \\
E_A + B & \xrightarrow{k_a, k_d} E_A B & E_B + A & \xrightarrow{k_a, k_d} E_B A \\
E_A B + B & \xrightarrow{k_a, k_d} E_A B_2 & E_B A + A & \xrightarrow{k_a, k_d} E_B A_2 \\
A & \xrightarrow{k_4} \emptyset & B & \xrightarrow{k_4} \emptyset
\end{align*}
\]

Slow/intermediate/fast diffusion in a simple model of an *S. cerevisiae* cell with internal structures in the form of a nucleus and a large vacuole. Molecules are not allowed to diffuse across the membranes and enter the organelles.
(a) Species A.  
(b) Species B.
Figure 2: The total number of $A$ and $B$ molecules as the diffusion constant is varied. Right: local bi-stability is lost.
Oscillations of proteins involved in the cell division of *Escherichia coli* bacterium:

- Five species, five reactions (*Fange/Elf*).
- “URDME” software (*Cullhed/Engblom/Hellander*).
- Mesoscopic stochastic kinetics (CTMC/master equation)
  -well-stirred chemical reactions
- Spatially inhomogeneous case:
  -local well-stirredness implies the reaction-diffusion master equation
  -unstructured meshes: consistency with macroscopic equations
- Expensive but structurally simple diffusion suggests hybrid schemes.
- Publicly available software ANSI-C99/Matlab/Comsol “URDME”.