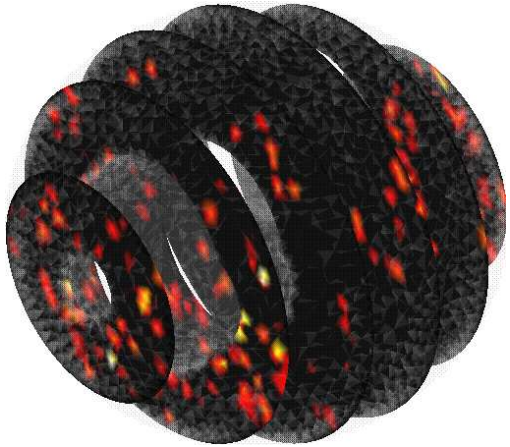
Simulation of stochastic reaction-diffusion processes on unstructured meshes



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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

System size Ω (# molecules)	Model	Idea
$\lesssim 10^2$	Micro	Movement of individual atoms/molecules
		Collisions $\rightarrow$ (Possible) reactions
$\sim 10^1$–10^6	Meso	Non-individual, assuming well-stirred mixture
		A *stochastic model* is used for reactions
$\gtrsim 10^6$	Macro	"Average"; —in the limit of many molecules

-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 $x \in \mathbf{Z}_+^D$ count the number of molecules of each of D species.

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

$$x \xrightarrow{w_r(x)} x - \mathbb{N}_r, \qquad \mathbb{N} \in \mathbf{Z}^{D\times R} \ (\textit{stoichiometric matrix})$$

where each transition intensity or *propensity* $w_r : \mathbf{Z}_+^D \to \mathbf{R}_+$ 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 Ω is subdivided into smaller computational cells Ω_j such that their individual volume $|\Omega_j|$ is small, then diffusion suffices to make each cell well-stirred.

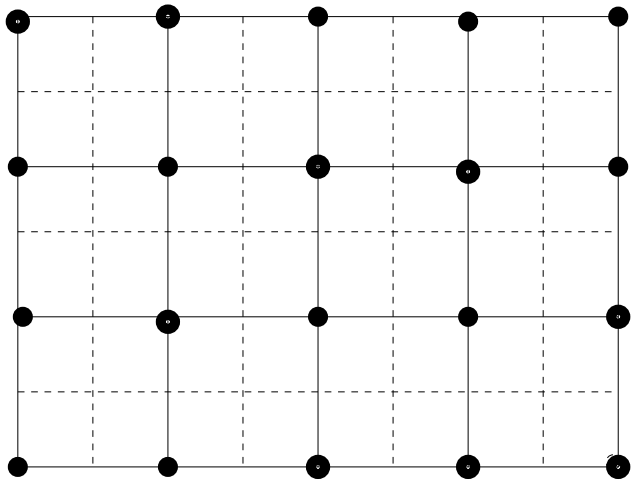


Figure 1: Primal mesh (solid), dual mesh (dashed). The nodal dofs are the # of molecules in each dual cell.

- 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 $\mathbf{x}$ with $D \times K$ elements.
- This state is changed by chemical reactions occurring between the molecules in the same cell (vertically in $\mathbf{x}$) *and* by diffusion where molecules move to adjacent cells (horizontally in $\mathbf{x}$).

Reactions

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

$$\frac{\partial p(\mathbf{x},t)}{\partial t} = \mathcal{M}p(\mathbf{x},t) := \sum_{j=1}^{K}\sum_{r=1}^{R} w_r(\mathbf{x}_{\cdot j} + \mathbb{N}_r)p(\mathbf{x}_{\cdot 1},\ldots,\mathbf{x}_{\cdot j}+\mathbb{N}_r,\ldots,\mathbf{x}_{\cdot K},t) - \sum_{j=1}^{K}\sum_{r=1}^{R} w_r(\mathbf{x}_{\cdot j})p(\mathbf{x},t).$$

Diffusion

A natural model of diffusion from one cell Ω_k to another cell Ω_j is

$$X_{ik} \xrightarrow{q_{kj}\mathbf{x}_{ik}} X_{ij},$$

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 Ω_k to Ω_j. $\Longrightarrow q_{kj} \propto \sigma^2/h^2$, where $\sigma^2/2$ is the macroscopic diffusion, h the local length.

The diffusion master equation can therefore be written

$$\frac{\partial p(\mathbf{x},t)}{\partial t} = \sum_{i=1}^{D}\sum_{k=1}^{K}\sum_{j=1}^{K} q_{kj}(\mathbf{x}_{ik} + \mathbb{M}_{kj,k})p(\mathbf{x}_{1\cdot},\ldots,\mathbf{x}_{i\cdot}+\mathbb{M}_{kj},\ldots,\mathbf{x}_{D\cdot},t)$$
$$-q_{kj}\mathbf{x}_{ik}p(\mathbf{x},t) =: \mathcal{D}p(\mathbf{x},t).$$

The transition vector $\mathbb{M}_{kj}$ is zero except for $\mathbb{M}_{kj,k} = -\mathbb{M}_{kj,j} = 1$.

The reaction-diffusion master equation (*Gardiner, van Kampen*)

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

-An *approximation*! Valid when

$$\rho^2 \ll h^2 \ll \sigma^2\tau_\Delta,$$

ρ the molecular radius, τ_Δ 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).

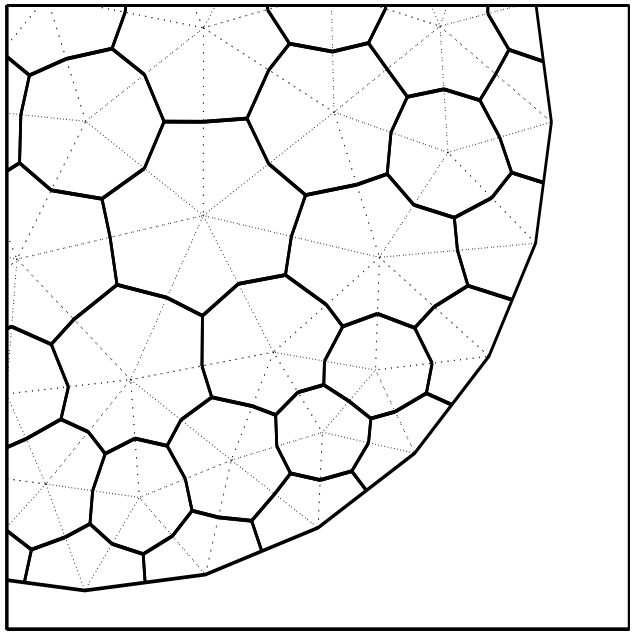
-A solution in the Cartesian case: ensure that the expected value limits to the macroscopic diffusion equation.

Define $\varphi_{ij} = E\,\Omega_j^{-1}\mathbf{x}_{ij}$. 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

$$\frac{d\varphi_{i\cdot}^T}{dt} = Q\varphi_{i\cdot}^T.$$



-FEM applied to the macroscopic equation $u_t = \sigma^2/2\,\Delta u$ with piecewise linear basis functions and lumped mass-matrix yields

$$\frac{d\mathbf{u}}{dt} = \frac{\sigma^2}{2} D\mathbf{u}.$$

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*)

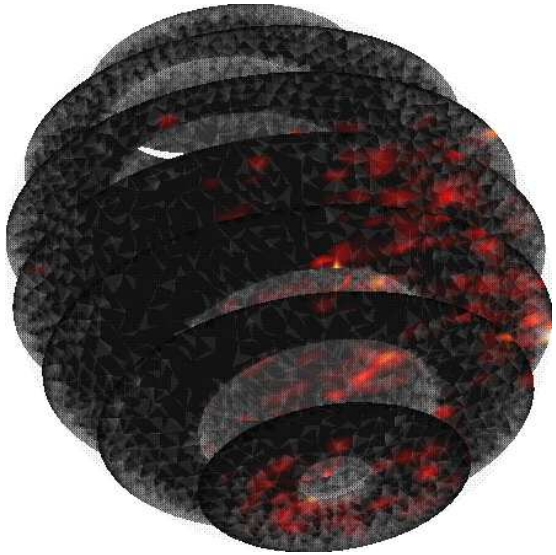
$$E_A \xrightarrow{k_1} E_A + A \qquad E_B \xrightarrow{k_1} E_B + B$$

$$E_A + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B \qquad E_B + A \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A$$

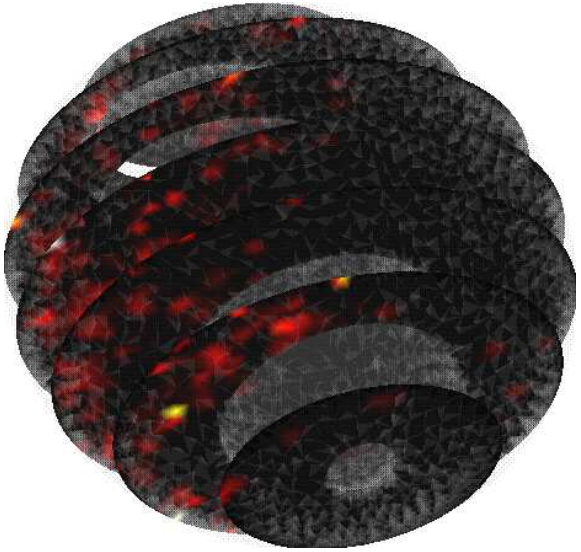
$$E_A B + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B_2 \qquad E_B A + A \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A_2$$

$$A \xrightarrow{k_4} \emptyset \qquad B \xrightarrow{k_4} \emptyset$$

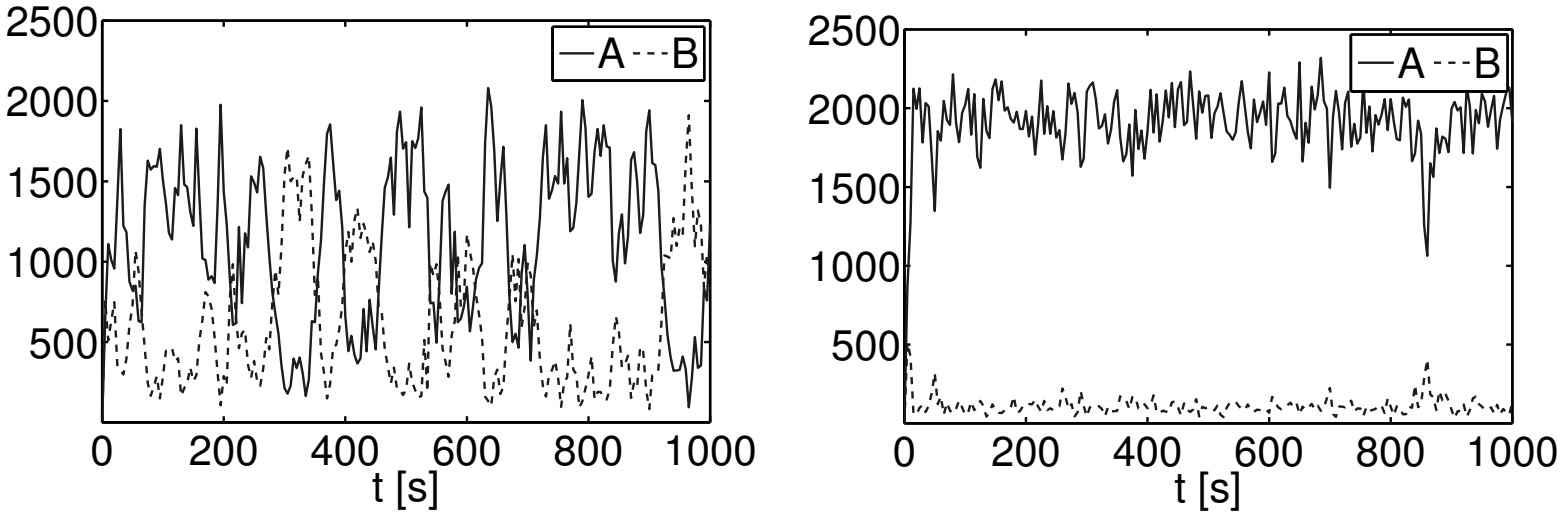
Slow/intermediate/fast diffusion in a simple model of an *S. cerevisiae* cell with internal structures in the form of a nucleus and a large vacuole. Molecules are not allowed to diffuse across the membranes and enter the organelles.



(a) Species A.



(b) Species B.



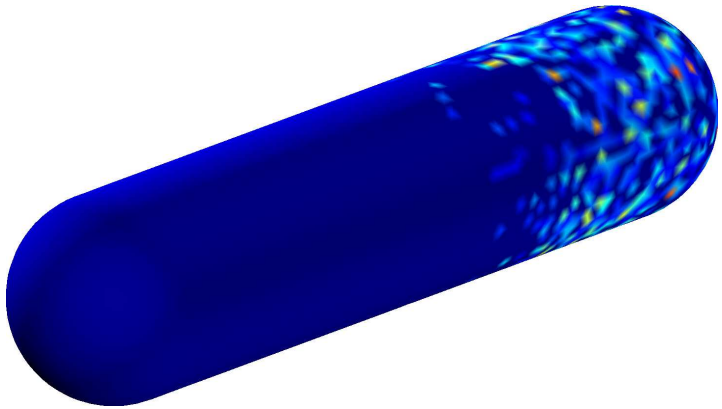
(c) $\sigma^2 = 2 \times 10^{-13}$ (d) $\sigma^2 = 4 \times 10^{-13}$

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".