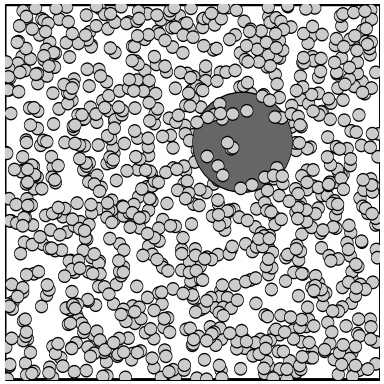
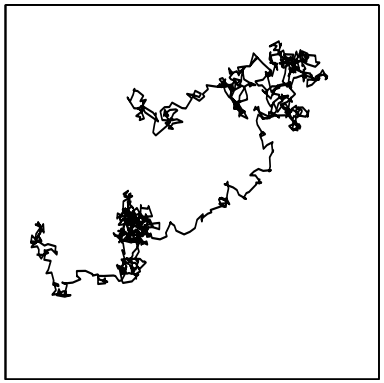
Mesoscopic Stochastic Modeling and the Diffusion Operator





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Minisymposium talk, ECMTB, June 15, 2014

1. Mesoscopic stochastic chemical kinetics
   - Brownian motion
   - (Bio-)Chemical kinetics
2. Mesoscopic stochastic spatial chemical kinetics
   - Unstructured meshes
   - Finite elements/volumes
3. Questions of convergence
4. Sample spatial effects
   - Stochastic focusing
   - Bistability

Conclusions

This talk also serves as an introduction to Lina Meinecke's talk *"Stochastic Simulation of Diffusion on Unstructured Meshes via First Exit Times"* (next).

The buzz

Stochastic

Stochastic *(Merriam-Webster Online Dictionary)*
Greek *stochastikos* skillful in aiming, from *stochazesthai* to aim at, guess at, from *stochos* target, aim, guess. Date: 1934.

1. Random; specifically: involving a random variable <*a stochastic process*>.
2. Involving chance or probability: probabilistic <*a stochastic model of radiation-induced mutation*>.

The buzz (cont)

Mesoscopic

Mesoscopic *(Merriam-Webster)*
No entries found. -Did you mean masochistic?

Mesoscopic scale *(Wikipedia, Oct 2008)*
In physics and chemistry, the **mesoscopic scale** refers to the length scale at which one can reasonably discuss the properties of a material or phenomenon without having to discuss the behavior of individual atoms, and concepts of averages such as density and temperature are useful.
Page removed in 2010!

Mesoscopic physics *(Wikipedia, Mar 2013)*
There is no rigid definition for mesoscopic physics, but the systems studied are normally in the range of $100nm$ (the size of a typical virus) to $1000nm$ (the size of a typical bacterium).

Scales in modeling 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

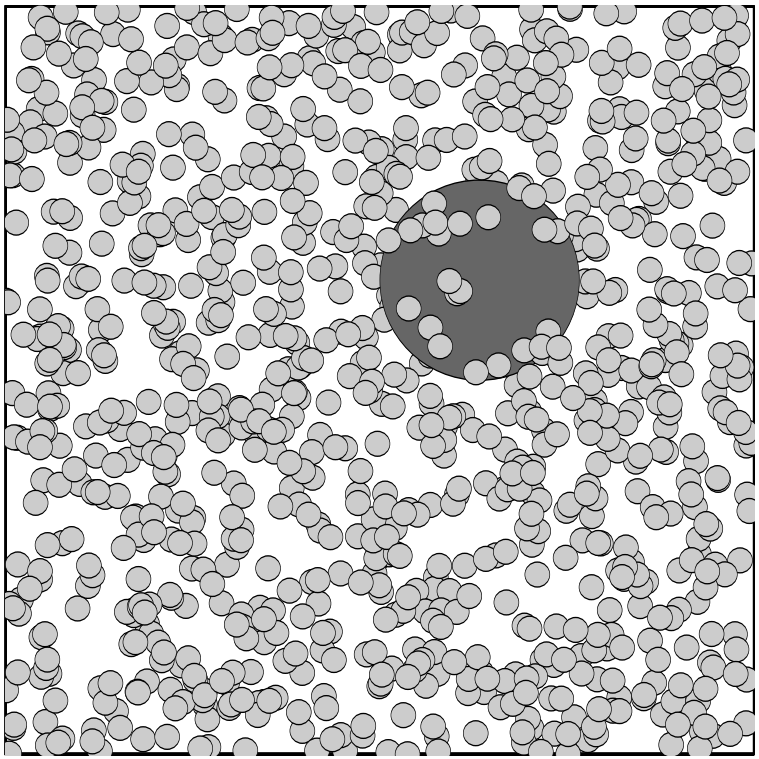
-With a mesoscopic viewpoint an accurate but still manageable *non-individual* model is possible thanks to stochasticity.

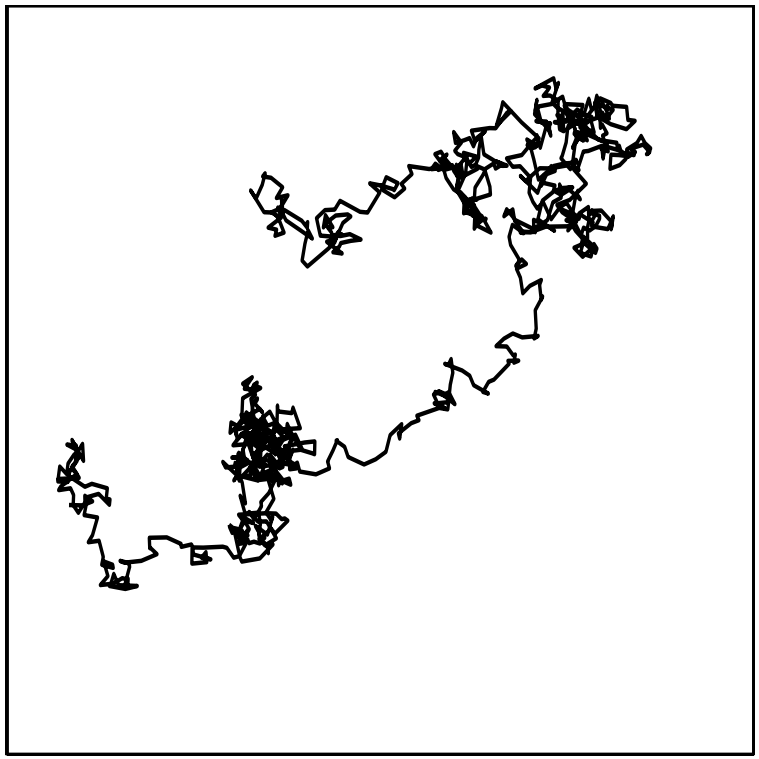
Diffusion-controlled kinetics

Model	Assumption
BD (Smoluchowski)	Brownian motion of individual molecules
CTMC (Master equation)	Non-individual, (locally) well-stirred
SDE (Langevin)	Continuous *approximation*
ODE (Reaction rate)	Continuous, deterministic

Brownian motion

Example: Particle in a fluid (Einstein 1905, & some others...).



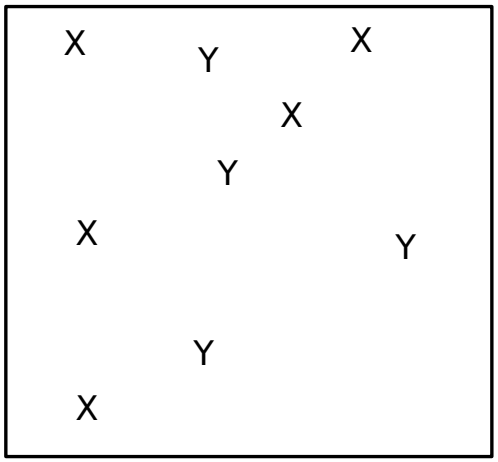


A stochastic model is simpler but depends on randomness.

Stochastic modeling of biochemical reactions

Example: Bimolecular reaction $X + Y \rightarrow Z$.

-What is the probability $P(1X \text{ and } 1Y \text{ reacts in the interval } [0, \Delta t])$?



V

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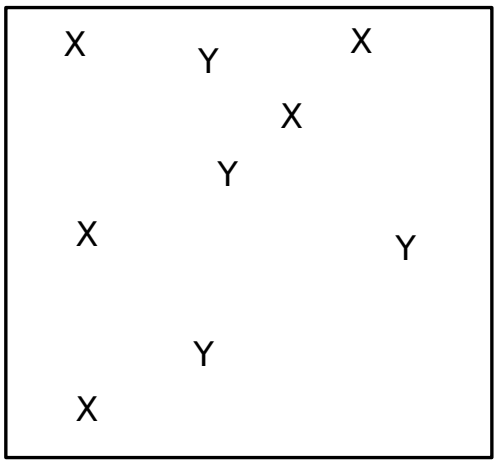

- $P \propto n_X$ ("number of X-molecules")
- $P \propto n_Y$

Stochastic modeling of biochemical reactions

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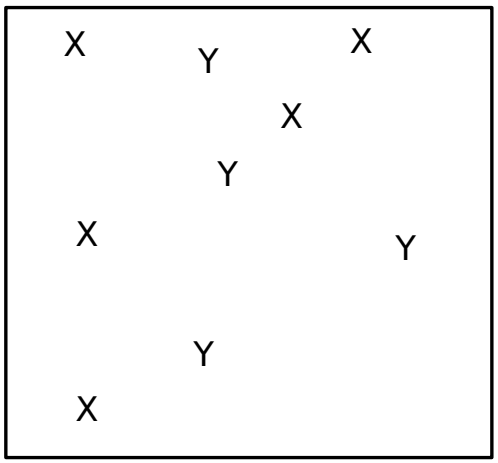


- $P \propto n_X$ ("number of X-molecules")
- $P \propto n_Y$
- $P \propto 1/V$
- $P \propto \Delta t$

$\Longrightarrow P(X + Y \to Z \text{ in the interval } [0, \Delta t]) = \text{const} \cdot n_X n_Y \, \Delta t / V.$

Let $\Delta t \to 0$. Then it so happens that this receipt describes a continuous-time Markov chain.

Well-stirred kinetics

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)*.

-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 these states,

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

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!*

"Direct method"

(*Doob* ∼'45, *Gillespie* '76)

Simulate a single stochastic trajectory $X(t)$ "an outcome":

0. Let $t = 0$ and set the state x to the initial number of molecules.
1. Compute the total reaction intensity $W := \sum_r w_r(x)$. Generate the *time to the next reaction* $\tau := -W^{-1} \log u_1$ where $u_1 \in (0, 1)$ is a uniform random number. Determine also the next reaction r by the requirement that

$$\sum_{s=1}^{r-1} w_s(x) < W u_2 \leq \sum_{s=1}^{r} w_s(x),$$

   where u_2 is again a uniform random deviate in $(0, 1)$.
2. Update the state of the system by setting $t := t + \tau$ and $x := x - \mathbb{N}_r$.
3. Repeat from step 1 until some final time T is reached.

Kolmogorov's forward differential system/Master equation

(Kolmogorov '31, Nordsieck/Lamb/Uhlenbeck '40)

With states $x \in \mathbf{Z}_+^D$, let $p(x,t) := P(X(t) = x | X(0))$. Then the *chemical master equation* (CME) is given by

$$\begin{aligned}\frac{\partial p(x,t)}{\partial t} &= \sum_{r=1}^{R} w_r(x + \mathbb{N}_r) p(x + \mathbb{N}_r, t) - \sum_{r=1}^{R} w_r(x) p(x,t) \\ &=: \mathcal{M} p.\end{aligned}$$

-A gain-loss discrete PDE in D dimensions for the probability density *conditioned upon an initial state*.

Inhomogeneous kinetics

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 *localized* — e.g. depend on an enzyme emitted from a precise position, or are located to, say, a membrane.

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.

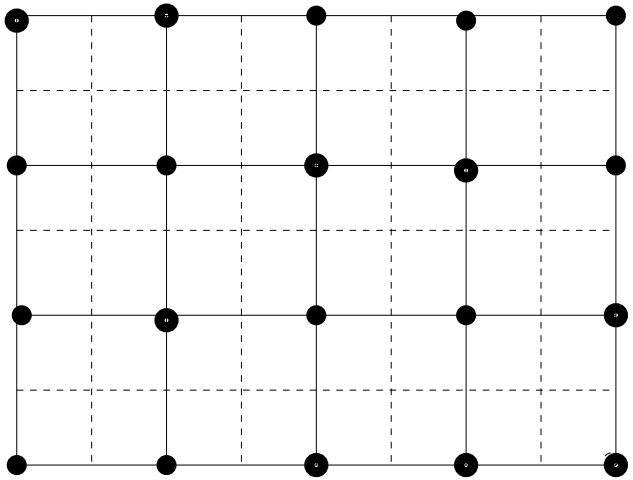


Figure: Primal mesh (solid), dual mesh (dashed). The nodal dofs are the # of molecules in each dual cell.

Mesoscopic spatial kinetics (cont)

- 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 now 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/transport 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. (**Meinecke's talk**)
The diffusion master equation can then 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

"RDME"

Combining reactions with diffusions,

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

-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 algorithm for sampling from the CME can also simulate the RDME. For a spatially resolved model, most of the simulation time is spent on diffusion events.

Unstructured meshes

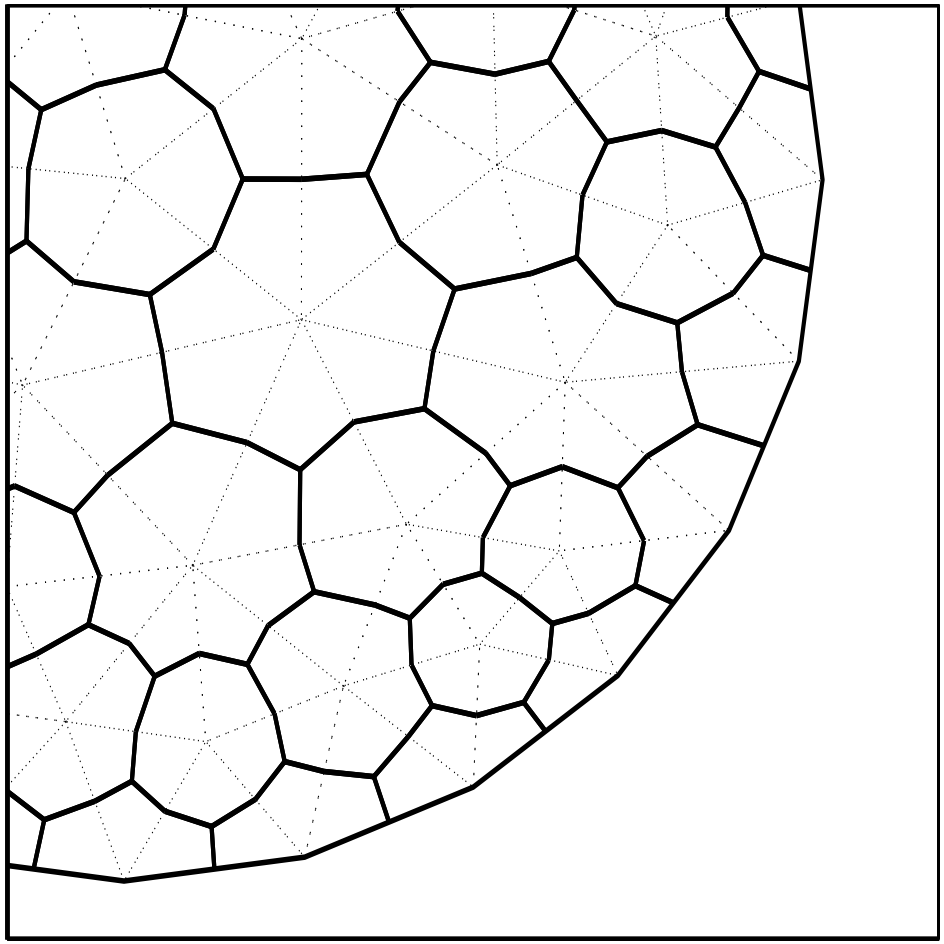
-Mean first exit time only known for very simple geometries (e.g. circles).
-*How to handle complicated geometries?* Attempt to converge in expectation to the macroscopic diffusion equation. A numerical method applied to $u_t = \sigma^2/2\,\Delta u$ yields the *discretized* form

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

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

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

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



FEM vs. FVM

An insane summary

Consider the strong formulation $u_t = \Delta u$ in Ω,

1. Variational form (Green's theorem): find $u \in V$ s.t. $(v, u_t) = -(\nabla v, \nabla u)$ for $\forall v \in V$, where $(f, g) \equiv \int_\Omega fg \, dx$.
2. A FEM is obtained by approximating $V \approx V_h = \text{span}_i \varphi_i \subset V$.
3. With $u_h = \sum_i \mathbf{u}_i(t)\varphi_i$ we get $M\mathbf{u}_t = -A\mathbf{u}$; $M_{ij} = (\varphi_i, \varphi_j)$, $A_{ij} = (\nabla\varphi_i, \nabla\varphi_j)$.

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1. Integrating over the ith finite volume and invoking the divergence theorem we get $\int_{\omega_j} u_t\, dx = \int_{\partial\omega_j} \mathbf{n} \cdot \nabla u\, da$.
2. Approximating ∇ with a difference and defining $\mathbf{u}_j$ as a volume average this gives $|\omega_j| d/dt\, \mathbf{u}_j = \sum_k |\partial\omega_{jk}||e_{jk}|^{-1}(\mathbf{u}_k - \mathbf{u}_j)$, e_{jk} the distance between nodes j and k.

Weak convergence

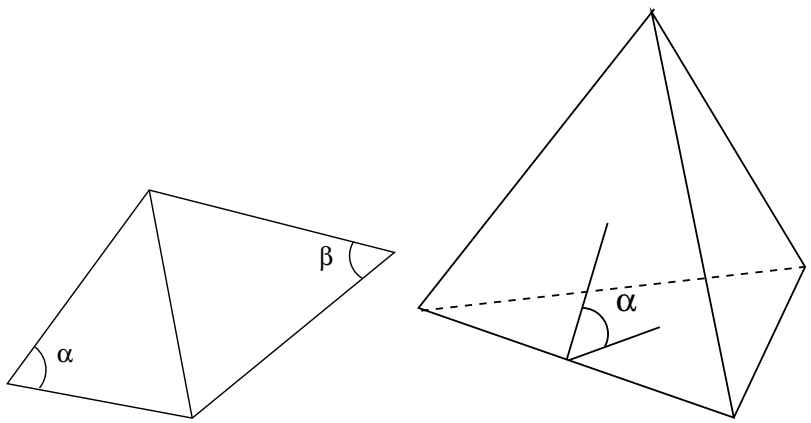
Observation: by linearity, the diffusion CTMC on the unstructured grid has an expected value which coincides with the exact solution to the deterministic numerical method.

FEM convergence

$M\mathbf{u}_t = -A\mathbf{u}$ or $\mathbf{u}_t = -M^{-1}A\mathbf{u} \approx -\tilde{M}^{-1}A\mathbf{u} =: D\mathbf{u}$.

1) Converges in L^2, $\|u_h - u\| = O(h^2)$ as $h \to 0$, under very mild assumptions on the mesh.

2) Under stringent conditions on the mesh, the maximum principle holds.



(a) $\alpha + \beta < \pi$ (b) $\alpha < \pi/2$

These conditions are needed to ensure that

$$D_{jk} \geq 0, \; D_{jj} < 0, \; \sum_{k=1}^{K} D_{jk} = 0.$$

FVM convergence

$$|\omega_j| d/dt\, \mathbf{u}_j = \sum_k |\partial\omega_{jk}||e_{jk}|^{-1}(\mathbf{u}_k - \mathbf{u}_j)$$

1) The maximum principle always holds.
2) If the mesh is a Delaunay triangulation, the method converges as $\|u_h - u\| = O(h^2)$. Unfortunately (in 3D) such meshes have a very poor quality except for very simple geometries. Then the "C" in $O(h^2)$ is very large.

On balance...

-With a (very) good mesh both methods converge as $h \to 0$ **and** satisfy the maximum principle.

-With an "average" mesh, (truncated) FEM seems to have an accuracy edge to FVM and is also amenable to backward analysis: the solution satisfies exactly a perturbed equation $u_t = \nabla \cdot (\tilde{\sigma}^2(x)/2 \times \nabla u)$ where $\|\tilde{\sigma} - \sigma\|$ is small and localized (**Meinecke's talk**).

-Challenges: *(i)* convergence *in distribution* — retrieving the correct Brownian motion, *(ii)* convergence *with reactions*, *(iii)* getting to grip of *when it matters*...

Stochastic focusing

Enzymatic reaction of a complex into a product,

$$C + E \xrightarrow{\nu\, C\cdot E} P + E.$$

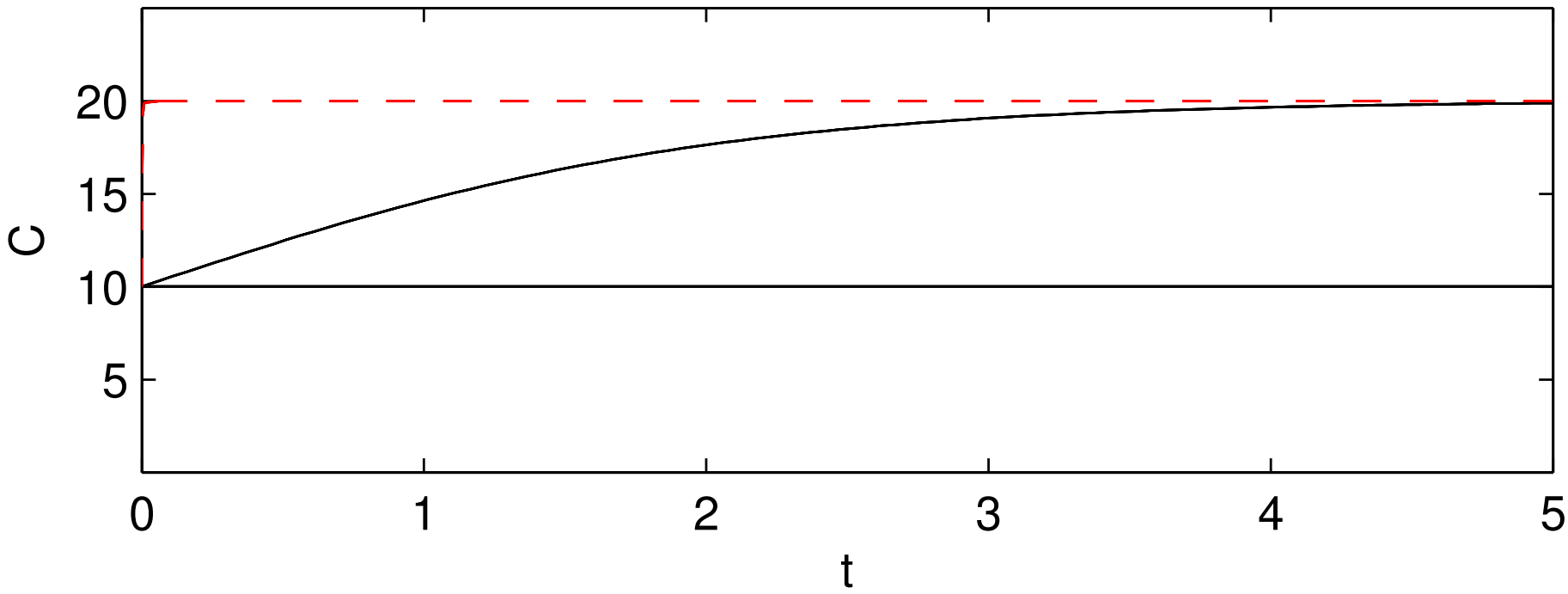
Combine with

$$\emptyset \underset{\mu_E E}{\overset{k_E}{\rightleftharpoons}} E, \quad \emptyset \underset{\mu_C C}{\overset{k_C}{\rightleftharpoons}} C, \quad P \xrightarrow{\mu_P P} \emptyset.$$

-Interested in $k_E \to (1+\delta)\cdot k_E$. *Example:* take $\delta = -1/2$.

Results in 0D (well-stirred)

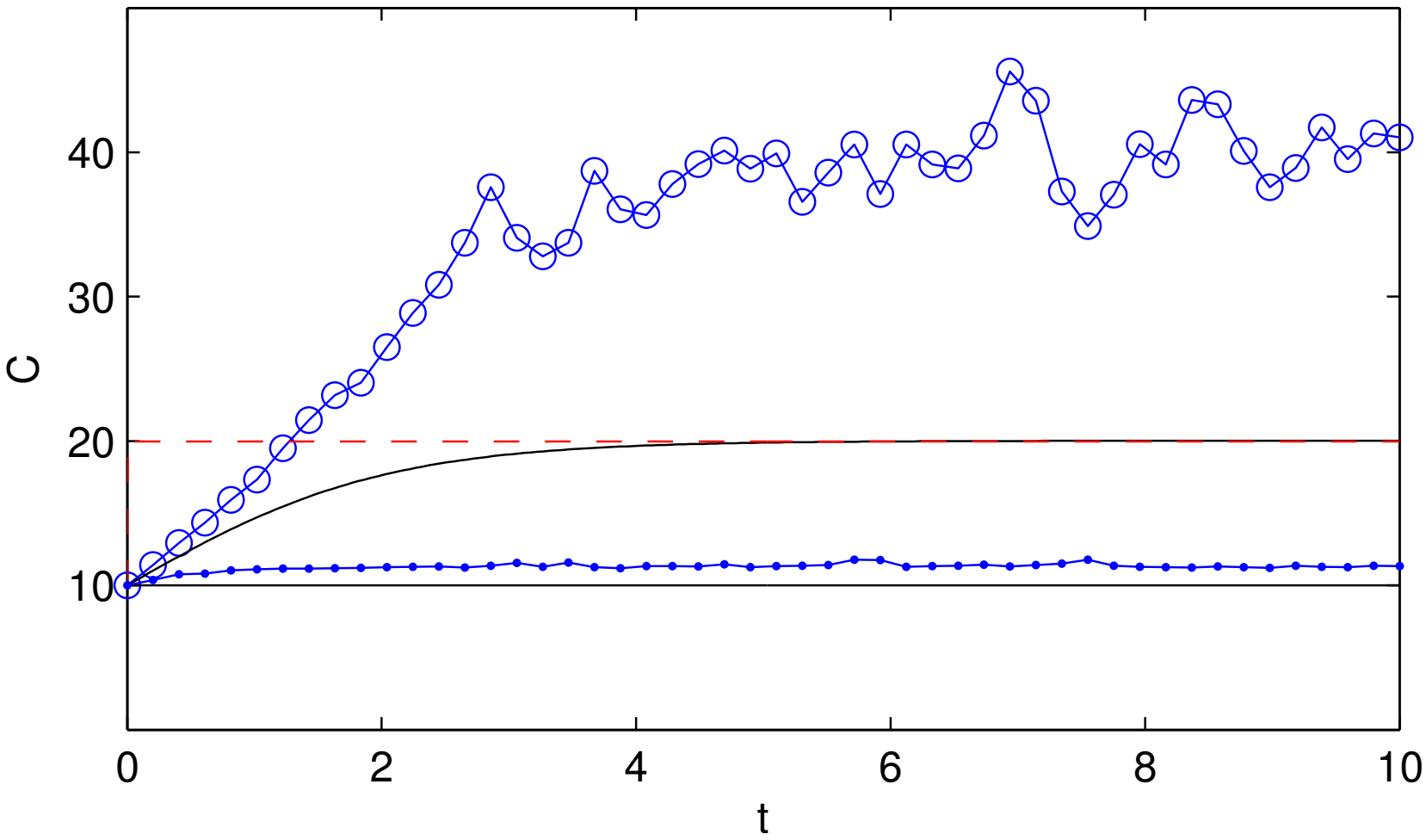
Deterministic equations



Expected: factor of 2 increase.

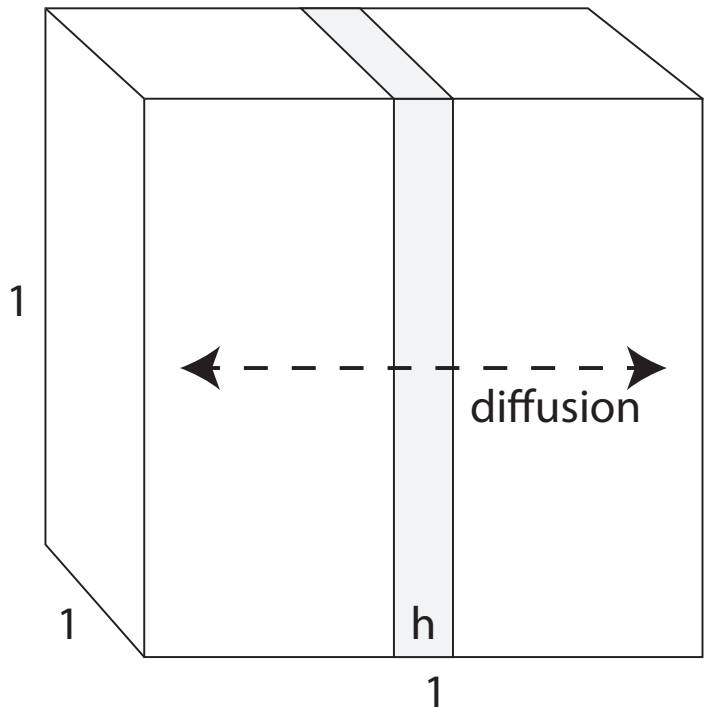
Results in 0D (well-stirred)

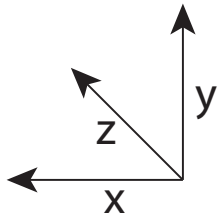
Stochastic equations - stochastic focusing effect



Results in 1D

Setup



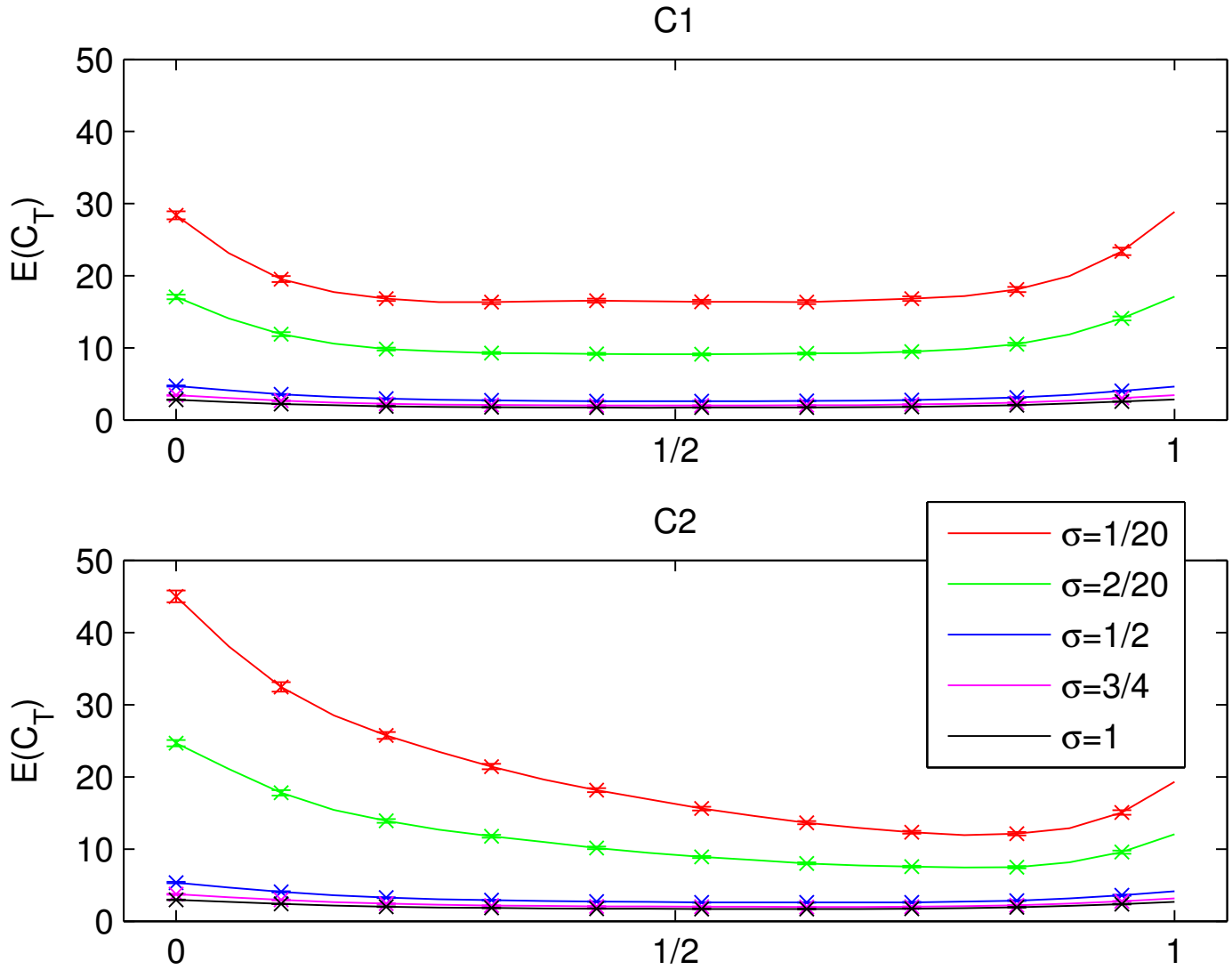


-Diffusion σ along the x-axis (assumed well-stirred in each yz-plane).

-In this case we compare with an *"unperturbed case"* with a birth-rate $k_E/2 \cdot (1 + 2x)$.
I.e. $\int k_E dV$ is unaffected and we can think of this as a *spatial* stochastic focusing.

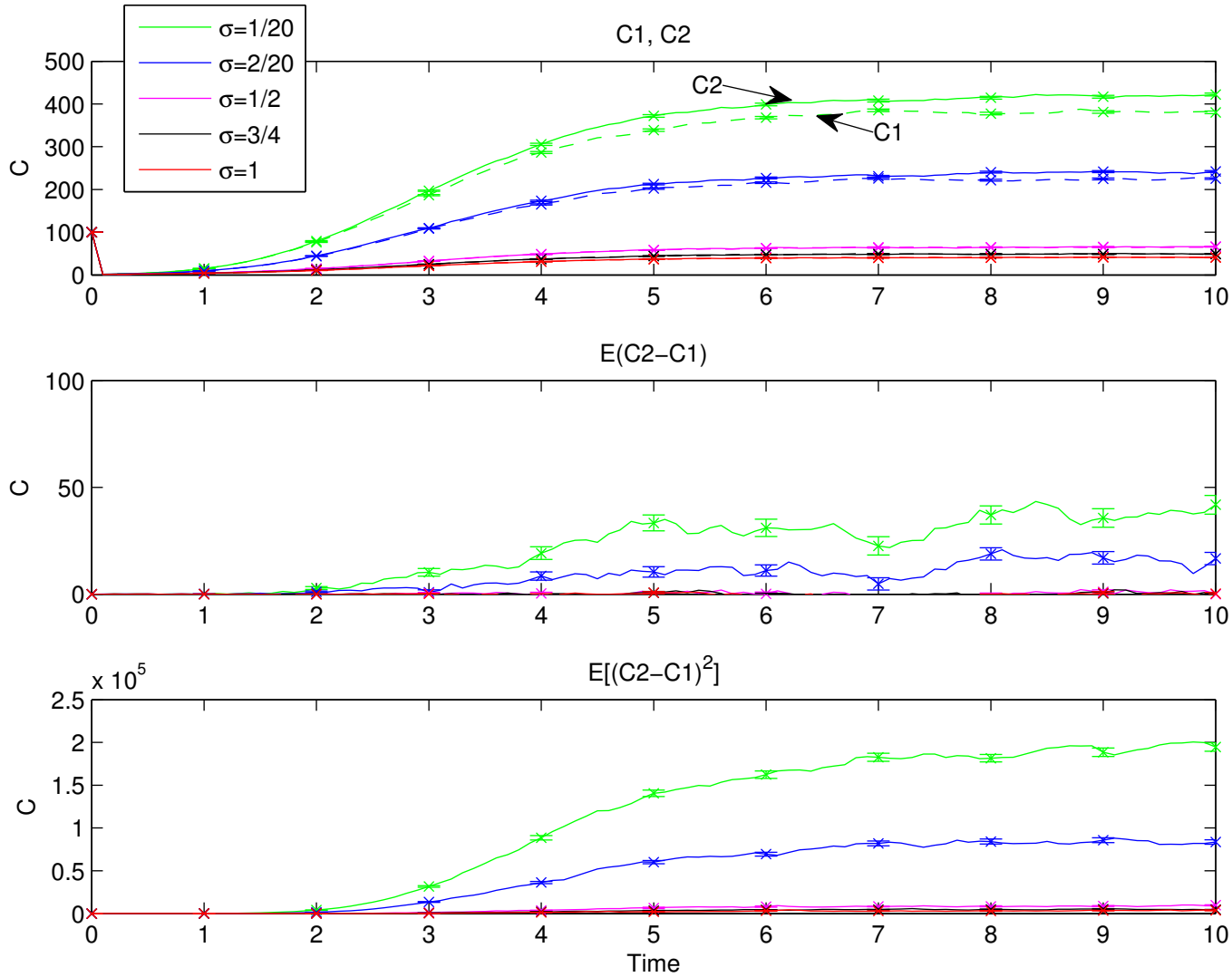
Results in 1D (cont)

Spatial profile



Results in 1D (cont)

Global effect is ∼10% increase



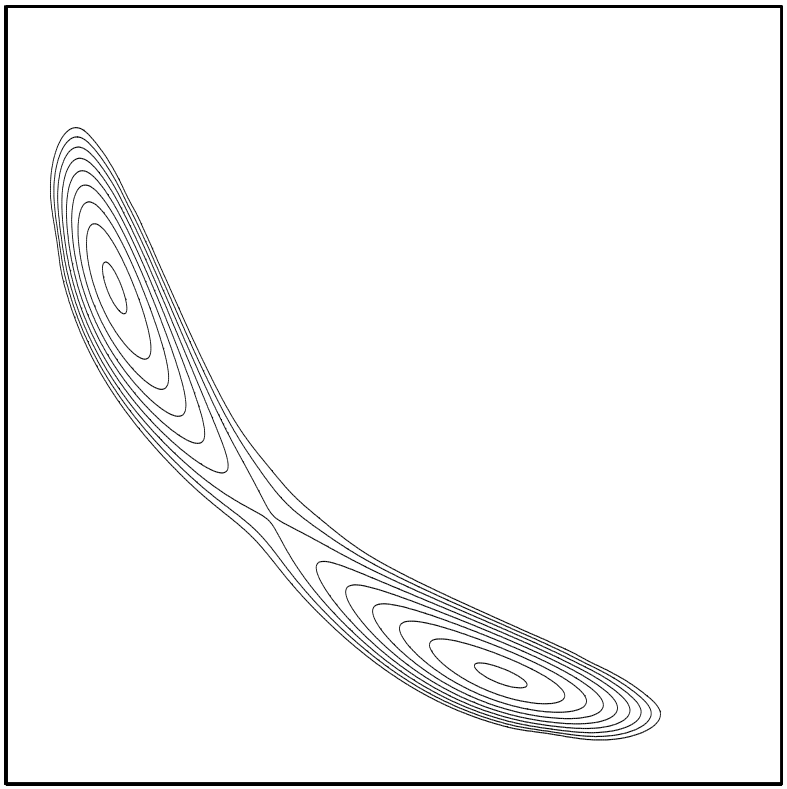
Bistable system, 2 competing species

Well-stirred

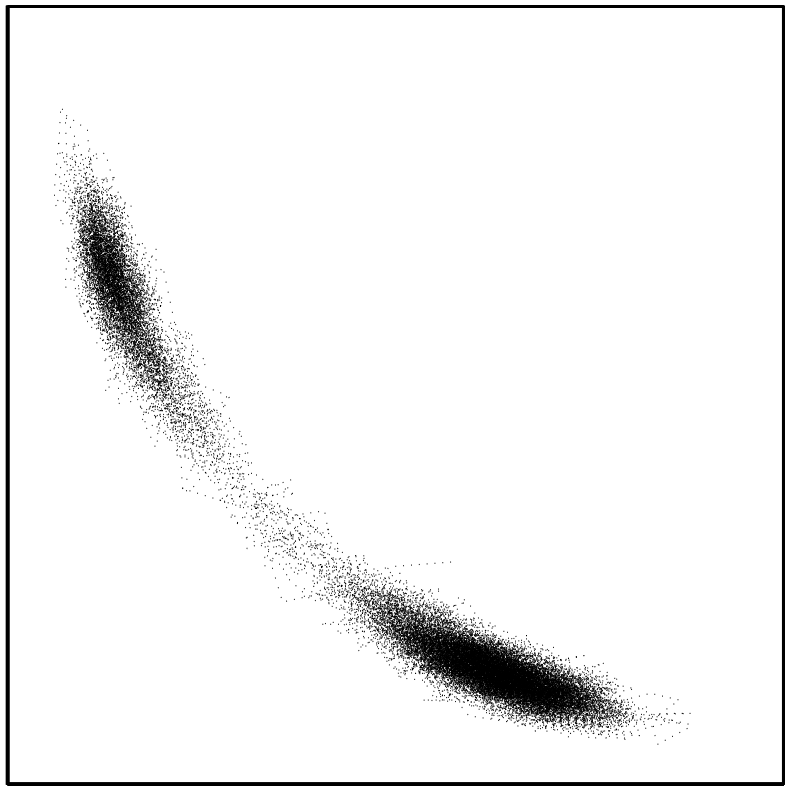
A simple model of two mutually cooperatively repressing gene products X and Y. Relying on adiabatic approximations the model is

$$\begin{array}{ccc} \emptyset & \xrightarrow{a/(b+y^2)} & X \\ X & \xrightarrow{\mu x} & \emptyset \end{array} \qquad \begin{array}{ccc} \emptyset & \xrightarrow{c/(d+x^2)} & Y \\ Y & \xrightarrow{\mu y} & \emptyset \end{array}$$

2 species/dimensions: the CME is a feasible approach.



(c) Solution to the master equation, discrete spectral method.



(d) Stochastic simulation.

Bistable double-negative feedback system

Spatial

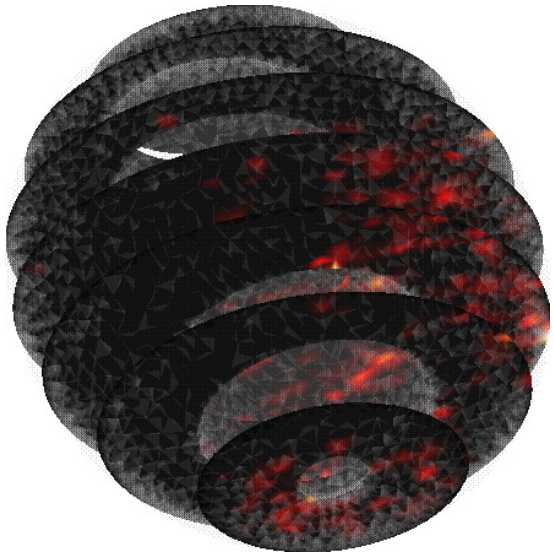
$$E_A \xrightarrow{k_1} E_A + A \qquad E_B \xrightarrow{k_1} E_B + B$$

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

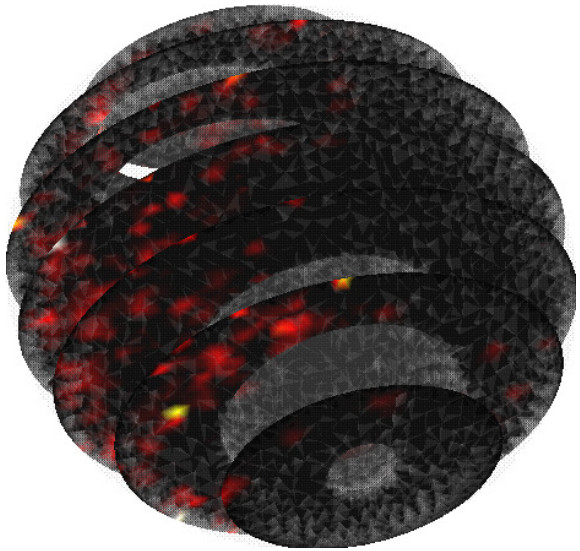
$$E_A B + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B_2 \qquad E_B A + A \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A_2$$

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

Slow/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.

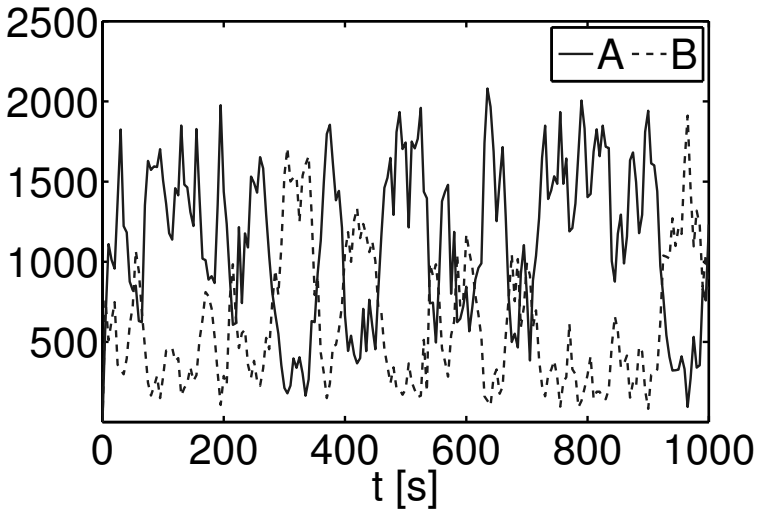


(e) Species A.

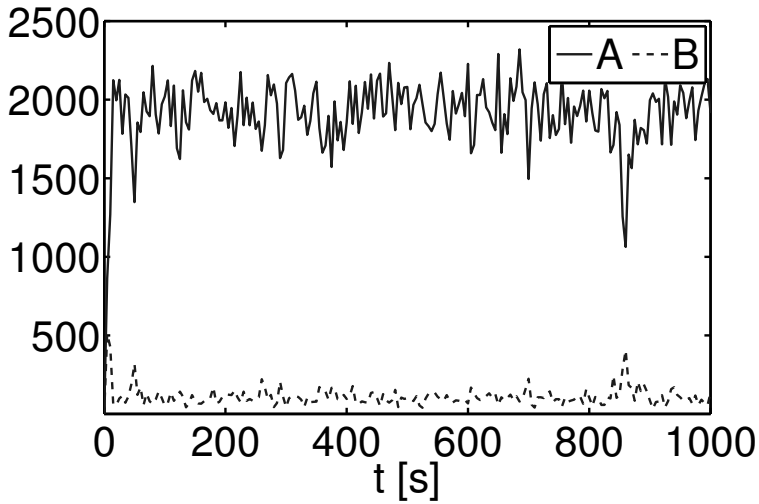


(f) Species B.

www.urdme.org.



(g) $\sigma^2 = 2 \times 10^{-13}$



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

Figure: The total number of A and B molecules as the diffusion constant is varied. *Right:* local bistability is lost.

Summary

- *Well stirred case*: stochastic mesoscopic modeling in chemical kinetics can combine *simplicity* with *accuracy*
- Spatially inhomogeneous case:
  -microscopic kinetics usually very expensive
  -local well-stirredness implies the reaction-diffusion master equation
  -the RDME is a computationally feasible alternative
- Unstructured meshes: consistency with macroscopic equations, and with microscopic diffusion. The numerical method's convergence to the macroscopic equation implies weak convergence of the corresponding stochastic model.
- Free software URDME (`www.urdme.org`). Currently relying on Matlab+Comsol.