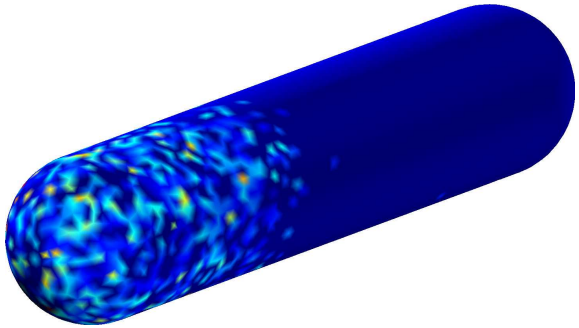
Numerical Solution Methods in Stochastic Chemical Kinetics



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- Stochastic chemical kinetics
  - Well-stirred mesoscopic kinetics
  - Motivation
  - Spatially inhomogeneous kinetics
- Numerical solution methods
  - Stochastic simulation
  - Moment equations
  - The master equation
  - Simulating spatial models

Stochastic chemical kinetics

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*>.

Kinetics (*Merriam-Webster*)

Date: circa 1859.

1 a. A branch of science that deals with the effects of forces upon the motions of material bodies or with changes in a physical or chemical system.

1 b. The rate of change in such a system.

2. The mechanism by which a physical or chemical change is effected.

Mesoscopic (*Merriam-Webster*)

No entries found. -Did you mean masochistic?

Mesoscopic scale (*Wikipedia*)

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. (- - -)

This article does not cite any references or sources. *(Nov 2007)*

Modeling chemical reactions

Model	Idea
Micro	Movement of individual atoms/molecules
	Collisions → (Possible) reactions
Meso	Non-individual, assuming well-stirred mixture
	A *stochastic model* is used for reactions
Macro	"Average"; —in the limit of many molecules

-With a mesoscopic model, an accurate but still manageable *non-individual* model is possible thanks to stochasticity (note that both the micro- and the macroscopic models are deterministic).

Well-stirred

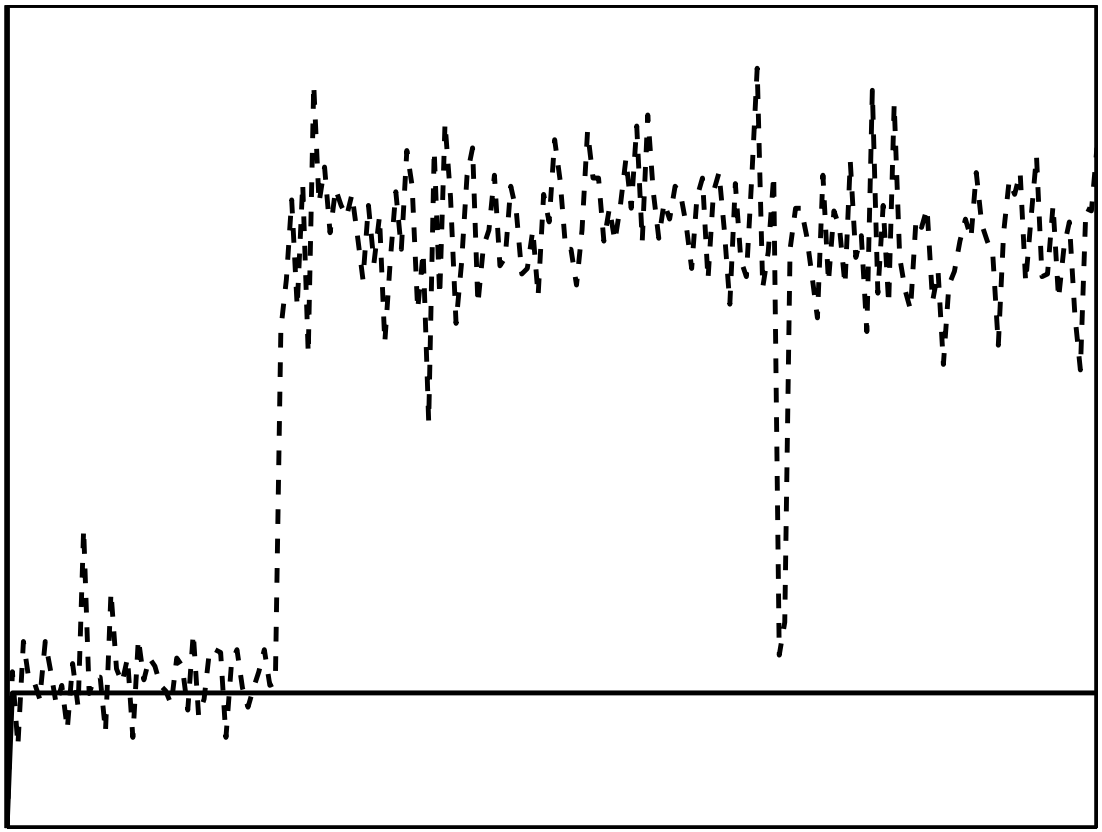
Assumption #1: the chance of finding a molecule is equal throughout the volume *(homogeneous)*.

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

-Under these assumptions there is a favorable stochastic model of chemical kinetics — a *continuous-time Markov chain*.

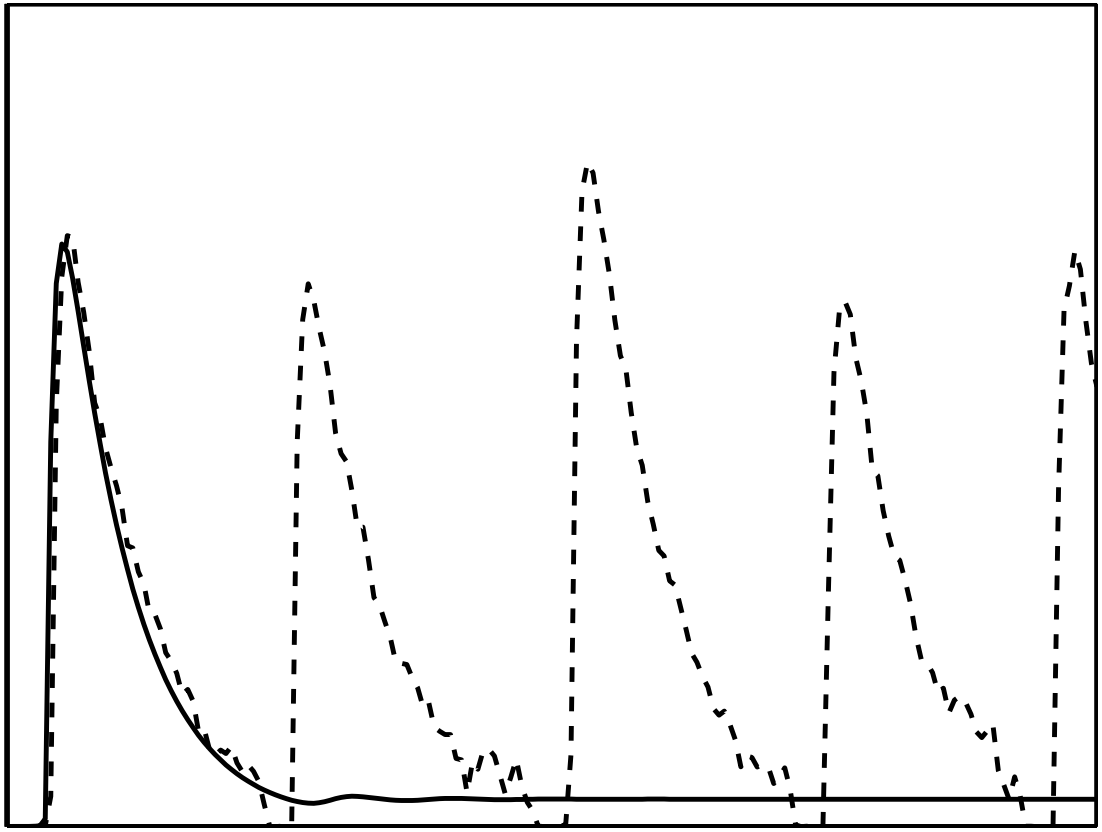
-There are many examples of when this model works better than macroscopic equations...

Multistability (*Gardner/Cantor/Collins*)



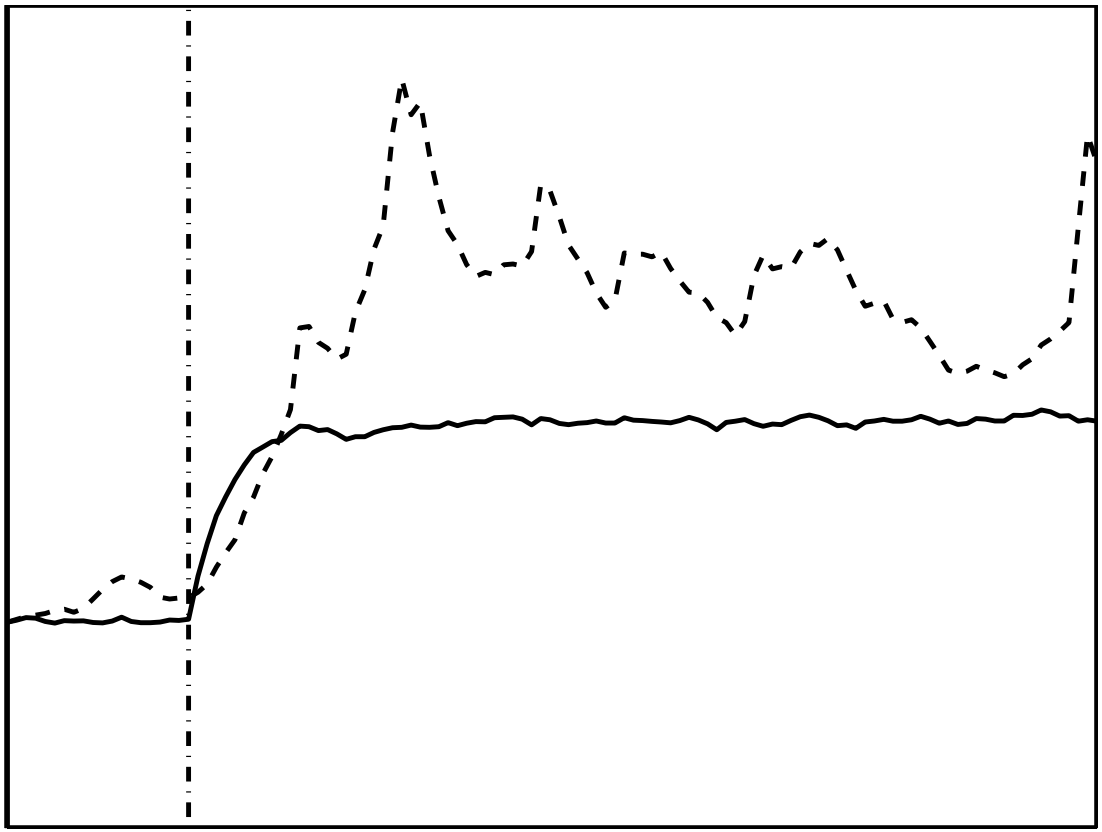
Solid: deterministic, dashed: stochastic.

Stochastic resonance (*Barkai/Leibler*)



Solid: deterministic, dashed: stochastic.

Stochastic focusing (*Paulsson/Berg/Ehrenberg*)



Solid: partially deterministic, dashed: fully stochastic.

Not well-stirred:

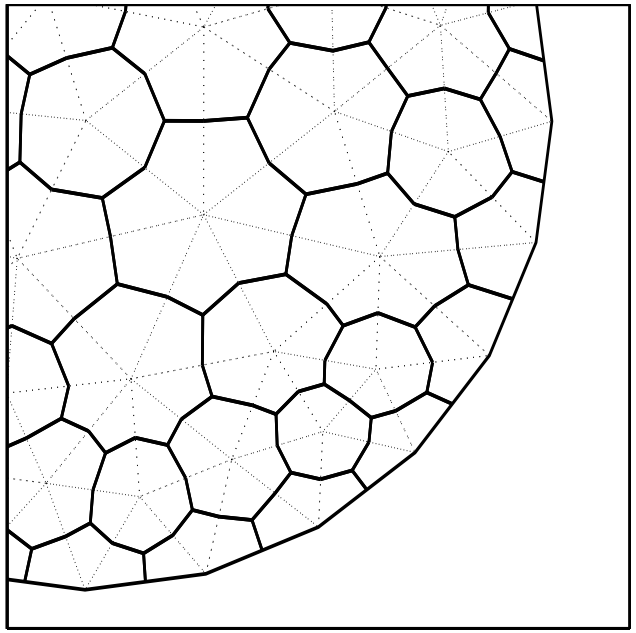
-When the molecular movement (diffusion) is slow compared to the reaction intensity — large *local* concentrations may easily build up.

-When some reactions are *localized* — e.g. depend on an enzyme 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 it is subdivided into smaller computational cells such that their individual volume is small, then diffusion suffices to make each cell well-stirred.



Smaller cells in a large volume.

Numerical solution methods

Direct method (*Gillespie '76*)

0. Let $t = 0$ and set the state x to the initial number of molecules.
1. Generate the *time to the next reaction* τ by picking a certain random number. Determine also *which reaction* from another random number. (...)
2. Update the state of the system by setting $t := t + \tau$ and $x := x + (\text{products of reaction})$.
3. Repeat from step 1 until some final time T is reached.

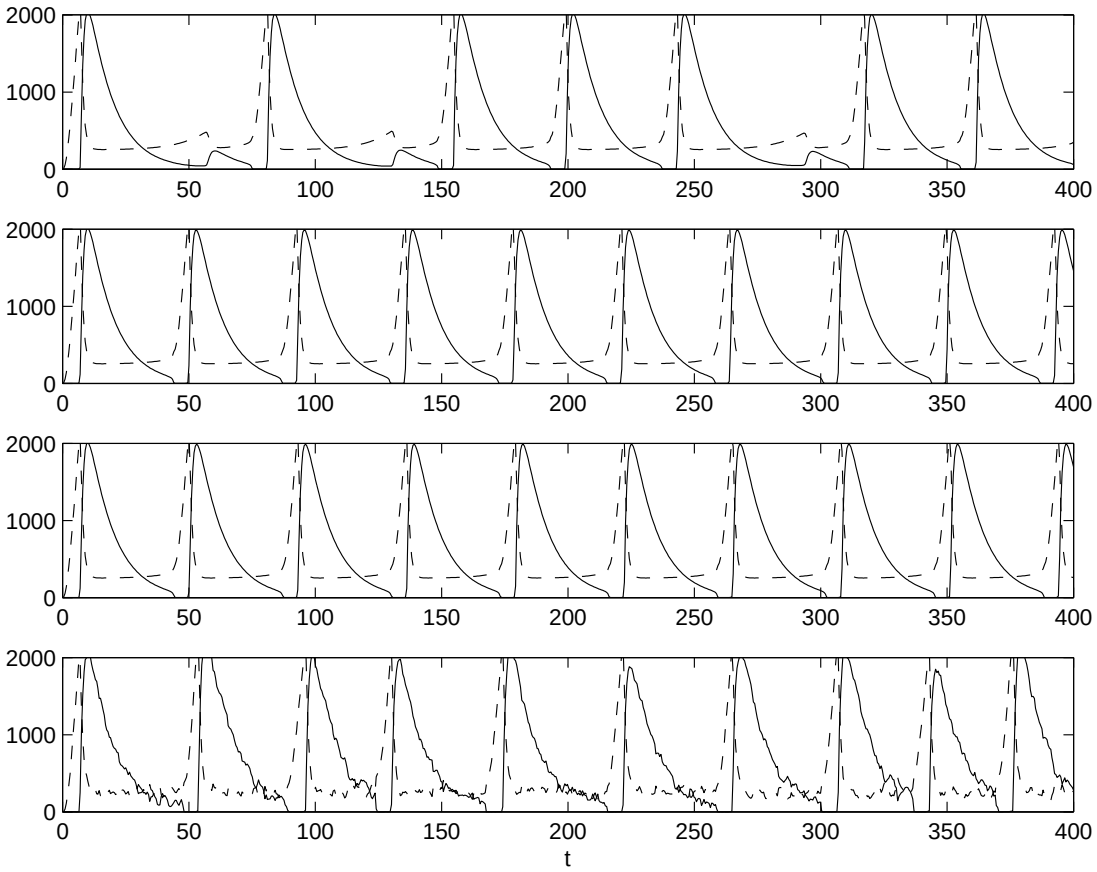
-Repeat *several* times to get an average value, to estimate the probability of reaching a certain state, to determine the average time before some event happens...

-Very expensive when typical times between reactions are small.

Averages

-Instead of simulating many times, it is possible to directly formulate equations for average quantities. However, the equation for the mean value (1st moment) depends on the covariance matrix (2nd moment). Generally the nth moment depends on the $(n+1)$th moment.

-Simply truncating at a certain order yields an *approximation*. Easy to compute, but the quality is difficult to evaluate. (*Paper I*)



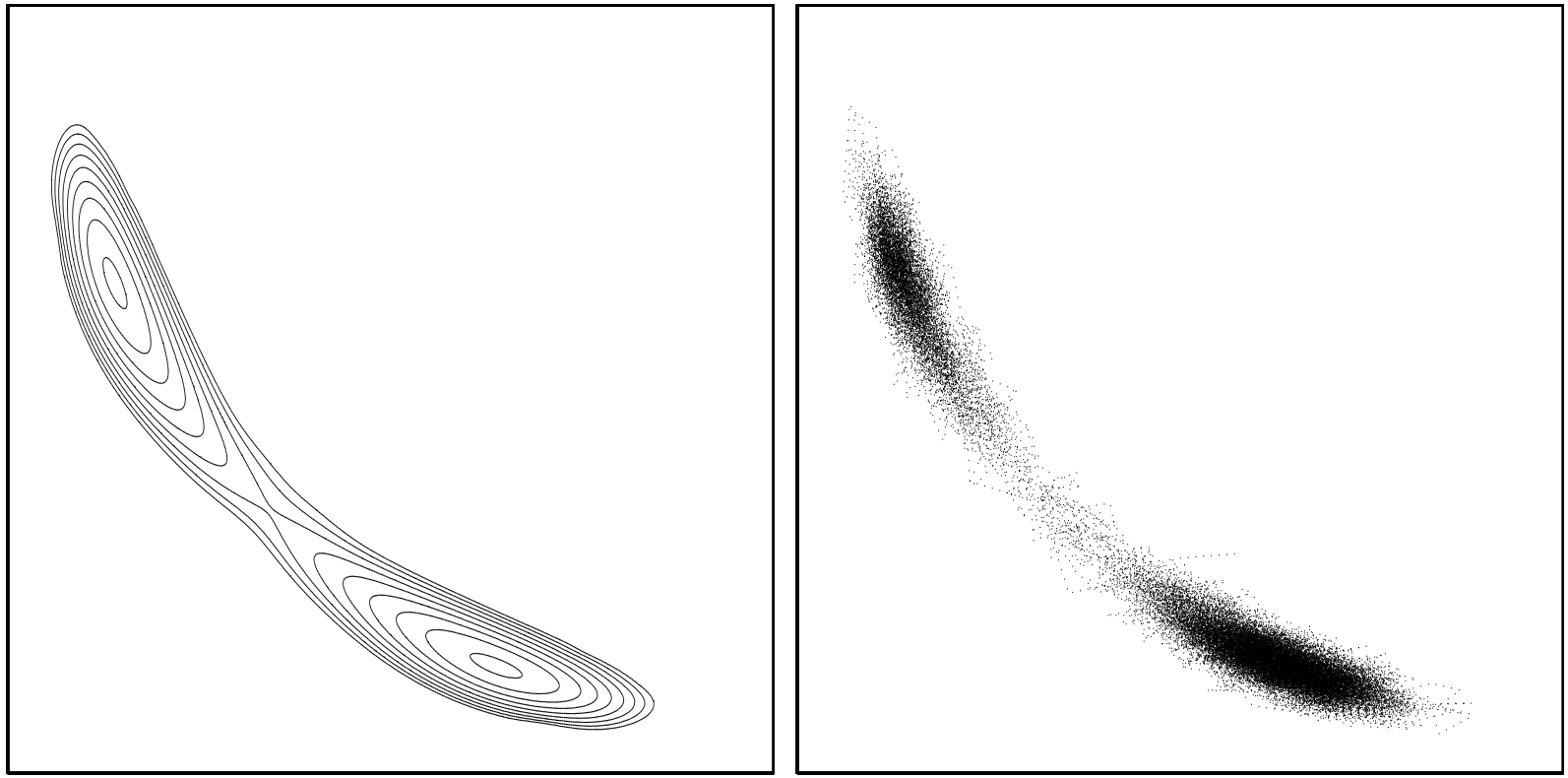
1st, 2nd and 3rd order equations, bottom: a stochastic simulations. # of molecules vs. time (*Paper I*).

Probabilities

-A different type of equation that gives the *probability* of reaching a certain state can also be derived. This is the master equation.

-Directly solving the master equation is extremely expensive since the number of states is huge. E.g. 4 different species that are present in less than 100 molecules yields 100 million states.

-A more efficient way of solving the master equation is investigated in *Paper II and III*.



(a) Solution to the master equation. (b) Stochastic simulation.

Adapted from *Paper III*.

Reactions inside a cell (*Paper IV*)

-Bistable double-negative feedback system (*Elf/Ehrenberg*):

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

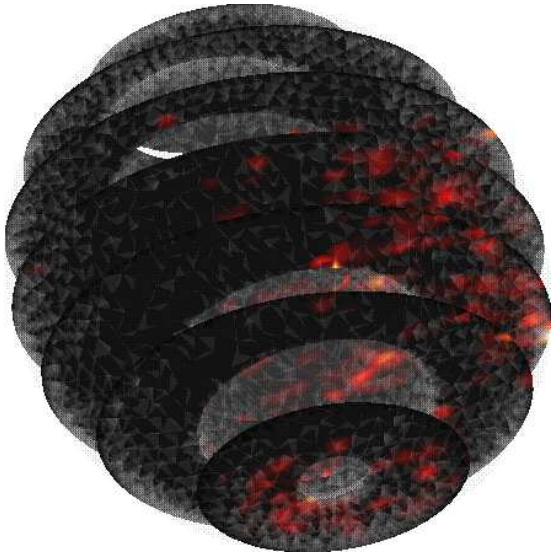
$$E_A + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B \qquad E_B + A \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A$$

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

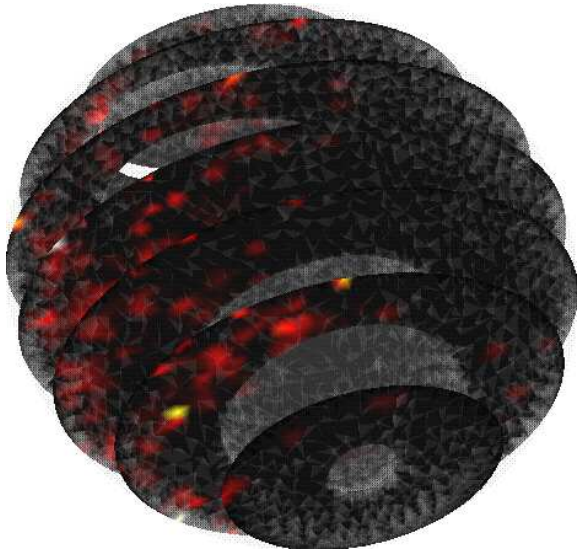
$$A \xrightarrow{k_4} \emptyset \qquad B \xrightarrow{k_4} \emptyset$$

-Diffusion in a model of an *S. cerevisiae* cell with internal structures in the form of a nucleus and a large vacuole. Molecules cannot diffuse across the membranes and enter the organelles.

-"URDME" software (*Cullhed/Engblom/Hellander, Paper IV*) implementing the "Next subvolume method" (*Fange/Elf*).



(a) Species A.

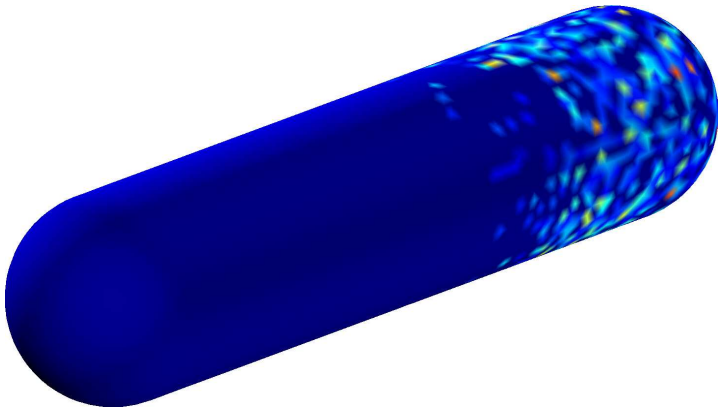


(b) Species B.

From *Paper IV*.

Oscillations in *E. coli* (*Fange/Elf, Cullhed/Engblom/Hellander*)

-Oscillations of proteins involved in the cell division of *Escherichia coli* bacterium; five species, five reactions.



Thank you for your attention!