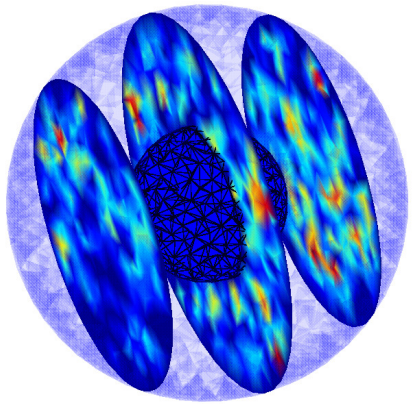
Mesoscopic Stochastic Modeling of Reaction-Transport Processes



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The buzz

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 *(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 (continuous-time Markov chain), an accurate but still manageable *non-individual* model is possible thanks to stochasticity.

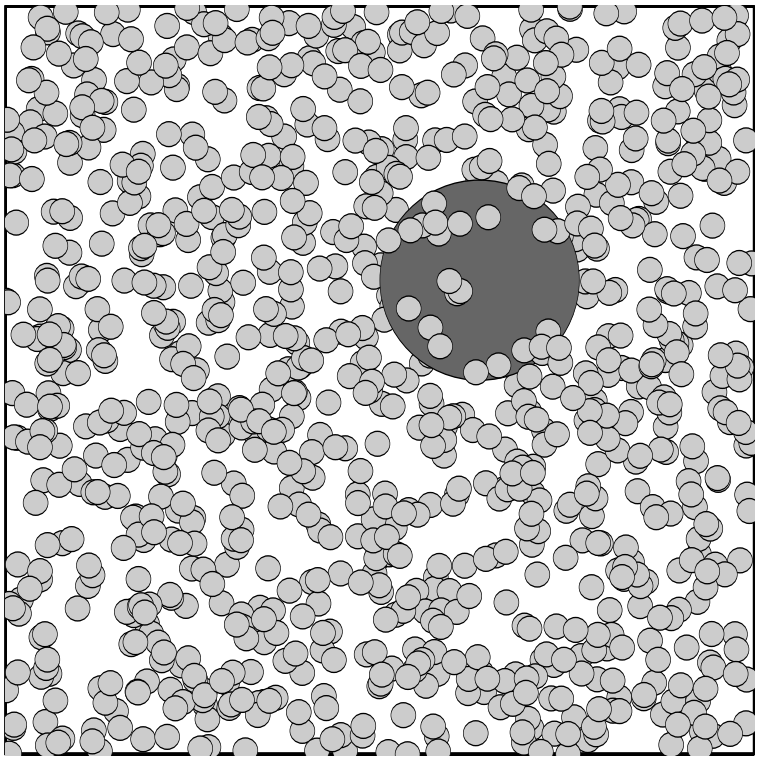
Diffusion-controlled kinetics

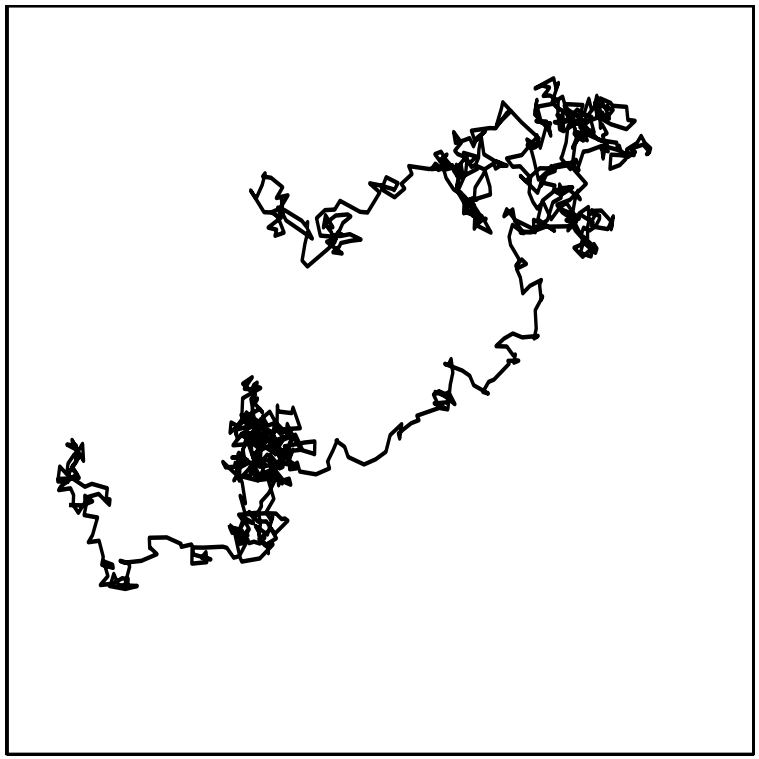
Model	Assumption
BD (Smoluchowski)	Brownian motion of individual molecules
CTMC (Master equation)	Non-individual, (locally) well-stirred
SDE (Langevin)	Continuous *approximation*
ODE (Reaction rate)	Continuous, deterministic

Up next: (1) Diffusion & (2) Stochastic chemical kinetics.

Brownian motion

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



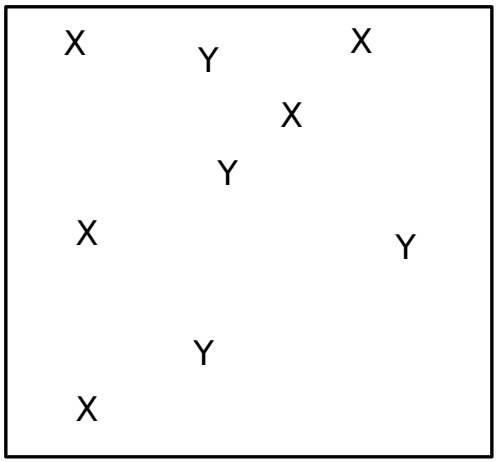


A stochastic model is simpler but depends on randomness.

Stochastic modeling of biochemical reactions

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

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



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

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

It so happens that this receipt describes a continuous-time Markov chain.

There are several examples of when stochastic models more easily can capture actual observed behavior...

Multistability

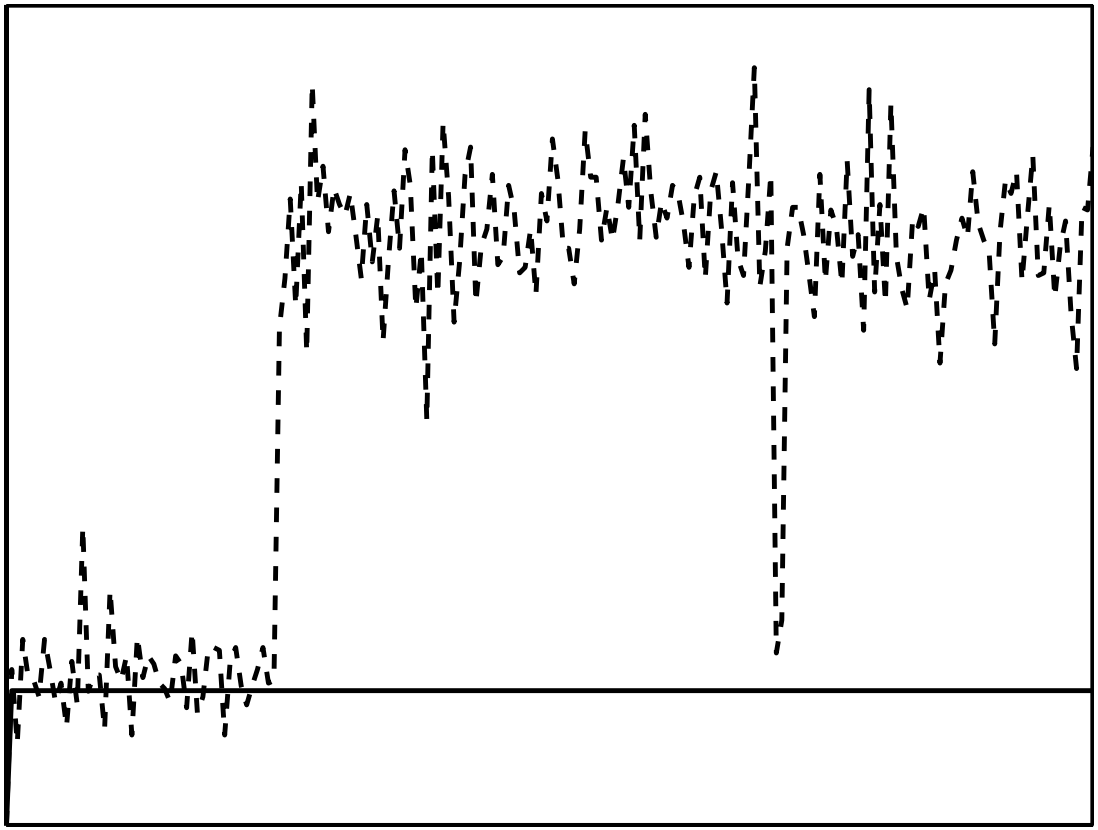


Figure: Solid: deterministic, dashed: stochastic.

Stochastic resonance

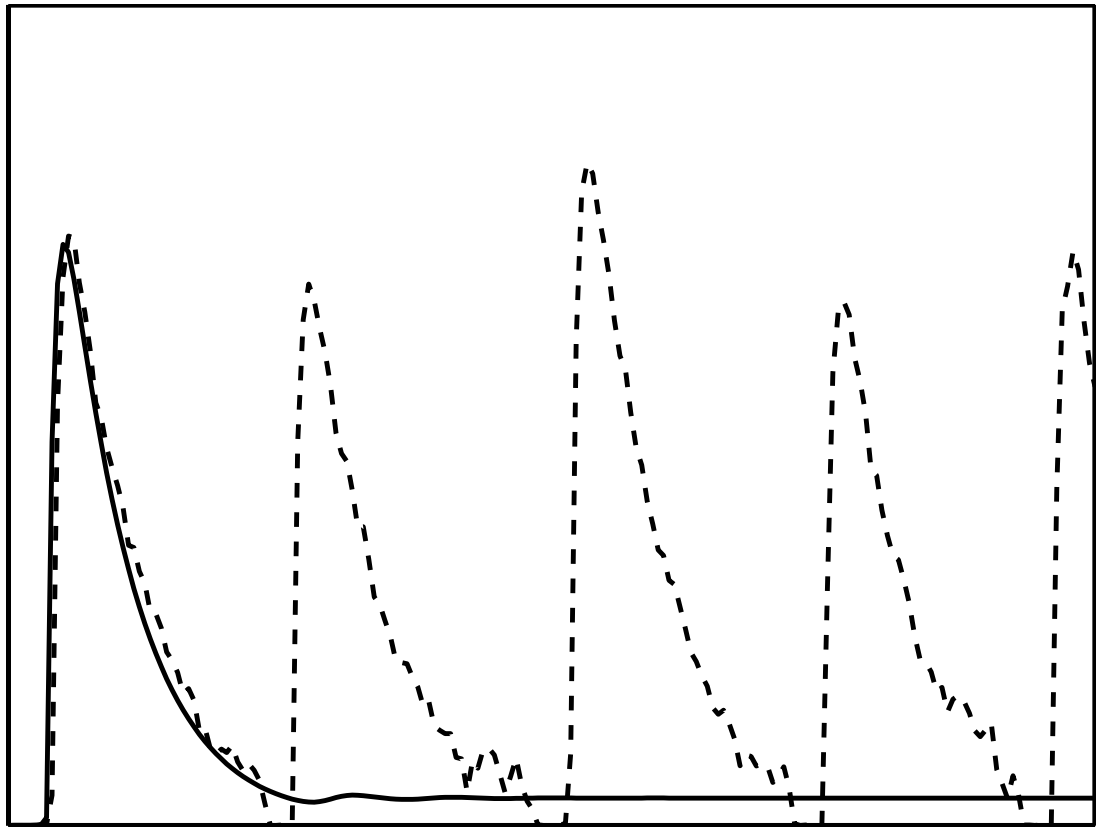


Figure: Solid: deterministic, dashed: stochastic.

Stochastic focusing

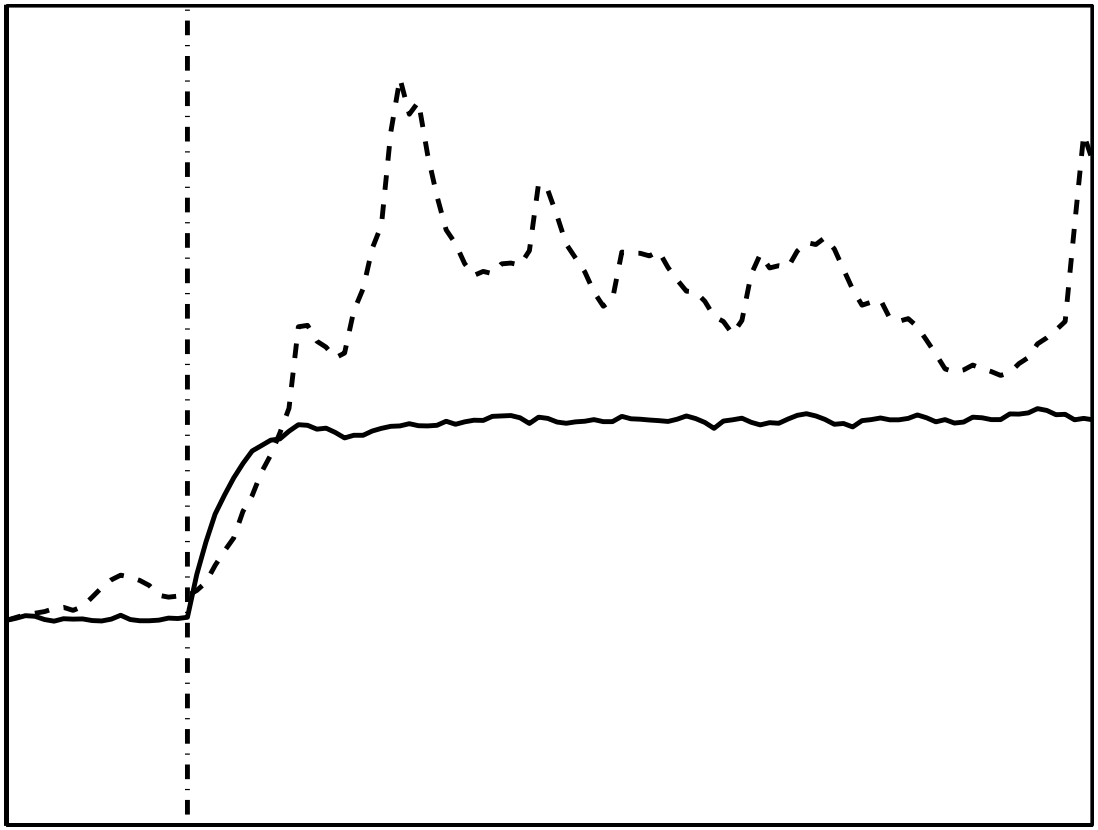


Figure: Nonlinear response to twofold signal increase; solid: partially deterministic, dashed: fully stochastic.

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.

"Next reaction method"

0. Let $t = 0$ and set the state x to the initial number of molecules. Generate the dependency graph G. Determine the *absolute* waiting times τ_r for all reactions r. Store those values in a heap H.
1. Remove the smallest time $\tau_r = H_0$ from the top of H, execute the rth reaction $x := x - N_r$ and set $t := \tau_r$.
2. For all dependencies $r \to j$ in G, update the jth waiting time by rescaling, thus accounting for the new propensity.
3. Also generate a new absolute time τ_r^{new}. Adjust the contents of H by replacing the old value of τ_r with the new one.

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!

Microscopic kinetics

- Molecular dynamics...
  -Many different algorithms, usually *very* expensive simulations.
- Smoluchowski kinetics (diffusion-controlled limit): individual coordinates of molecules, Brownian motion in space. The *Smoluchowski PDE* evolves the spatial probability density in time and the reactions are to be incorporated as boundary conditions.
  -One exact algorithm: Green's function reaction dynamics (GFRD).
  -Various software for approximations: "MCell", "SmolDyn", "ChemCell"...

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.

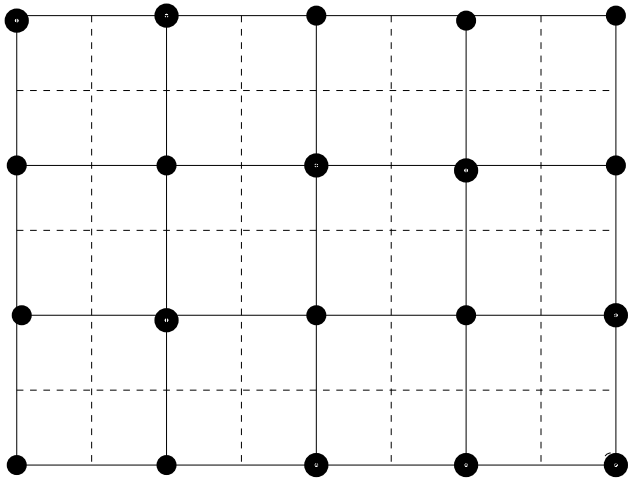


Figure: Primal mesh (solid), dual mesh (dashed). The nodal dofs are the # of molecules in each dual cell.

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.
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

"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.

"Next subvolume method"

0. *Initialize:* Compute the sum σ_k^r of all reaction rates w_{rk} and the sum σ_k^d of all diffusion rates in all subvolumes $k = 1, \ldots, N_{\text{cells}}$. Compute the time until the next event in each subvolume and store all times in a heap H.
1. Select the next subvolume ζ_n where an event takes place by extracting the minimum τ_n from the top of H, set $t = \tau_n$.
2. Determine if the event in ζ_n is a reaction or a diffusion event. Let it be a reaction if $(\sigma_n^r + \sigma_n^d) \times \text{rand} < \sigma_n^r$, otherwise it is a diffusion event.

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2. Determine if the event in ζ_n is a reaction or a diffusion event. Let it be a reaction if $(\sigma_n^r + \sigma_n^d) \times \text{rand} < \sigma_n^r$, otherwise it is a diffusion event.
3. *Reaction event:* determine the reaction channel that fires. This is done as in the Direct method. Update $\mathbf{x}(:, n) := \mathbf{x}(:, n) - \mathbb{N}_r$.
4. *Diffusion event:* determine which species diffuses and subsequently, determine to which neighboring subvolume $\zeta_{n'}$. This is again done as in the Direct method. Update: $\mathbf{x}(s, n) := \mathbf{x}(s, n) - 1$ and $\mathbf{x}(s, n') + 1$.
5. Update the reaction- and diffusion rates of subvolumes ζ_n and $\zeta_{n'}$ using G. Compute a new waiting time τ_n for subvolume ζ_n and add it to the heap H.

Unstructured meshes

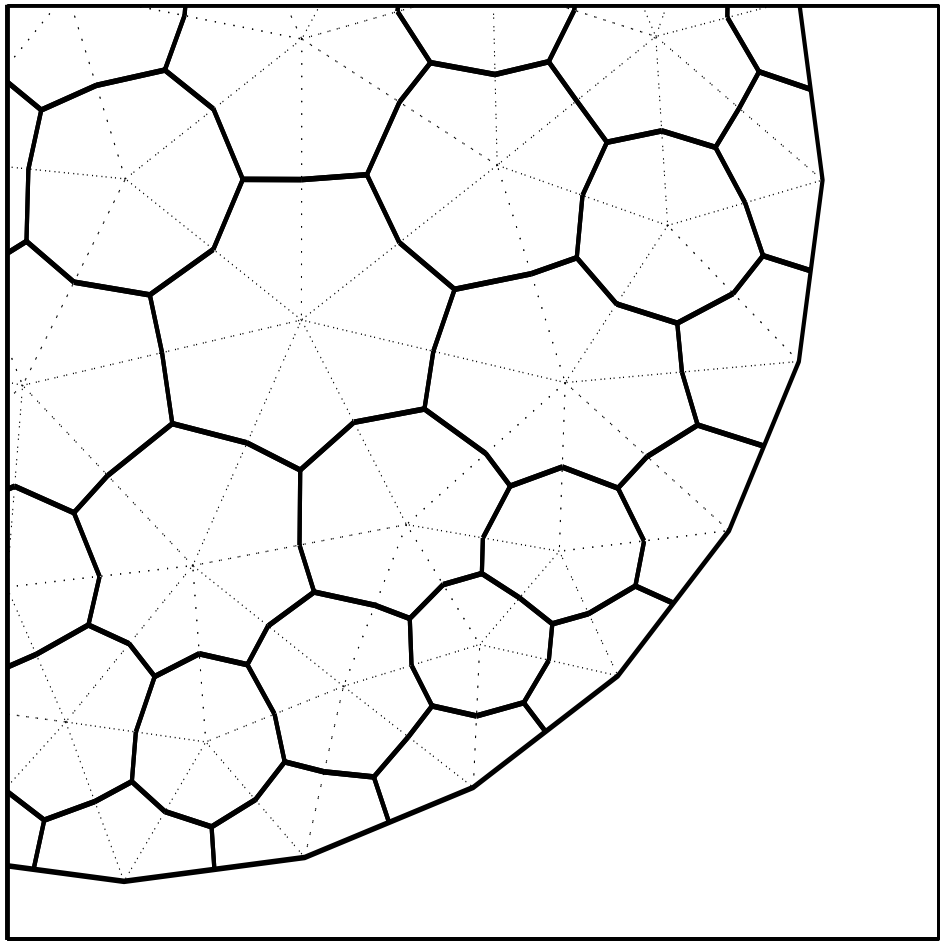
-Mean first exit time only known for very simple geometries (e.g. circles).
-*How to handle complicated geometries?* Attempt to converge in expectation to the macroscopic diffusion equation. Briefly, a numerical method applied to $u_t = \sigma^2/2\,\Delta u$ yields the *discretized* form

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

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

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

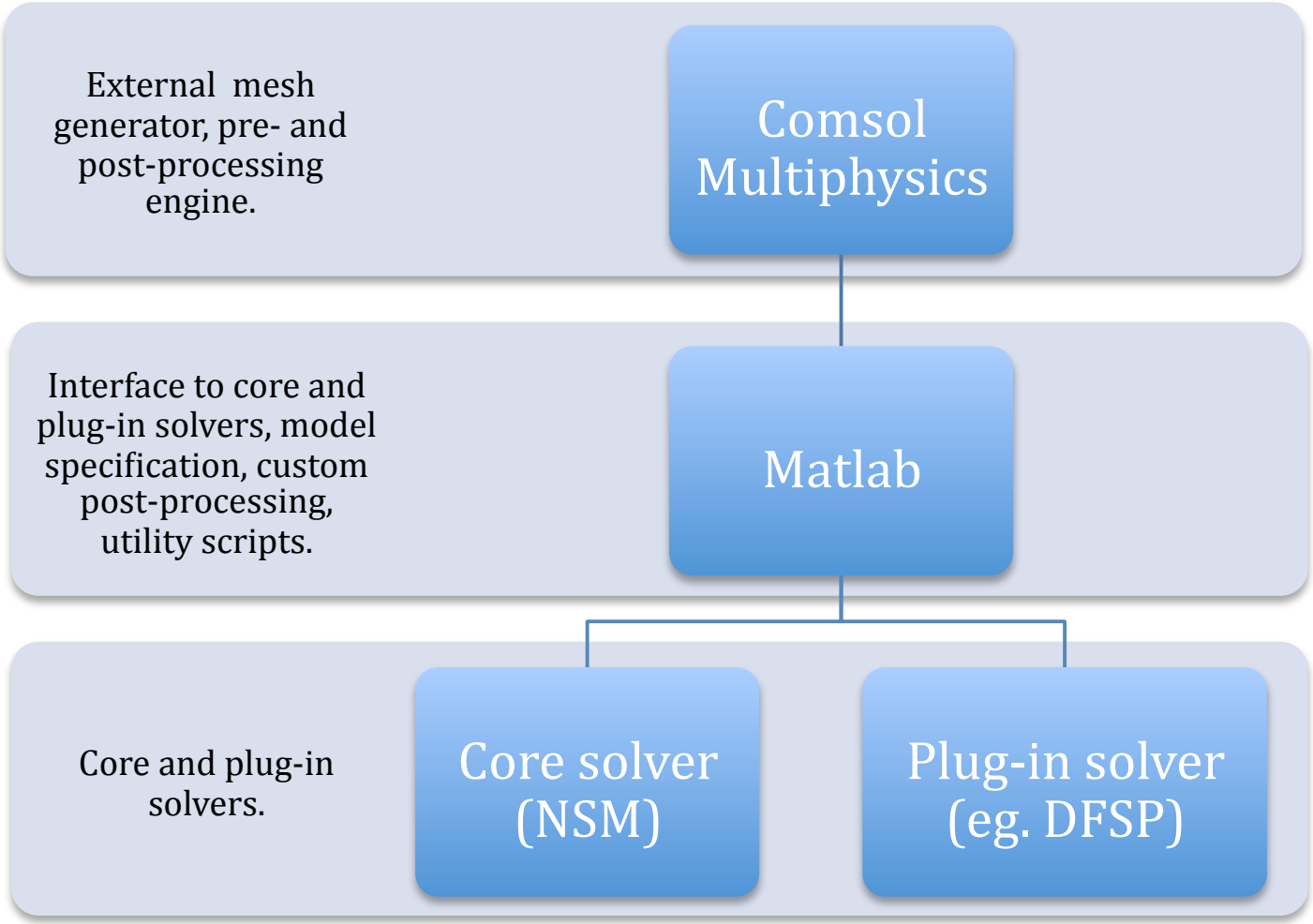
$$\iff \frac{d\varphi_{i\cdot}^T}{dt} = Q\varphi_{i\cdot}^T.$$



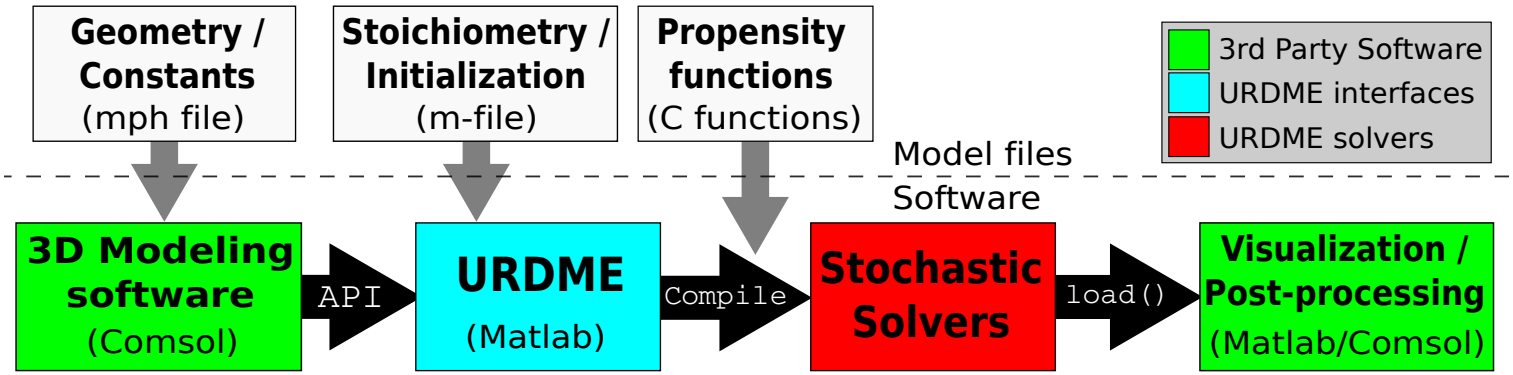
Assuming point-wise convergence of the numerical discretization $\rightarrow$ diffusion PDE, the consistency in this interpretation ensures convergence in distribution to the correct Brownian motion as the mesh-size $h \rightarrow 0$.

URDME

Unstructured **R**eaction-**D**iffusion **M**aster **E**quation

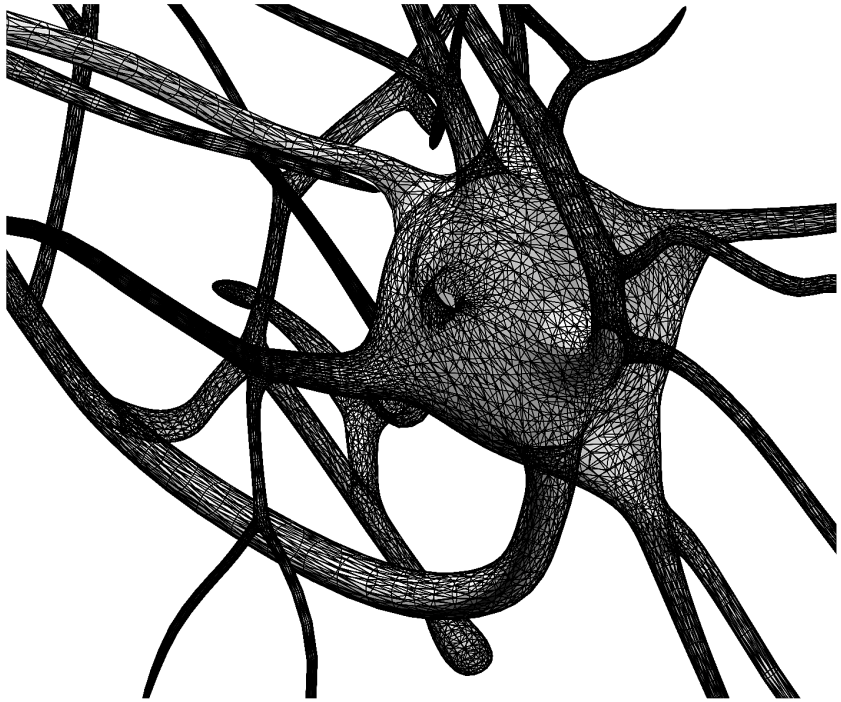


URDME


Geometry / Constants (mph file)
Stoichiometry / Initialization (m-file)
Propensity functions (C functions)
3rd Party Software
URDME interfaces
URDME solvers
Model files
Software
3D Modeling software (Comsol)
API
URDME (Matlab)
Compile
Stochastic Solvers
load()
Visualization / Post-processing (Matlab/Comsol)

Computations

- *"Semi-live"*: $X + Y \longleftrightarrow Z$.
- Bistable models;
  - non-spatial (hence non-URDME!)
  - spatial
- Spatial oscillations in *E. coli*.

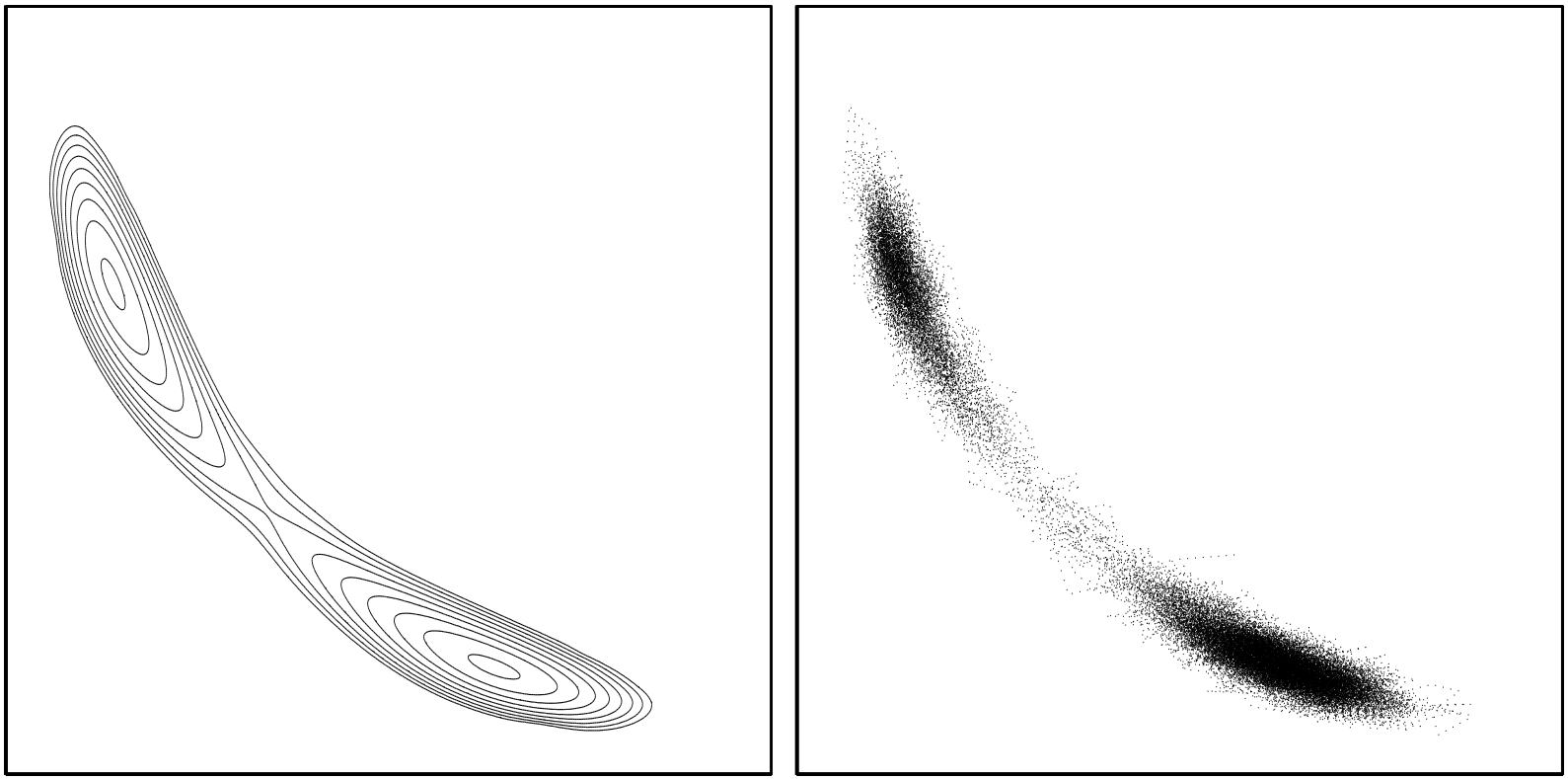


Bistable system, 2 competing species (non-spatial)

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.



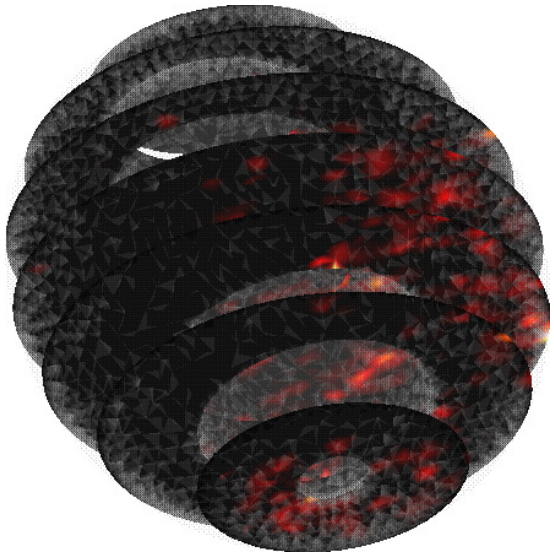
(a) Solution to the master equation, discrete spectral method.

(b) Stochastic simulation.

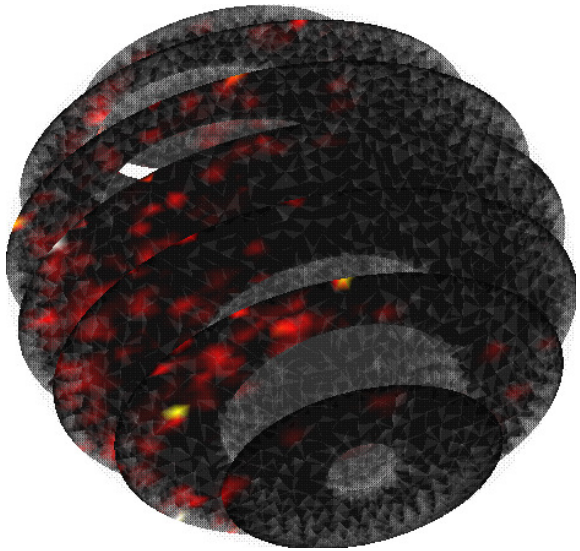
Bistable double-negative feedback system (spatial)

$$
\begin{aligned}
E_A &\xrightarrow{k_1} E_A + A & \qquad E_B &\xrightarrow{k_1} E_B + B \\
E_A + B &\underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B & \qquad E_B + A &\underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A \\
E_A B + B &\underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B_2 & \qquad E_B A + A &\underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A_2 \\
A &\xrightarrow{k_4} \emptyset & \qquad B &\xrightarrow{k_4} \emptyset
\end{aligned}
$$

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.

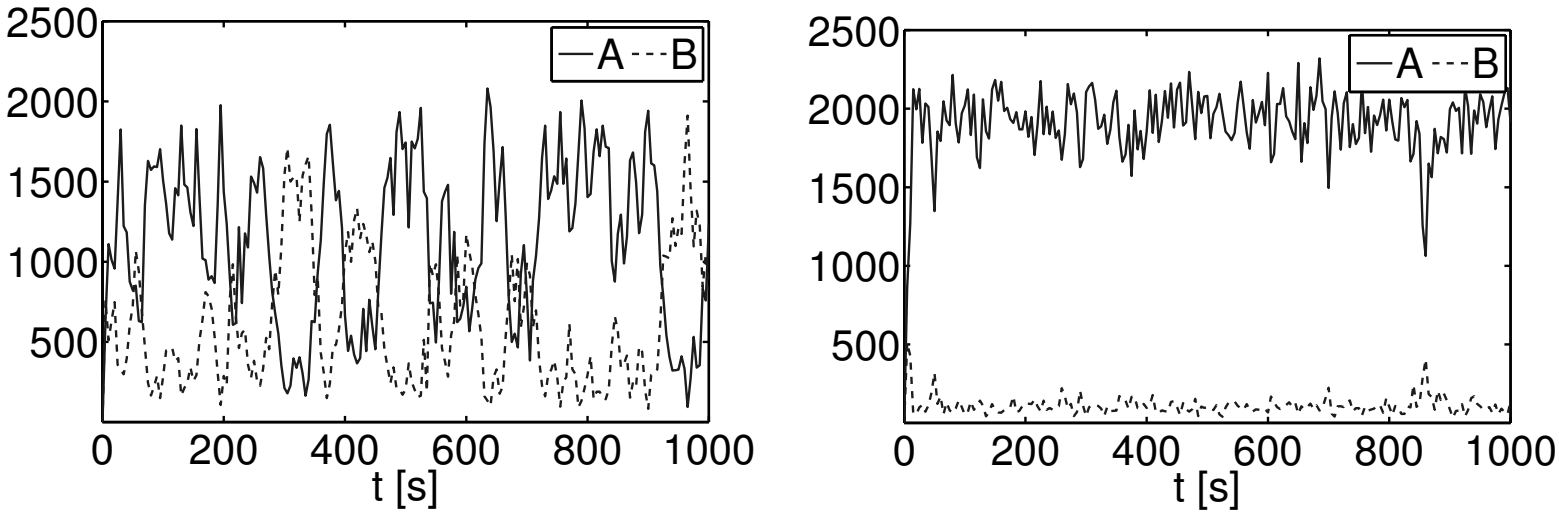


(c) Species A.



(d) Species B.

www.urdme.org.



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

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

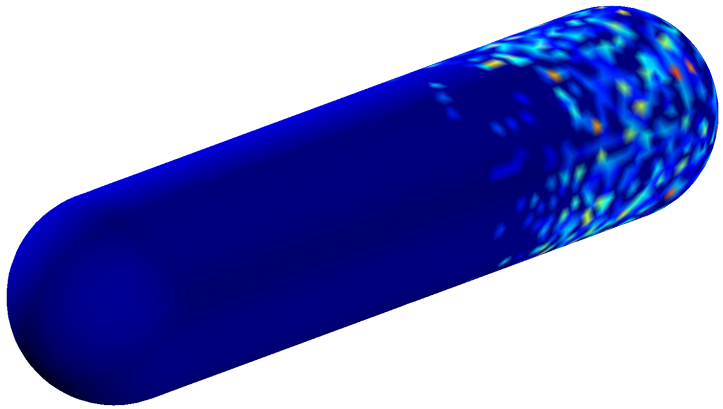
MinD oscillations

Oscillations of proteins involved in the cell division of *E. coli*:

$$\text{MinD\_c\_atp} \xrightarrow{k_d} \text{MinD\_m} \qquad \text{MinD\_c\_atp} + \text{MinD\_m} \xrightarrow{k_{dD}} 2\text{MinD\_m}$$

$$\text{Min\_e} + \text{MinD\_m} \xrightarrow{k_{de}} \text{MinDE} \qquad \text{MinDE} \xrightarrow{k_e} \text{MinD\_c\_adp} + \text{Min\_e}$$

$$\text{MinD\_c\_adp} \xrightarrow{k_p} \text{MinD\_c\_atp}$$



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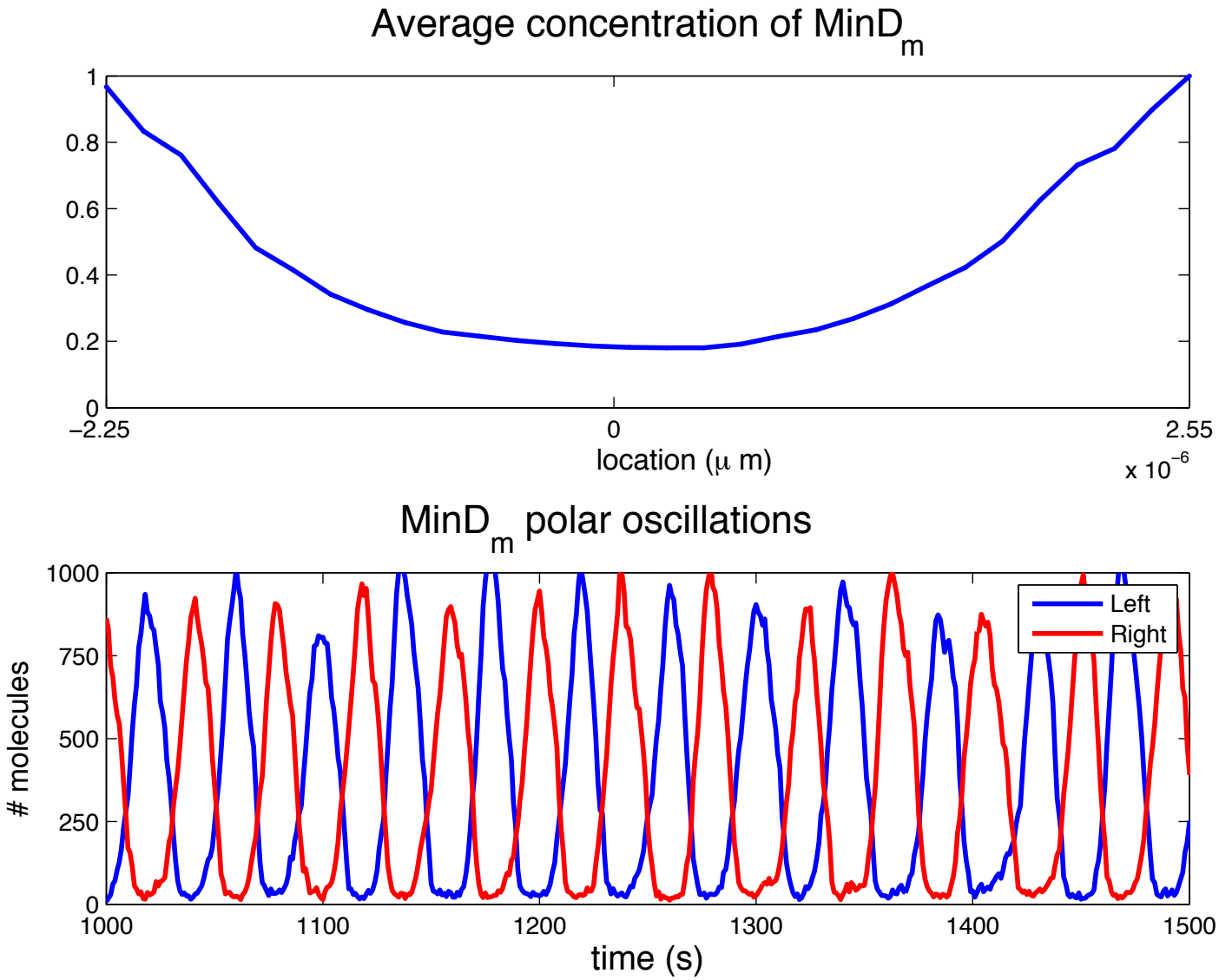
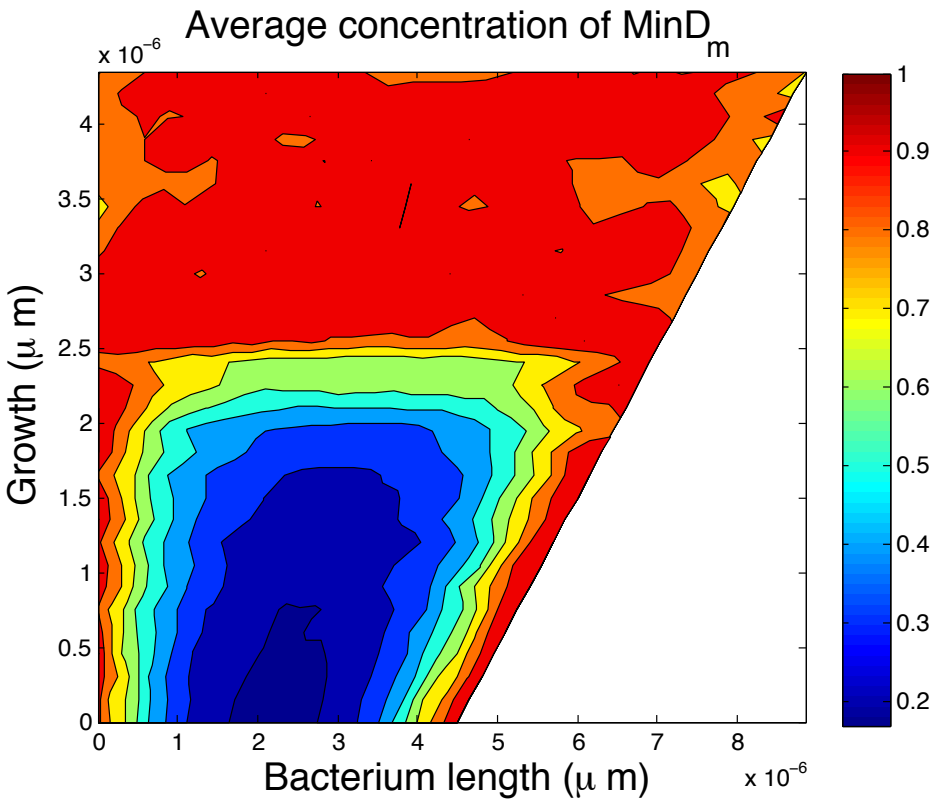
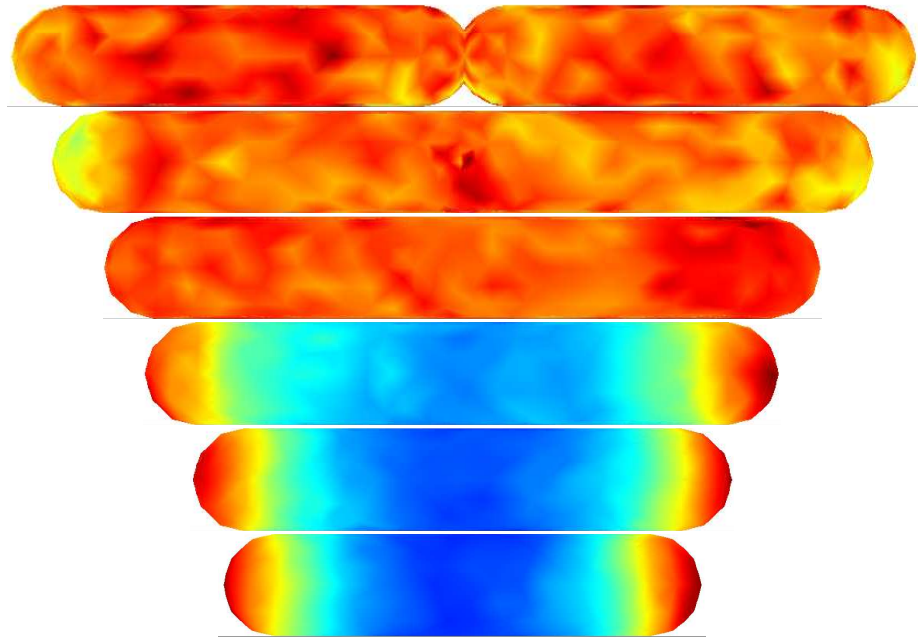

Average concentration of MinD m
1
0.8
0.6
0.4
0.2
0
−2.25
0
2.55
location (μ m)
x 10−6
MinD m polar oscillations
1000
750
500
250
0
molecules
1000
1100
1200
1300
1400
1500
time (s)
Left
Right


Average concentration of MinD$_m$
x 10^{-6}
Growth (μ m)
Bacterium length (μ m)
x 10^{-6}
0
0.5
1
1.5
2
2.5
3
3.5
4
0
1
2
3
4
5
6
7
8
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2



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
- Computational issues arise due to high temporal resolution
- Free software URDME (`www.urdme.org`). Currently relying on Matlab+Comsol. *Ongoing:* support for R and Python.