Spatial Stochastic Modeling in URDME: consistency, software, and applications to neuronal processes

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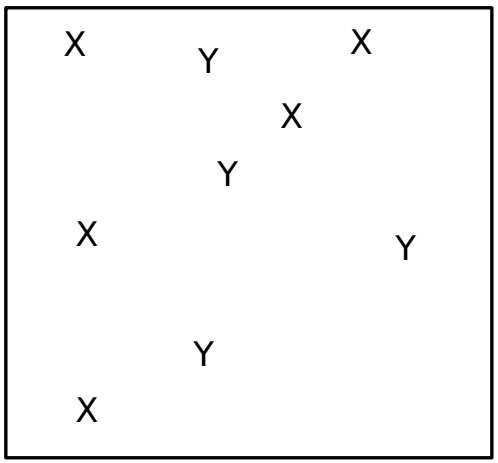
Stochastic modeling of biochemical reactions

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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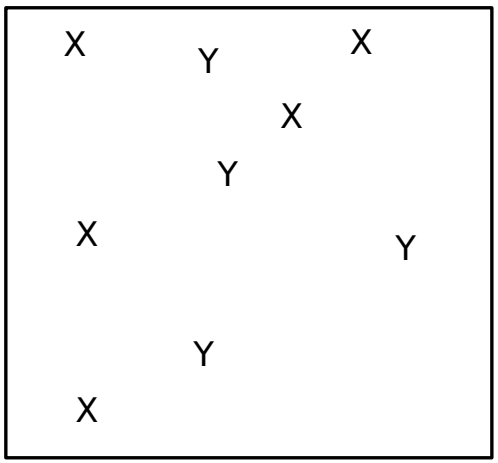


- $P \propto n_X$ ("number of X-molecules")
- $P \propto n_Y$
- $P \propto 1/V$
- $P \propto \Delta t$

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

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

Kolmogorov's forward differential system/Master equation

Well-stirred stochastic chemical kinetics

-State $x \in \mathbf{Z}_+^D$, counting the number of molecules of each of D species.
-R specified reactions defined as *transitions* between these states,

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

under a transition intensity or *propensity* w_r.

Let $p(x,t) := P(X(t) = x|X(0))$. Then the *chemical master equation* (CME) is given by

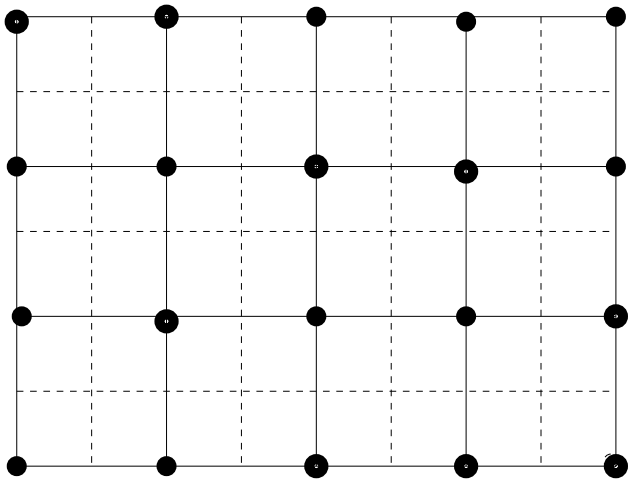
$$\begin{aligned}\frac{\partial p(x,t)}{\partial t} &= \sum_{r=1}^{R} w_r(x+\mathbb{N}_r)p(x+\mathbb{N}_r,t) - \sum_{r=1}^{R} w_r(x)p(x,t)\\ &=: \mathcal{M}p,\end{aligned}$$

a gain-loss discrete PDE in D dimensions for the probability.

Mesoscopic spatial kinetics

Not well-stirred

-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.



Diffusion

Not well-stirred

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.
-*For best consistency*, q_{kj} should be taken as the inverse of the mean first exit time. $\Longrightarrow q_{kj} \propto \sigma^2/h^2$, 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"

- 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 $\mathbf{x}$).

Hence when combining reactions with diffusions,

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

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-An *approximation*! Valid when

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

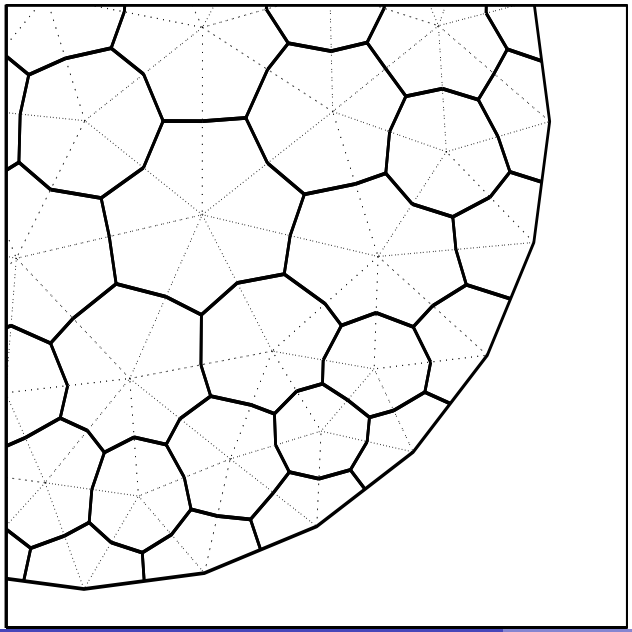
ρ the molecular radius, τ_Δ average molecular survival time.

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

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

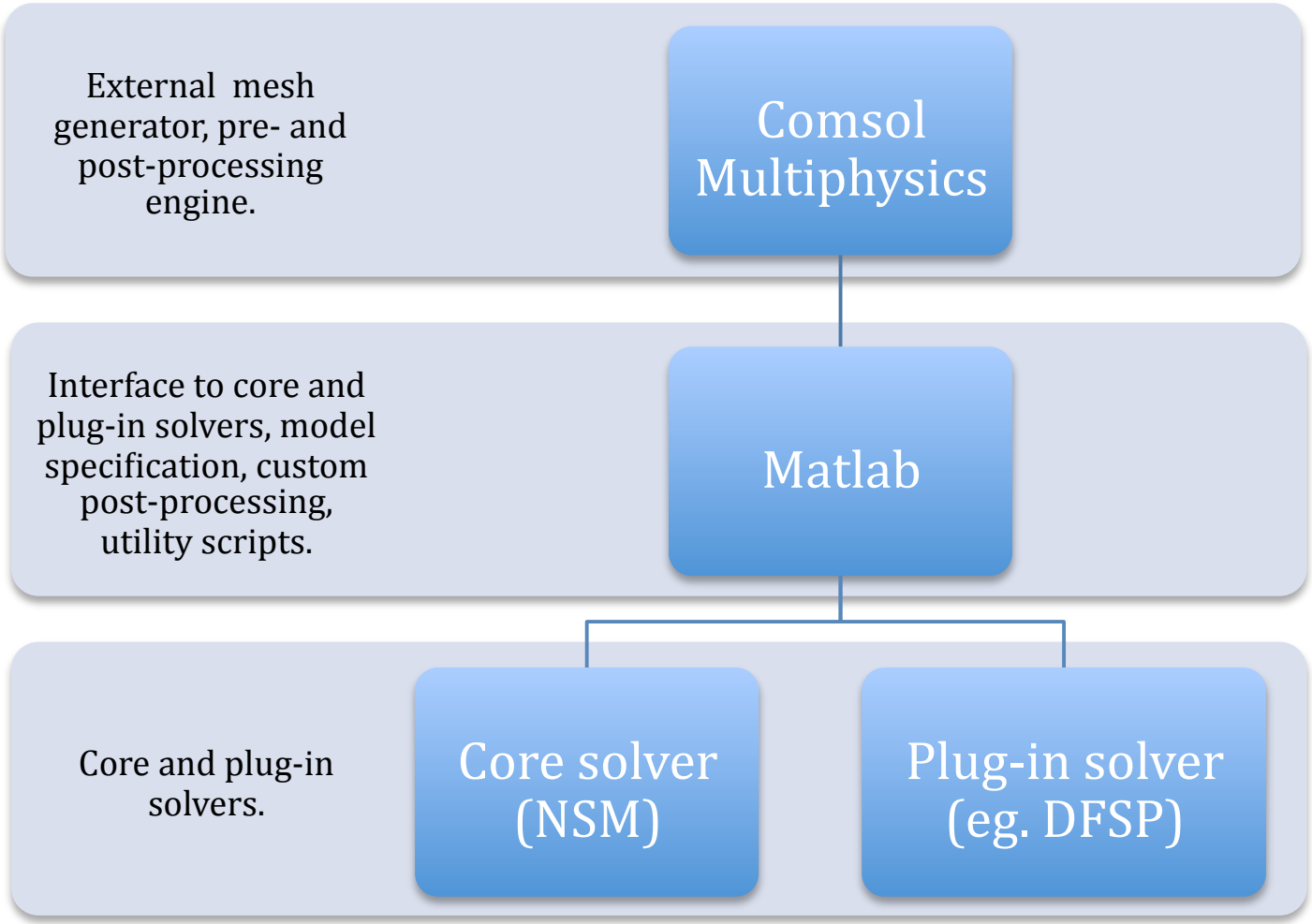
Can now obtain $\mathcal{D}$ from the numerical $\sigma^2/2\ D$.



- Assume point-wise convergence of the numerical discretization $\rightarrow$ diffusion PDE
- Then 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



www.urdme.org.

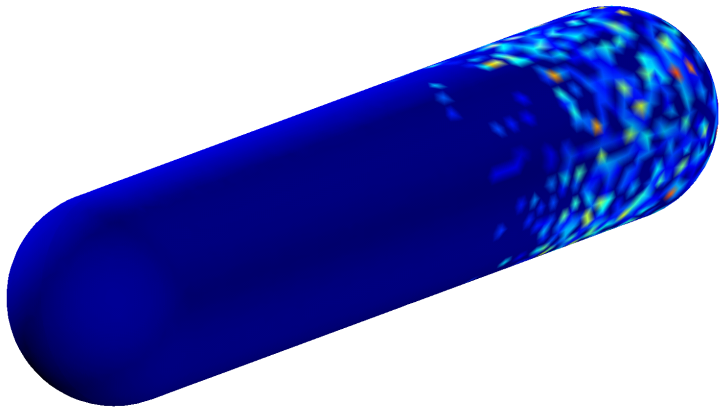
MinD oscillations

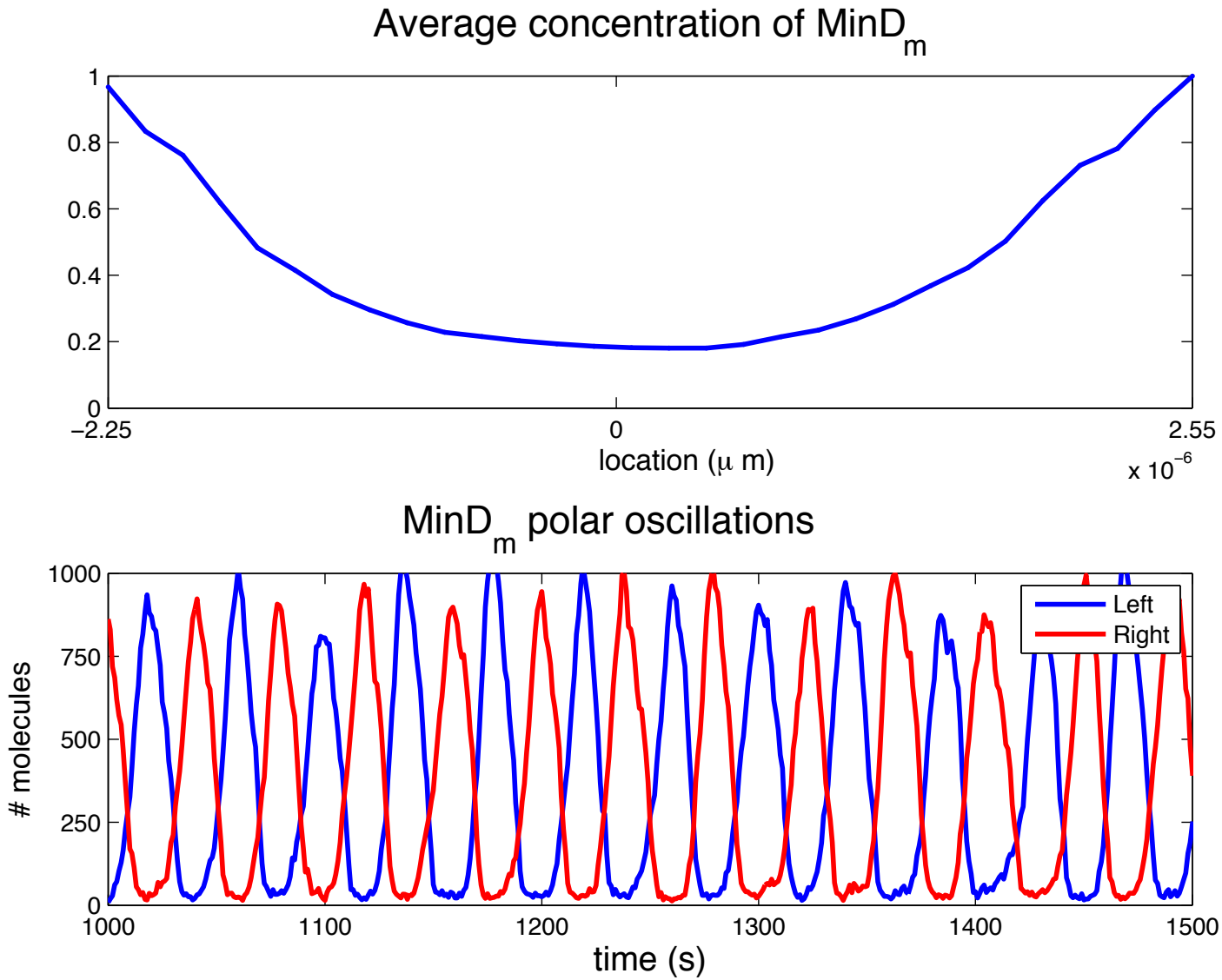
Oscillations of proteins involved in the cell division of *E. coli*:

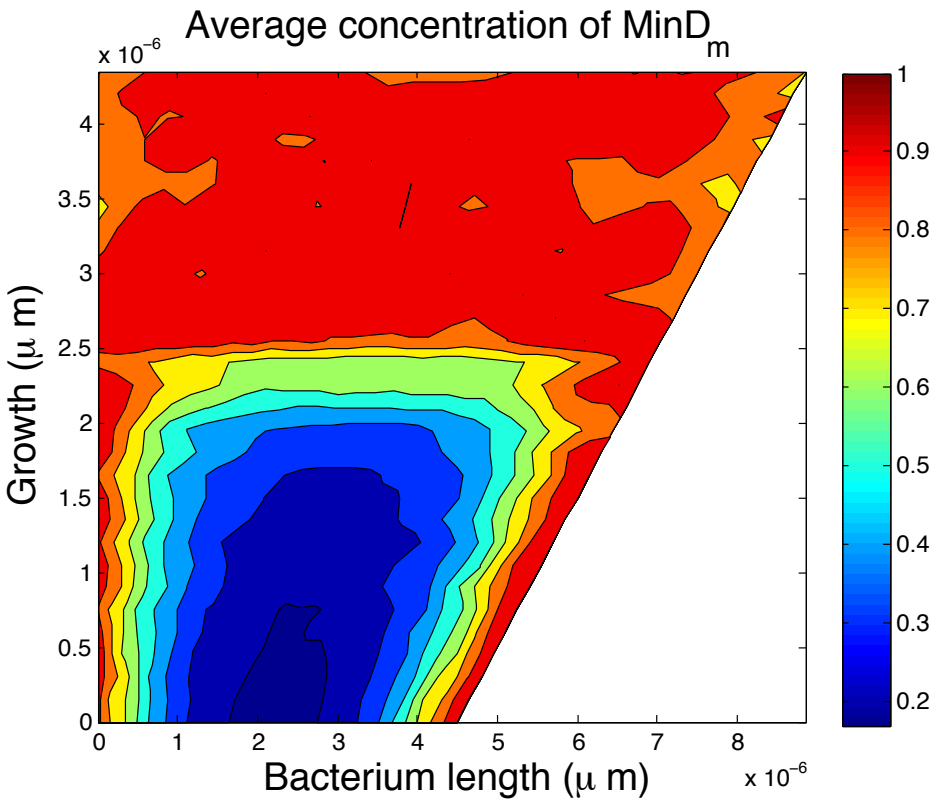
$$\text{MinD\_c\_atp} \xrightarrow{k_d} \text{MinD\_m} \qquad \text{MinD\_c\_atp} + \text{MinD\_m} \xrightarrow{k_{dD}} 2\text{MinD\_m}$$

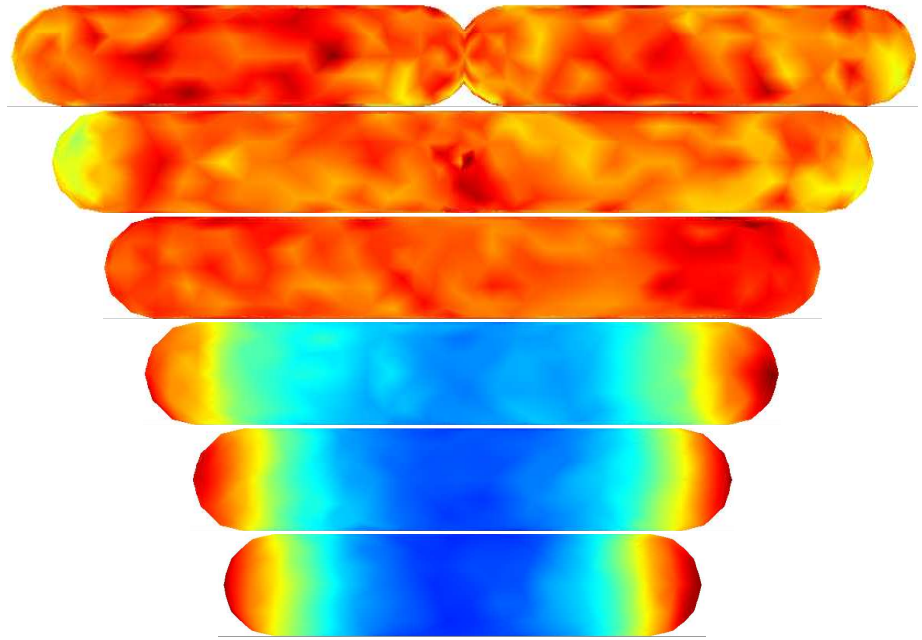
$$\text{Min\_e} + \text{MinD\_m} \xrightarrow{k_{de}} \text{MinDE} \qquad \text{MinDE} \xrightarrow{k_e} \text{MinD\_c\_adp} + \text{Min\_e}$$

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

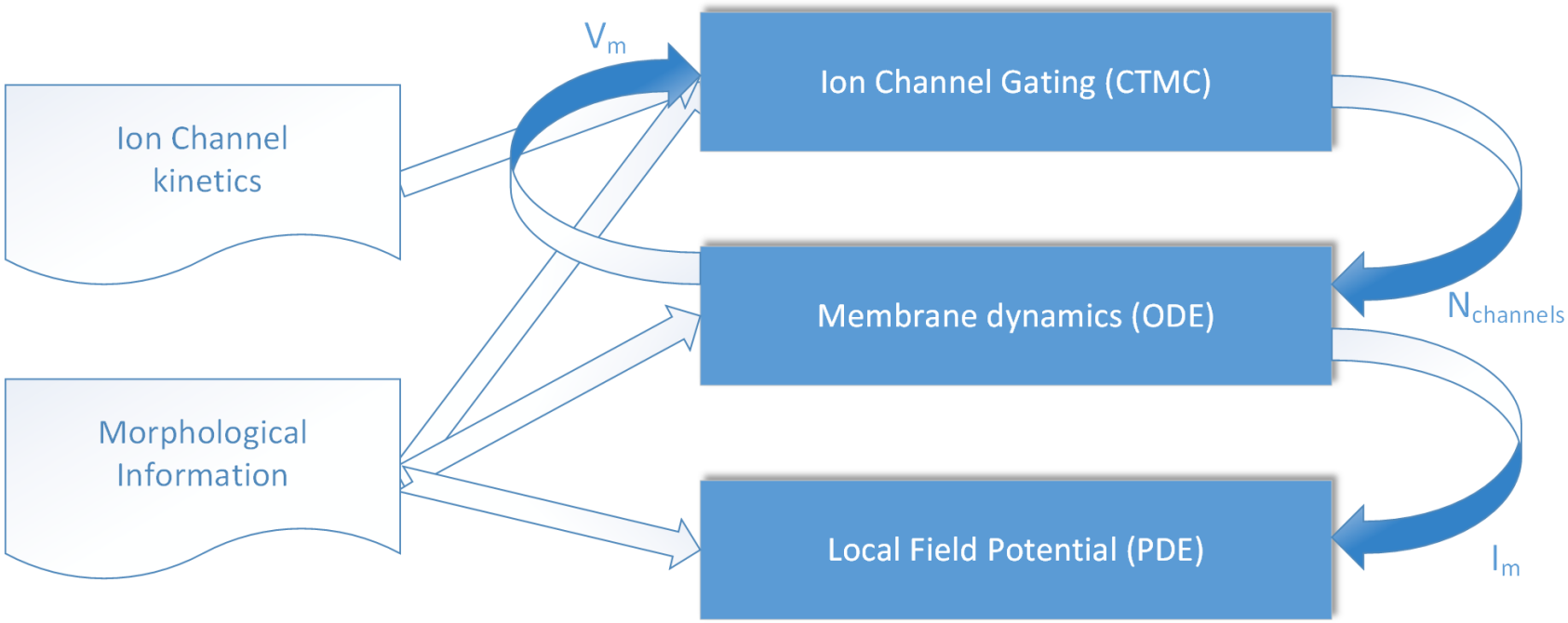



Average concentration of MinD m
1
0.8
0.6
0.4
0.2
0
−2.25
0
2.55
location (μ m)
x 10−6
MinD m polar oscillations
1000
750
500
250
0
molecules
1000
1100
1200
1300
1400
1500
time (s)
Left
Right


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



Application: multiscale neuronal model



Joint work: Stefan Engblom, Pavol Bauer, Emil Berwald

Bottom level

Ion channel gating

The gating process of ion channels can be mesoscopically described as

$$N_0 \underset{\beta_m(V_m)N_1}{\overset{3\alpha_m(V_m)N_o}{\rightleftharpoons}} N_1 \underset{2\beta_m(V_m)N_2}{\overset{2\alpha_m(V_m)N_1}{\rightleftharpoons}} N_2 \underset{3\beta_m(V_m)N_3}{\overset{\alpha_m(V_m)N_2}{\rightleftharpoons}} N_3,$$

again a *continuous-time Markov chain*. *Output:* N_3, the number of open gates.
For efficient model coupling we use *"tau-leaping"* - which is a consistent time discretization method (Euler method):

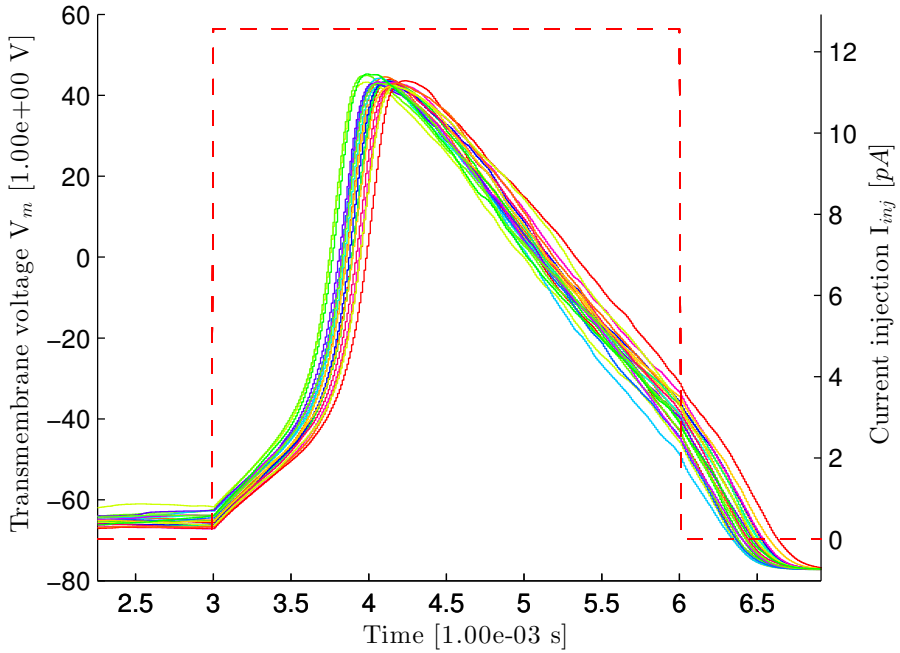
$$\mathbf{X}_{n+1} = \mathbf{X}_n - \sum_r \mathbb{N}_r P_r(w_r(\mathbf{X_n})\tau),$$

$\mathbf{X}$ state variable, P_r Poisson random variable, w_r propensity, and τ timestep.

Middle level

Membrane dynamics

- Morphological information extracted using the *Trees toolbox*
- System of current-balance and cable equations is solved for each time step τ



$$I_m = c_m \frac{dV_m}{dt} + \sum_{i \in C_v} \gamma_i N_3^i(t)[V_m(t) - E_i]$$

Top level

Maxwell's equations, potential form

We seek the *electric field intensity* $\mathbf{E}$ in terms of the *electric scalar potential* V,

$$\mathbf{E} = -\nabla V.$$

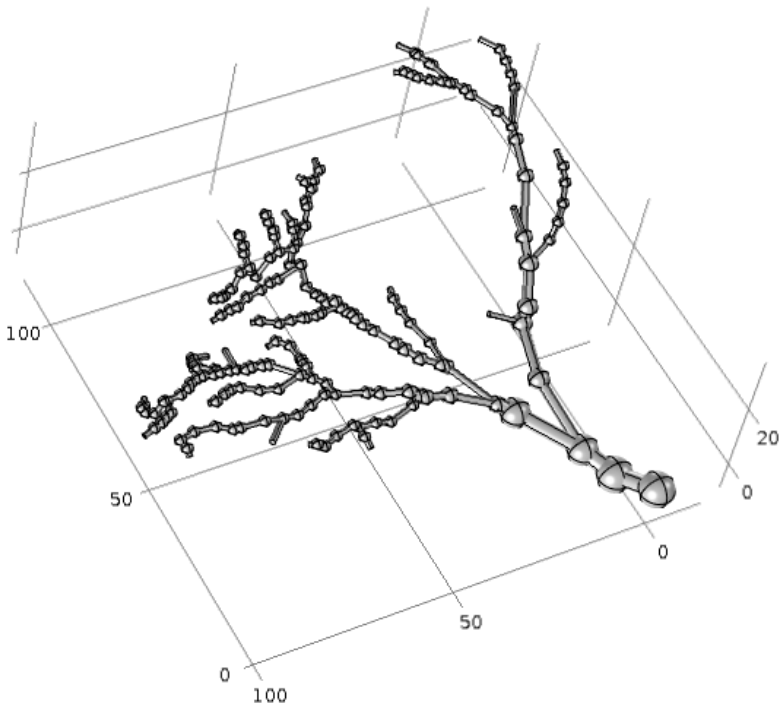
Trans-membrane current I_m is scaled with the compartement surface area and coupled as a current source,

$$-\nabla \cdot \left(\sigma \nabla V + \varepsilon_0 \varepsilon_r \frac{\partial}{\partial t} \nabla V \right) = \frac{1}{\Omega_c} I_m,$$

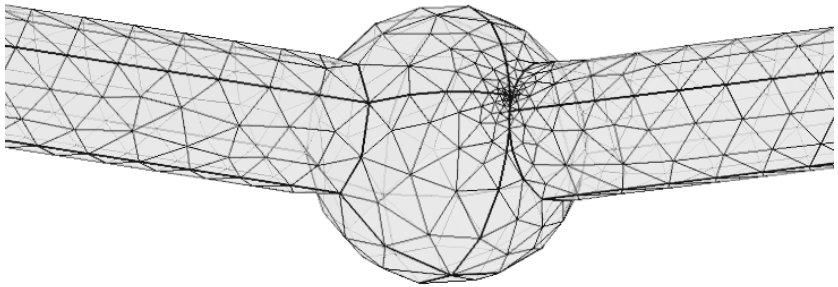
with conductivity σ and permittivity ε. Finally, the time dependent potential V is solved via finite element methods.

Top level

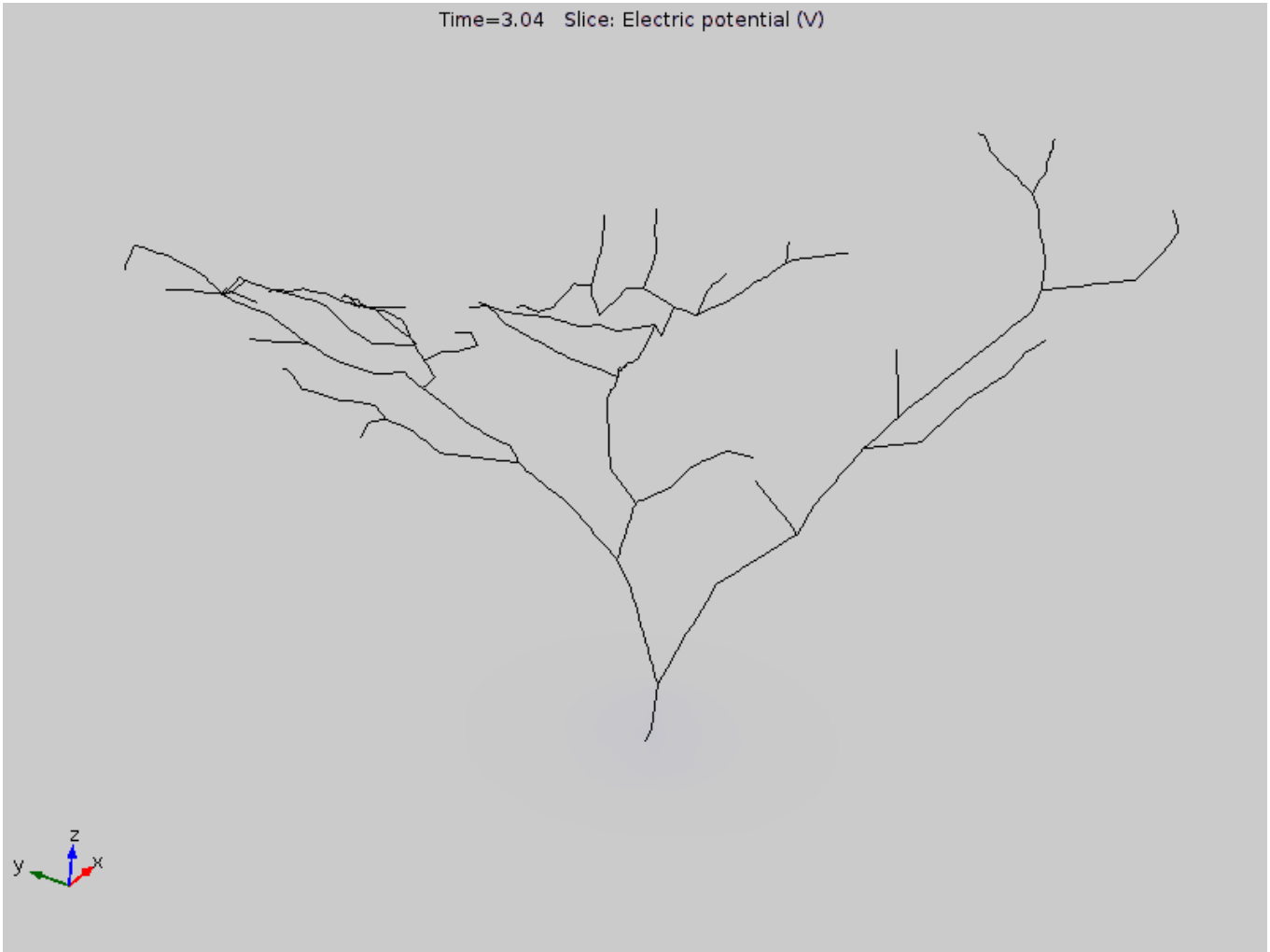
Geometry coupling



- Bottom and middle level: compartments (cylindrical volumes)
- Coupling with PDE requires a mesh
- Approximation with curves much more efficient than volumetric elements



Coupled solution



Summary & Conclusions

- Stochastic mesoscopic modeling in chemical kinetics can combine *simplicity* with *accuracy*
- Spatial modeling is also possible and often necessary, consistency through numerical methods
- Free software URDME (`www.urdme.org`), organized in loosely coupled layers, easy to extend and modify
- Sample neuronal application: coupling very different types of models was possible thanks to this software architecture

Thank you for listening

Input and exchange of ideas is very much welcome!