ETH zürich

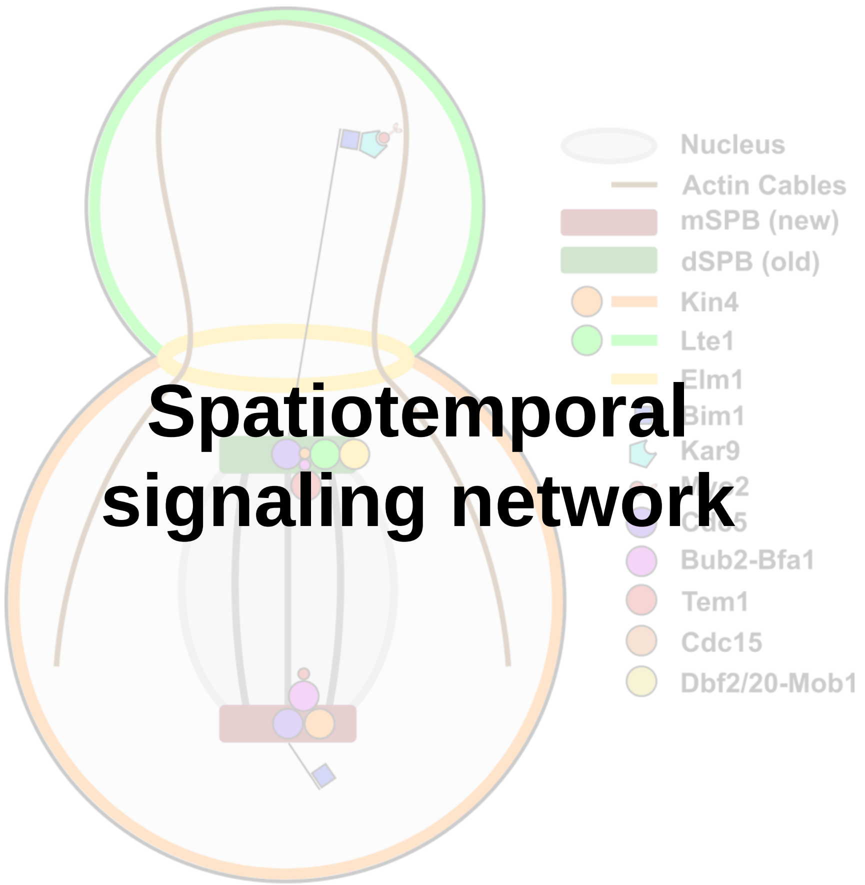
Efficiently Solving the Stochastic Reaction-Diffusion Master Equation in C++ with a COMSOL Interface

Lukas Widmer
Computational Biology & Bioinformatics MSc

Computational Systems Biology Group
D-BSSE, Basel, Switzerland

csb

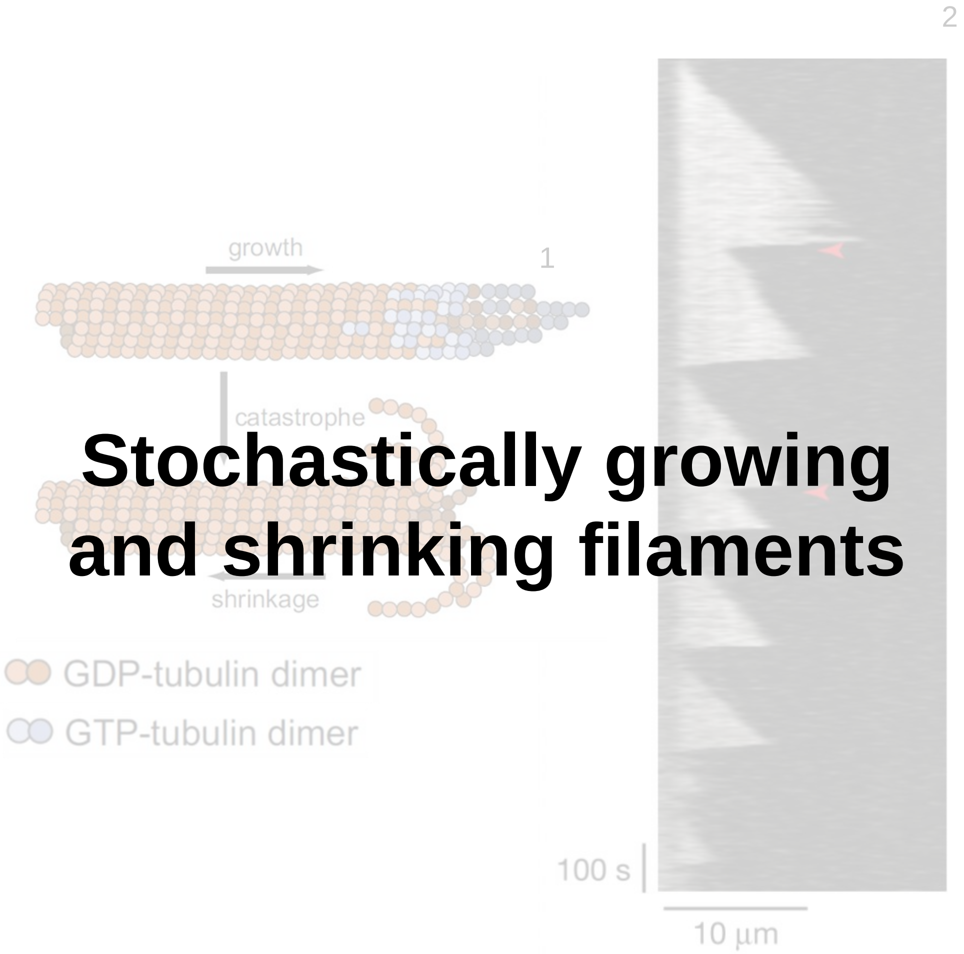
How to model yeast signaling influencing microtubule dynamics?



Spatiotemporal signaling network

+

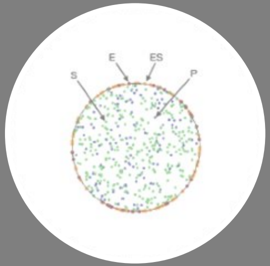
Stochastically growing and shrinking filaments



1. Bowne-Anderson, H., Zanic, M., Kauer, M. & Howard, J. Microtubule dynamic instability: a new model with coupled GTP hydrolysis and multistep catastrophe. *Bioessays* **35,** 452–61 (2013).
2. Aumeier, C. *et al.* Self-repair promotes microtubule rescue. *Nat. Cell Biol.* **18,** (2016)..

Numerical simulation methods for biochemical reaction-diffusion problems in biological cells

Stochastic | **Deterministic**

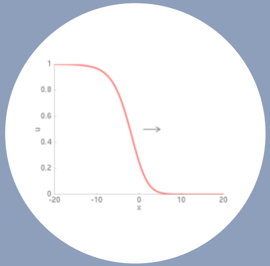


Smoluchowski Dynamics: Stochastic

Tracks a particle for each molecule

Reaction-Diffusion Master Equation (RDME)

Tracks # molecules in subvolume



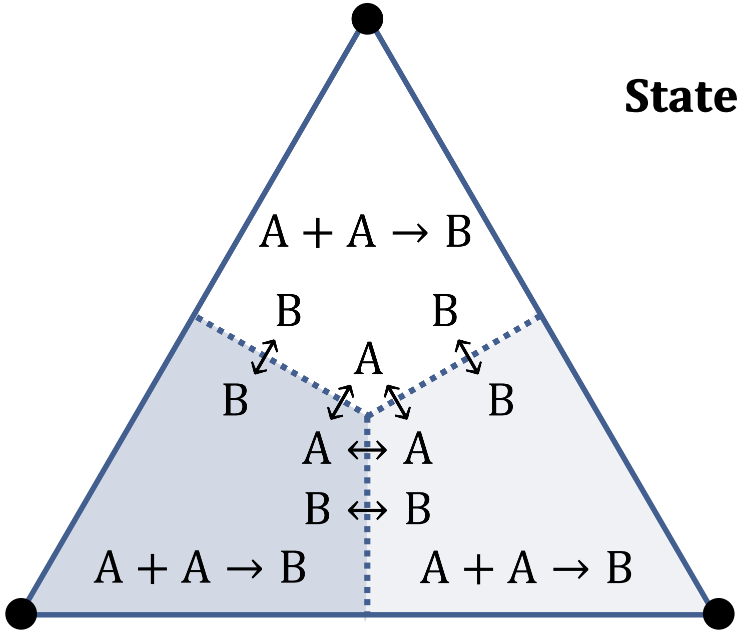
Continuum Methods: Deterministic

Tracks concentration on mesh

Off-Lattice ⟷ Discretized (Mesh)

Smoldyn | COMSOL + RDMEcpp | COMSOL

Reaction-Diffusion Master Equation 101



$$\textbf{State } \boldsymbol{x} = \begin{pmatrix} \#A \\ \#B \\ \begin{pmatrix} \#A \\ \#B \end{pmatrix} \\ \#A \\ \#B \end{pmatrix}$$

- Discretized reaction subvolumes
- Diffusion between neighboring ones

- Describes the probability of the state $p(\boldsymbol{x}, t)$ given stochastic reaction and diffusion events

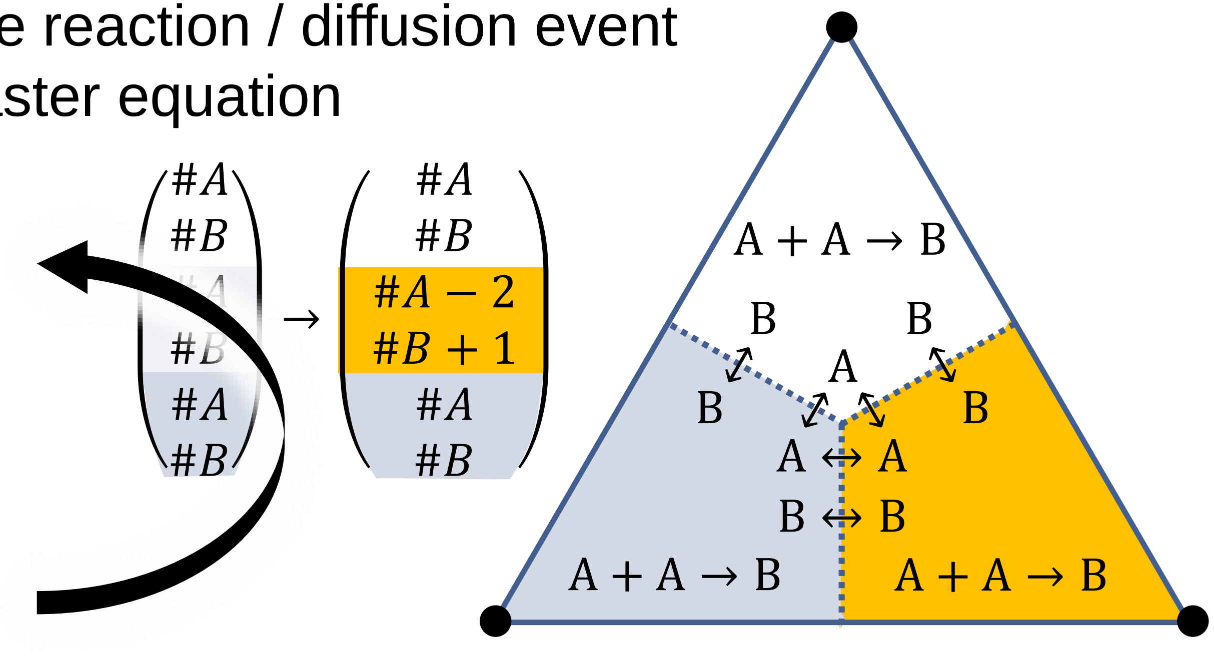
- Realistic models cannot be solved analytically → sampling

csb

Simulating trajectories from the reaction-diffusion master equation with the Next Subvolume Method

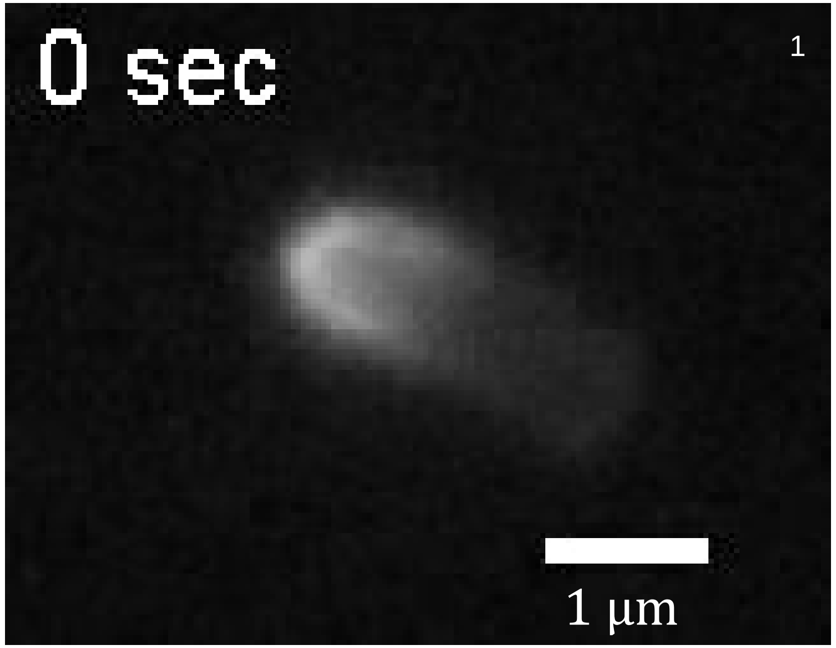
1. Compute next occurrence of every possible reaction / diffusion event by sampling from the reaction-diffusion master equation

2. Determine subvolume of earliest event
3. Determine if reaction or diffusion event
4. Execute event / update state
5. Update dependent events, simulation time
6. Goto 2, until simulation end time reached

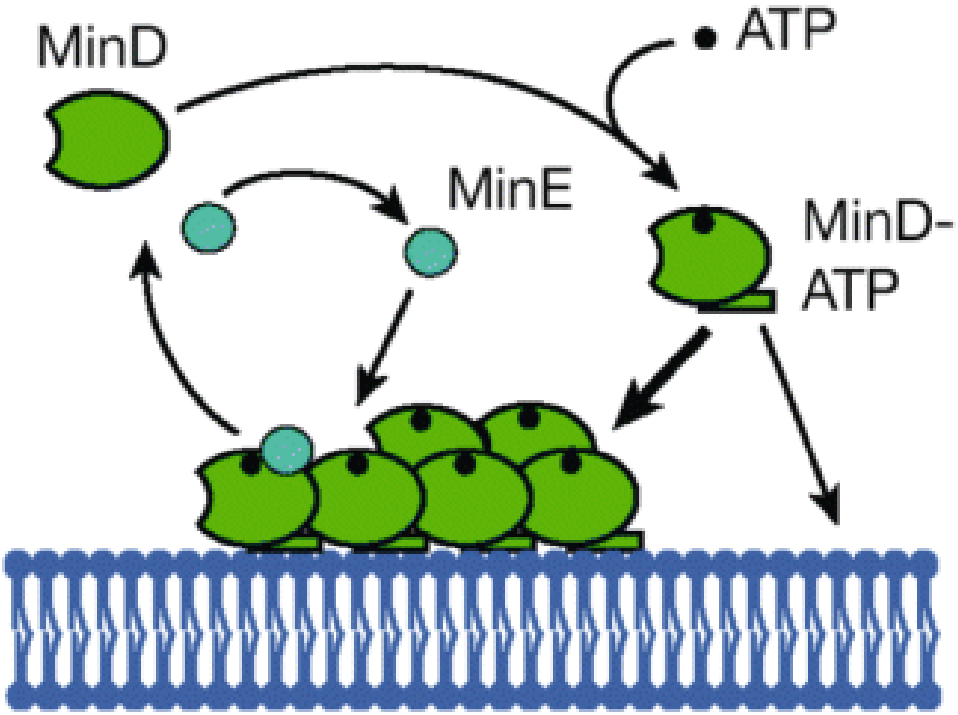


Example: modelling MinD oscillations in *E. coli* cell division

- Biological observation: MinD oscillations preceding cell division



- Biochemical Model

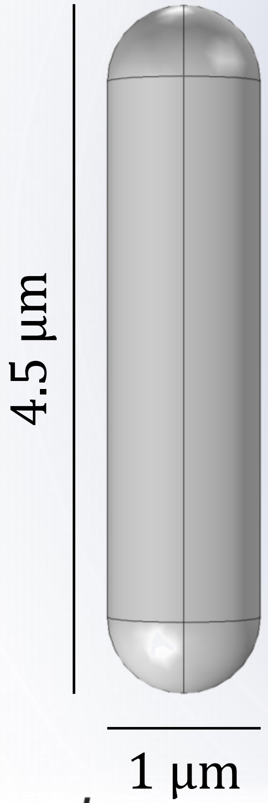


1. Männik, J. *et al.* Robustness and accuracy of cell division in Escherichia coli in diverse cell shapes. *Proc. Natl. Acad. Sci. U. S. A.* **109,** 6957–62 (2012).
2. Kruse, K., Howard, M. & Margolin, W. An experimentalist's guide to computational modelling of the Min system. *Mol. Microbiol.* **63,** 1279–84 (2007).

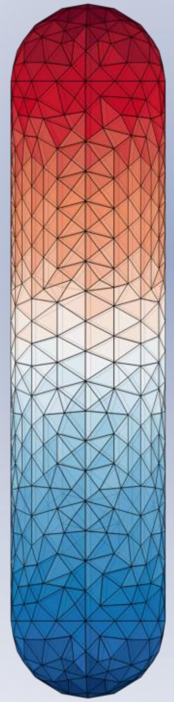
Setting up the *E. coli* MinD oscillation model using RDMEcpp

COMSOL

1. Geometry Specification



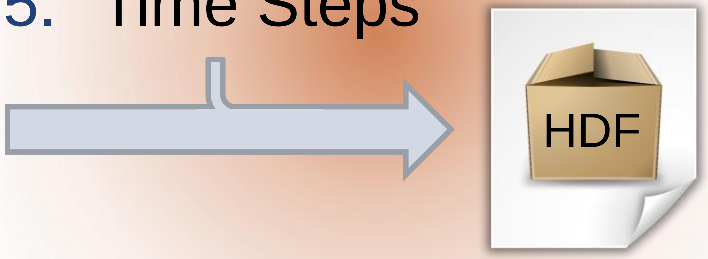
2. Meshing



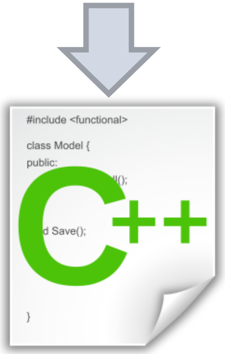
3. Matrix Assembly
   - Dual Mesh Element Volume
     - (Row-sum lumped) Damping Matrix
   - Diffusion Coefficients

MATLAB

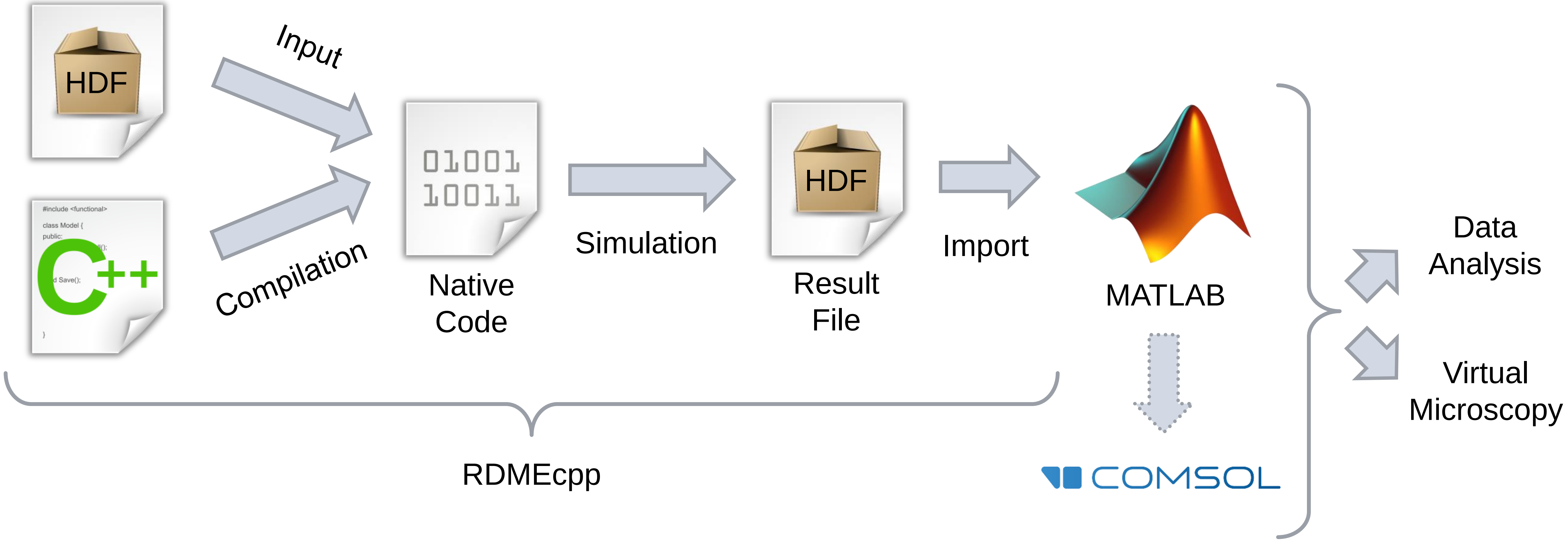
4. Initial State Definition
5. Time Steps



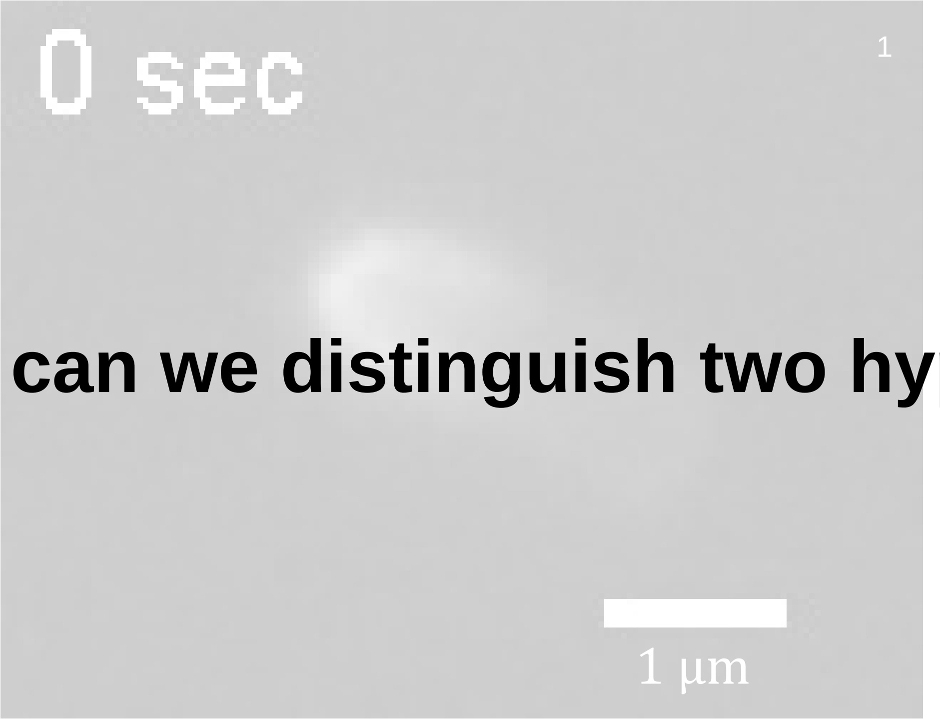
6. Reaction Propensity Specification



Simulating the *E. coli* MinD oscillation model using RDMEcpp

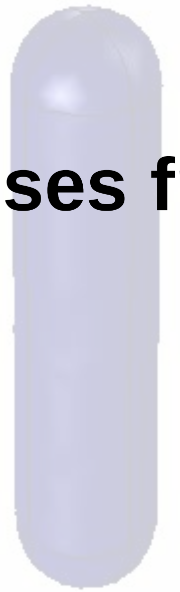


MinD oscillations in *E. coli* cell division – observation & model



$[\mathrm{MinD}_{\mathrm{membrane}}](t, \boldsymbol{x})$ $\overline{[\mathrm{MinD}_{\mathrm{membrane}}]}(\boldsymbol{x})$

$t = 0 \ldots 900s$



Explains location of cell division!

Q: can we distinguish two hypotheses from our microscopy data?

1. Männik, J. *et al.* Robustness and accuracy of cell division in Escherichia coli in diverse cell shapes. *Proc. Natl. Acad. Sci. U. S. A.* **109,** 6957–62 (2012).

Virtual Microscopy: the forward problem in the modeling cycle

Forward Problem
integrating
a priori knowledge

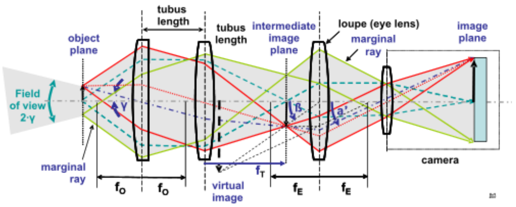

[1]

Inverse Problem
aiming at reconstructing ***geometry*** and ***photometry*** from an **observed image**

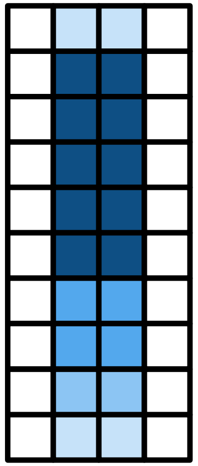
1. Hale, C. a., Meinhardt, H. & De Boer, P. a J.
Dynamic localization cycle of the cell division regulator MinE in Escherichia coli. *EMBO J.* **20,** 1563–1572 (2001).

Virtual Microscope: a physically-based model of fluorescence microscopy

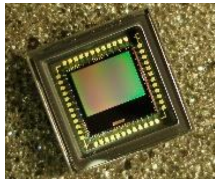
Object Space



Optics & Sampling



Pixel Space



Noise & Quantization

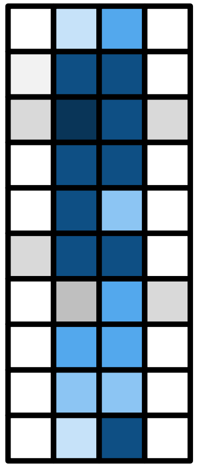


Image Space

Geometry → Subset of space where light sources are restricted

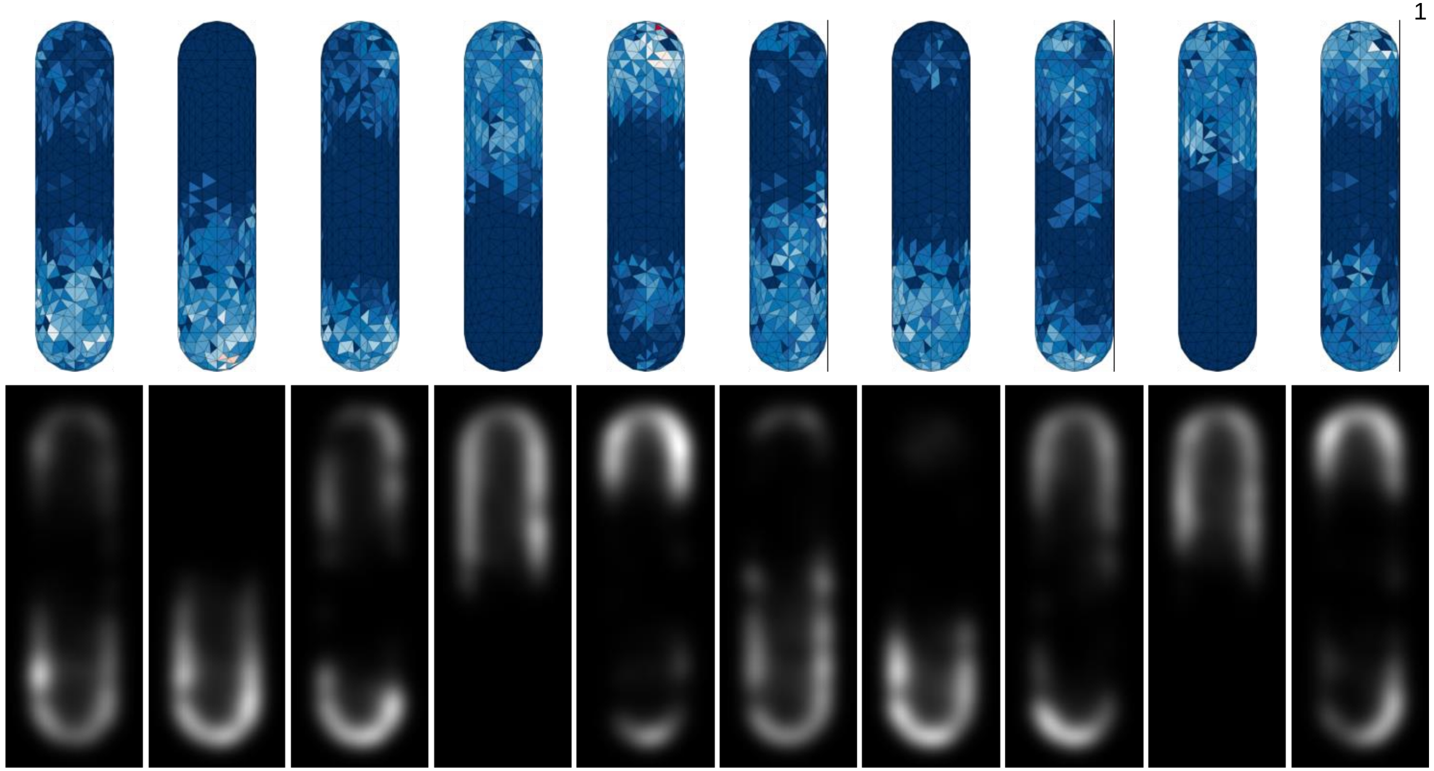
\+

Photometry → Distribution in space & time of light source intensities

Example: Virtual imaging of MinD oscillations in *E. coli*

Object Space

Virtual[1] Microscope



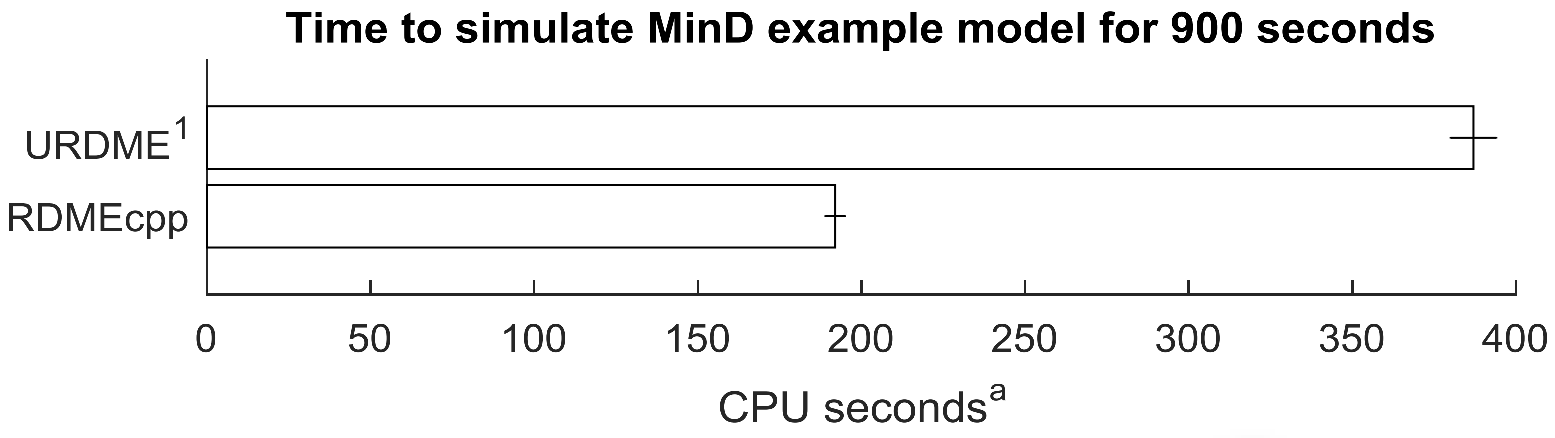
Acquisition start time (seconds)

Real[2] Microscope

1. Samuylov, D. K., **Widmer, L. A.**, Szekely, G. & Paul, G.
Mapping Complex Spatio-Temporal Models to Image Space: The Virtual Microscope. *ISBI 2015* (2015).
2. Hale, C. a., Meinhardt, H. & De Boer, P. a J.
Dynamic localization cycle of the cell division regulator MinE in Escherichia coli. *EMBO J.* **20,** 1563–1572 (2001).

RDMEcpp – Summary

- Factor two speedup[a] over the state-of-the-art C-solver, URDME[1]

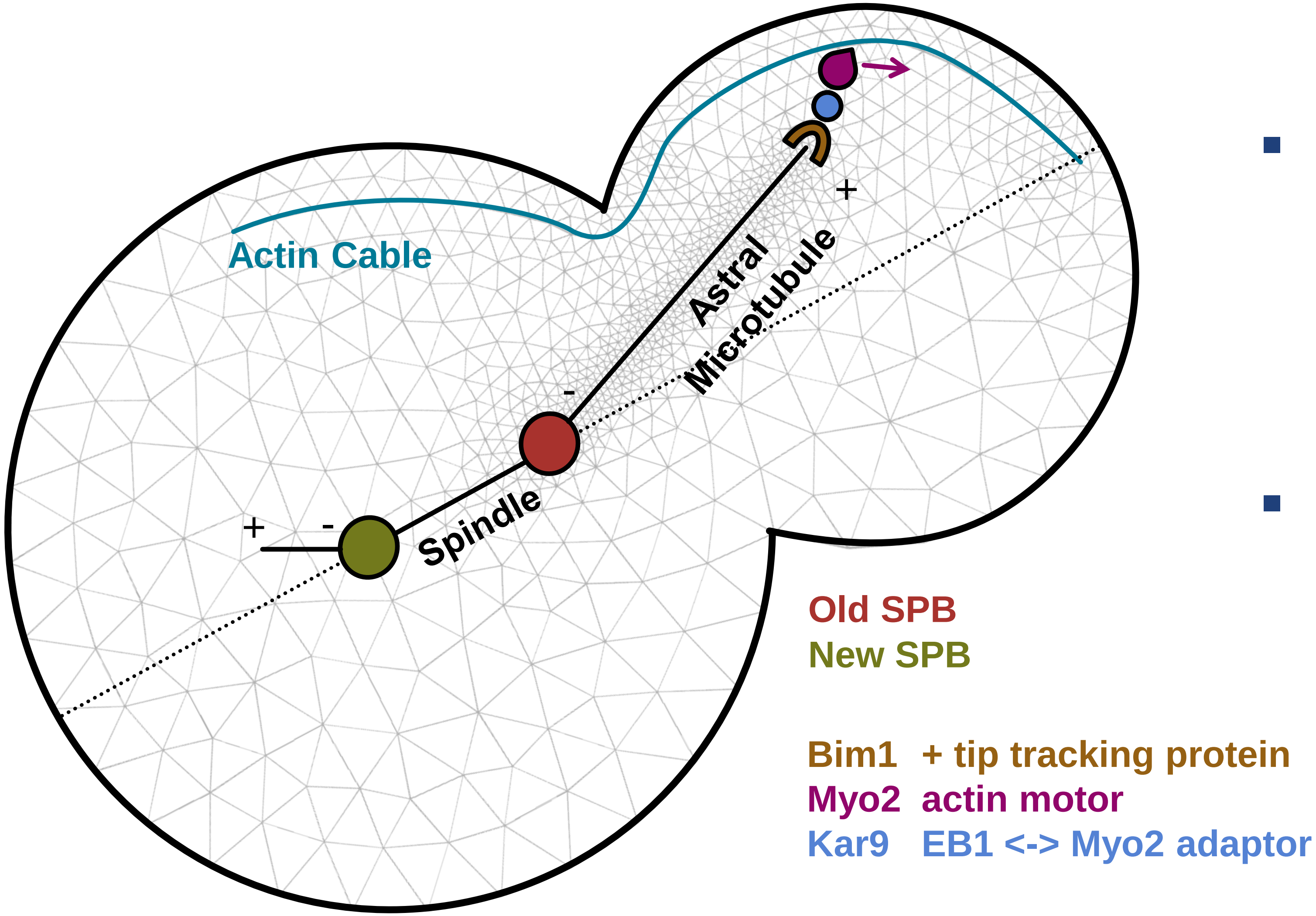


- ✓ Currently the only cross-platform RDME solver
  - ✓ In contrast to [1], simulations can be shared with users that do not have COMSOL or MATLAB
  - ✓ Only solver that works with COMSOL 5.2a
- ✓ Can be used together with our virtual microscope, e.g. for experimental design

1. Drawert, B., Engblom, S. & Hellander, A. URDME: a modular framework for stochastic simulation of reaction-transport processes in complex geometries. *BMC Syst. Biol.* **6,** 76 (2012).

a. Thinkpad W520 w/ Intel i7-2720QM CPU, 16 GB RAM

Ongoing Work



- Building a model with embedded microtubules that captures dynamics during cell division
- Hybrid deterministic / stochastic reaction-diffusion with the odeSD[1] ODE solver

csb

1. Gonnet, P., Dimopoulos, S., **Widmer, L. A.** & Stelling, J. A specialized ODE integrator for the efficient computation of parameter sensitivities. *BMC Systems Biology,* **6,** 13 (2012).

Thanks go to…

Gregory
Paul

TubeX
Multiscale Biophysics of
Microtubule Dynamics

CMake

HDF

SystemsX.ch
The Swiss Initiative in Systems Biology

SIB
Swiss Institute of
Bioinformatics

LSGSZ
Systems
Biology

… and you for your attention!

Poster #223