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

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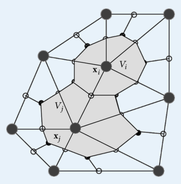
In budding yeast, we model stochastic microtubule dynamics and their regulation in 2D- and 3D geometries created with COMSOL. Our C++ simulation engine improves on state-of-the-art in performance. Its results can be used for virtual microscopy and experimental design.

Stochastic Reaction-Diffusion Modeling

We use models based on the *reaction-diffusion master equation (RDME)* to combine stochastic microtubule dynamics with reacting & diffusing regulatory and signaling molecules:

Domain Discretization



In the RDME, reactions and diffusion events are defined on the *voxels* spanned by the *dual mesh.*

$j \in \{1, \dots, K\}$: voxel in dual mesh

V_j: Volume of voxel j

System State

$i \in \{1, \dots, N\}$: chemical species

x_{ij}: # molecules of chemical species i in voxel j

$\boldsymbol{x}(t) \in \mathbb{N}_{\geq 0}^{N \times K}$: state (of all species in all voxels) at time t

Reactions & Diffusion

$r \in \{1, \dots, R\}$: reaction

$\boldsymbol{\nu}_r$: change vector of reaction r

$\boldsymbol{\eta}_{kj}$: change vector of diffusion from k to j

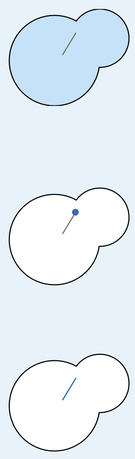
Master Equation of the Probability Density Function

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

$$\mathcal{M}p(\boldsymbol{x},t) = \sum_{j=1}^{K}\sum_{r=1}^{R} a_j(\boldsymbol{x}_{\cdot j} - \boldsymbol{\nu}_r)\, p(\boldsymbol{x}_{\cdot 1}, \dots, \boldsymbol{x}_{\cdot j} - \boldsymbol{\nu}_r, \dots, \boldsymbol{x}_{\cdot K}, t) - \sum_{j=1}^{K}\sum_{r=1}^{R} a_j(\boldsymbol{x}_{\cdot j})\, p(\boldsymbol{x},t)$$

$$\mathcal{D}p(\boldsymbol{x},t) = \sum_{i=1}^{N}\sum_{j=1}^{K}\sum_{k=1}^{K} b_{kj}(\boldsymbol{x}_{\cdot j} - \boldsymbol{\eta}_r) p(\boldsymbol{x}_{\cdot 1}, \dots, \boldsymbol{x}_{\cdot j} - \boldsymbol{\eta}_{kj}, \dots, \boldsymbol{x}_{\cdot K}, t) - \sum_{i=1}^{N}\sum_{j=1}^{K}\sum_{k=1}^{K} b_{kj}(\boldsymbol{x}_{i\cdot})\, p(\boldsymbol{x},t)$$

Reaction-Diffusion Model on Dynamic Subdomains (Microtubules)



Cytosol

GTP- to GDP-tubulin

Diffusion

Signaling & Regulation

Microtubule Plus-Tip

GTP-tubulin attachment

GTP- and GDP-tubulin dissociation

Whole Microtubule

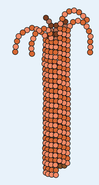
GTP-tubulin -> GDP-tubulin (hydrolysis)

Rescue

Occurs as a result of regulatory microtubule-associated proteins *in vivo*.

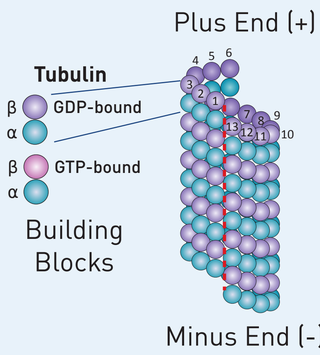
Catastrophe

When 3/13 protofilaments GDP-exposed[3]



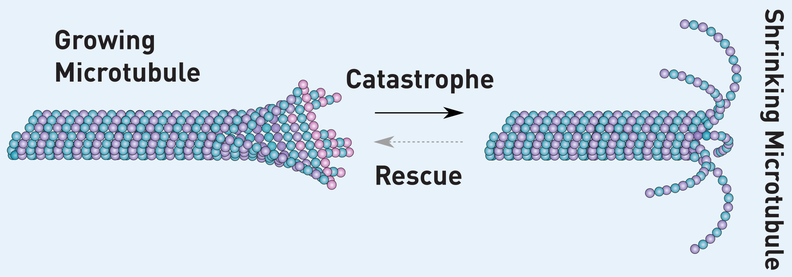
Microtubule Structure and Function

Microtubule Structure



A single microtubule consists of 13 *protofilaments*.

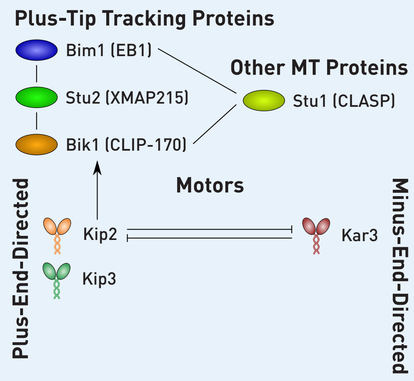
Microtubule Dynamics

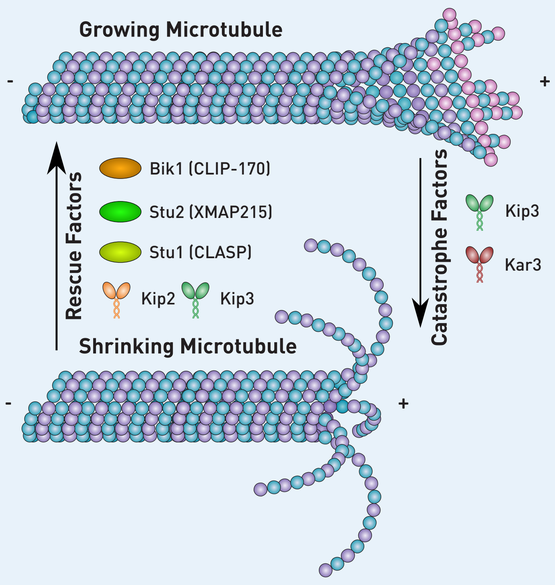


GTP-tubulin subunits attach and subsequently hydrolyze to GDP-tubulin. Once GDP-tubulin reaches the growing plus tip, the microtubule rapidly starts depolymerizing, giving rise to a highly dynamic system.

Microtubule Interaction with Diffusing Regulatory Molecules

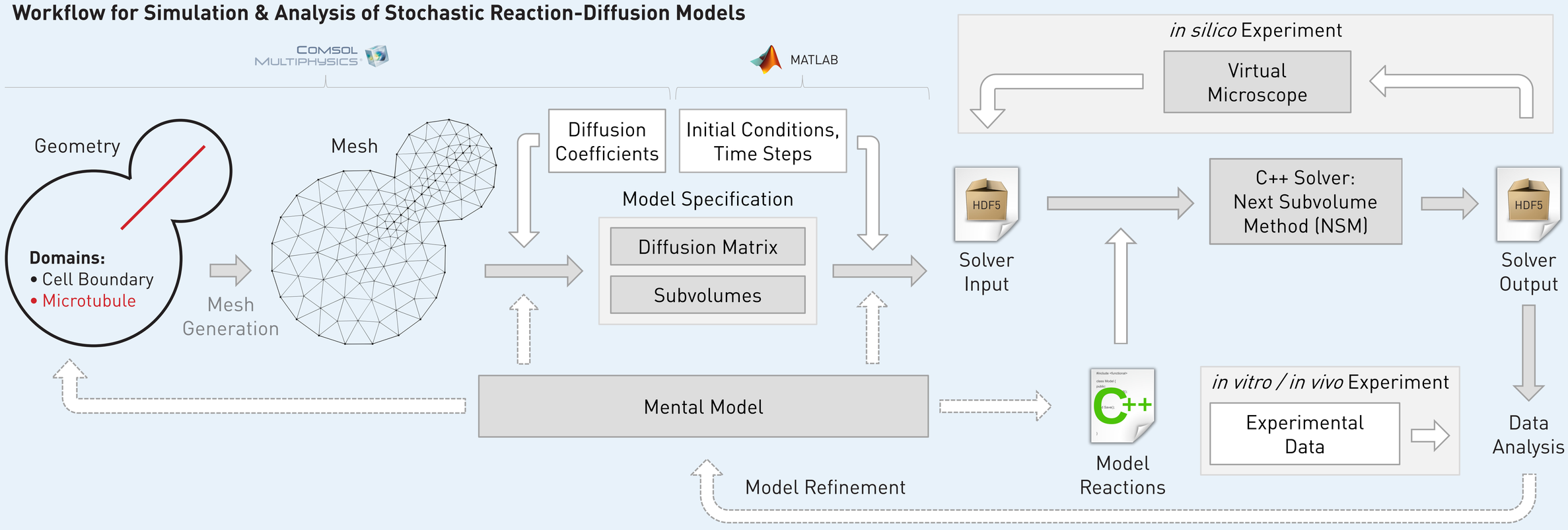
We are currently step-by-step adding regulatory molecules that modify microtubule dynamics in budding yeast cells, testing different hypotheses about their interaction network:





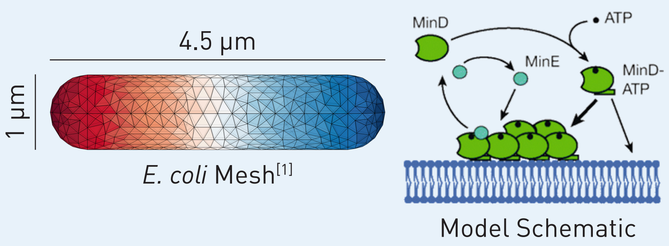
Modeling & Simulation Framework

Workflow for Simulation & Analysis of Stochastic Reaction-Diffusion Models

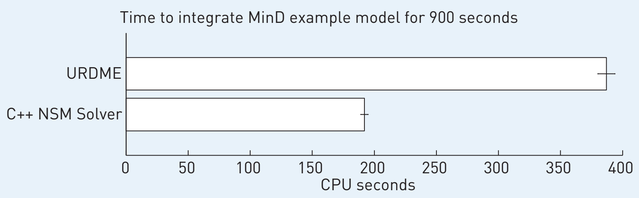


Performance Evaluation: MinD Oscillations in *E. coli*

We tested our C++ Next Subvolume Method (NSM) solver against the state-of-the-art C solver URDME[1] on the well-known MinD model from *E. coli*:



We achieved a 2-fold performance increase:



in vivo, we often image at the resolution limit, where distinguishing hypotheses may not be trivial.

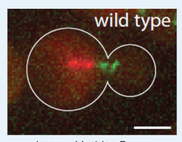
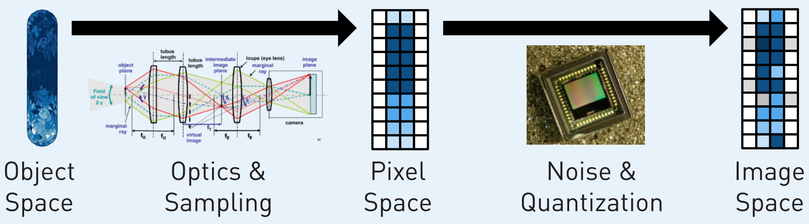


Image: Mathias Bayer

To accurately simulate a fluorescence microscopy experiment *in silico*, our collaborators and us developed[2] a method to enable physically-based microscopy of our simulation results:



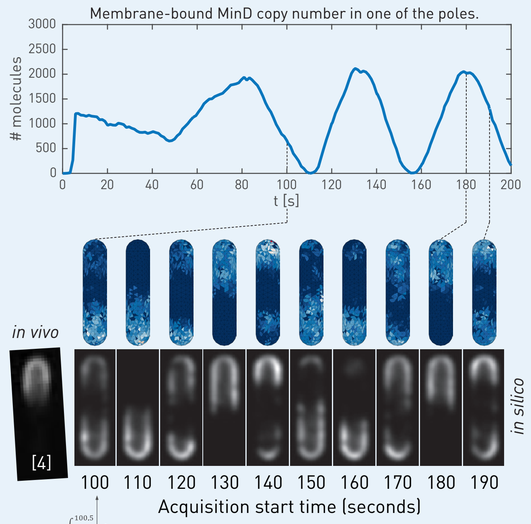
Usage Scenarios

in silico experiments, experimental design

Reconstruction of Geometry / Photometry

Benchmarking image analysis pipelines

Example: GFP-MinD Timelapse



State samples are recorded at the acquisition times of the virtual microscope (T_{int} = .5s)

Comparison to *in vivo* Data by Virtual Microscopy

B. Drawert, S. Engblom, and A. Hellander, BMC Systems Biology 6, 76 (2012). [1]

D. K. Samuylov, L. A. Widmer, G. Székely, and G. Paul, ISBI (2015). [2]

[3] H. Bowne-Anderson et al, Bioessays 35, 452–61 (2013).

[4] C. A. Hale *et al*, EMBO J. 20, 1563–1572 (2001).

Excerpt from the Proceedings of the 2016 COMSOL Conference in Munich