Stochastic Simulation at Your Service

Linda Petzold
University of California Santa Barbara

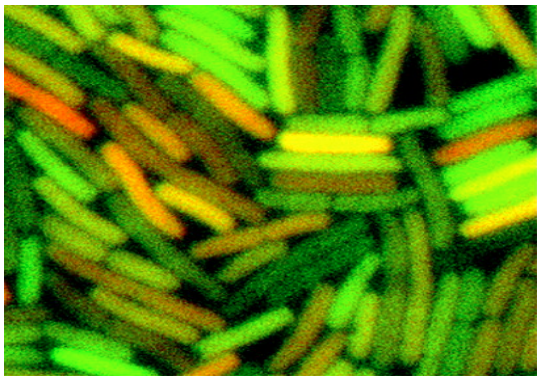
Outline

- Stochastic effects in biological systems
- Brief review of discrete stochastic simulation for well-mixed systems
- StochKit2 software for well-mixed systems
- Spatial stochasticity in biological systems
- Spatial stochastic simulation
- PyURDME
- StochSS
- Future plans

Stochasticity in Biochemical Systems

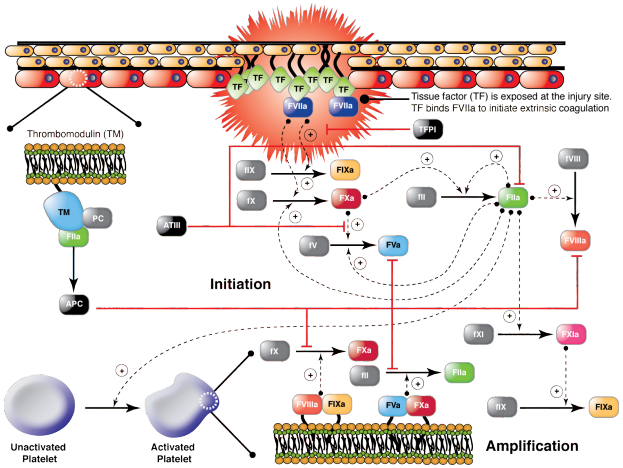
Small populations of key chemical species give rise to stochastic behavior

Intrinsic stochasticity revealed by experiment



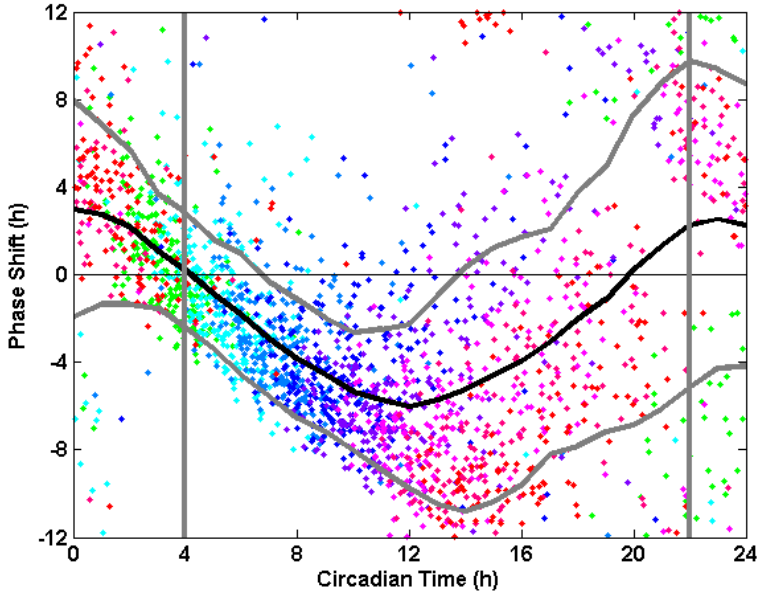
Elowitz M B et al. Science 2002;297:1183-1186
©2002 by AAAS

Coagulation cascade



Stochastic Effects

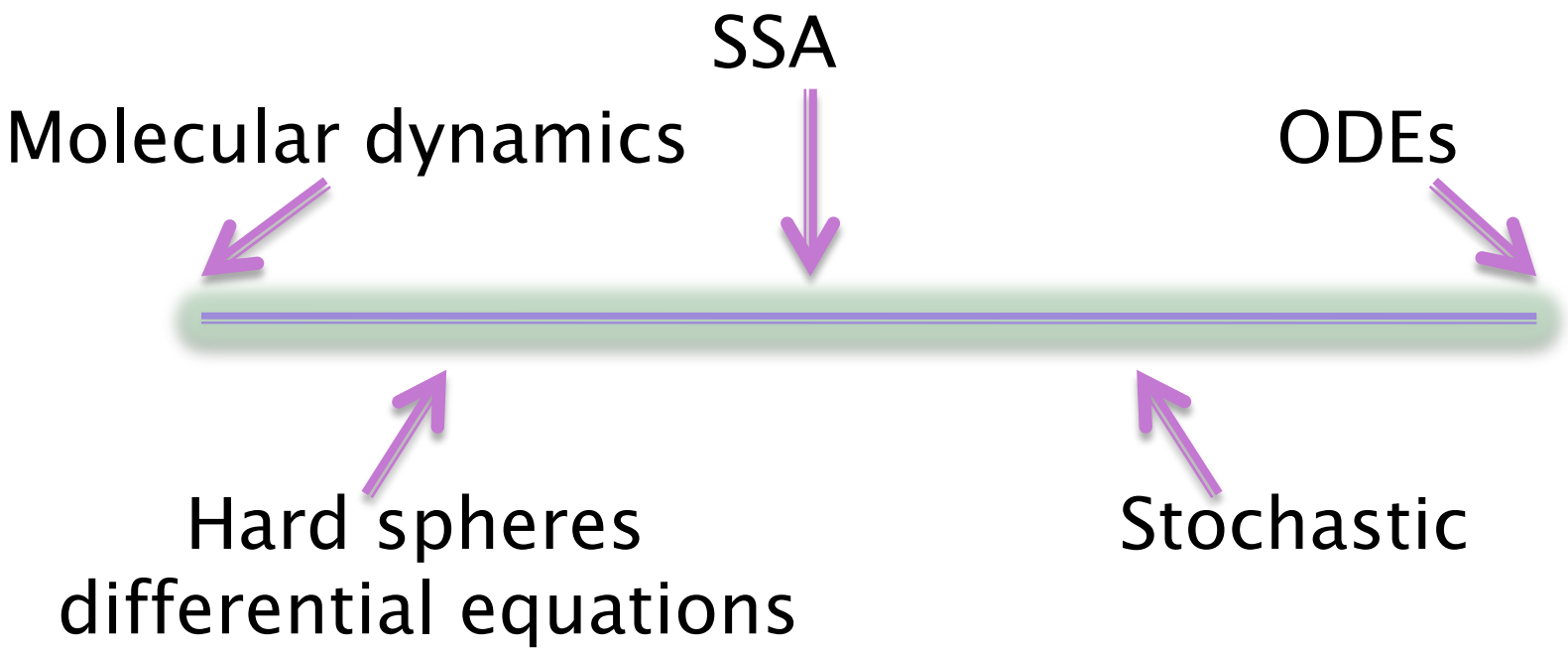
Circadian rhythm:
phase response distribution



An et al., PNAS 2013

Extinction

Spectrum of chemical reaction simulation regimes



Discrete Stochastic Simulation

- Stochastic Simulation Algorithm (SSA) for well-mixed, chemically reacting systems *(Gillespie, 1976)*
- Virtually fire each reaction event according to its propensity (probability)

$$A + B \xrightarrow{c} C + D$$

- A large ensemble of these simulations must be computed to estimate the pdfs with even modest accuracy

Properties of Discrete Stochastic Models

- Stochastic (mass-action) model converges to the corresponding deterministic model, in the thermodynamic limit
- There is often no need to include non-physical terms such as highly nonlinear Hill kinetics or delays, to explain experimental results
- Stochastic model captures the intrinsic variability in system response – Important for coupled models and medical applications

Algorithms for Discrete Stochastic Simulation of Well-Mixed Chemical Systems

- Fast formulations of SSA
  - *Next Reaction method (Gibson & Bruck, 2000), Optimized Direct Method (Li & Petzold, 2004), Sorting Direct Method (McCollumna et al., 2004), Logarithmic Direct Method (Li & Petzold, 2006), Constant Time Method (Slepoy et al., 2008), SSA on GPU (Li & Petzold, 2009)*
- Tau leaping *(Gillespie, 2001)*
  - *Implicit (Rathinam et al., 2003), R-leaping (Auger et al., 2006), adaptive stepsize selection and preservation of non-negativity (Cao et al. 2006), unbiased post-leap rejection (Anderson 2008)*
- Hybrid SSA/ODE
  - *(Haseltine & Rawlings, 2002), (Mattheyses, Kiehl & Simmons, 2002), (Puchalka & Kierzek, 2004), (Salis & Kaznessis, 2005)*
- Slow scale/multiscale SSA
  - *(Cao, Gillespie & Petzold, 2005)*
- *Multilevel Monte Carlo*
  - *(Anderson & Higham, 2012)*

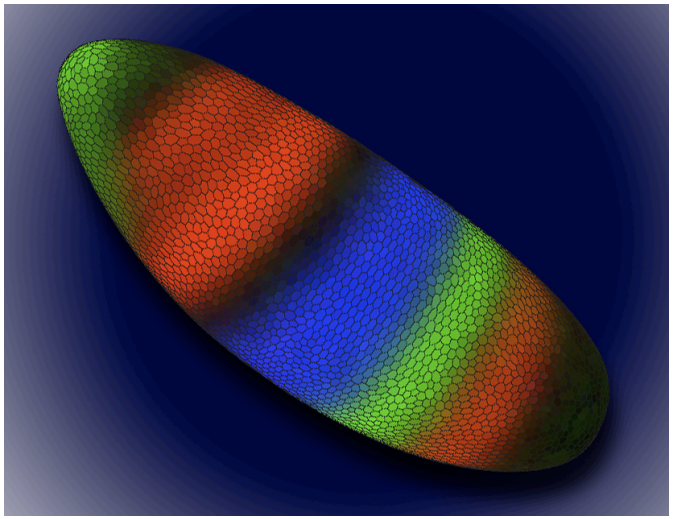
StochKit2
Stochastic Simulation Toolkit

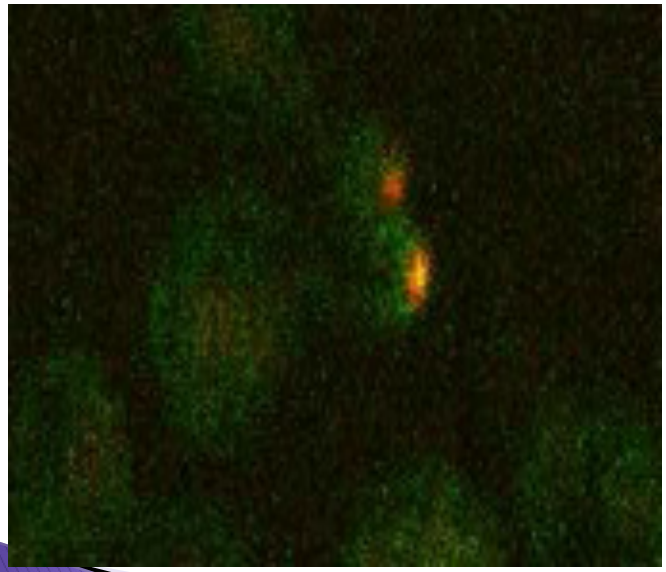
- Features:
  - StochKitML: Simple XML-based model input
  - SSA driver automatically selects the fastest solver
  - Tau-leaping driver adaptively selects stepsize, preserves nonnegativity, and dynamically switches to SSA when tau-leaping is not advantageous
  - Event handling
  - Automatic parallelism utilizes multi-core technology
  - Flexible output options: trajectories, statistics, histograms
- Tools
  - Convert SBML models to StochKitML format
  - Display histograms and trajectories using Matlab-compatible functions

Sanft et al., Bioinformatics 2011

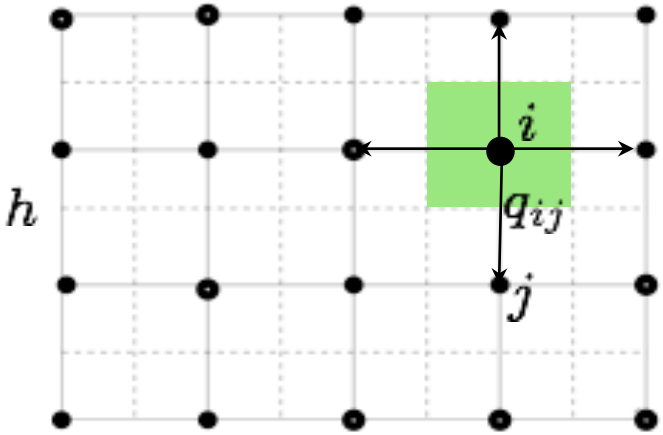
Spatial Stochastic Simulation

- Morphogenesis
- Polarization
- Chemotaxis





Inhomogeneous SSA (ISSA)



Introduce a discretization of the domain into subvolumes (voxels) and assume that the well-stirred assumption is fulfilled within each subvolume (green). Diffusion is introduced as jumps from one subvolume to adjacent subvolumes.

Cartesian, uniform mesh: $q_{ij} = \frac{\gamma}{h^2}$ $\qquad X_i \xrightarrow{q_{ij}} X_j$

Fundamental Issues and Complications

- The limit h -> 0 is not attainable for physical reasons. Must choose the mesh parameter h to be small enough to capture the desired features of the system, but large enough so that the system is well-mixed in each grid cell

Elf & Ehrenberg, 2004

- For reaction-diffusion systems, for small enough h, molecules never react!

Isaacson, 2009

- Theory and proposed improvement on algorithm

Erban & Chapman, 2009; Fange & Elf, 2011
Hellander, Hellander & Petzold, 2012; Isaacson, 2013

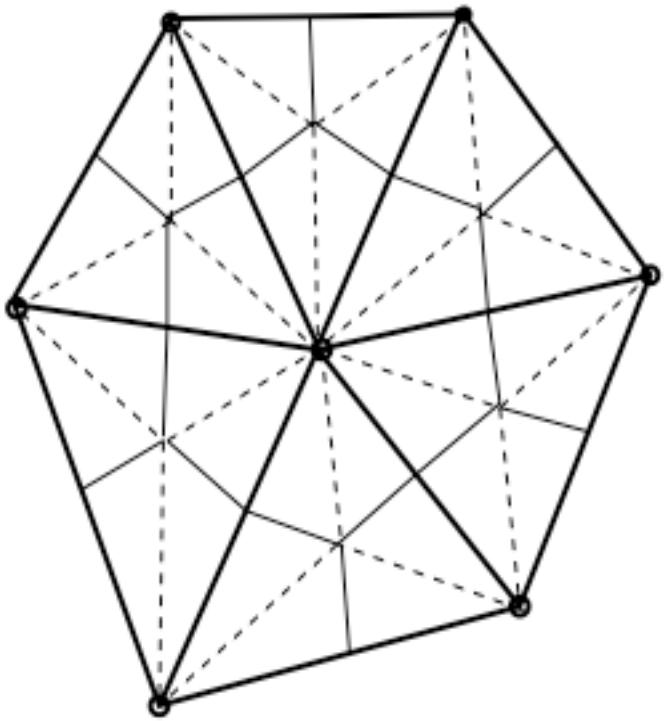
- Propensities vary with molecular crowding, roughly as a function of the size of the molecules

Lampoudi, Gillespie, Petzold, 2007, 2009; Ellis, 2001; Despa, 2009

Simulation of Diffusion

- Gold standard exact algorithm: Next Subvolume Method (Elf, Ehrenberg, 2004)
- Problem: Large number of fast diffusive transfers
- Solution: Aggregate the diffusive transfers
  - Multinomial Simulation Algorithm *(Lampoudi, Gillespie, Petzold 2009)*, Diffusive FSP (DFSP) *(Drawert, Lawson, Khammash, Petzold, 2010)*
  - For reaction/diffusion, reactions are incorporated by operator splitting
  - Fewer communication events, more computation between communication events

Complicated Geometries and Unstructured Meshes



- Early work on complicated geometries *(Isaacson & Peskin, 2006)*
- Unstructured meshes and complicated geometries *(Engblom, Ferm, Hellander, Lötstedt, 2009)*
- Adaptive hybrid method, reactions by operator splitting *(Ferm, Hellander, Lötstedt, 2009)*

Common Characteristics of Biochemical Simulations

- Often begins with an ODE model
- Independent models of subcellular mechanisms may be developed and combined later
- Spatial stochastic simulation, rare event characterization, and/or stochastic parameter estimation may be employed
- Many of the rate parameters are unknown (or known only to an order of magnitude or two)
- Global parameter sweeps may be done to determine overall behavior as well as regions of parameter space of particular interest
- Large amounts of data are generated and need to be analyzed

StochSS: Stochastic Simulation as a Service

Integrated Development Environment

- Build a model(s) – multiphysics
- Scale it up to increasing levels of complexity
- Explore the parameter space
- Seamlessly deploy the appropriate computing resources as needed
- Building on Powerful Existing Tools:
  - StochKit2, PyURDME, ODE and sensitivity
- Available for Mac, Linux and Windows at

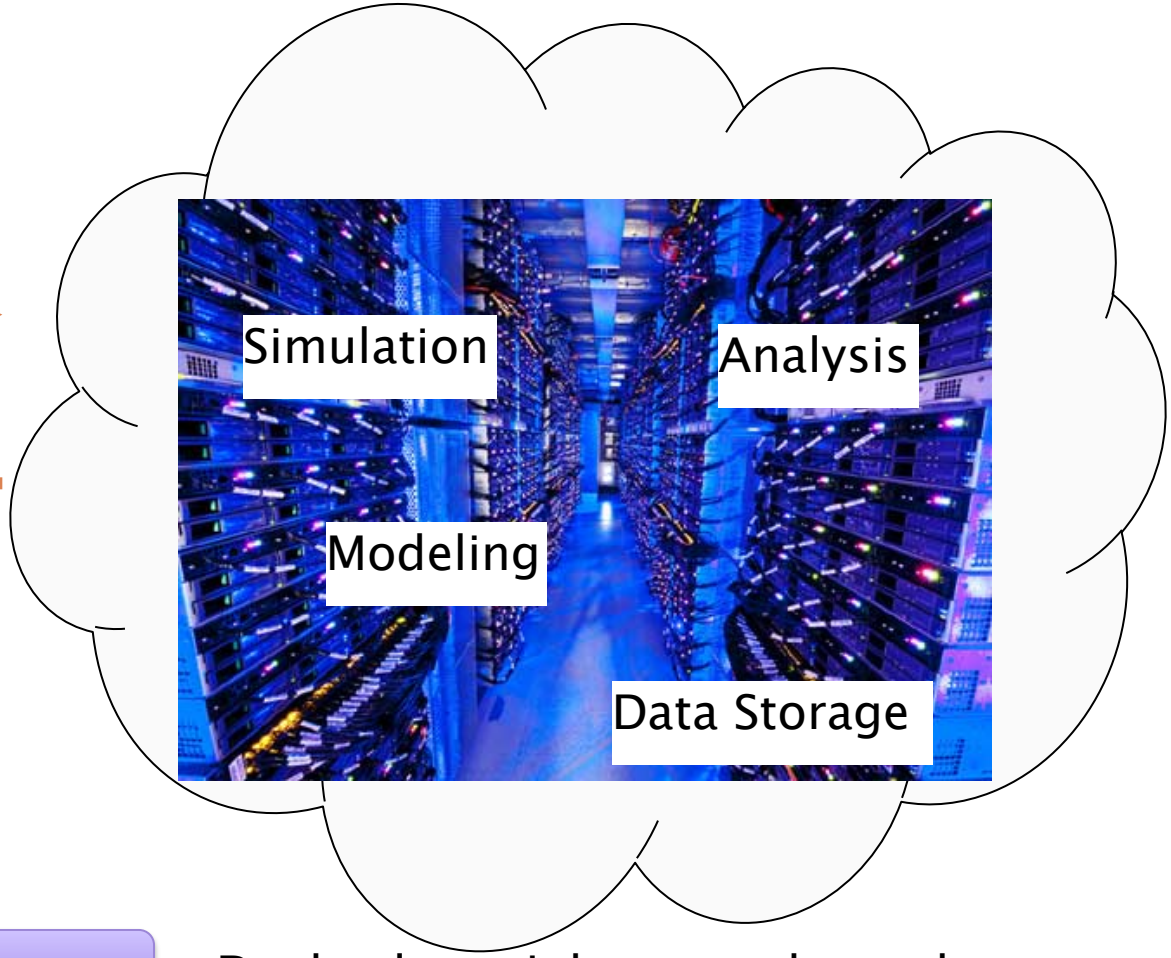
www.stochss.org

Version 1.6 supports ODE and well-mixed stochastic simulation via StochKit2, parameter estimation for discrete stochastic systems, spatial stochastic simulation via PyURDME

StochSS: Simplifying Large-Scale Stochastic Simulation and Data Analysis

Run Locally

- Deploy small jobs locally
- Experiment and explore
- Visualize/download results



Run Via Cloud

- Deploy large jobs, store large datasets
- Trade-off time and monetary cost
- On-premise or public clouds

Output and Visualization Tools
Summary Data
Plots
Problem Specification
Problem Description
Model Workflow
Data Analysis Tools
Parameter Sweeps
Automated Discovery
Model Analysis Tools
Rare Events
Parameter Estimation
Simulation Tools
ODE
Stochastic Well-Mixed
PDE
Spatial Stochastic

StochSS v1.6 Example

Letters to Nature

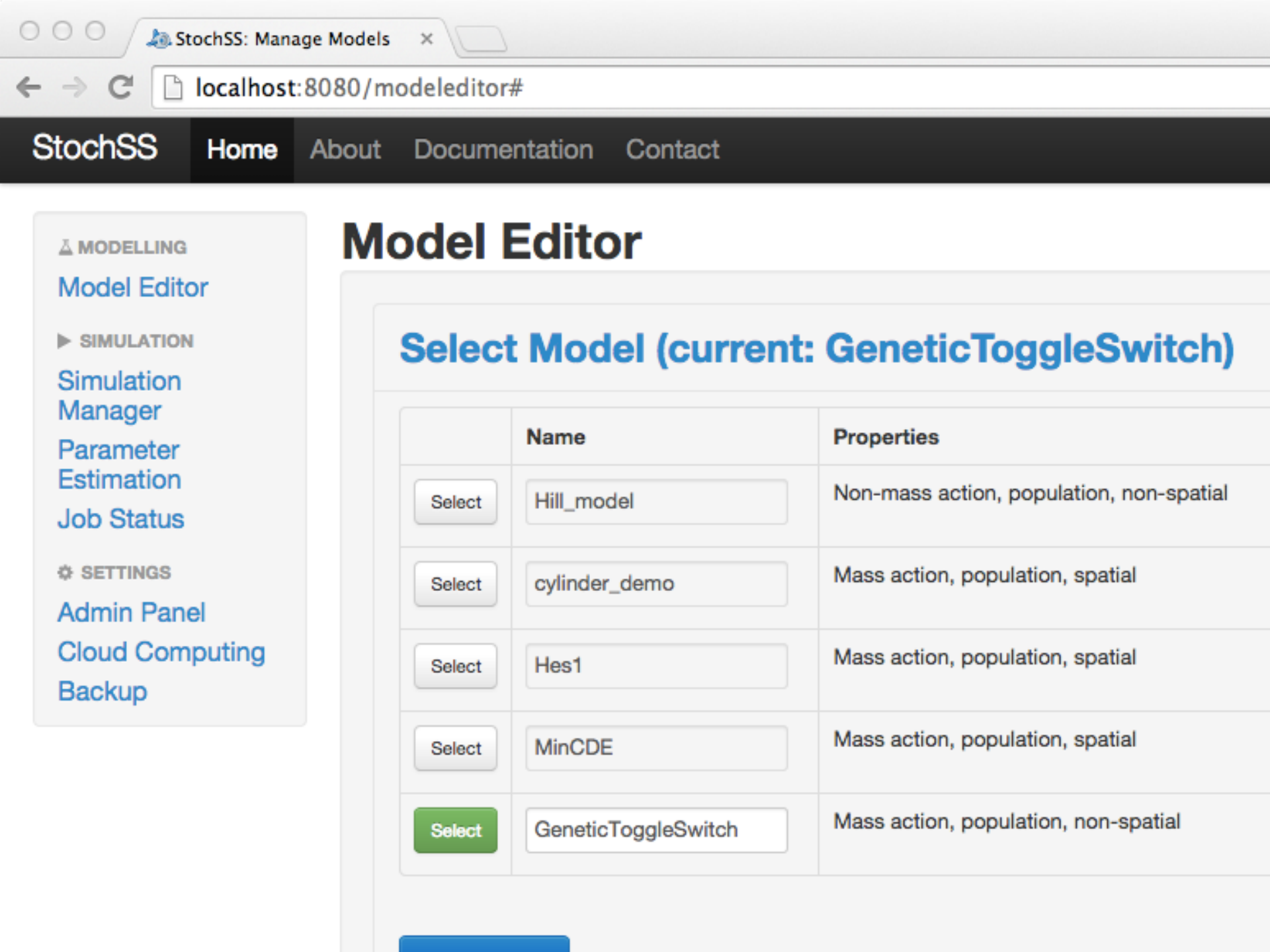
Nature **403**, 339-342 (20 January 2000) | doi:10.1038/35002131; Received 15 September 1999; Accepted 23 November 1999

Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner[1,2], Charles R. Cantor[1] & James J. Collins[1,2]

$$\frac{du}{dt} = \frac{\alpha_1}{1 + v^{\beta}} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1 + u^{\gamma}} - v$$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Model Editor
Select Model (current: GeneticToggleSwitch)
Name
Properties
Select
Hill_model
Non-mass action, population, non-spatial
Select
cylinder_demo
Mass action, population, spatial
Select
Hes1
Mass action, population, spatial
Select
MinCDE
Mass action, population, spatial
Select
GeneticToggleSwitch
Mass action, population, non-spatial

Manage Models ×

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Species Editor

Define species and their initial conditions. For concentration models this is a positive floating point value and for population models this is an integer.

Name	Initial Condition	
U	10	x
V	10	x

Add Species

Parameters Editor

Define the model parameters. Parameter constants are used to defined reaction rates in the simulation. Stochkit syntax is used to define the parameters. They can be functions of other parameters or simple math operations.

Name	Value	
alpha1	5	x

V	10	x

Add Species

Parameters Editor

Define the model parameters. Parameter constants are used to defined reaction rates in the simulation. Stochkit syntax is used to define the parameters. They can be functions of other parameters or simple math operations.

Name	Value	
alpha1	5	x
alpha2	5	x
beta	2	x
gamma	2	x
mu1	1	x
mu2	1	x

Add Parameter

Reactions Editor

Add Parameter

Reactions Editor

Define reactions. Select from the given reaction templates, or use the custom types. Using templated reaction types will help eliminate errors. For non-linear reactions, use the custom propensity type.

Edit	Name	Summary	Delete
◉	create_u	∅→U	x
○	create_v	∅→∅	x
○	destroy_u	∅→U	x
○	destroy_v	∅→V	x

∅→U

Reaction Type:

Custom propensity

Custom rate equation:

alpha1/(1+pow(V,

Reactants

Add species

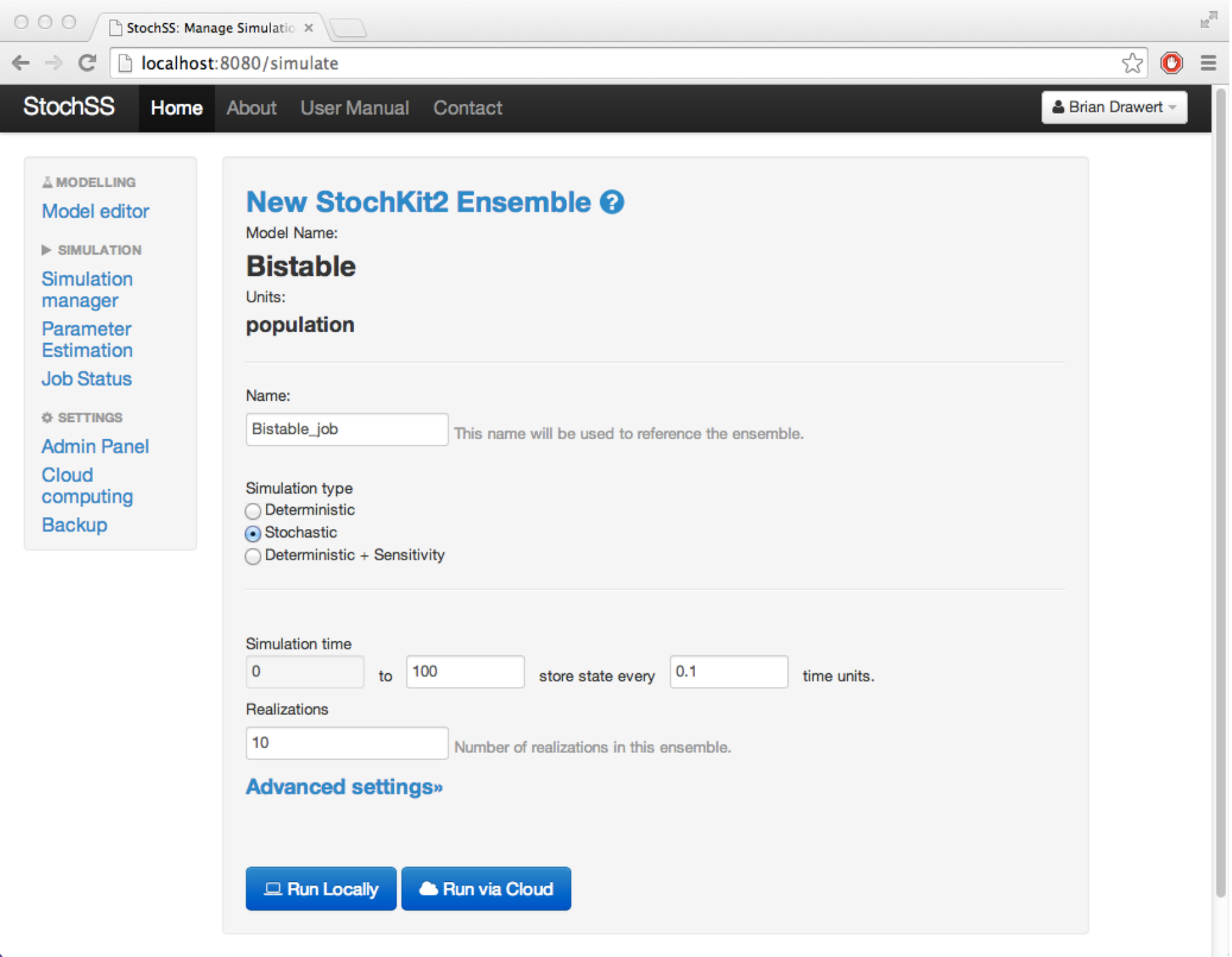
Add

Products

+ 1 - U x

Add species Add

Add Reaction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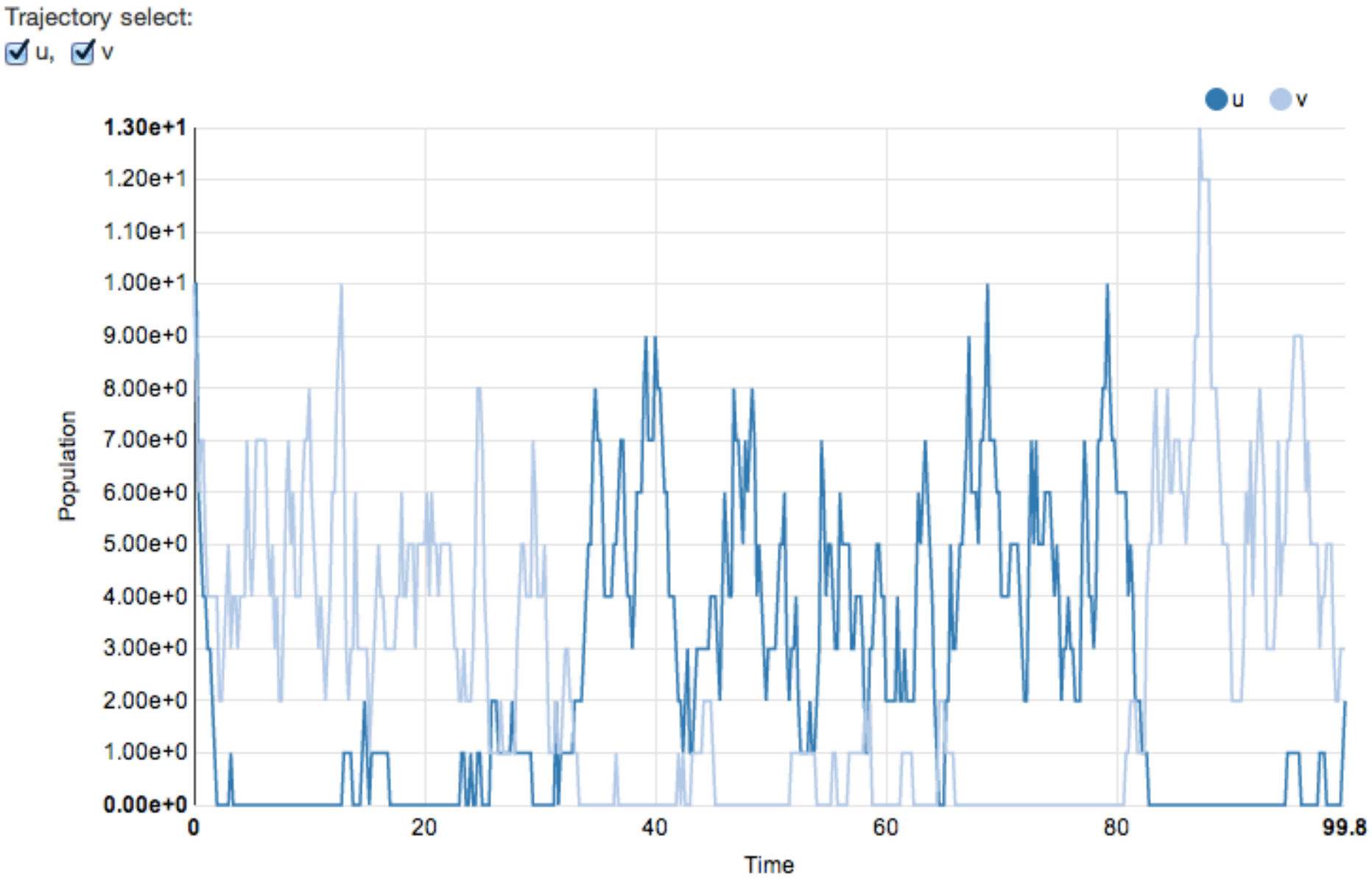
New StochKit2 Ensemble
Model Name:
Bistable
Units:
population
Name:
Bistable_job
This name will be used to reference the ensemble.
Simulation type
Deterministic
Stochastic
Deterministic + Sensitivity
Simulation time
0
to
100
store state every
0.1
time units.
Realizations
10
Number of realizations in this ensemble.
Advanced settings»
Run Locally
Run via Cloud

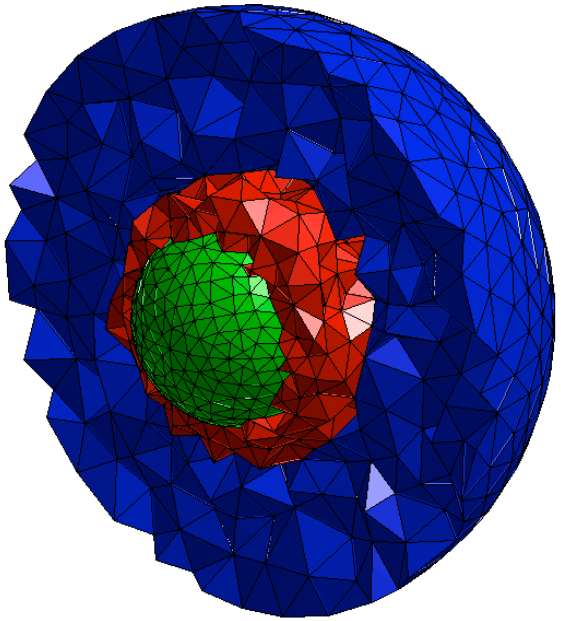

Trajectory select:
u, v
u
v
1.30e+1
1.20e+1
1.10e+1
1.00e+1
9.00e+0
8.00e+0
7.00e+0
6.00e+0
5.00e+0
4.00e+0
3.00e+0
2.00e+0
1.00e+0
0.00e+0
Population
0
20
40
60
80
99.8
Time

Spatial Stochastic Simulation with StochSS

- Integration of PyURDME
- Easy to build spatial models
- Local and Cloud execution
- Interactive dynamic visualization with WebGL
  - Three.JS library

PyURDME

Python framework for Spatial Stochastic Modeling and Simulation with complex geometries

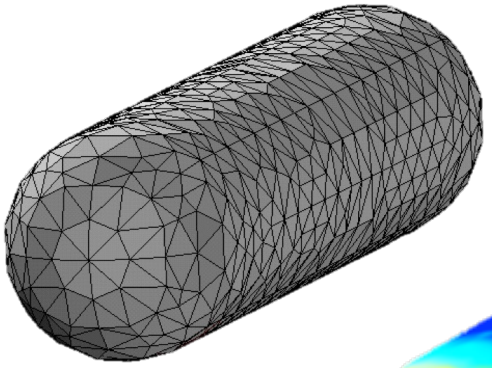


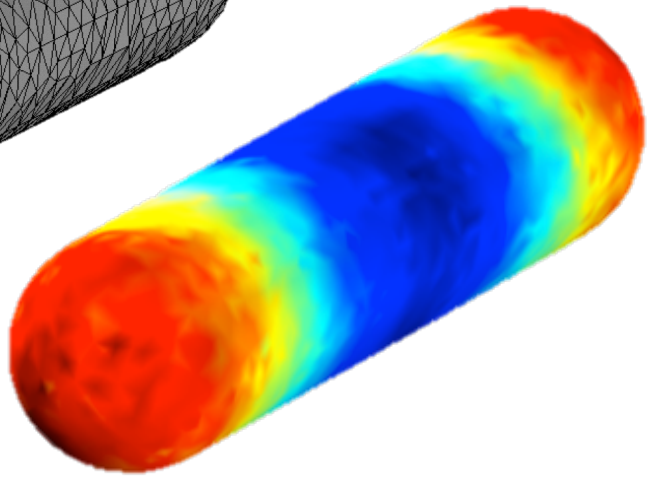
- **Features**
  - Easy model development using Python
  - FEniCS/Dolfin library for geometry and meshing
  - Fast efficient solvers written in C
  - Exact and approximate algorithms:
    - NSM
    - DFSP (w/GPU)
    - Hybrid Methods
- Extensible solver interface

www.pyurdme.org

http://github.com/pyurdme/pyurdme

Drawert, Engblom, Hellander, 2012

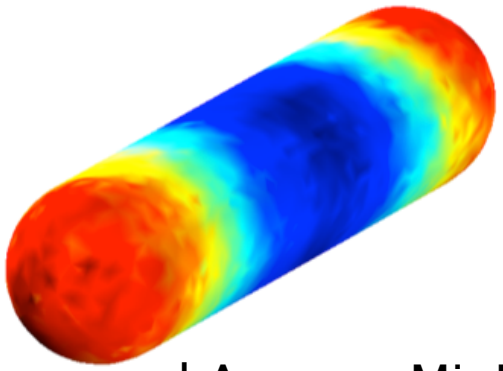




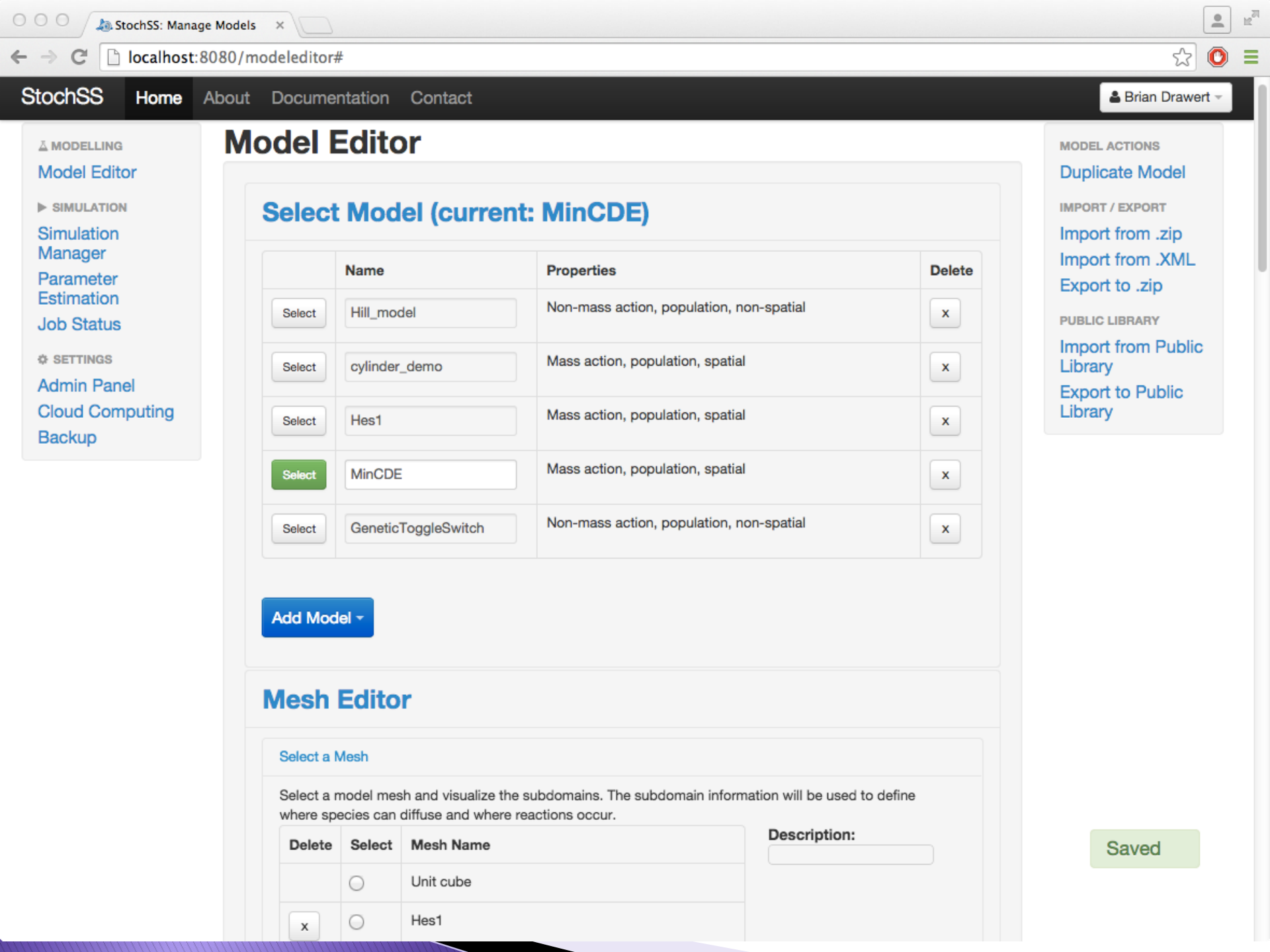
PyURDME Example: MinD Oscillations in *E. coli*

- Cell division in *E. coli* is regulated by polar oscillations of MinD protein.
  - Act to inhibit enzymes that sever the cell wall
- Pole-to-pole oscillations force the temporal average of MinD to be high at the poles and low at the cell center
  - Cells always divide at the center
  - Cells only divide when they grow large enough for oscillations to form

Fange et al. (2006)



Temporal Average MinD Concentration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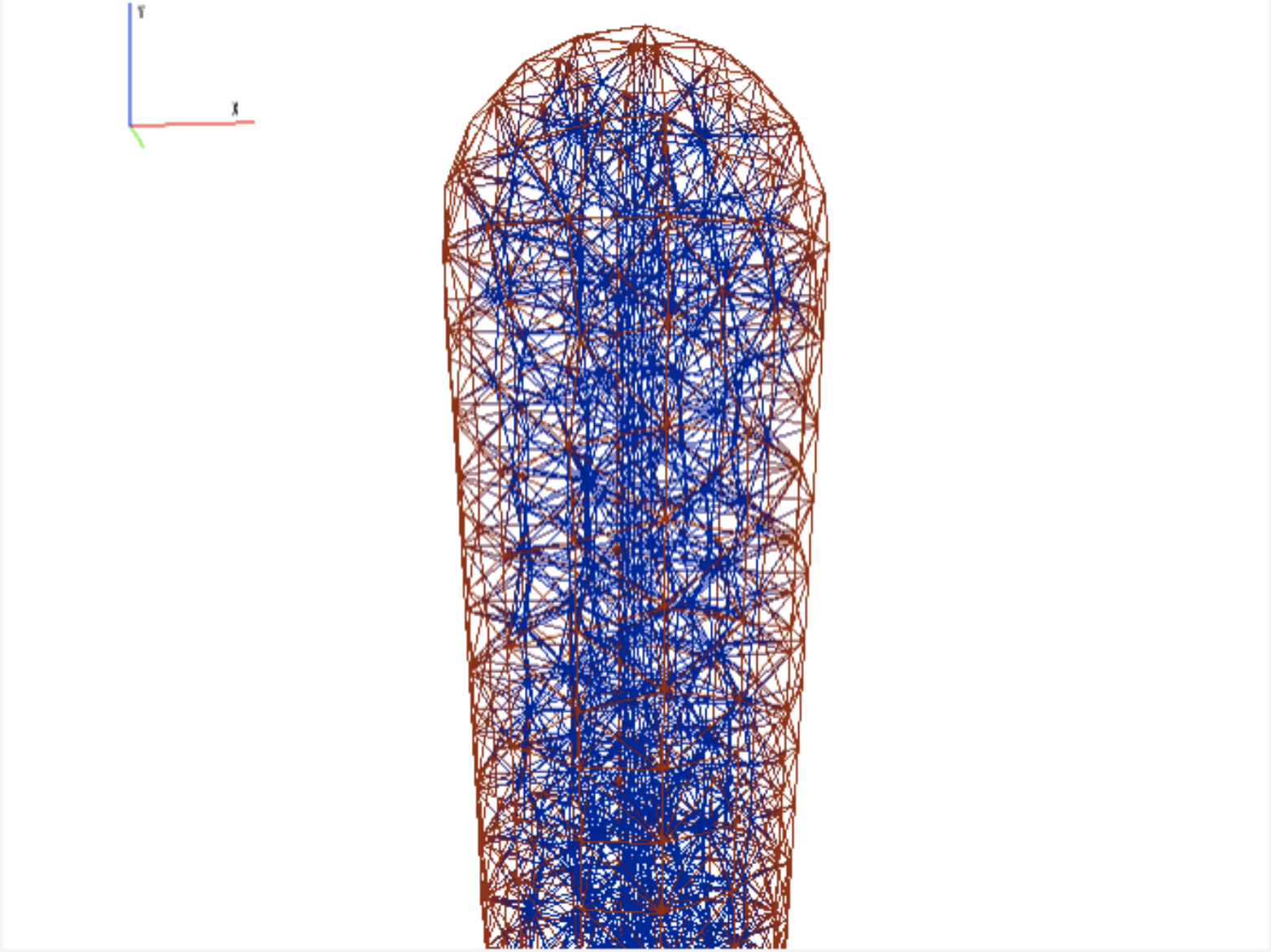
Model Editor
Select Model (current: MinCDE)
Name
Properties
Delete
Select
Hill_model
Non-mass action, population, non-spatial
x
Select
cylinder_demo
Mass action, population, spatial
x
Select
Hes1
Mass action, population, spatial
x
Select
MinCDE
Mass action, population, spatial
x
Select
GeneticToggleSwitch
Non-mass action, population, non-spatial
x
Add Model
Mesh Editor
Select a Mesh
Select a model mesh and visualize the subdomains. The subdomain information will be used to define where species can diffuse and where reactions occur.
Delete
Select
Mesh Name
Description:
Unit cube
x
Hes1
MODEL ACTIONS
Duplicate Model
IMPORT / EXPORT
Import from .zip
Import from .XML
Export to .zip
PUBLIC LIBRARY
Import from Public Library
Export to Public Library
Saved

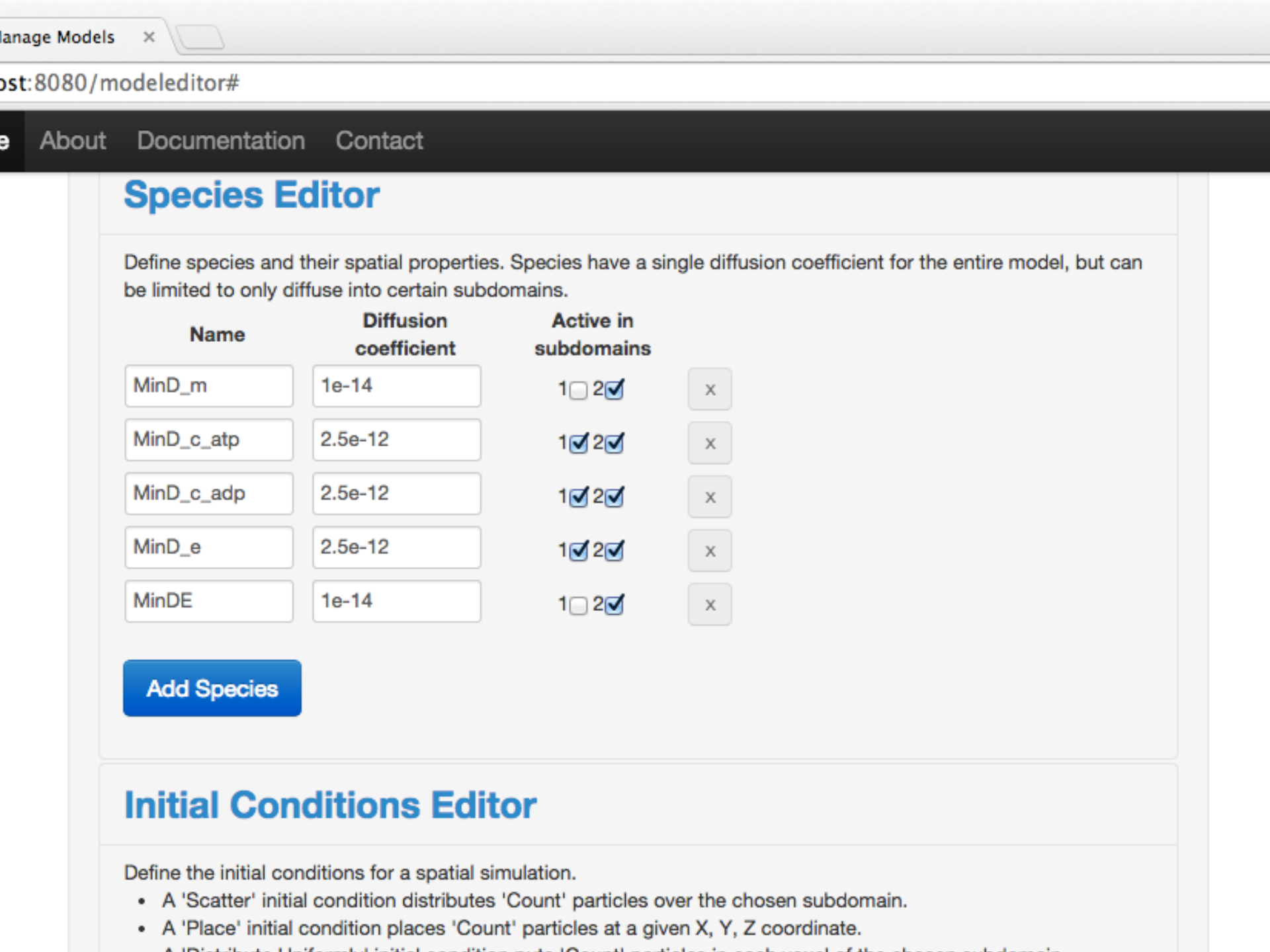
Mesh Preview

Zoom Pan Rotate Reset



Highlight Subdomains

1 2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Species Editor
Define species and their spatial properties. Species have a single diffusion coefficient for the entire model, but can be limited to only diffuse into certain subdomains.
Name
Diffusion coefficient
Active in subdomains
MinD_m
1e-14
1 2
x
MinD_c_atp
2.5e-12
1 2
x
MinD_c_adp
2.5e-12
1 2
x
MinD_e
2.5e-12
1 2
x
MinDE
1e-14
1 2
x
Add Species
Initial Conditions Editor
Define the initial conditions for a spatial simulation.
A 'Scatter' initial condition distributes 'Count' particles over the chosen subdomain.
A 'Place' initial condition places 'Count' particles at a given X, Y, Z coordinate.

x | Scatter | MinD_c_ad | Count: 4500

Subdomain 1

Add Initial Condition

Parameters Editor

Define the model parameters. Parameter constants are used to defined reaction rates in the simulation. Stochkit syntax is used to define the parameters. They can be functions of other parameters or simple math operations.

Name	Value	
sigma_d	0.384615384615	x
sigma_dD	1.6e-21	x
sigma_e	9.3e-20	x
sigma_de	0.7	x
sigma_dt	1	x

Add Parameter

Reactions Editor

	coefficient	subdomains	
MinD_m	1e-14	1 ☐ 2 ☑	x
MinD_c_atp	2.5e-12	1 ☑ 2 ☑	x
MinD_c_adp	2.5e-12	1 ☑ 2 ☑	x
MinD_e	2.5e-12	1 ☑ 2 ☑	x
MinDE	1e-14	1 ☐ 2 ☑	x

Add Species

Initial Conditions Editor

Define the initial conditions for a spatial simulation.

- A 'Scatter' initial condition distributes 'Count' particles over the chosen subdomain.
- A 'Place' initial condition places 'Count' particles at a given X, Y, Z coordinate.
- A 'Distribute Uniformly' initial condition puts 'Count' particles in each voxel of the chosen subdomain.

	Type	Specie	Details	
x	Scatter	MinD_e	Count:	1575
			Subdomain	1
x	Scatter	MinD_c_ad	Count:	4500
			Subdomain	1

Add Initial Condition

Sav

Reactions Editor

Define reactions. Select from the given reaction templates, or use the custom types. Using templated reaction types will help eliminate errors. For non-linear reactions, use the custom propensity type. Reactions can be restricted to specific subdomains.

Edit	Name	Summary	Delete
◉	R1	MinD_c_atp→MinD_m	x
○	R3	MinD_e+MinD_m→MinDE	x
○	R4	MinDE→MinD_c_adp+MinD_e	x
○	R2	MinD_c_atp+MinD_m→2MinD_m	x
○	R5	MinD_c_adp→MinD_c_atp	x
○	R6	MinD_c_atp+MinDE→MinD_m+MinDE	x

MinD_c_atp→MinD_m

Reaction Type:

Custom mass action

Rate parameter:

sigma_d

Subdomains reaction can occur in:

1☐ 2☑

Reactants

\+ 1 - MinD_c_atp x

Add species Add

Products

\+ 1 - MinD_m x

Add species Add

Add Reaction

StochSS: Spatial Simulation | New Tab

localhost:8080/spatial?id=5556931766779904

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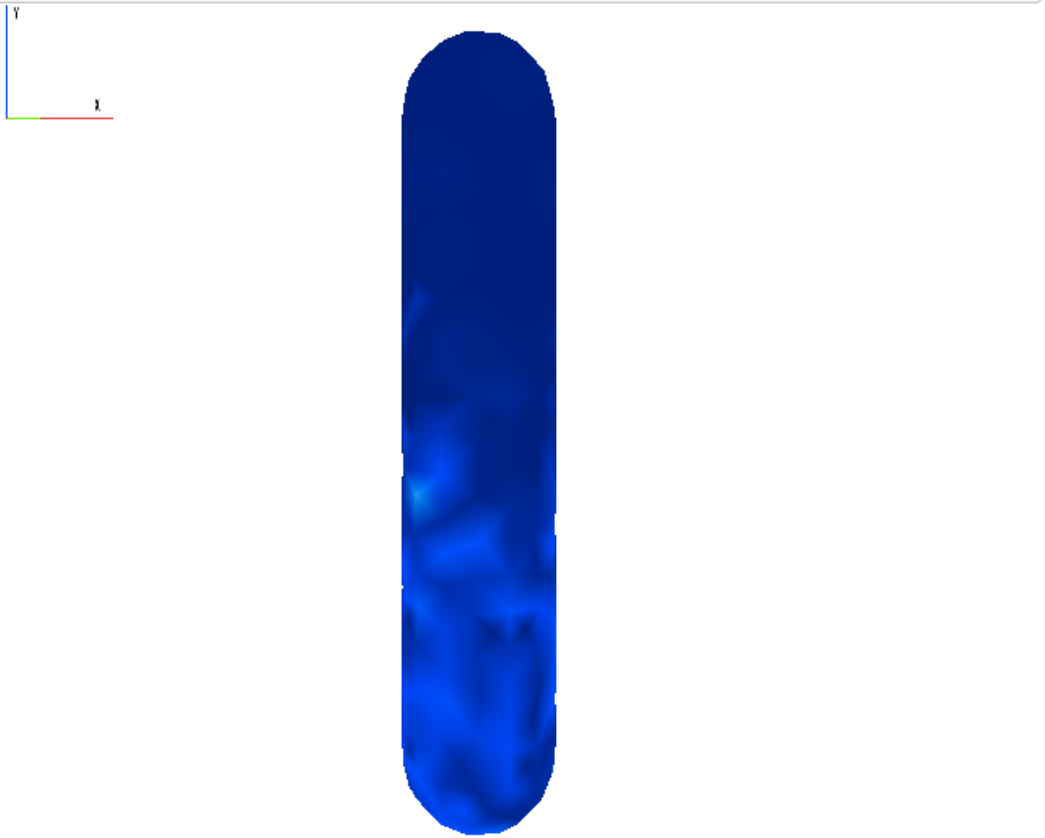
- Cloud Computing
- Backup

Select Time: 57

Select Trajectory: Trajectory 0

Select species: MinD_m

Zoom | Pan | Rotate | Reset



Maximum voxel population: 18

Minimum voxel population: 0

Output

StochSS: Spatial Simulation

localhost:8080/spatial?id=5556931766779904

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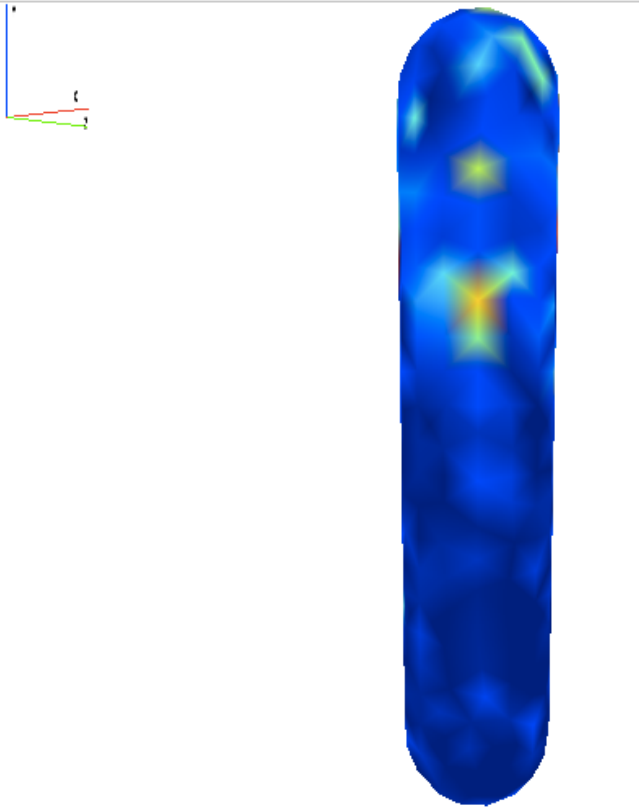
Select Time: 97

Select Trajectory: Trajectory 0

Select species: MinD_m

Zoom | Pan | Rotate | Reset

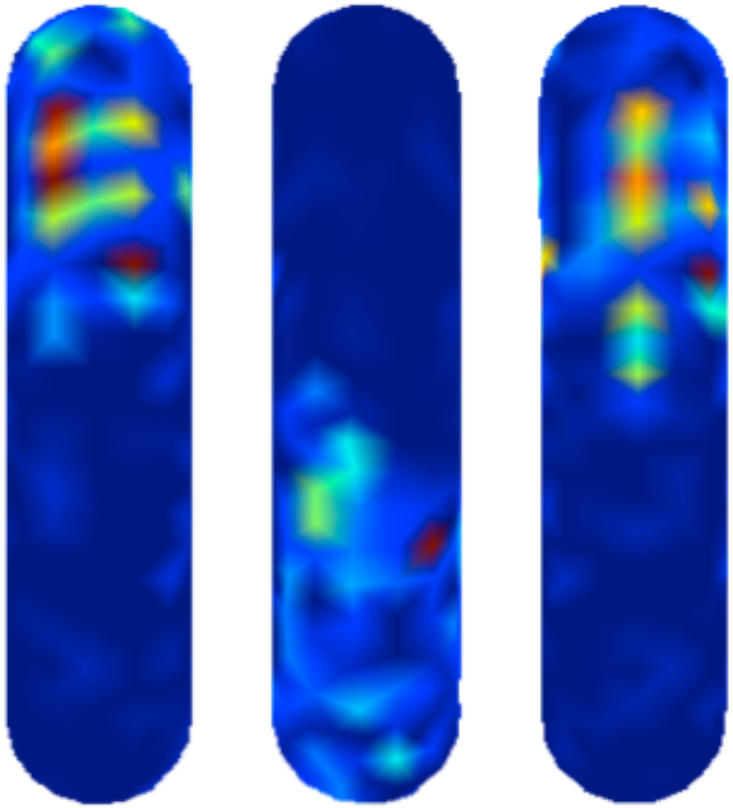


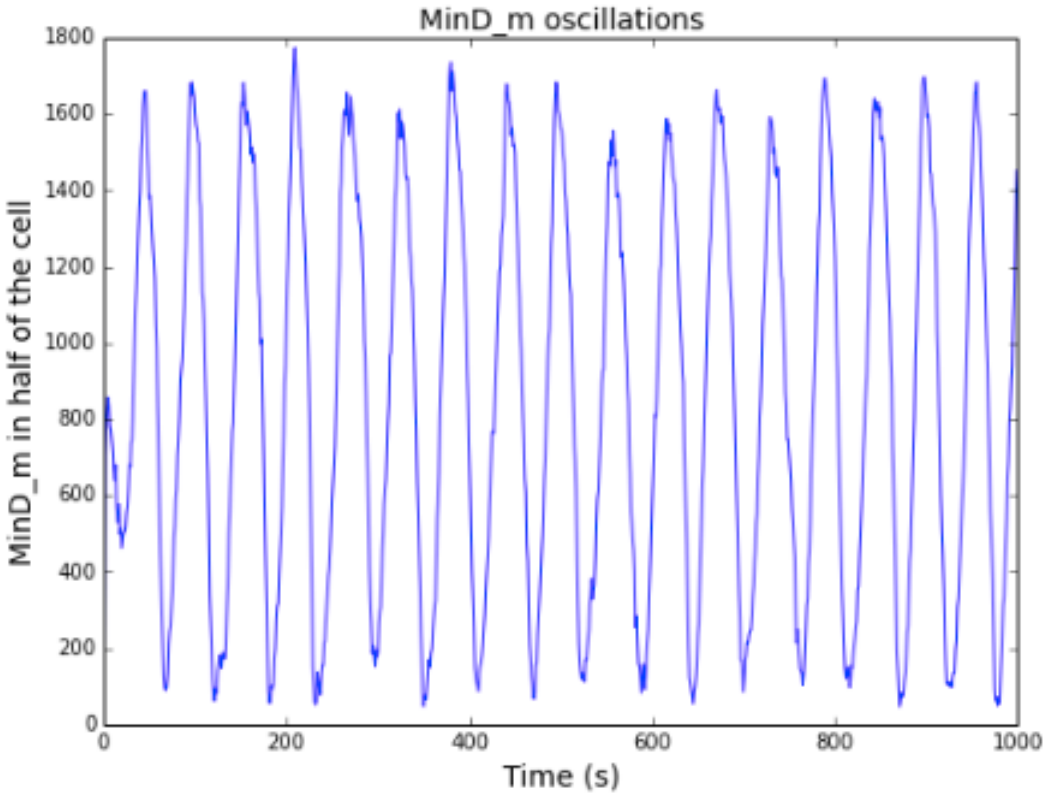
Maximum voxel population: 15

Minimum voxel population: 0

Output

Oscillations of MinCDE system





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- Sponsored by NIH
- Multidisciplinary Team
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  - Andreas Hellander (Uppsala), Brian Drawert, Benjamin B. Bales, Stefan Hellander, and a host of others!