V I I
SBML und Modell-Erstellung

9. Januar 2014

Übersicht

Austausch und Archivierung von biochemischen Modellen
=> SBML

Diffusion plus Reaktionen
=> Virtual Cell

Komplexität der Modelle
=> BioNetGen

Systems Biology Markup Language

XML-Dialekt für Speicherung und Austausch biochemischer Modelle

=> Archivierung

=> Transfer von Modellen in andere Softwaretools

Acknowledgements

We are deeply indebted to the many funding agencies and organizations that have supported SBML over the years.

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von http://sbml.org/Acknowledgments

SBML <= XML

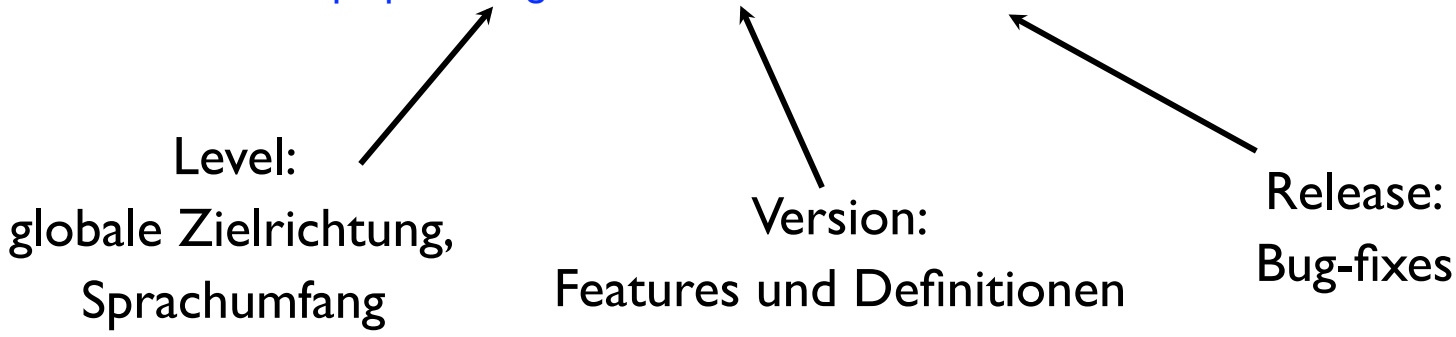
XML = eXtensible Markup Language

- hierarchische Baumstruktur:
  => Schachtelung von <Object> … </Object> oder <Objekt [Parameter…]/>
- genau ein Wurzelobjekt: <sbml…>

Aktuelle Dialekte: siehe http://sbml.org/Documents/Specifications

SBML Level 1, Version 2
http://www.sbml.org/specifications/sbml-level-1/version-2/sbml-level-1-v2.pdf

SBML Level 2, Version 4, Release 1
http://precedings.nature.com/documents/2715/version/1



Was ist enthalten?

beginning of model definition
- list of function definitions (optional)
- list of unit definitions (optional)
- list of compartment types (optional)
- list of species types (optional)
- list of compartments (optional)
- list of species (optional)
- list of parameters (optional)
- list of initial assignments (optional)
- list of rules (optional)
- list of constraints (optional)
- list of reactions (optional)
- list of events (optional)

end of model definition

http://sbml.org/More_Detailed_Summary_of_SBML

Ein Beispiel

$$E + S \underset{k_{off}}{\overset{k_{on}}{<=>}} ES \overset{k_{cat}}{=>} E + P$$

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="3" xmlns="http://www.sbml.org/sbml/level2/version3">
  <model name="EnzymaticReaction">
    <listOfUnitDefinitions>
      <unitDefinition id="per_second">
        <listOfUnits>
          <unit kind="second" exponent="-1"/>
        </listOfUnits>
      </unitDefinition>
      <unitDefinition id="litre_per_mole_per_second">
        <listOfUnits>
          <unit kind="mole"   exponent="-1"/>
          <unit kind="litre"  exponent="1"/>
          <unit kind="second" exponent="-1"/>
        </listOfUnits>
      </unitDefinition>
    </listOfUnitDefinitions>
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      <compartment id="cytosol" size="1e-14"/>
    </listOfCompartments>
    <listOfSpecies>
      <species compartment="cytosol" id="ES" initialAmount="0"     name="ES"/>
      <species compartment="cytosol" id="P"  initialAmount="0"     name="P"/>
      <species compartment="cytosol" id="S"  initialAmount="1e-20" name="S"/>
      <species compartment="cytosol" id="E"  initialAmount="5e-21" name="E"/>
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    <listOfReactions>
      <reaction id="veq">
        <listOfReactants>
          <speciesReference species="E"/>
          <speciesReference species="S"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="ES"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci>cytosol</ci>
              <apply>
                <minus/>
                <apply>
                  <times/>
                  <ci>kon</ci>
                  <ci>E</ci>
                  <ci>S</ci>
                </apply>
                <apply>
                  <times/>
                  <ci>koff</ci>
                  <ci>ES</ci>
                </apply>
              </apply>
            </apply>
          </math>
          <listOfParameters>
            <parameter id="kon"  value="1000000" units="litre_per_mole_per_second"/>
            <parameter id="koff" value="0.2"     units="per_second"/>
          </listOfParameters>
        </kineticLaw>
      </reaction>
      <reaction id="vcat" reversible="false">
        <listOfReactants>
          <speciesReference species="ES"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="E"/>
          <speciesReference species="P"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci>cytosol</ci>
              <ci>kcat</ci>
              <ci>ES</ci>
            </apply>
          </math>
          <listOfParameters>
            <parameter id="kcat" value="0.1" units="per_second"/>
          </listOfParameters>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

Nochmal:

$$E + S \underset{k_{off}}{\overset{k_{on}}{<=>}} ES \overset{k_{cat}}{=>} E + P$$

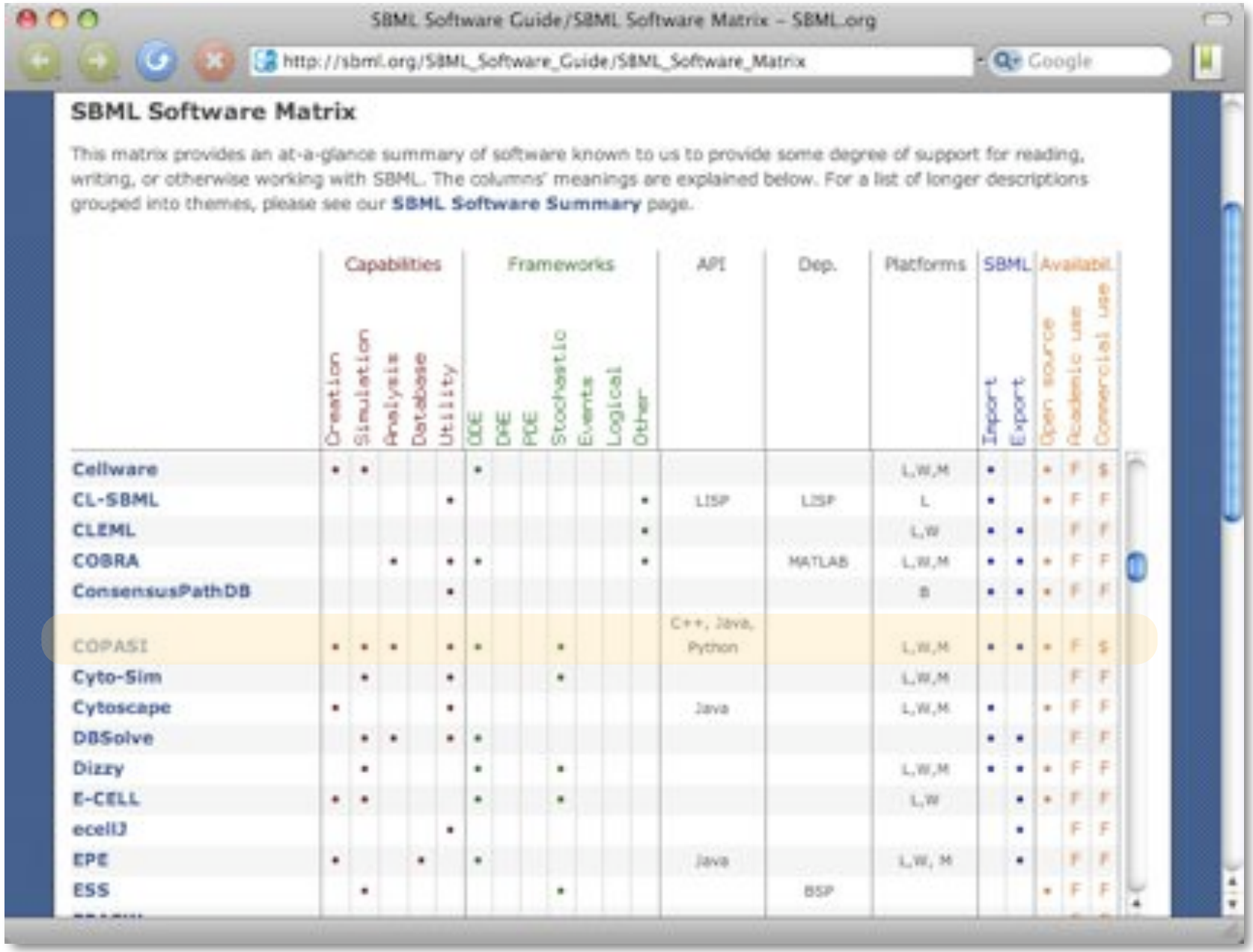
```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="3" xmlns="http://www.sbml.org/sbml/level2/version3">
  <model name="EnzymaticReaction">
    <listOfUnitDefinitions>
      :
    </listOfUnitDefinitions>
    <listOfCompartments>
      <compartment id="cytosol" size="1e-14"/>
    </listOfCompartments>
    <listOfSpecies>
      <species compartment="cytosol" id="ES" initialAmount="0"    name="ES"/>
      <species compartment="cytosol" id="P"  initialAmount="0"    name="P"/>
      <species compartment="cytosol" id="S"  initialAmount="1e-20" name="S"/>
      <species compartment="cytosol" id="E"  initialAmount="5e-21" name="E"/>
    </listOfSpecies>
    <listOfReactions>
      :
    </listOfReactions>
  </model>
</sbml>
```

Details: Einheiten

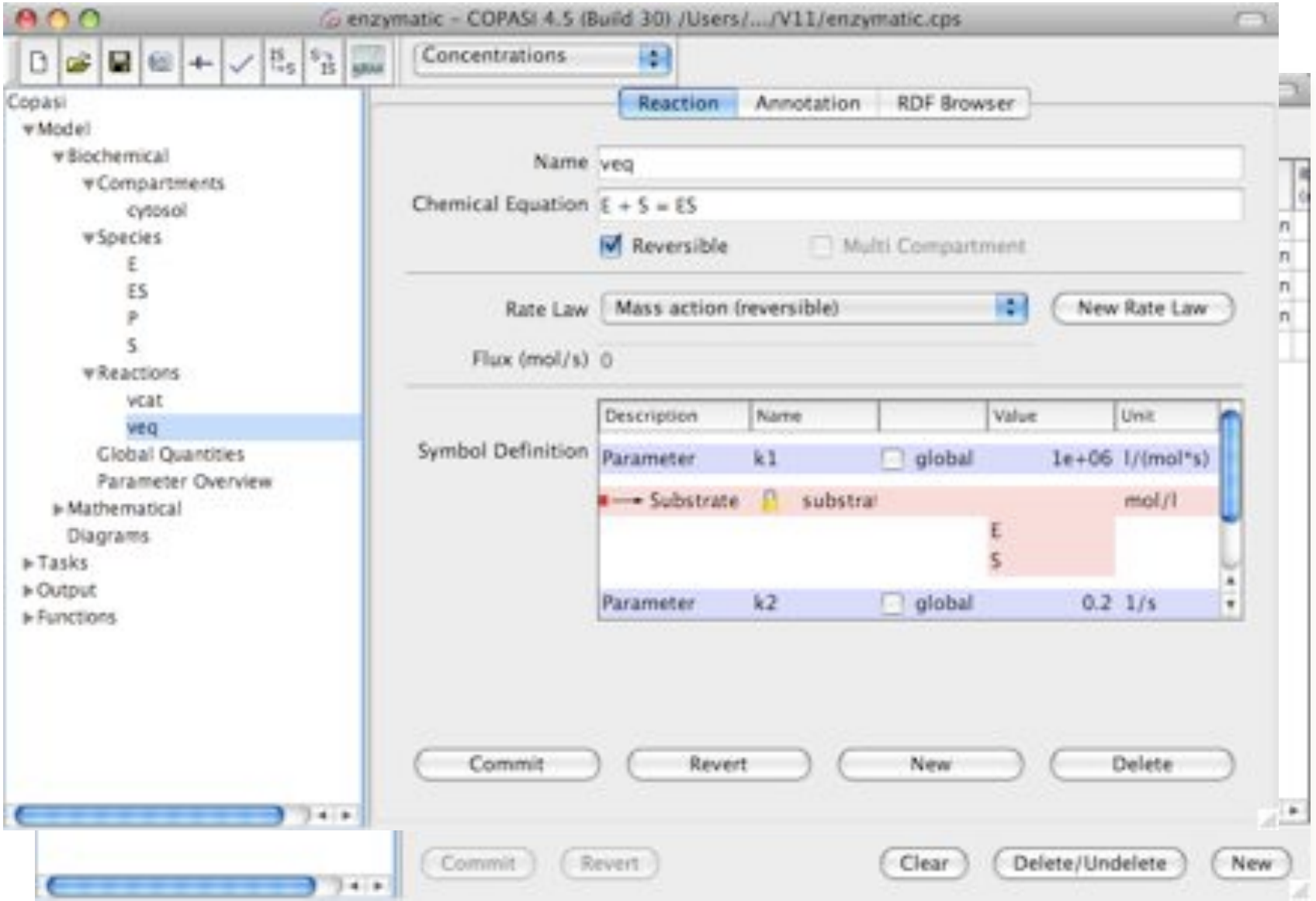
```
<listOfUnitDefinitions>
        <unitDefinition id="per_second">
                <listOfUnits>
            <unit kind="second" exponent="-1"/>
        </listOfUnits>
    </unitDefinition>
    <unitDefinition id="litre_per_mole_per_second">
        <listOfUnits>
            <unit kind="mole"   exponent="-1"/>
            <unit kind="litre"  exponent="1"/>
            <unit kind="second" exponent="-1"/>
        </listOfUnits>
    </unitDefinition>
</listOfUnitDefinitions>
```

per_seconds := s^{-1}

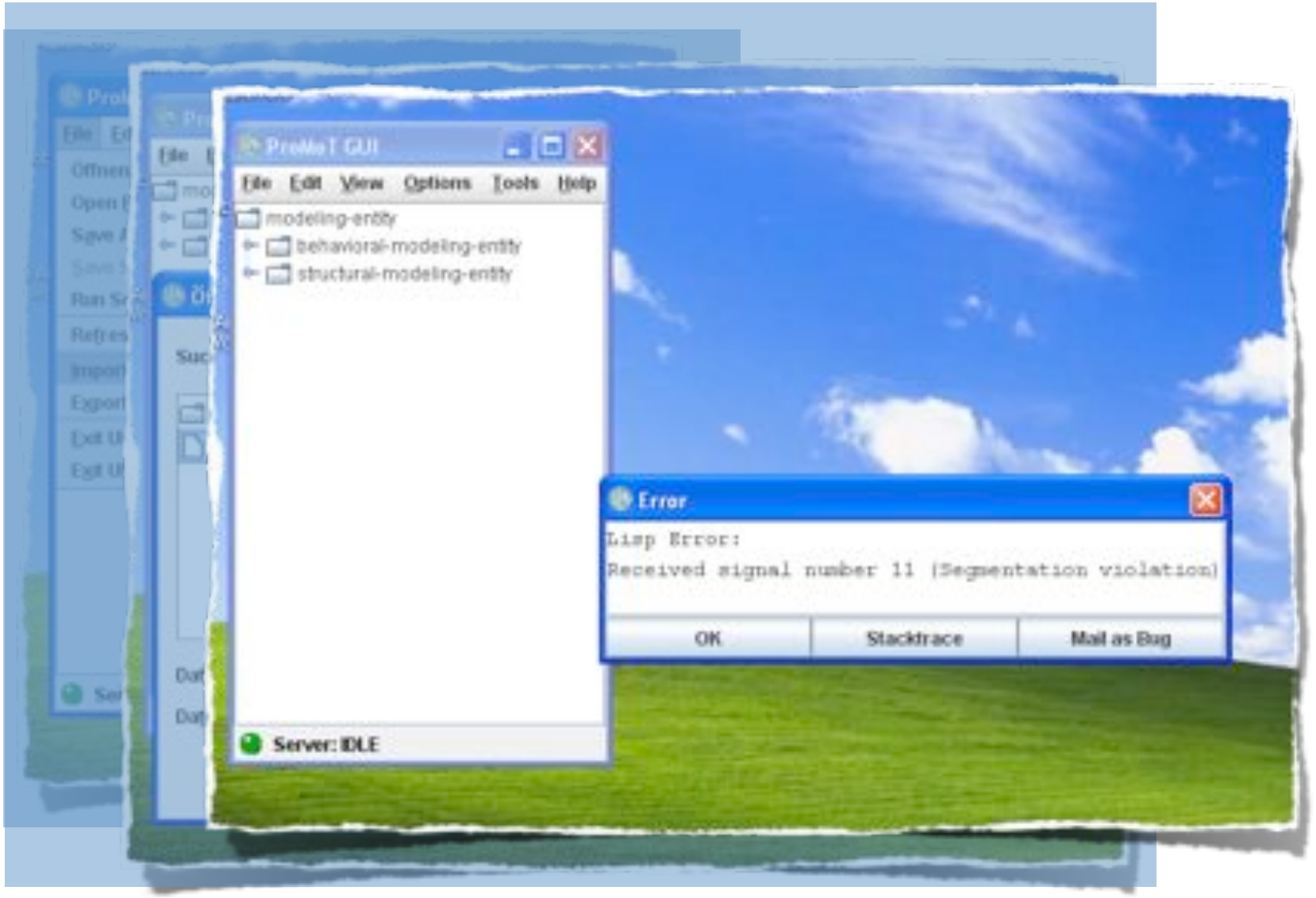
$$\frac{\text{litre}}{\text{mol s}}$$


SBML Software Guide/SBML Software Matrix – SBML.org
http://sbml.org/SBML_Software_Guide/SBML_Software_Matrix
Google
SBML Software Matrix
This matrix provides an at-a-glance summary of software known to us to provide some degree of support for reading, writing, or otherwise working with SBML. The columns' meanings are explained below. For a list of longer descriptions grouped into themes, please see our SBML Software Summary page.
Capabilities
Frameworks
API
Dep.
Platforms
SBML
Availabil.
Creation
Simulation
Analysis
Database
Utility
ODE
DAE
PDE
Stochastic
Events
Logical
Other
Import
Export
Open source
Academic use
Commercial use
Cellware L,W,M
CL-SBML LISP LISP L
CLEML L,W
COBRA MATLAB L,W,M
ConsensusPathDB B
COPASI C++, Java, Python L,W,M
Cyto-Sim L,W,M
Cytoscape Java L,W,M
DBSolve
Dizzy L,W,M
E-CELL L,W
eceli3
EPE Java L,W, M
ESS BSP

Import nach Copasi



Interoperabilität?



Details: eine Reaktion

```
<listOfReactions>
      :
  <reaction id="vcat" reversible="false">
    <listOfReactants>
        <speciesReference species="ES"/>
    </listOfReactants>
    <listOfProducts>
        <speciesReference species="E"/>
        <speciesReference species="P"/>
    </listOfProducts>
    <kineticLaw>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
                <times/>
                <ci>cytosol</ci>
                <ci>kcat</ci>
                <ci>ES</ci>
            </apply>
        </math>
        <listOfParameters>
            <parameter id="kcat" value="0.1" units="per_second"/>
        </listOfParameters>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

$$E + S \underset{k_{off}}{\overset{k_{on}}{<=>}} ES \overset{k_{cat}}{=>} E + P$$

$$\Rightarrow \frac{dN}{dt} = V_{cytosol}\, k_{cat}\, [ES]$$

lokaler Parameter!

SBML lesbar machen

SBML2LaTeX

Conversion of SBML files into human-readable reports

http://webservices.cs.uni-tuebingen.de/

Dräger A, Planatscher H, Wouamba DM, Schröder A, Hucka M, Endler L, Golebiewski M, Müller W, and Zell A: "SBML2LaTeX: Conversion of SBML files into human-readable reports", Bioinformatics 2009

Drei Minuten später:

convert

Please download your result here: 07ff0064-6af4-4eb5-bea1-906da1fbcd86-request.pdf

Submit another file

SBML Model Report

Model name: "EnzymaticReaction"

June 30, 2009

1 General Overview

This is a document in SBML Level 2 Version 3 format. Table 1 gives an overview of the quantities of all components of this model.

Table 1: The SBML components in this model.
All components are described in more detail in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	1
species types	0	species	4
events	0	constraints	0
reactions	2	function definitions	0
global parameters	0	unit definitions	2
rules	0	initial assignments	0

2 Unit Definitions

This is an overview of seven unit definitions. The units `substance`, `volume`, `area`, `length`, and `time` are predefined by SBML and not mentioned in the model.

2.1 Unit `per_second`

Definition s^{-1}

2.2 Unit `litre_per_mole_per_second`

Definition $mol^{-1} \cdot l \cdot s^{-1}$

2.3 Unit `substance`

Notes Mole is the predefined SBML unit for `substance`.

Definition mol

2.4 Unit `volume`

Notes Litre is the predefined SBML unit for `volume`.

Definition l

2.5 Unit `area`

Notes Square metre is the predefined SBML unit for `area` since SBML Level 2 Version 1.

Definition m^2

2.6 Unit `length`

Notes Metre is the predefined SBML unit for `length` since SBML Level 2 Version 1.

Definition m

2.7 Unit `time`

Notes Second is the predefined SBML unit for `time`.

Definition s

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
cytosol			3	10^{-14}	l	☑	

3.1 Compartment cytosol

This is a three-dimensional compartment with a constant size of 10^{-14} litre.

4 Species

This model contains four species. Section 6 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
ES	ES	cytosol	$mol \cdot l^{-1}$	☐	☐
P	P	cytosol	$mol \cdot l^{-1}$	☐	☐
S	S	cytosol	$mol \cdot l^{-1}$	☐	☐
E	E	cytosol	$mol \cdot l^{-1}$	☐	☐

5 Reactions

This model contains two reactions. All reactions are listed in the following table and are subsequently described in detail. If a reaction is affected by one or more modifiers, the identifiers of the modifier species are written above the reaction arrow.

Table 4: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	veq		$E + S \rightleftarrows ES$	
2	vcat		$ES \longrightarrow E + P$	

5.1 Reaction veq

This is a reversible reaction of two reactants forming one product.

Reaction equation

$$E + S \longrightarrow ES \tag{1}$$

Reactants

Table 5: Properties of each reactant.

Id	Name	SBO
E	E	
S	S	

Product

Table 6: Properties of each product.

Id	Name	SBO
ES	ES	

Kinetic Law

Derived unit $s^{-1} \cdot mol$

$$v_1 = \text{vol}(\texttt{cytosol}) \cdot (\texttt{kon} \cdot [E] \cdot [S] - \texttt{koff} \cdot [ES]) \tag{2}$$

Table 7: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kon			1000000.0	$mol^{-1} \cdot l \cdot s^{-1}$	☑
koff			0.2	s^{-1}	☑

6 Derived Rate Equations

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rates of change of each species.

6.1 Species ES

Name ES

Initial amount 0 mol

This species takes part in two reactions (as a reactant in vcat and as a product in veq).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ES} = v_1 - v_2 \tag{5}$$

6.2 Species P

Name P

Initial amount 0 mol

This species takes part in one reaction (as a product in vcat).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P} = v_2 \tag{6}$$

6.3 Species S

Name S

Initial amount 10^{-20} mol

This species takes part in one reaction (as a reactant in veq).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{S} = -v_1 \tag{7}$$

6.4 Species E

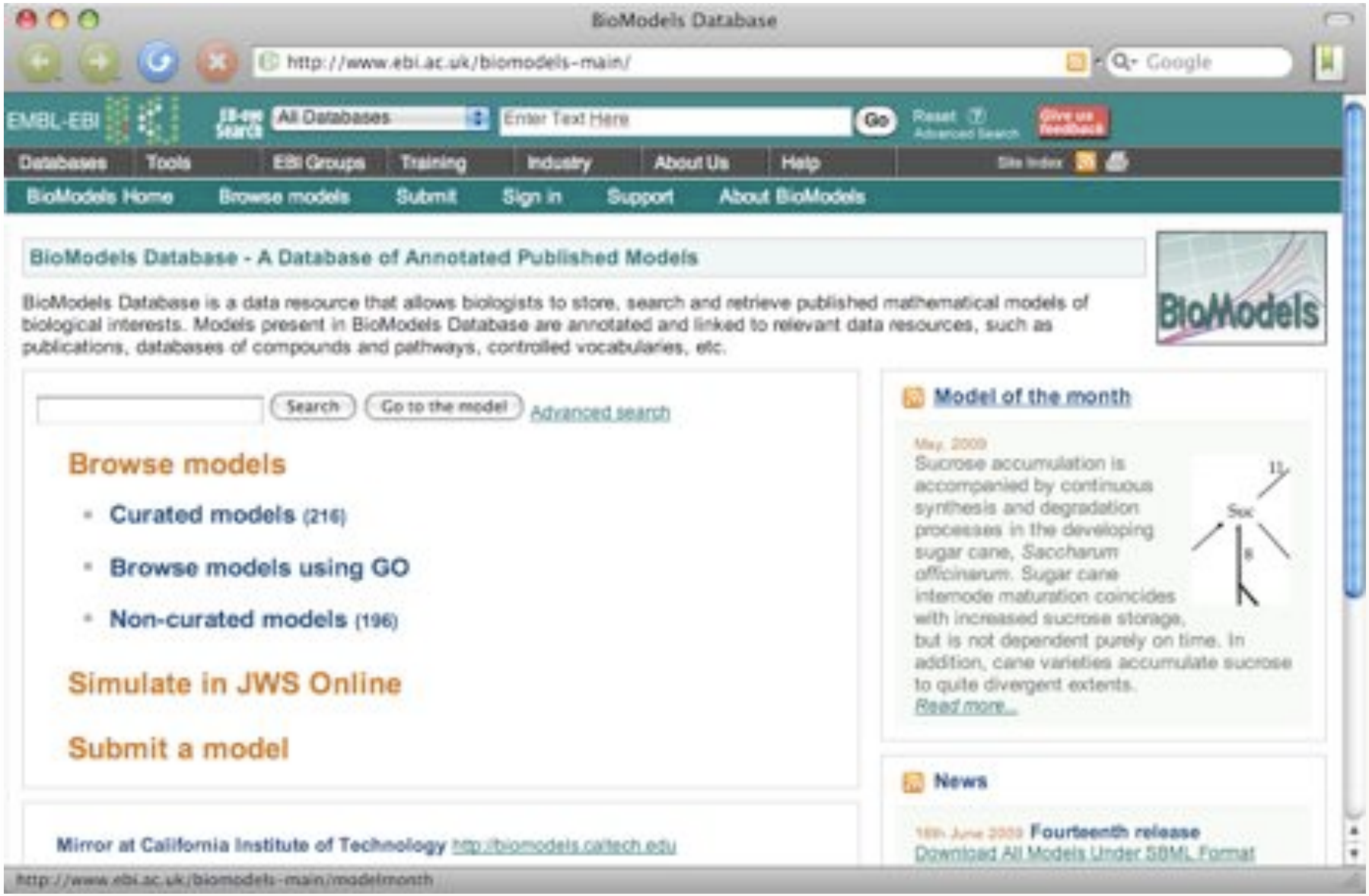
Name E

Initial amount $5 \cdot 10^{-21}$ mol

This species takes part in two reactions (as a reactant in veq and as a product in vcat).

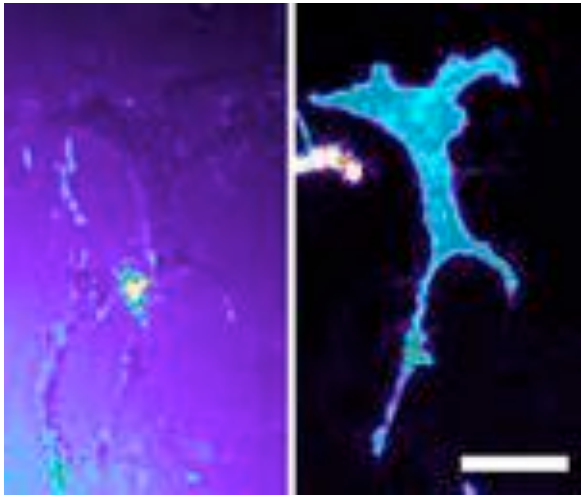
$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E} = v_2 - v_1 \tag{8}$$

es gibt bereits sehr viele Modelle



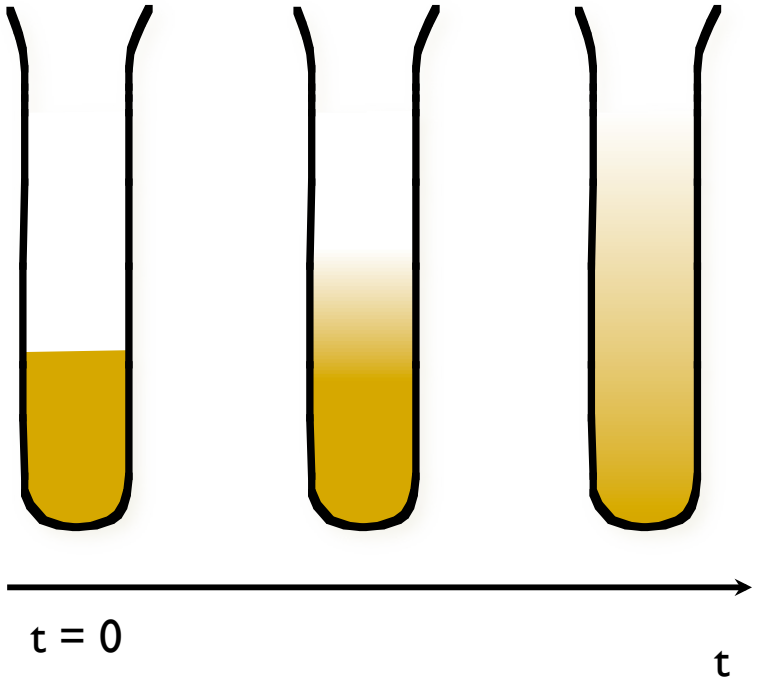
Prozesse in einer Zelle

Schneider und Haugh "Quantitative elucidation of a distinct spatial gradient-sensing mechanism in fibroblasts", *JCB* **171** (2005) 883



PI 3-kinase signaling in response to a transient PDGF gradient. The video depicts the experiment presented in Fig. 5 A of the paper, with TIRF time courses of the extracellular OG 514-dextran gradient (left) and intracellular CFP-AktPH translocation response (right). A CFP-AktPH-transfected fibroblast was stimulated with a moving PDGF gradient for 21 min, after which a uniform bolus of 10 nM PDGF and subsequently wortmannin were added (additions indicated by the flashing screen). The video plays at 7.5 frames/s (150x speed up). Bar, 30 µm.

Diffusion



Diffusion
=> verschmiert Unterschiede

Entwicklung der ortsabh. Dichte
<=> Diffusionsgleichung

$$\rho(\vec{r},t) = \frac{\Delta N(\vec{r},t)}{\Delta V}$$

+ ortsabhängige Quellen und Senken

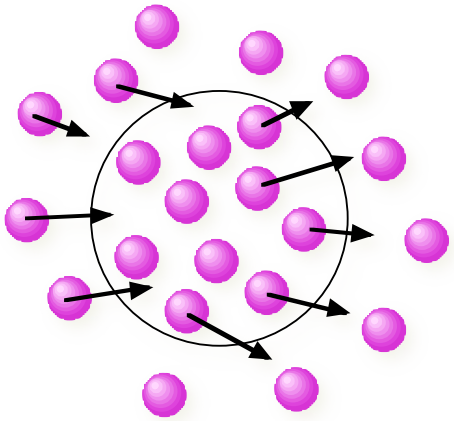
Kontinuitätsgleichung

Zwei Beiträge zur Diffusionsgleichung:

1) Kontinuitätsgleichung: wo bleibt das Material?

$$\frac{\partial \rho(\vec{r},t)}{\partial t} = -\nabla \vec{j}(\vec{r},t) = -\mathrm{div}\ \vec{j}(\vec{r},t)$$

Änderung der Dichte ρ bei (r, t) — Divergenz des Stromes = Quellen und Senken für Teilchen



partielle Ableitung:
=> betrachte nur Änderungen von ρ in der Zeit an einem festgehaltenen Ort r (nicht: Ortsverschiebungen r = r(t))

$$\Delta N = N_{in} - N_{out} = 3 - 5 = -2$$

Diffusionsstrom

2) Diffusionsstrom durch Dichteunterschiede (Gradienten) – Fick'sches Gesetz:

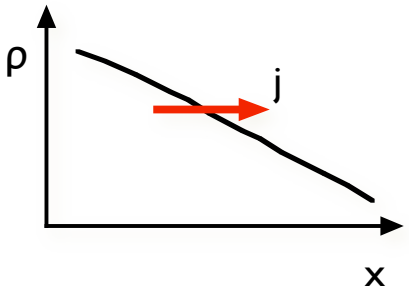
$$\vec{j}(\vec{r},t) = -D\ \nabla\rho(\vec{r},t) = -D\ \text{grad}\ \rho(\vec{r},t)$$

Diffusionstrom bei (r, t)

Strom fließt weg von hohen Dichten

Diffusions–koeffizient

Dichte-fluktuationen (=Gradienten)

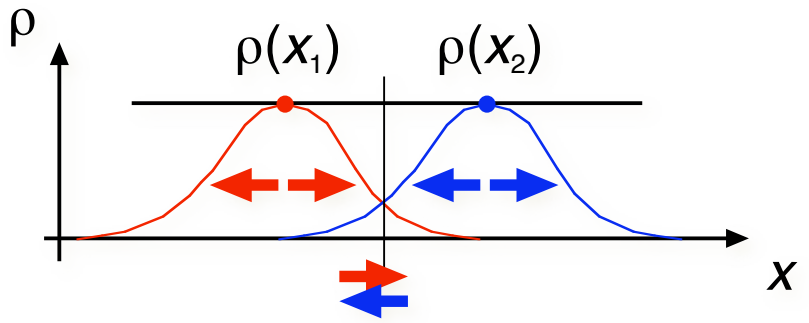


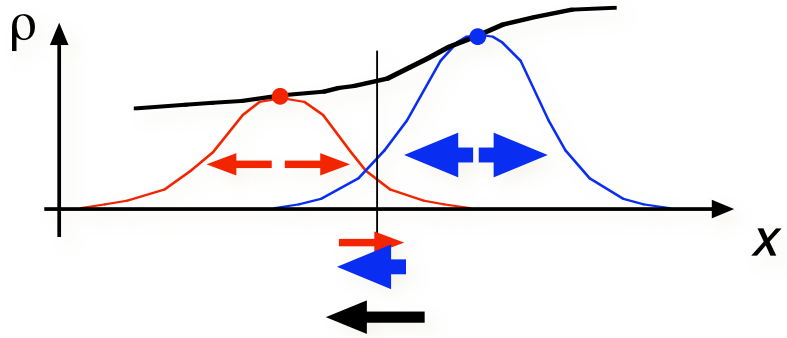
hier: phänomenologischer Umrechnungsfaktor von Dichteunterschieden in Teilchenströme

Diffusion mikroskopisch

Ohne externe Kräfte

=> Teilchen bewegen sich in alle Richtungen gleich wahrscheinlich
(Gauss'sche Wahrscheinlichkeit)





$\rho(x_1) = \rho(x_2) \Rightarrow j_{diff} = 0$

$\rho(x_1) < \rho(x_2) \Rightarrow j_{diff} < 0$

$$j_{diff} \propto -\frac{\rho(x_2) - \rho(x_1)}{x_2 - x_1} \Rightarrow \frac{d\rho}{dx}$$

Gleiche Dichten an x_1 und x_2:
=> gleiche Anzahl Teilchen springt
von x_1 => x_2 wie von x_2 => x_1

Unterschiedliche Dichten:
=> mehr Teilchen springen
von x_2 => x_1 als von x_1 => x_2

Diffusionsgleichung: partielle DGL

Diffusionsstrom

$$\vec{j}(\vec{r},t) = -D\ \nabla\rho(\vec{r},t) = -D\ \text{grad}\ \rho(\vec{r},t)$$

in Kontinuitätsgleichung einsetzen

$$\frac{\partial\rho(\vec{r},t)}{\partial t} = -\nabla\vec{j}(\vec{r},t) = -\text{div}\ \vec{j}(\vec{r},t)$$

=> Diffusionsgleichung:

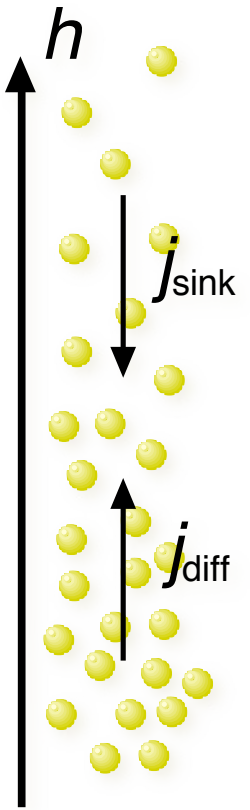
$D(\vec{r},t) = \text{const}$

$$\frac{\partial\rho(\vec{r},t)}{\partial t} = -\nabla(-D\,\nabla\rho(\vec{r},t)) = D\,\Delta\rho(\vec{r},t)$$

=> Vollständige Beschreibung der zeitabhängigen Dichteverteilung
(ohne externe Kräfte)

Zur Boltzmann-Verteilung

Diffusion unter dem Einfluß einer externen Kraft (z.B. Schwerkraft)
=> stationäre Lösung der Diffusionsgleichung



zwei Beiträge

Gravitation
=> Moleküle sinken

$$j_{sink}(h) = v\rho(h) = -\frac{mg}{\gamma}\rho(h)$$

Dichteunterschied
=> Diffusionsstrom

$$j_{diff}(h) = -D\frac{d\rho(h)}{dh}$$

stationärer Zustand: $j_{sink}(h) + j_{diff}(h) = 0$

Mit $D = \frac{k_B T}{\gamma}$ => $\frac{d\rho(h)}{dh} = -\frac{mg}{k_B T}\rho(h)$

$$\rho(h) = \rho_0 \exp\left[-\frac{mgh}{k_B T}\right]$$

stationärer Zustand ist unabhängig von D (aber: Relaxationszeit)

Integration

Bisher: (System von) ODEs

$$\frac{d}{dt}X_i = f_i(X_1, X_2, \ldots)$$

- Zeitentwicklung abhängig von den **lokalen** Werten der Systemparameter
- alle Ableitungen nach der Zeit

Jetzt: Diffusionsgl. mit konstantem D:

$$\frac{\partial \rho(\vec{r},t)}{\partial t} = D\,\Delta\rho(\vec{r},t)$$

- Zeitentwicklung bestimmt durch **globale** Werte (Verteilungen) der Variablen (gesamte Dichte ρ(r) nötig für Gradient)
- Ableitungen nach **Zeit und Ort**

FTCS–Integrator

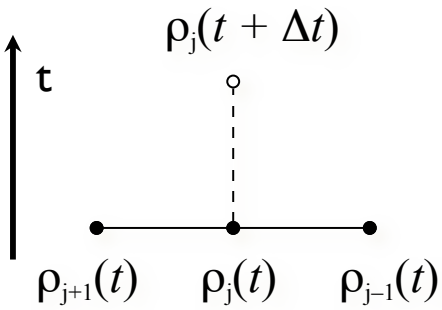
Diffusionsgleichung mit konstantem D in 1D:

$$\frac{\partial \rho(\vec{x},t)}{\partial t} = D \frac{\partial^2 \rho(\vec{x},t)}{\partial x^2}$$

Direkte Implementierung auf einem Gitter $\{\rho(x_i)\}$ mit Abstand Δx:

$$\frac{\rho_j(t+\Delta t)-\rho_j(t)}{\Delta t} = D \frac{\rho_{j+1}(t)-2\rho_j(t)+\rho_{j-1}(t)}{\Delta x^2}$$

Forward in **T**ime **C**entered in **S**pace



Propagationsschritt:

$$\rho_j(t+\Delta t) = \rho_j(t) + \Delta t\, D \frac{\rho_{j+1}(t)-2\rho_j(t)+\rho_{j-1}(t)}{\Delta x^2}$$

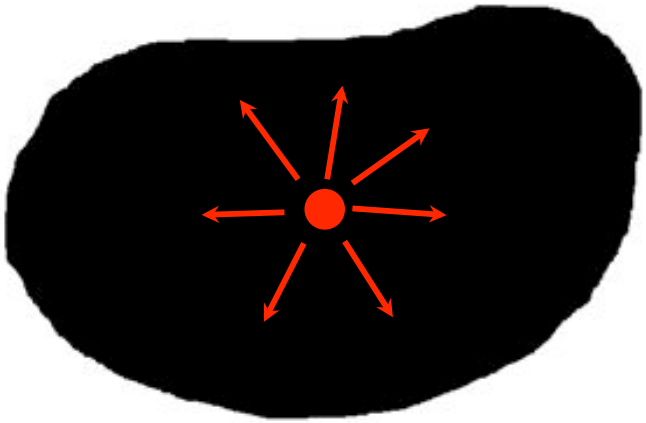
Stabil für: $\Delta t \leq \frac{\Delta x^2}{2D}$ (Δt < DIffusionszeit über Abstand Δx)

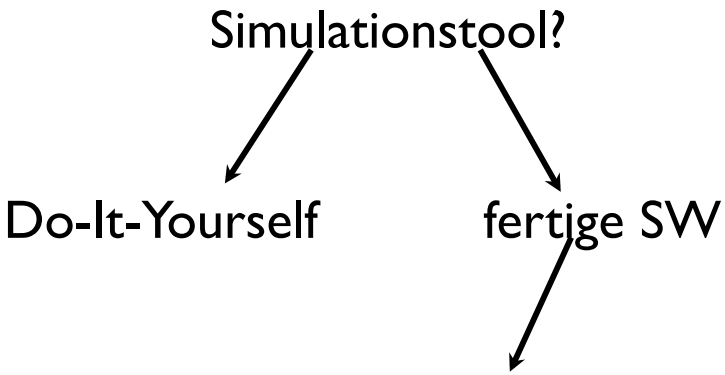
Beispiel: Diffusion

Moleküle werden bei x_s produziert und in der ganzen Zelle abgebaut

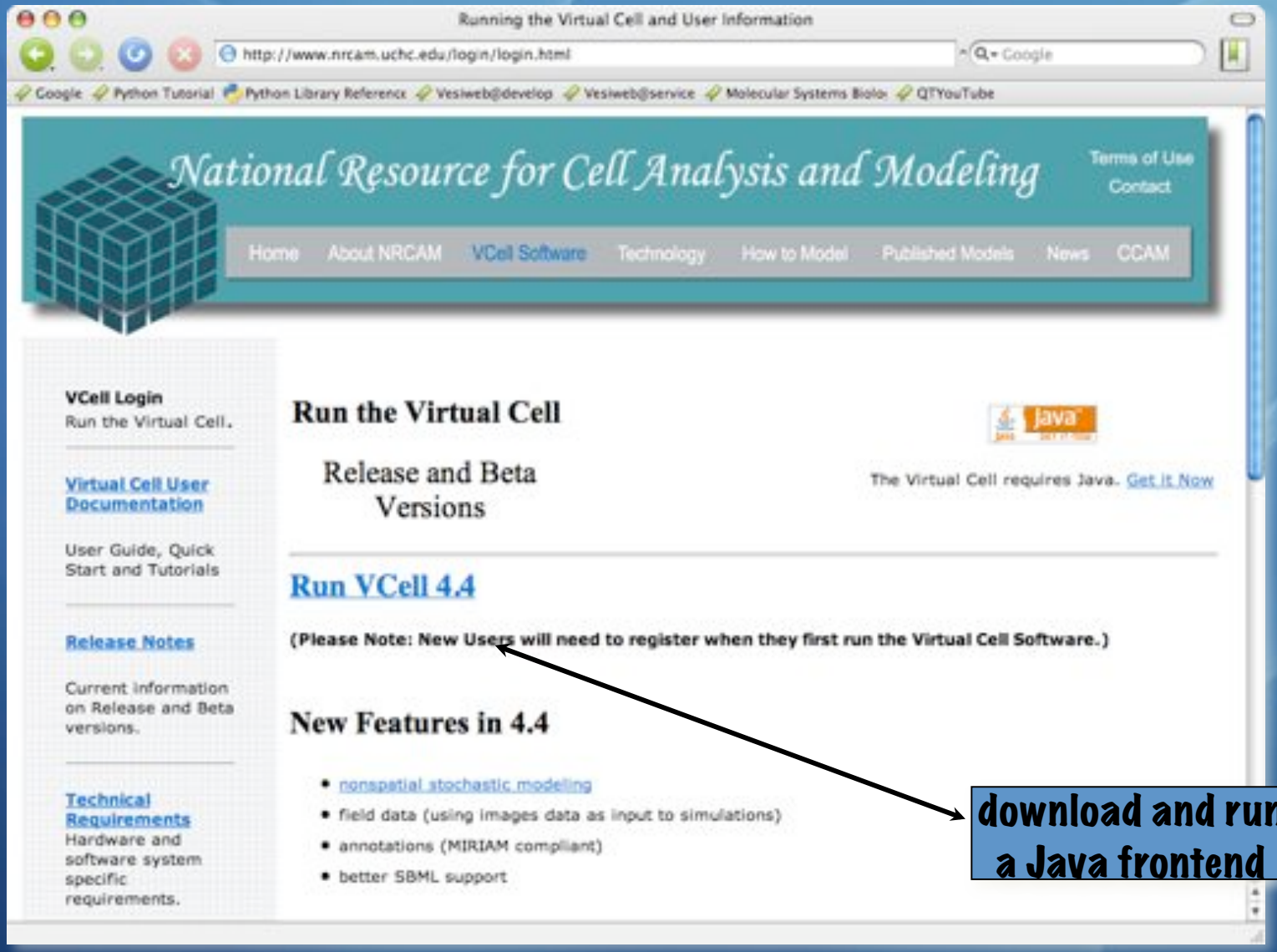
Diffusion in beliebiger Geometrie:

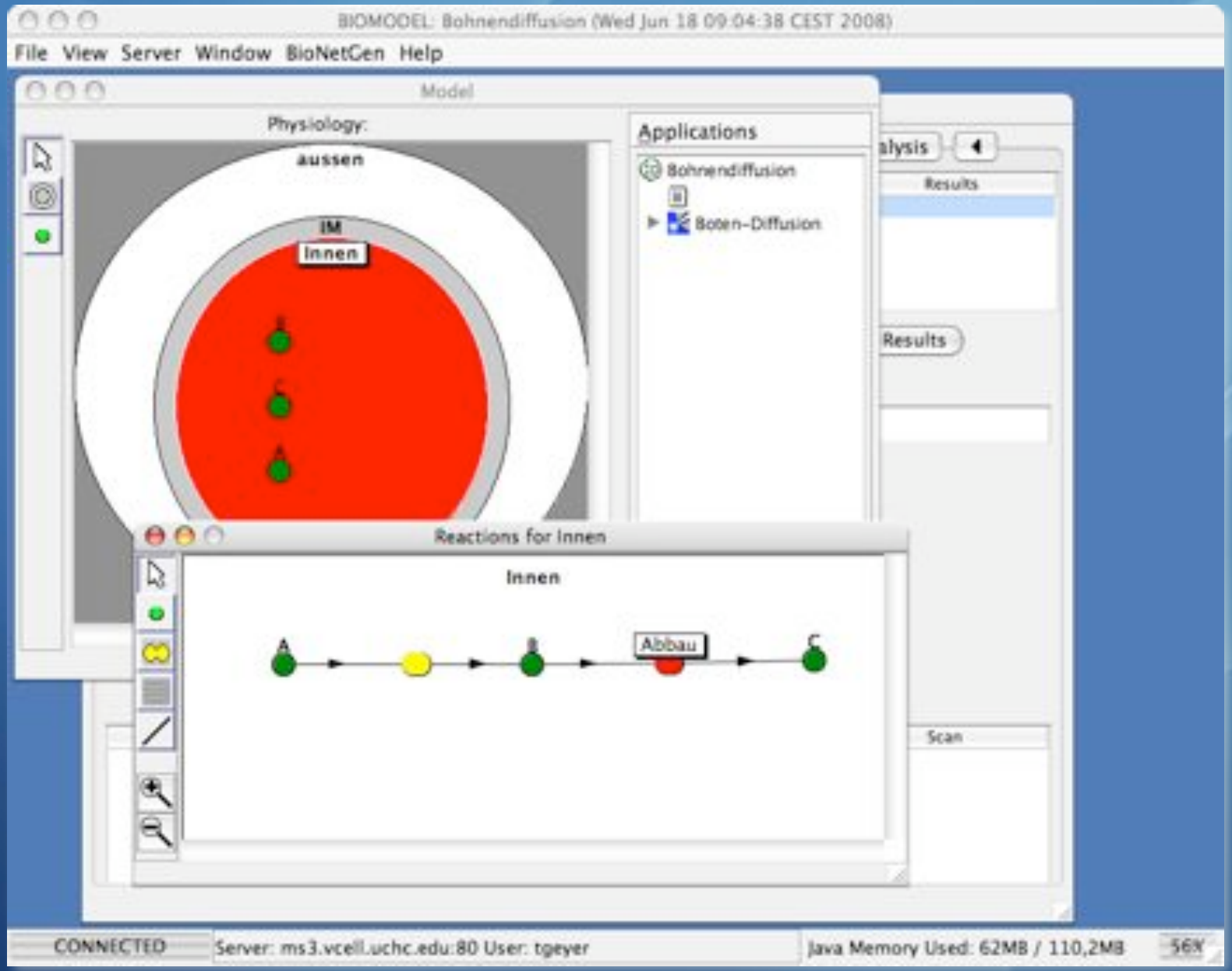
=> Einfluß der Wände?

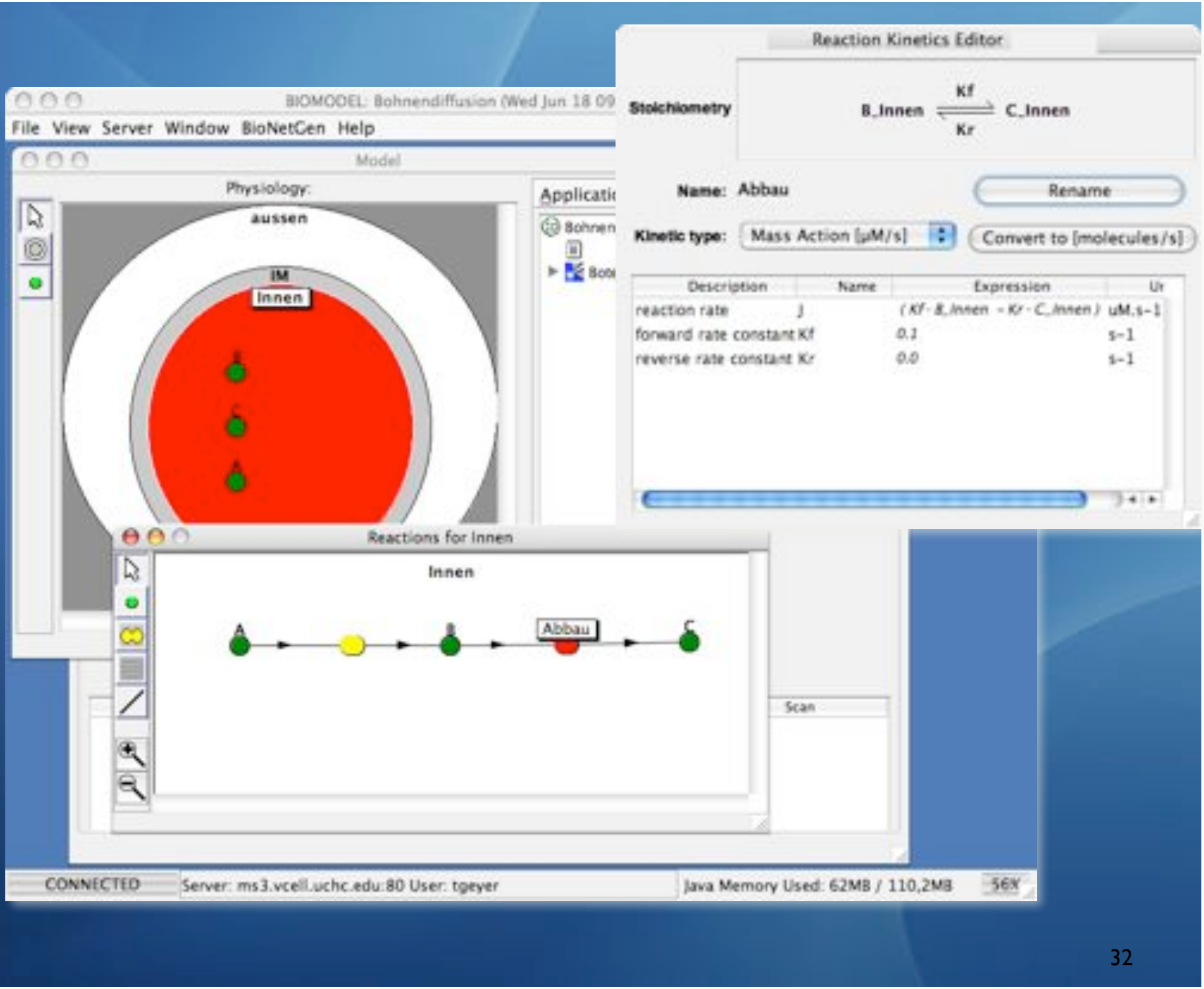


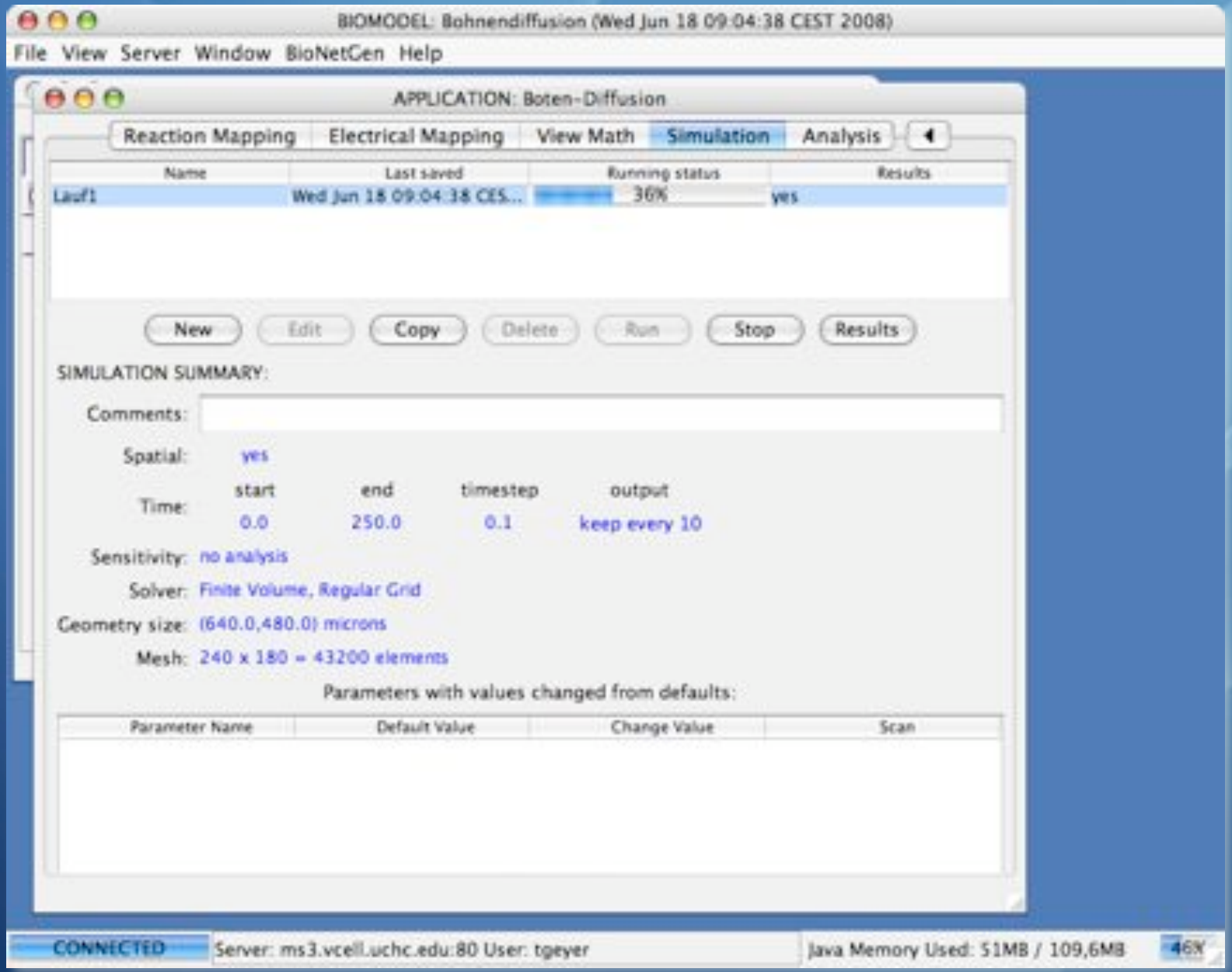


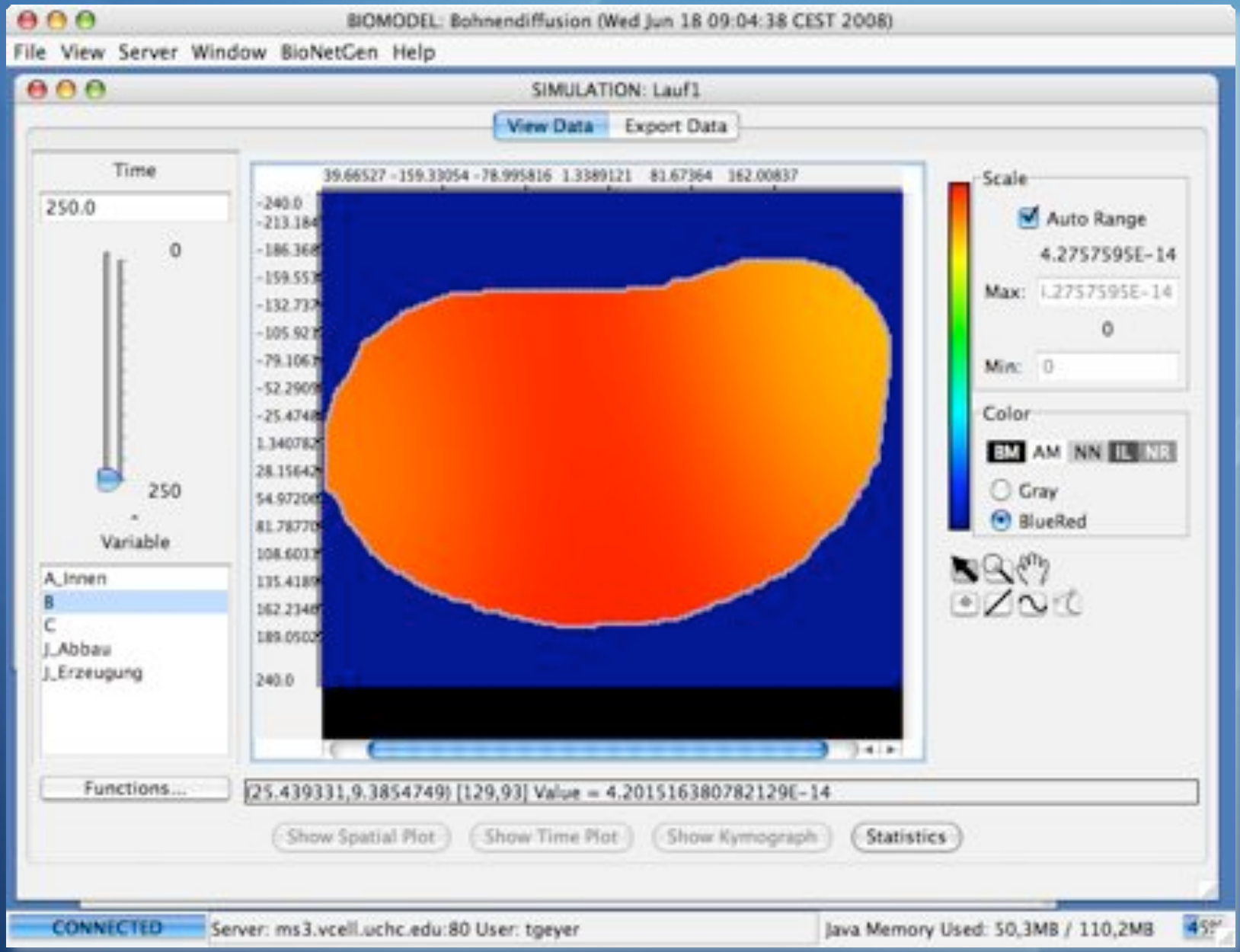
- Reaktions-Diffusions-Systeme
- kontinuierliche und stochastische Integration
- frei definierbare Geometrien (Fotos)
- lokales Java-Frontend + Cluster @ NRCAM


Running the Virtual Cell and User Information
http://www.nrcam.uchc.edu/login/login.html
National Resource for Cell Analysis and Modeling
Terms of Use
Contact
Home
About NRCAM
VCell Software
Technology
How to Model
Published Models
News
CCAM
VCell Login
Run the Virtual Cell.
Virtual Cell User Documentation
User Guide, Quick Start and Tutorials
Release Notes
Current information on Release and Beta versions.
Technical Requirements
Hardware and software system specific requirements.
Run the Virtual Cell
Release and Beta Versions
The Virtual Cell requires Java. Get It Now
Run VCell 4.4
(Please Note: New Users will need to register when they first run the Virtual Cell Software.)
New Features in 4.4
nonspatial stochastic modeling
field data (using images data as input to simulations)
annotations (MIRIAM compliant)
better SBML support
download and run a Java frontend


BIOMODEL: Bohnendiffusion (Wed Jun 18 09:04:38 CEST 2008)
File View Server Window BioNetGen Help
Model
Physiology:
aussen
IM
Innen
Applications
Bohnendiffusion
Boten-Diffusion
Results
Results
Scan
Reactions for Innen
Innen
Abbau
CONNECTED
Server: ms3.vcell.uchc.edu:80 User: tgeyer
Java Memory Used: 62MB / 110,2MB


Reaction Kinetics Editor
Stoichiometry
B_Innen
Kf
Kr
C_Innen
Name: Abbau
Rename
Kinetic type: Mass Action [μM/s]
Convert to [molecules/s]
Description
Name
Expression
reaction rate
forward rate constant
reverse rate constant
BIOMODEL: Bohnendiffusion (Wed Jun 18 09
File View Server Window BioNetGen Help
Model
Physiology:
aussen
IM
Innen
Reactions for Innen
Innen
Abbau
Scan
CONNECTED
Server: ms3.vcell.uchc.edu:80 User: tgeyer
Java Memory Used: 62MB / 110,2MB

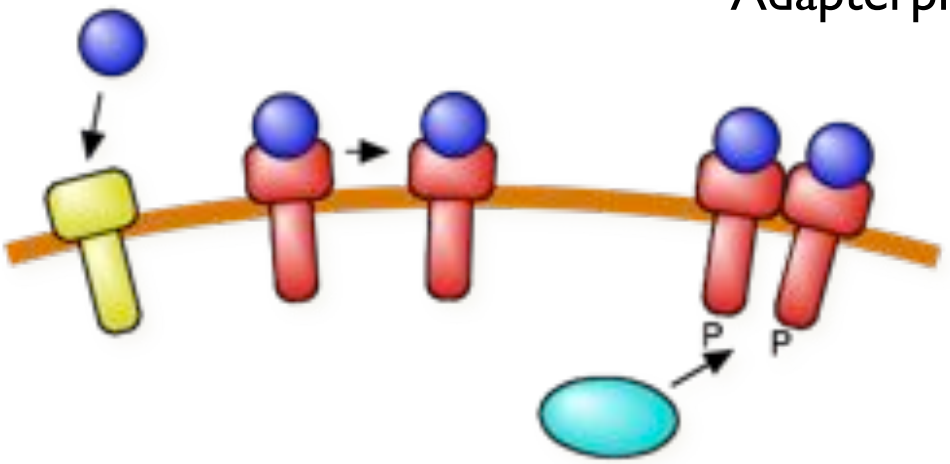

BIOMODEL: Bohnendiffusion (Wed Jun 18 09:04:38 CEST 2008)
File View Server Window BioNetGen Help
APPLICATION: Boten-Diffusion
Reaction Mapping
Electrical Mapping
View Math
Simulation
Analysis
Name
Last saved
Running status
Results
Lauf1
Wed Jun 18 09:04:38 CES...
36%
yes
New
Edit
Copy
Delete
Run
Stop
Results
SIMULATION SUMMARY:
Comments:
Spatial: yes
Time:
start
end
timestep
output
0.0
250.0
0.1
keep every 10
Sensitivity: no analysis
Solver: Finite Volume, Regular Grid
Geometry size: (640.0,480.0) microns
Mesh: 240 x 180 = 43200 elements
Parameters with values changed from defaults:
Parameter Name
Default Value
Change Value
Scan
CONNECTED
Server: ms3.vcell.uchc.edu:80 User: tgeyer
Java Memory Used: 51MB / 109,6MB


BIOMODEL: Bohnendiffusion (Wed Jun 18 09:04:38 CEST 2008)
File View Server Window BioNetGen Help
SIMULATION: Lauf1
View Data
Export Data
Time
250.0
0
250
Variable
A_Innen
B
C
J_Abbau
J_Erzeugung
Scale
Auto Range
4.2757595E-14
Max:
0
Min:
0
Color
BM AM NN IL NR
Gray
BlueRed
Functions...
Show Spatial Plot
Show Time Plot
Show Kymograph
Statistics
CONNECTED
Server: ms3.vcell.uchc.edu:80 User: tgeyer
Java Memory Used: 50,3MB / 110,2MB

Kombinatorische Komplexität

Einfaches Modellsystem:

- externer monovalenter Ligand
- monovalente Rezeptor-Kinase
- Adapterprotein im Zytosol



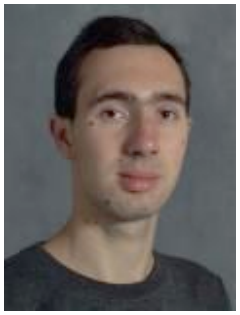
Reaktionen:

- Rezeptor + Ligand
- Rezeptor-Dimere
- Phosphorylierung des Rezeptors
- Bindung des Adapterproteins

3 Spezies + 5 Regeln => 14 Kombinationen im Modell

BioNetGen: Regelbasierter "Biological Network Generator"

BioNetGen


J. R. Faeder, M. L. Blinov, and W. S. Hlavacek. "Rule-Based Modeling of Biochemical Systems with BioNetGen."
In Methods in Molecular Biology: Systems Biology, Ed. I.V. Maly, Humana Press, Totowa, NJ, 2009

BioNetGen@VirtualCell

toy1.bngl

```
begin parameters
  1 L0   1
  2 R0   1
  3 A0   5
  4 kp1  0.5
  5 km1  0.1
  6 kp2  1.1
  7 km2  0.1
  8 p1   10
  9 d1   5
 10 kpA  1e1
 11 kmA  0.02
end parameters

begin species
  1  L(r)       L0  # Ligand has one site for binding to receptor.
                    # L0 is initial concentration
  2  R(l,d,Y~U) R0  # Dimer has three sites: l for binding to a ligand,
                    # d for binding to another receptor, and
                    # Y - tyrosine. Initially Y is unphosphorylated, Y~U.
  3  A(SH2)     A0  # A has a single SH2 domain that binds phosphotyrosine
end species


begin reaction rules

# Ligand binding (L+R)
# Note: specifying r in R here means that the r component must not
#       be bound.  This prevents dissociation of ligand from R
#       when R is in a dimer.
  1  L(r) + R(l,d) <-> L(r!1).R(l!1,d) kp1, km1

# Aggregation (R-L + R-L)
# Note:  R must be bound to ligand to dimerize.
  2  R(l!+,d) + R(l!+,d) <-> R(l!+,d!2).R(l!+,d!2) kp2, km2

# Transphosphorylation
# Note:  R must be bound to another R to be transphosphorylated.
  3  R(d!+,Y~U) -> R(d!+,Y~P) p1

# Dephosphorylation
# Note:  R can be in any complex, but tyrosine is not protected by bound A.
  4  R(Y~P) -> R(Y~U) d1

# Adaptor binding phosphotyrosine (reversible).
# Note: Doesn't depend on whether R is bound to
#       receptor, i.e. binding rate is same whether R is a monomer, is
#       in association with a ligand, in a dimer, or in a complex.

  5  R(Y~P) + A(SH2) <-> R(Y~P!1).A(SH2!1) kpA, kmA
end reaction rules

begin observables
  Molecules R_dim  R(d!+)      # All receptors in dimer
  Molecules R_phos R(Y~P!?)    # Total of all phosphotyrosines
  Molecules A_R    A(SH2!1).R(Y~P!1) # Total of all A's associated with phosphotyrosines
  Molecules A_tot  A()     # Total of A. Should be a constant during simulation.
  Molecules R_tot  R()     # Total of R. Should be a constant during simulation.
  Molecules L_tot  L()     # Total of L. Should be a constant during simulation.
end observables


generate_network();
writeSBML();
simulate_ode({t_end=>50,n_steps=>20});
```

BioNetGen-Input für das Rezeptor-System von S 35

Zusammenfassung

SBML:

- hierarchisches XML-Schema
- es gibt viel Software, die SBML lesen und schreiben kann

Diffusion:

- Diffusionsgleichung
- Simulation mit "The Virtual Cell" im Tutorial nächste Woche

Kombinatorische Komplexität

- BioNetGen