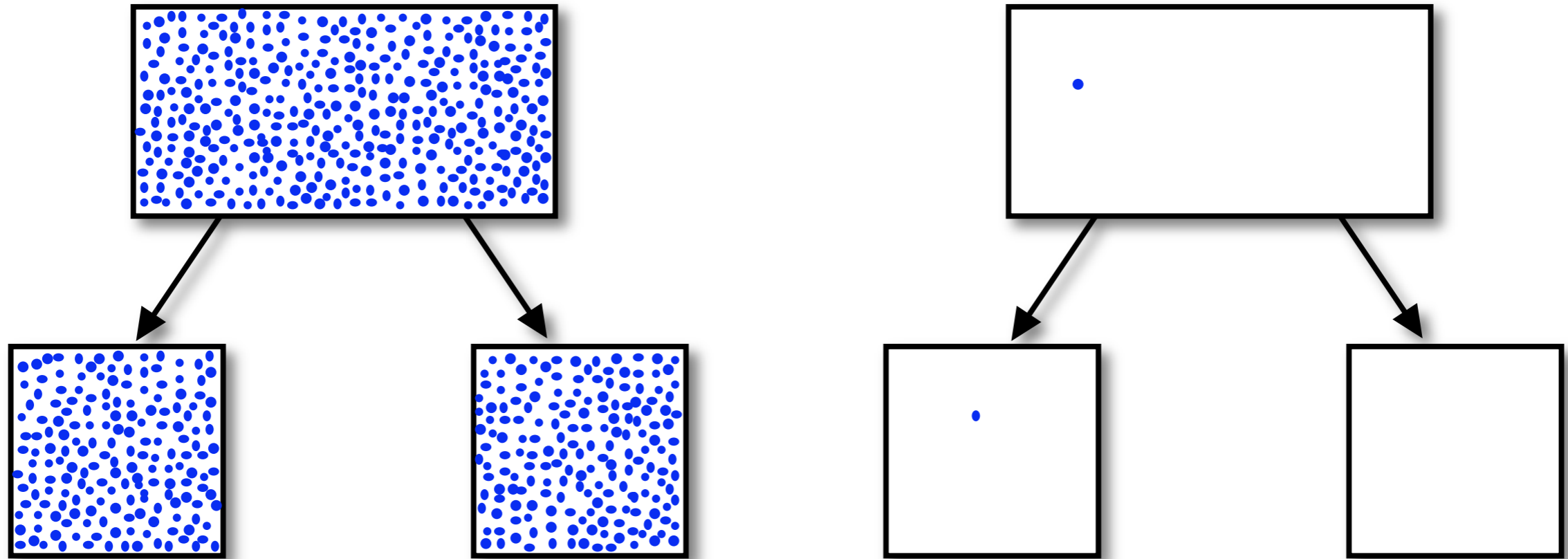


V12

Stochastische Effekte + Diffusion

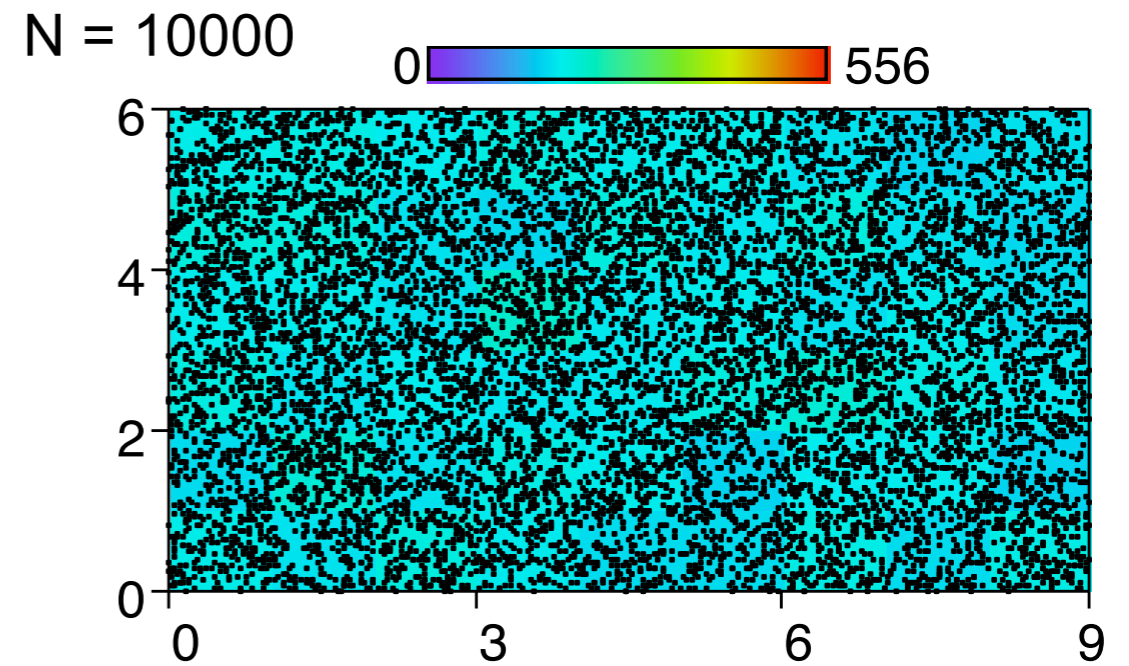
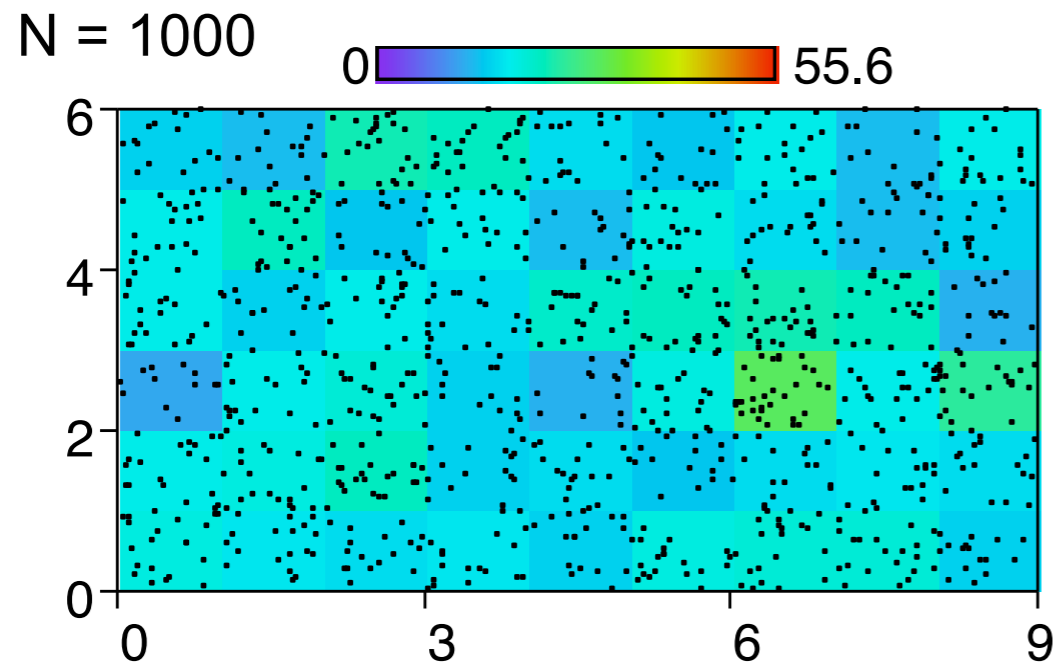
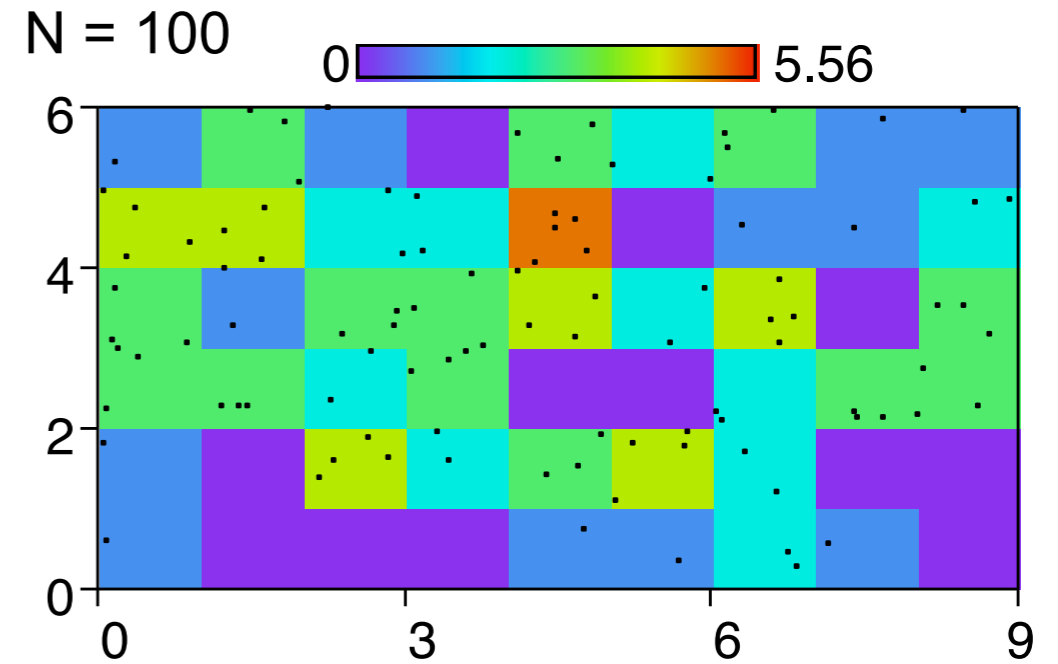
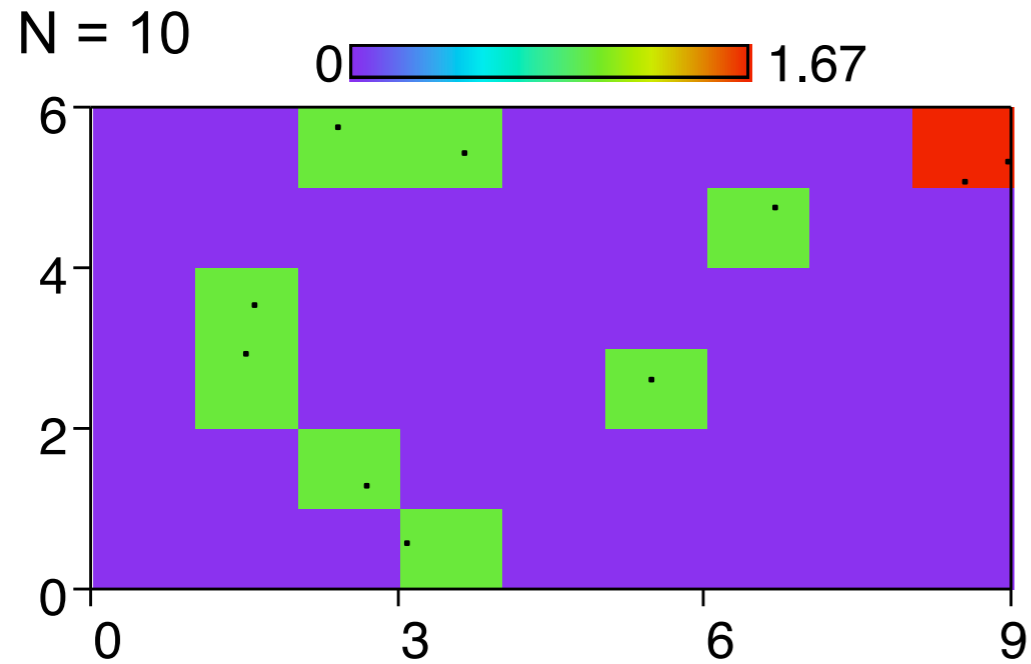
29. Januar 2015

Stochastische Effekte



$$\text{Dichte} = \frac{\text{ununterscheidbare Teilchen}}{\text{Volumen}}$$

Dichtefluktuationen



Poisson-Verteilung

Betrachte Kontinuum w mit im Mittel λ Ereignissen pro Einheitsintervall Δw

Annahmen:

- i) Seltenheit: $\ll 1$ Ereignisse in $[w, w+\Delta w]$, höchstens ein Ereignis
- ii) Proportionalität: $\langle N \rangle = \lambda \Delta w$
- iii) Geschichtslosigkeit (Markov-Prozess)

Wahrscheinlichkeit, dass k Ereignisse pro Einheitszeitintervall auftreten:

$$p_k = \frac{\lambda^k}{k!} e^{-\lambda}$$

Mittelwert: $\langle k \rangle = \sum k p_k = \lambda$

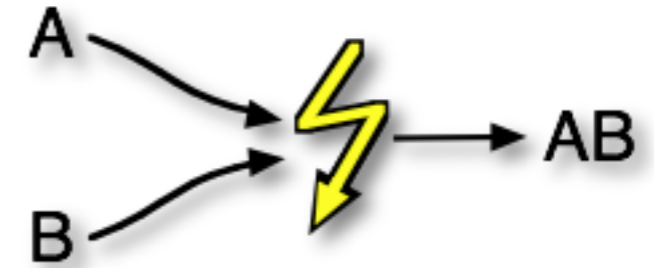
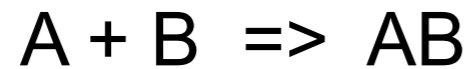
Varianz: $\sigma^2 = \sum p_k (k - \langle k \rangle)^2 = \lambda$

Relative Streuung (Fehler): $\frac{\Delta k}{k} = \frac{\sigma}{\langle k \rangle} = \frac{1}{\sqrt{\lambda}}$

Mittlere Teilchenzahl	100	1000	1 Mol
relative Unsicherheit	10%	3%	1e-12

Reaktionen im Teilchenbild

Assoziation:



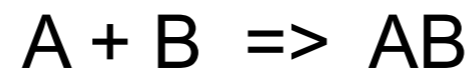
Kontinuierliche Ratengleichung: $\frac{d[AB]}{dt} = k[A][B]$

Anzahl neuer AB in V während Δt :

$$\begin{aligned}\Delta N_{AB} &= \frac{d[AB]}{dt} V \Delta t \\ &= k_{AB} \frac{N_A}{V} \frac{N_B}{V} V \Delta t \\ &= \frac{k_{AB} \Delta t}{V} N_A N_B \\ &= P_{AB} N_A N_B\end{aligned}$$

Reaktionsrate $k_{AB} \Rightarrow$ Reaktionswahrscheinlichkeit P_{AB}

Direkte Implementierung



```
Continuous_AB.py
# continuous association of A and B

# parameter
tEnd = 5.0
dt = 0.01
volume = 100.0

# rate and probability
kAB = 1.0
prob = kAB * dt / volume

# initial conditions: particle numbers
A = 1000
B = 1000
AB = 0

# convert to densities
A = A/volume
B = B/volume
AB = AB/volume

# main loop
t = 0.0
print t, "\t", A, "\t", B, "\t", AB

while(t<tEnd):
    dAB = dt * kAB * A * B

    AB += dAB
    A -= dAB
    B -= dAB

    # increment time and output
    t += dt
    print t, "\t", A, "\t", B, "\t", AB
```

```
Stochastic_AB.py
# Stochastic association of A + B => AB

import random

# parameter
tEnd = 5.0
dt = 0.01
volume = 100.0

# rate and probability
kAB = 1.0
prob = kAB * dt / volume

# initial conditions
A = 1000
B = 1000
AB = 0

# main loop
t = 0.0
print t, "\t", A/volume, "\t", B/volume, "\t", AB/volume

while(t<tEnd):
    dAB = 0
    # check for every pair A, B
    for ia in xrange(A):
        for ib in xrange(B):
            r = random.random()
            if (r < prob):
                dAB+=1

    AB += dAB
    A -= dAB
    B -= dAB

    # increment time and output
    t += dt
    print t, "\t", A/volume, "\t", B/volume, "\t", AB/volume
```

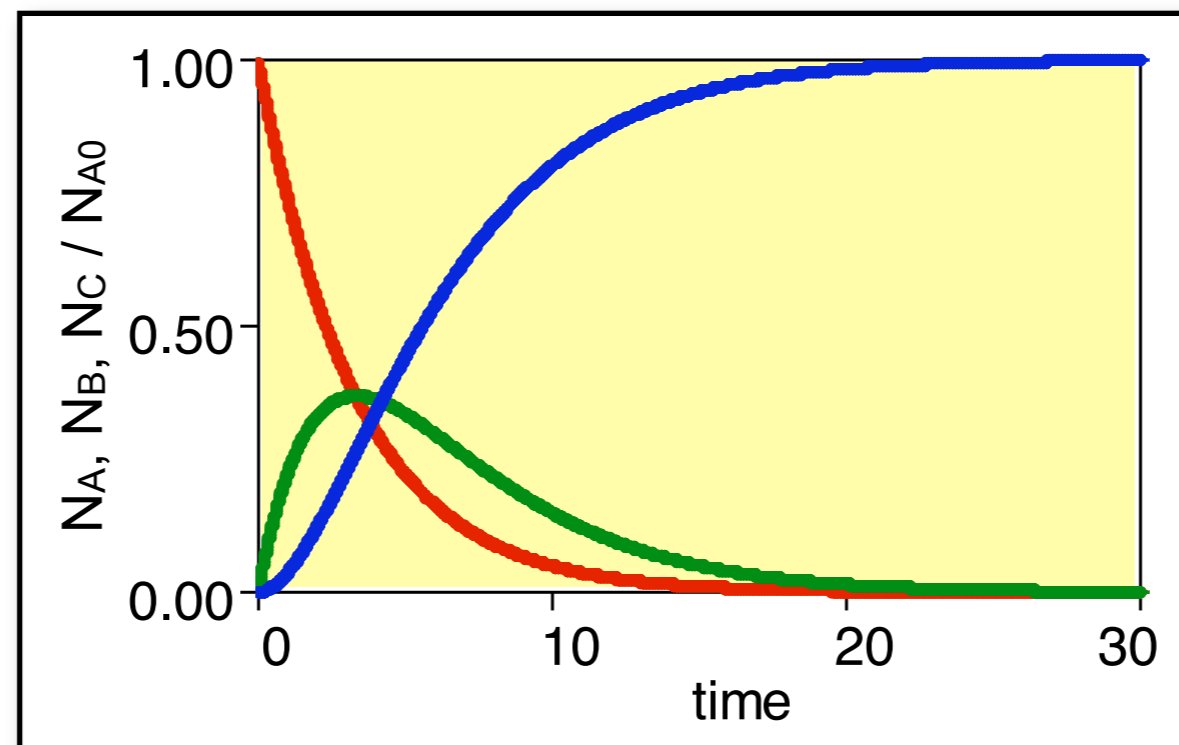
Achtung: didaktische Implementierungen!

Beispiel: Reaktions-Kette



Raten: $\frac{dA}{dt} = -k_1 A$ $\frac{dB}{dt} = k_1 A - k_2 B$ $\frac{dC}{dt} = k_2 B$

Zeitentwicklung aus den kontinuierlichen Raten:



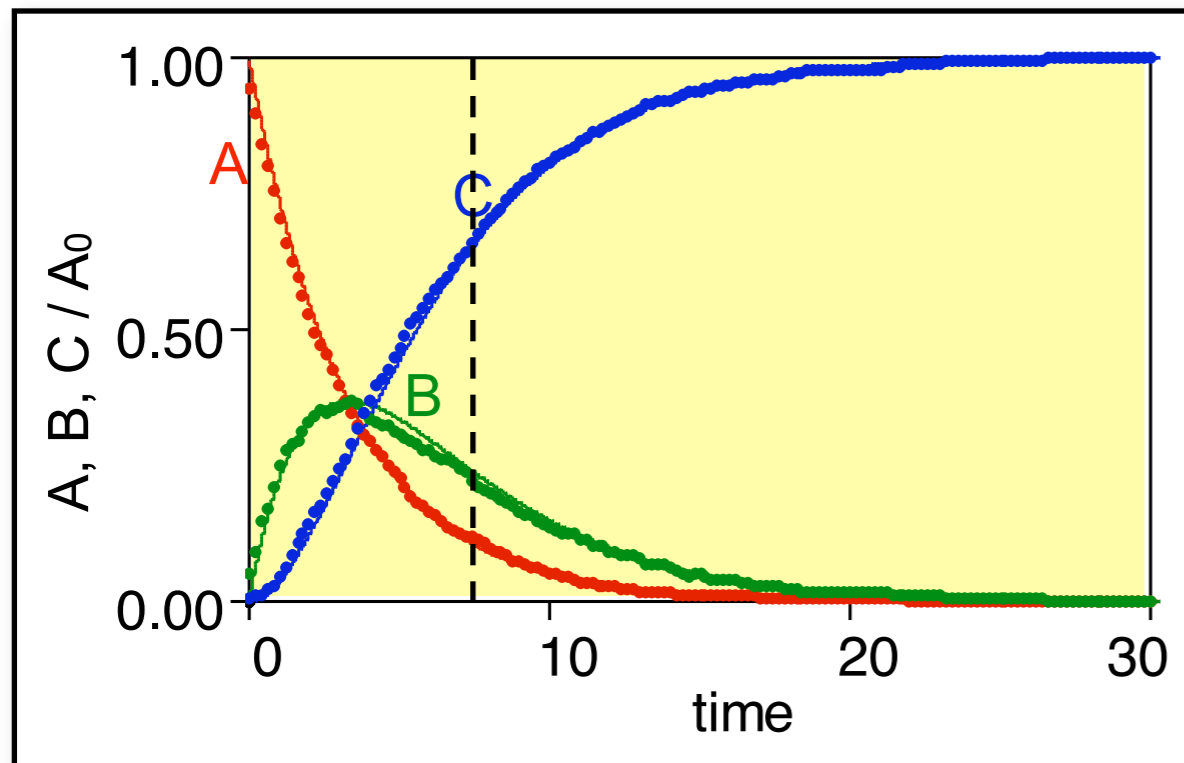
$$k_1 = k_2 = 0.3$$

Stochastische Simulation

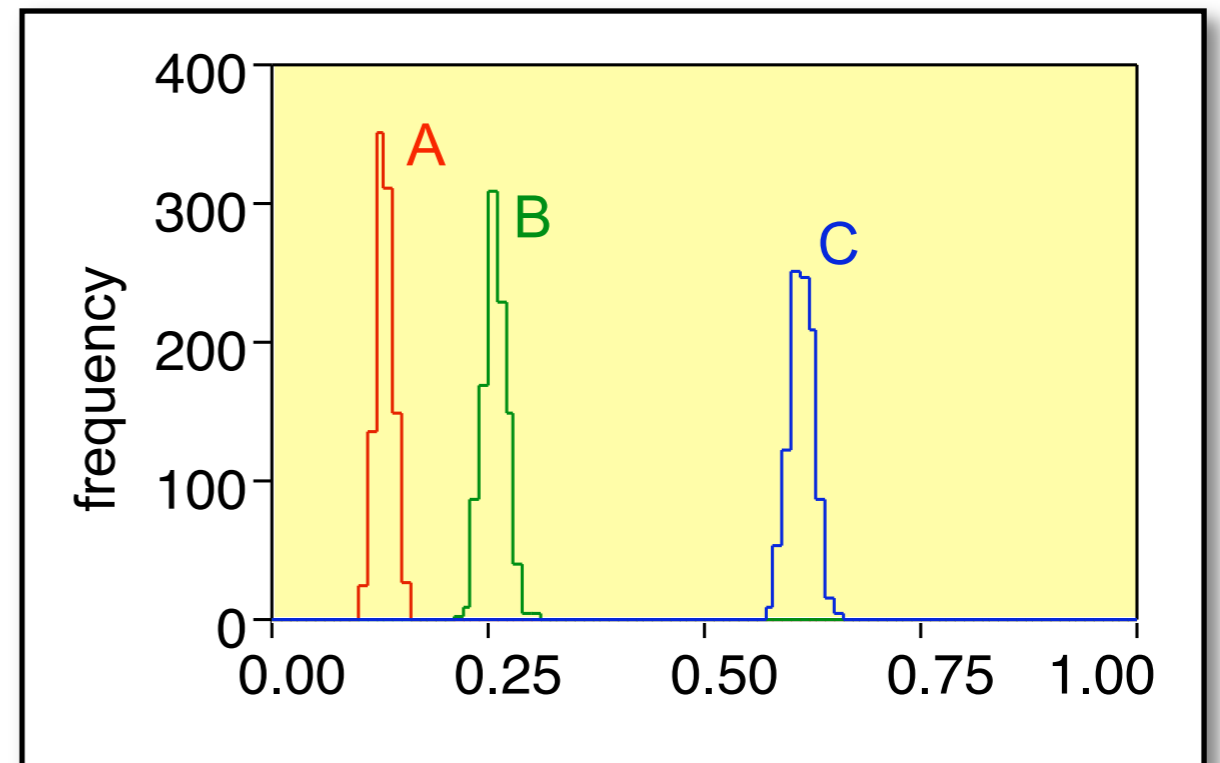


$A_0 = 1000$ Teilchen bei $t = 0$

$t = 7$



$k_1 = k_2 = 0.3$

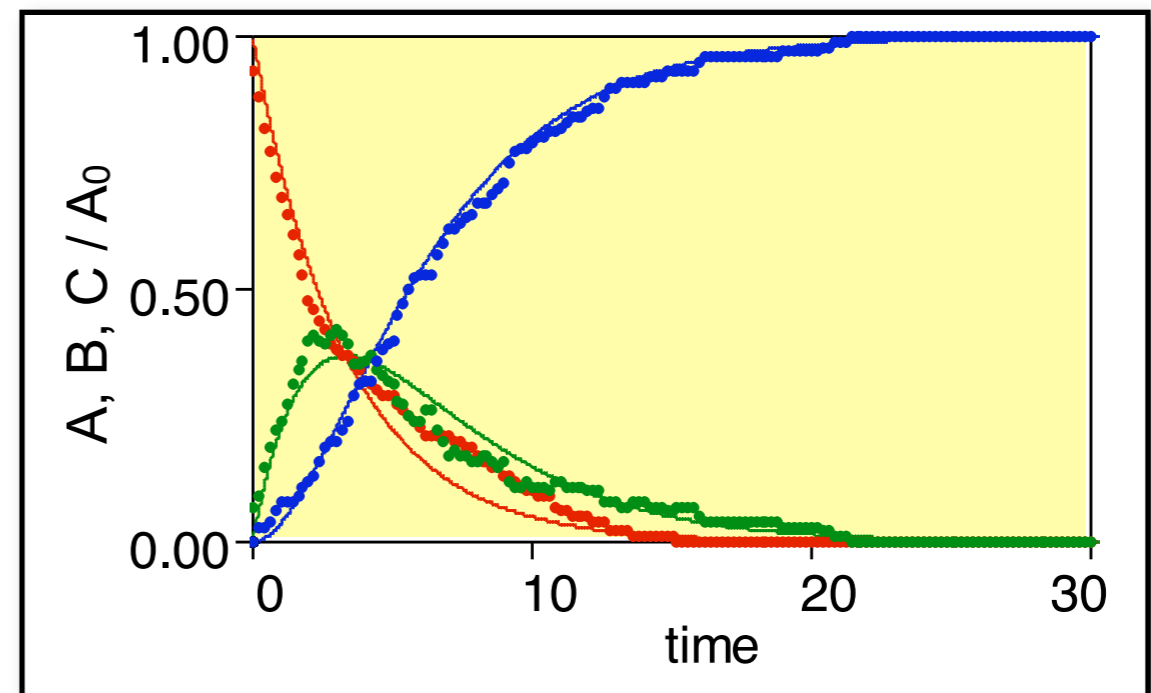
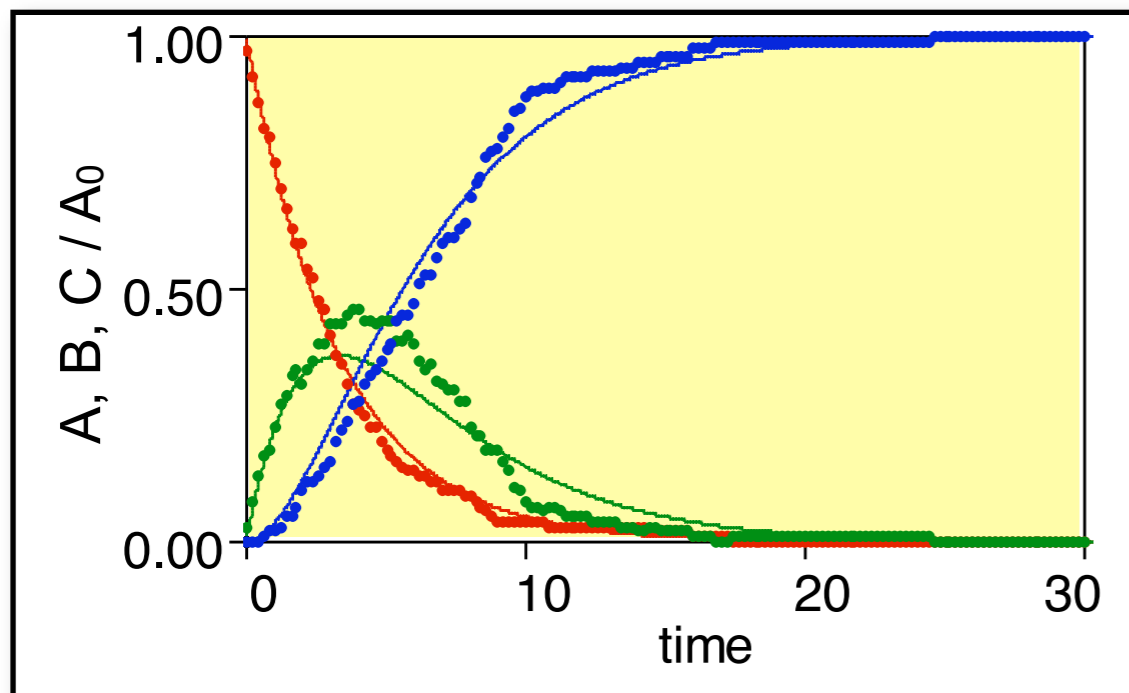
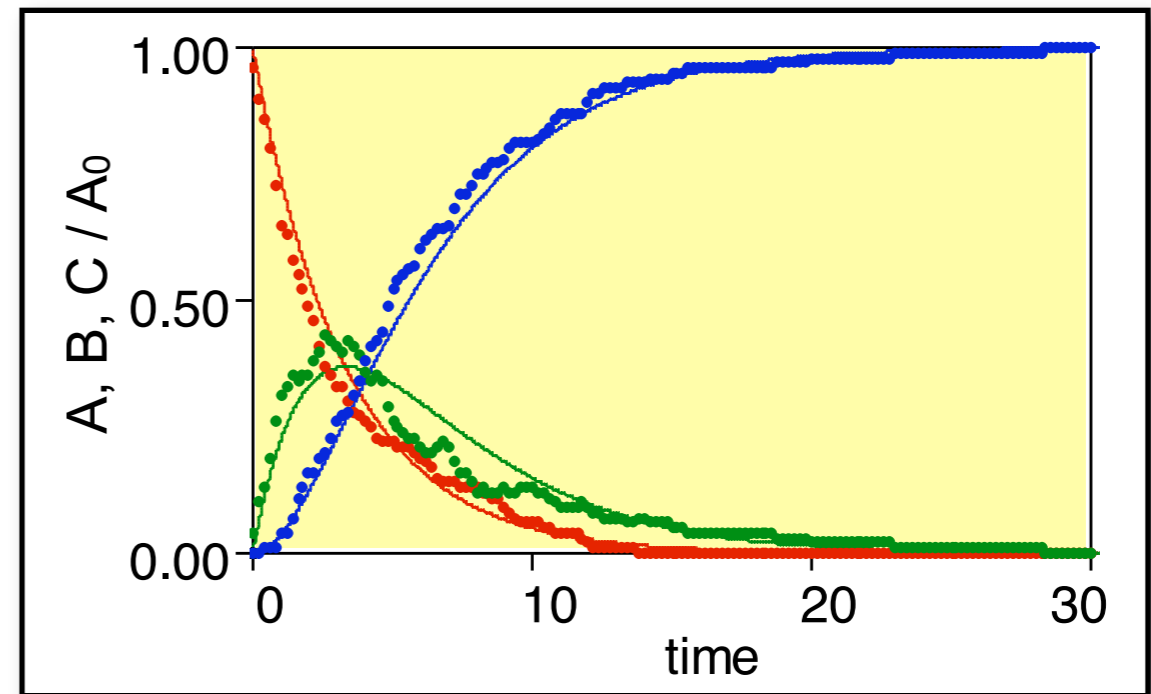
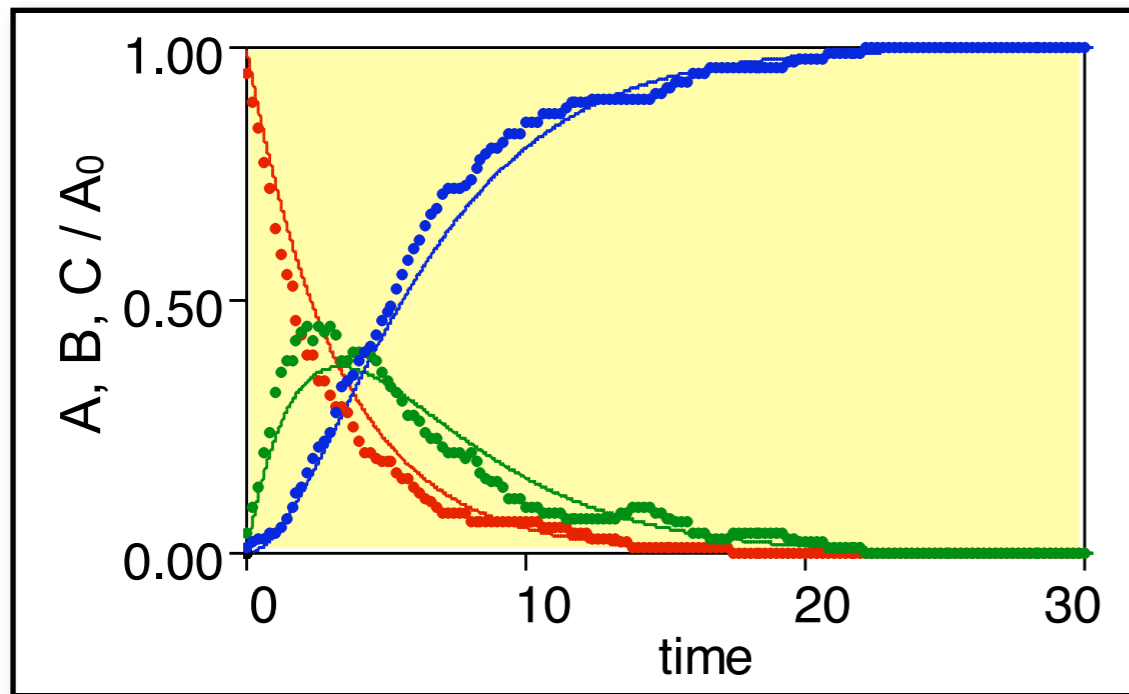


Werte bei $t = 7$ (1000 Läufe)

=> Fluktuationen

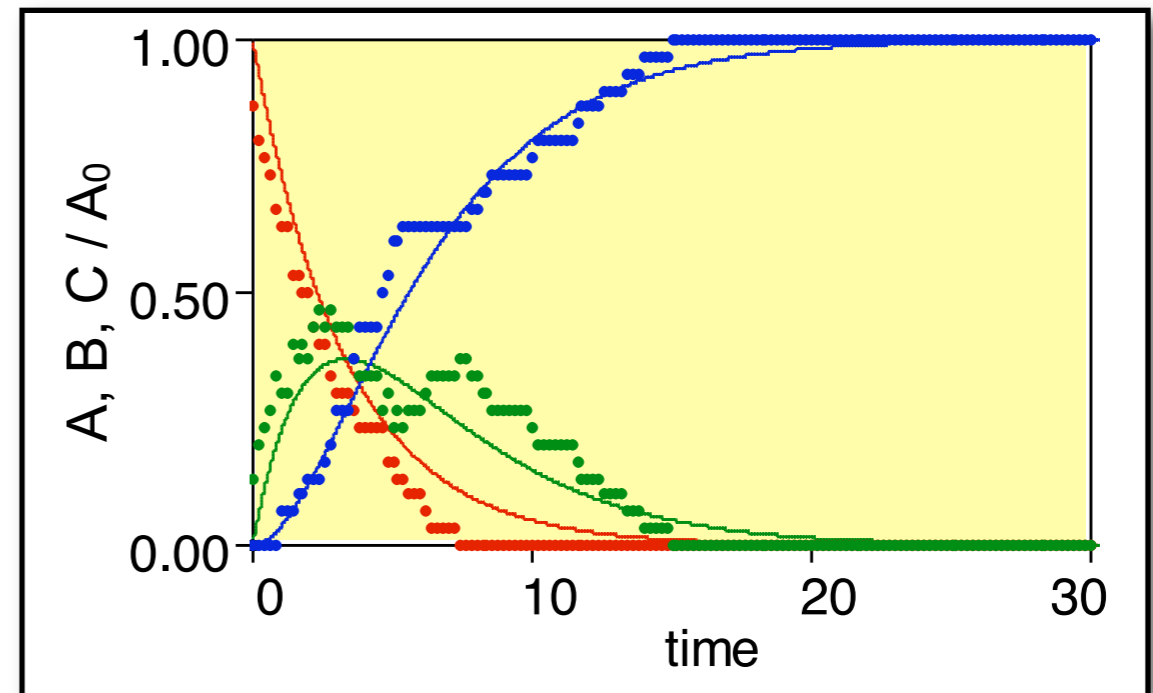
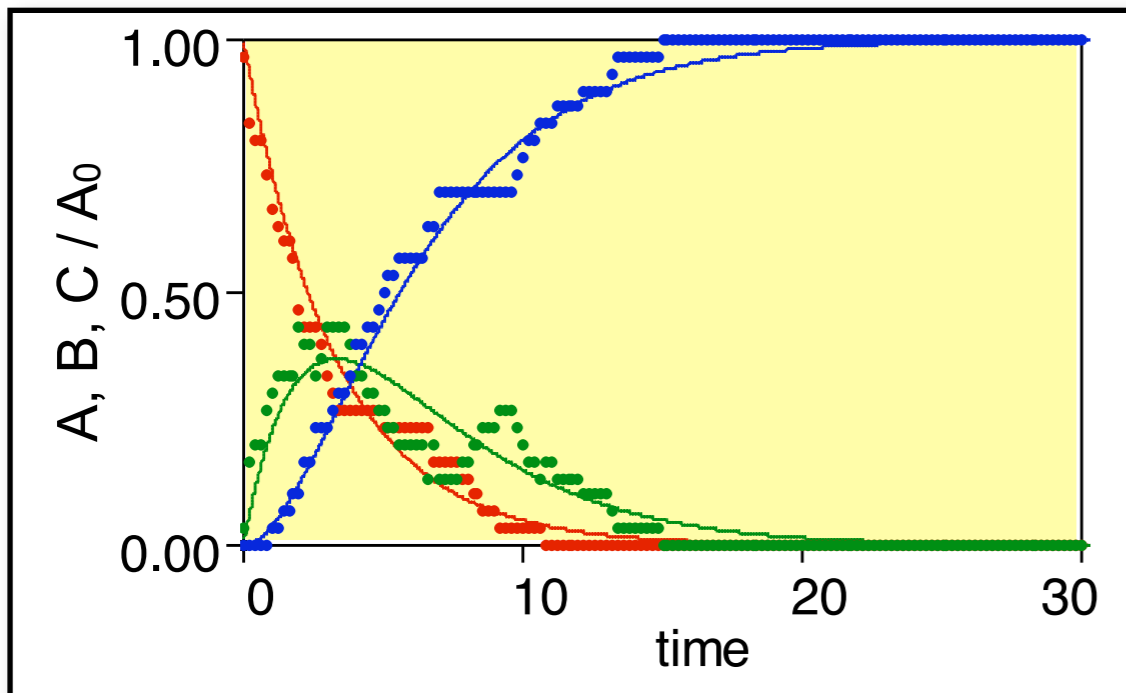
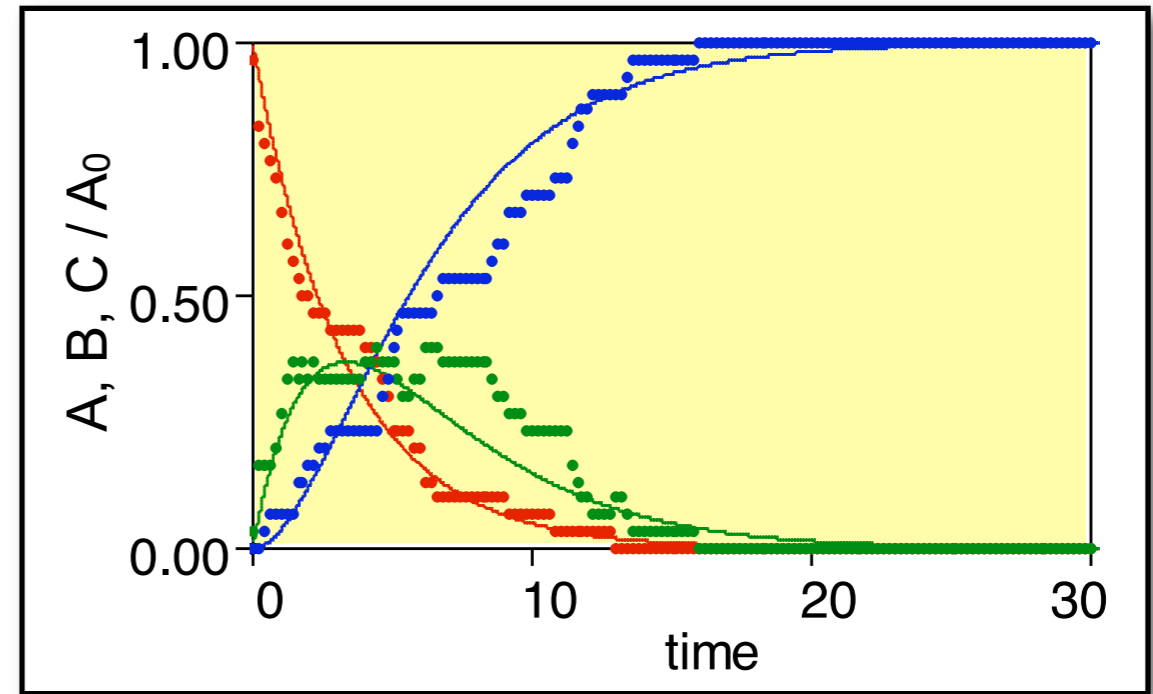
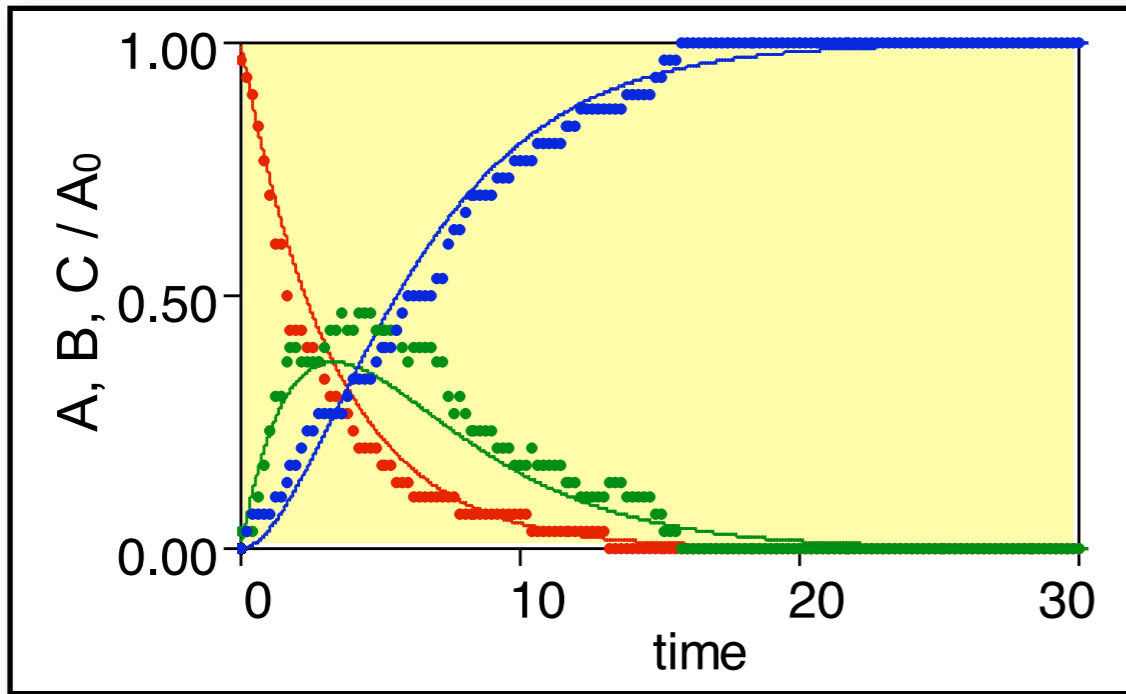
Weniger Teilchen => Mehr Rauschen

$A_0 = 100$



Noch weniger Teilchen

$A_0 = 30$



Varianz vs. Teilchenanzahl

Poisson:

relative Abweichung $\propto 1/\sqrt{N}$

1000 Simulationsläufe,
Werte sichern bei $t = 7$.

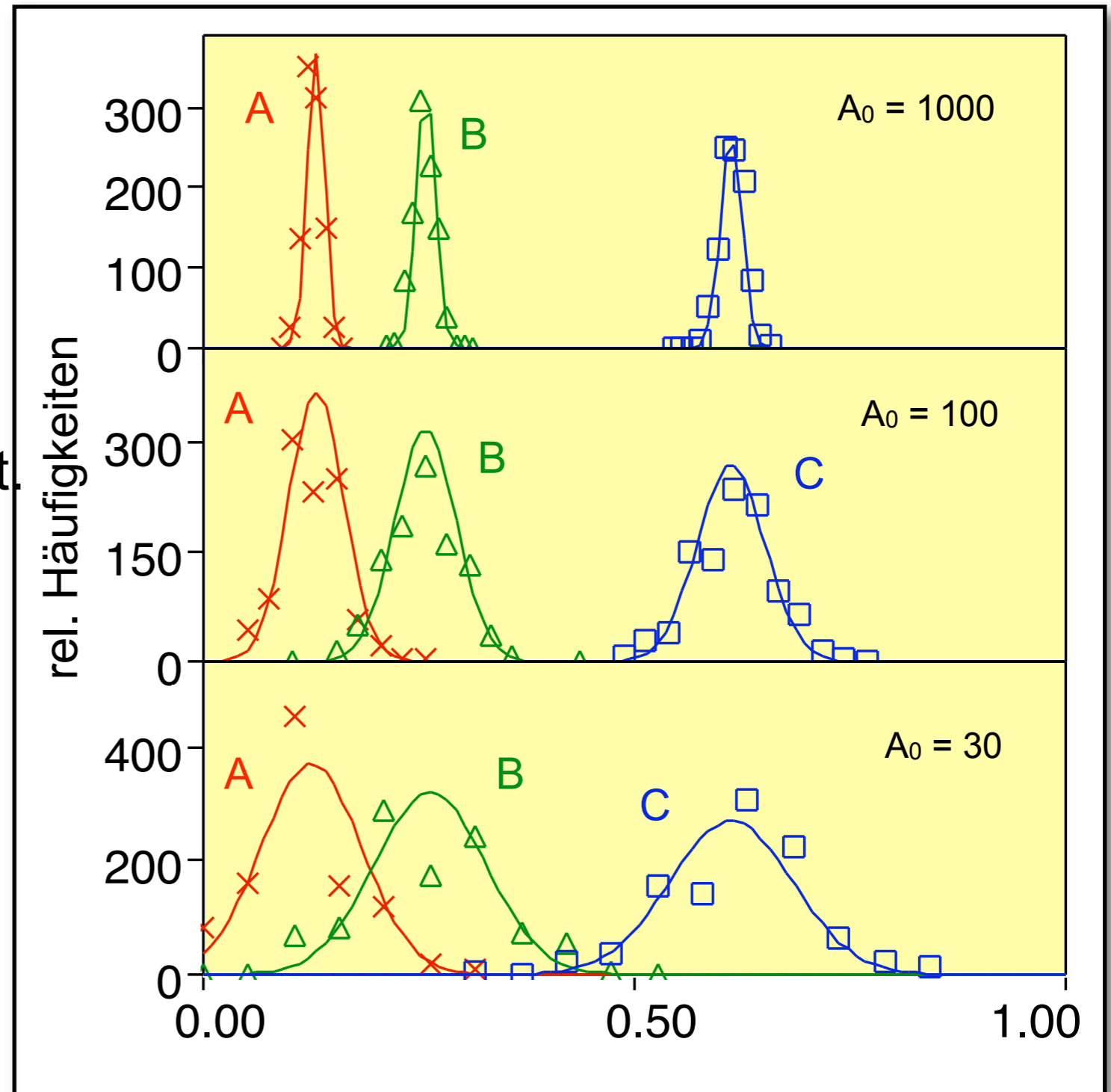
Fit der Verteilung mit Gaussvert.
(Normalverteilung)

$$g(x) = \exp \left[-\frac{(x - \langle x \rangle)^2}{w/\sqrt{A_0}} \right]$$

$$\langle A \rangle = 0.13, \quad w_A = 0.45$$

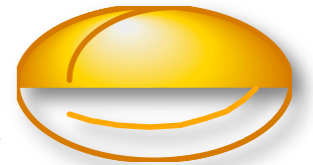
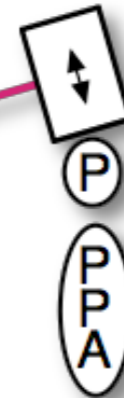
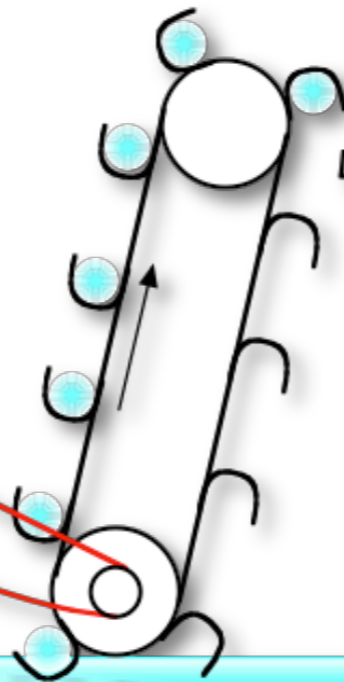
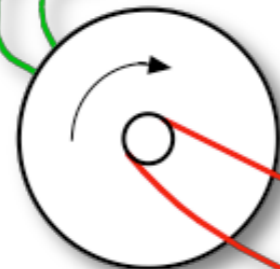
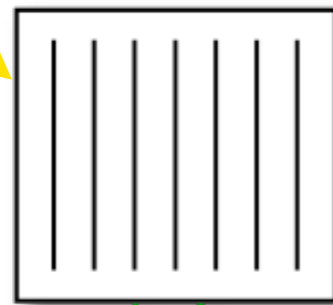
$$\langle B \rangle = 0.26, \quad w_B = 0.55$$

$$\langle C \rangle = 0.61, \quad w_C = 0.45$$



Photosynthese ist...

...die Umwandlung von Lichtenergie in chemische Energie
(einer der wichtigsten Prozesse weltweit)



biologischer Überblick

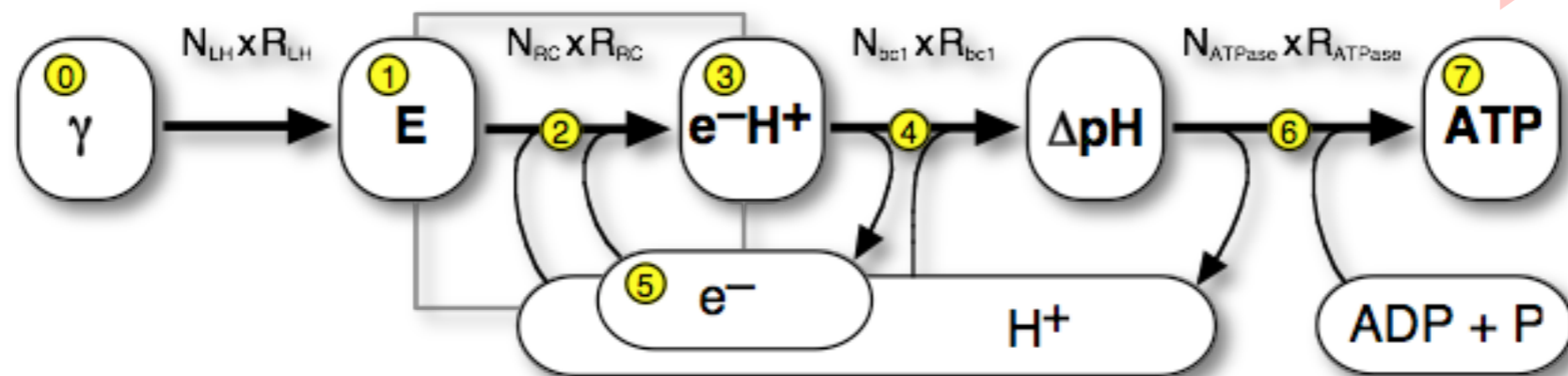
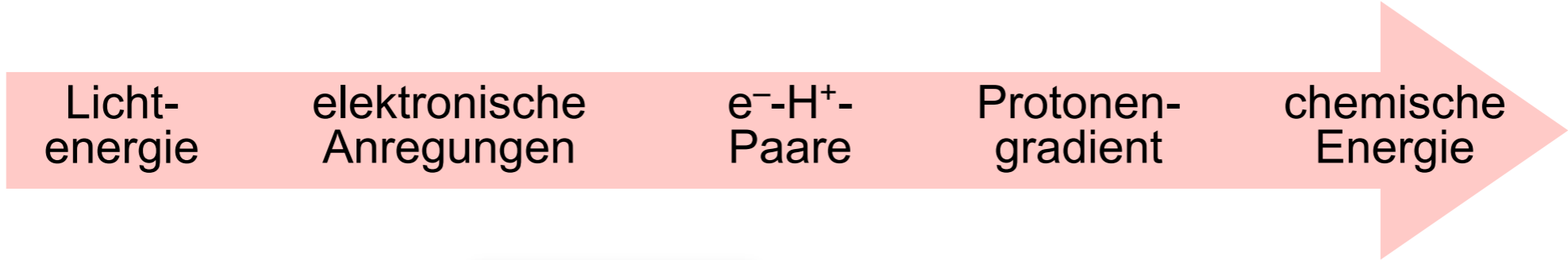
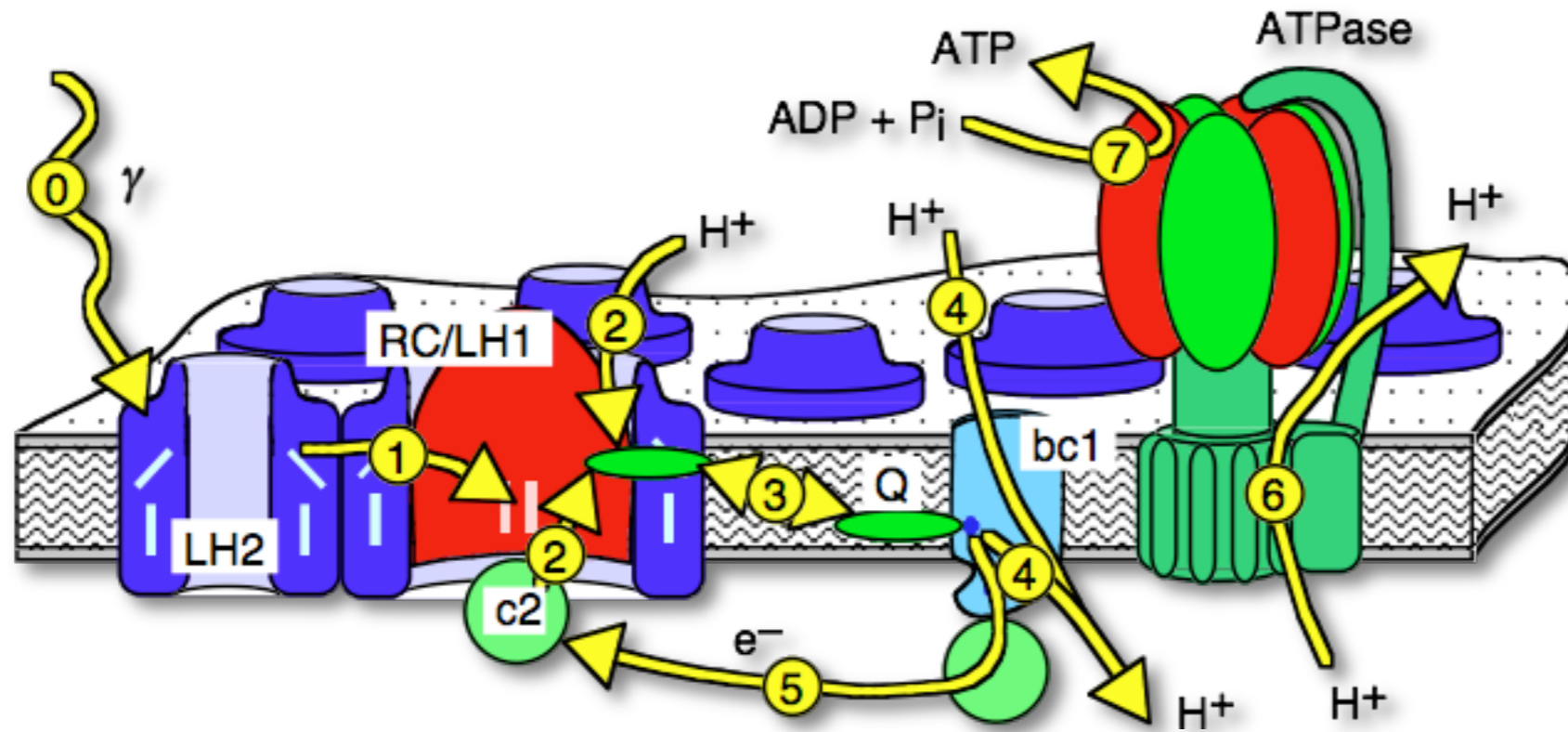
Stochastische Simulation aus einzelnen Reaktionen

=> Unterschiede zu Gillespie?

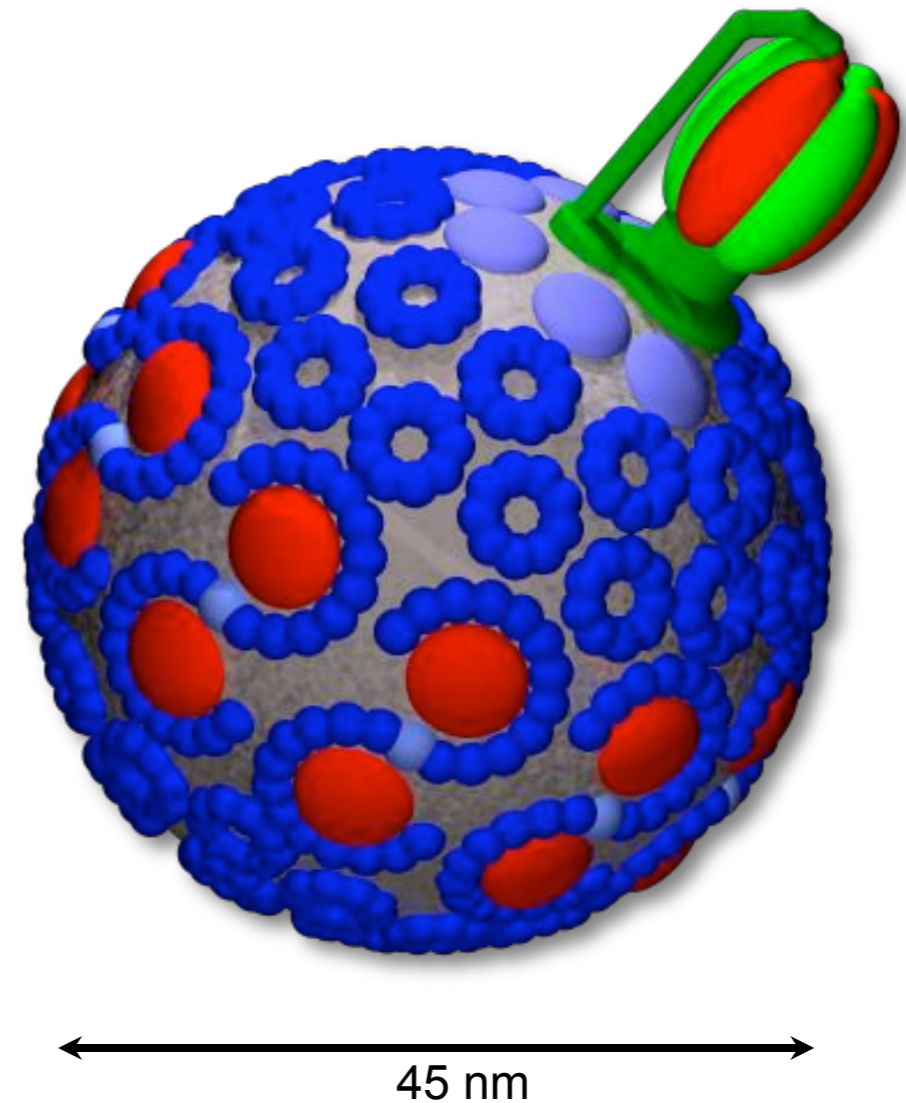
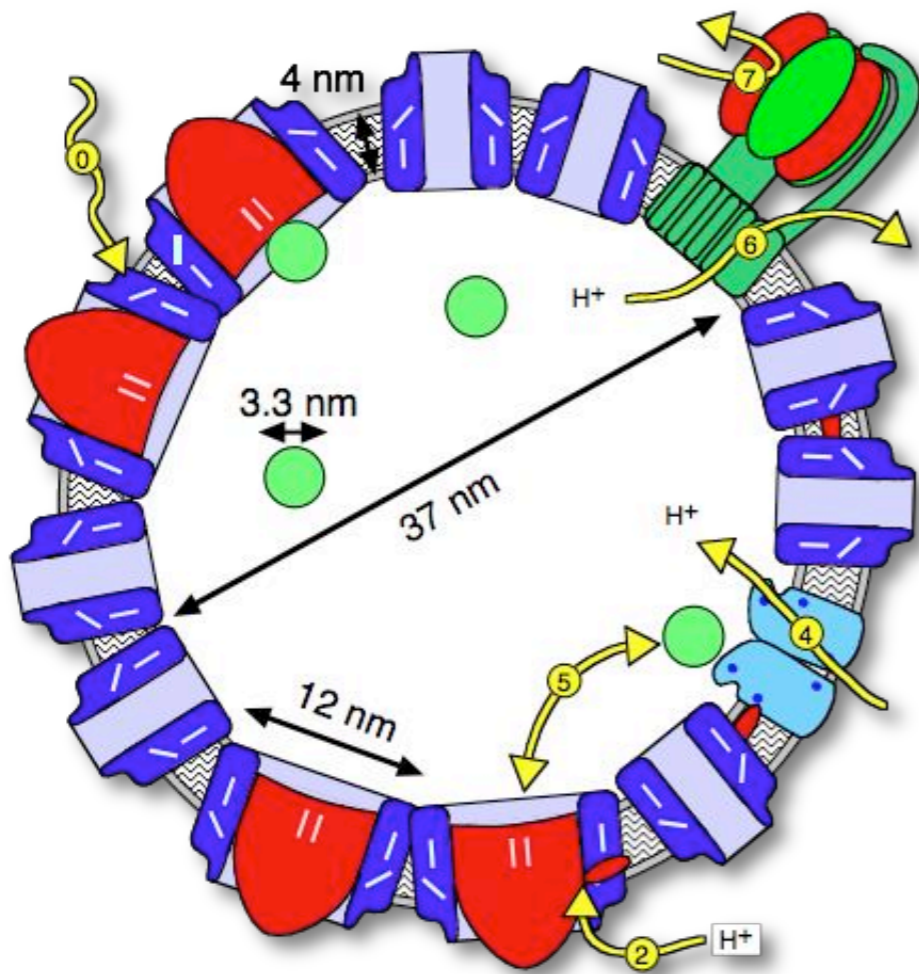
=> Reihenfolge von Näherung und Simulation

Vesiweb

Photosynthese in *Rb. sphaeroides*



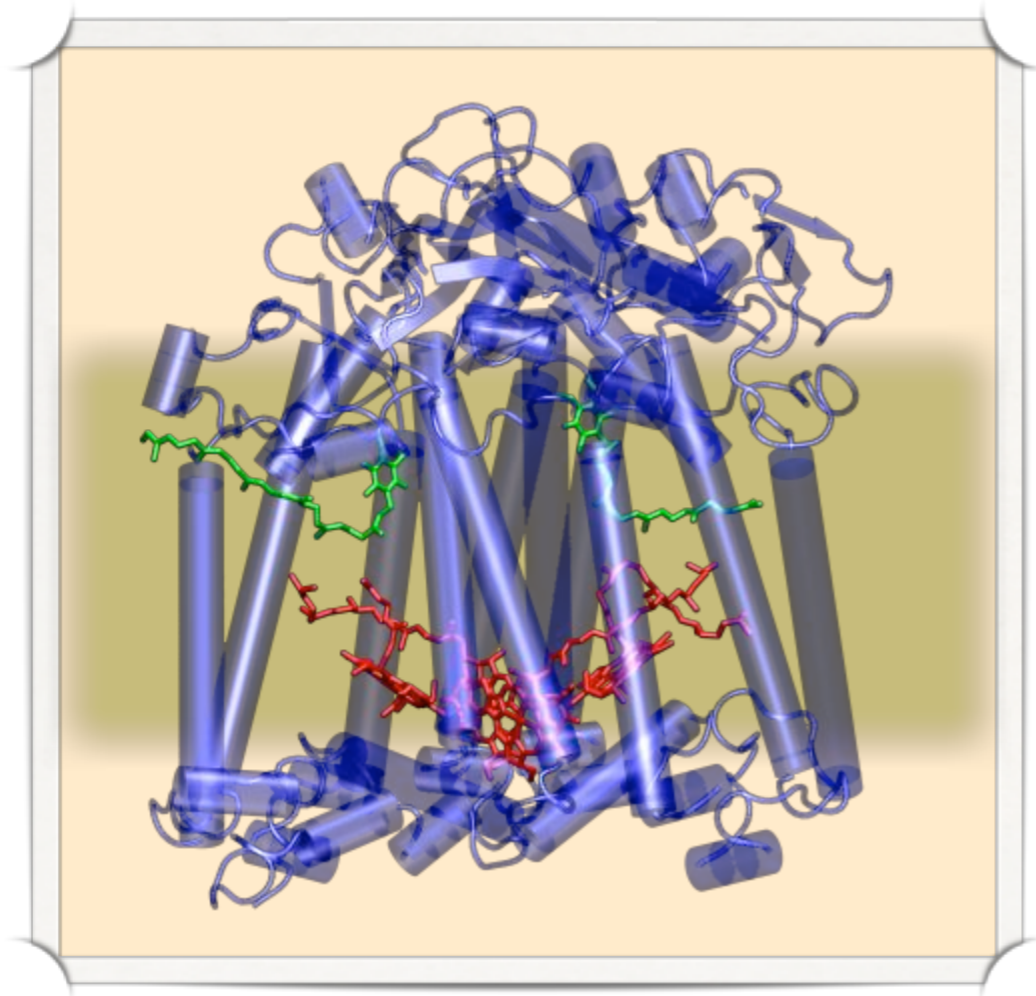
Chromatophoren-Vesikel



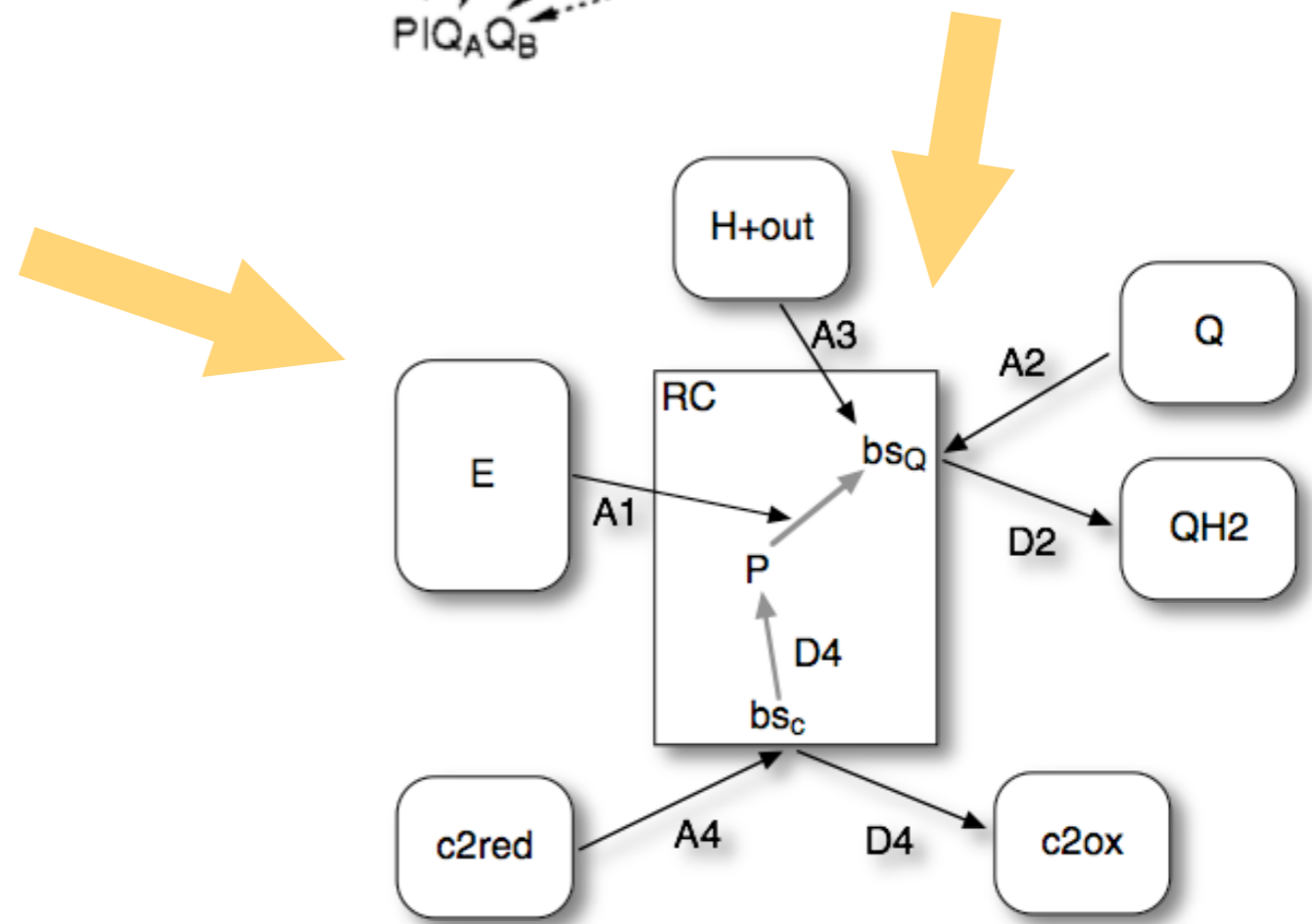
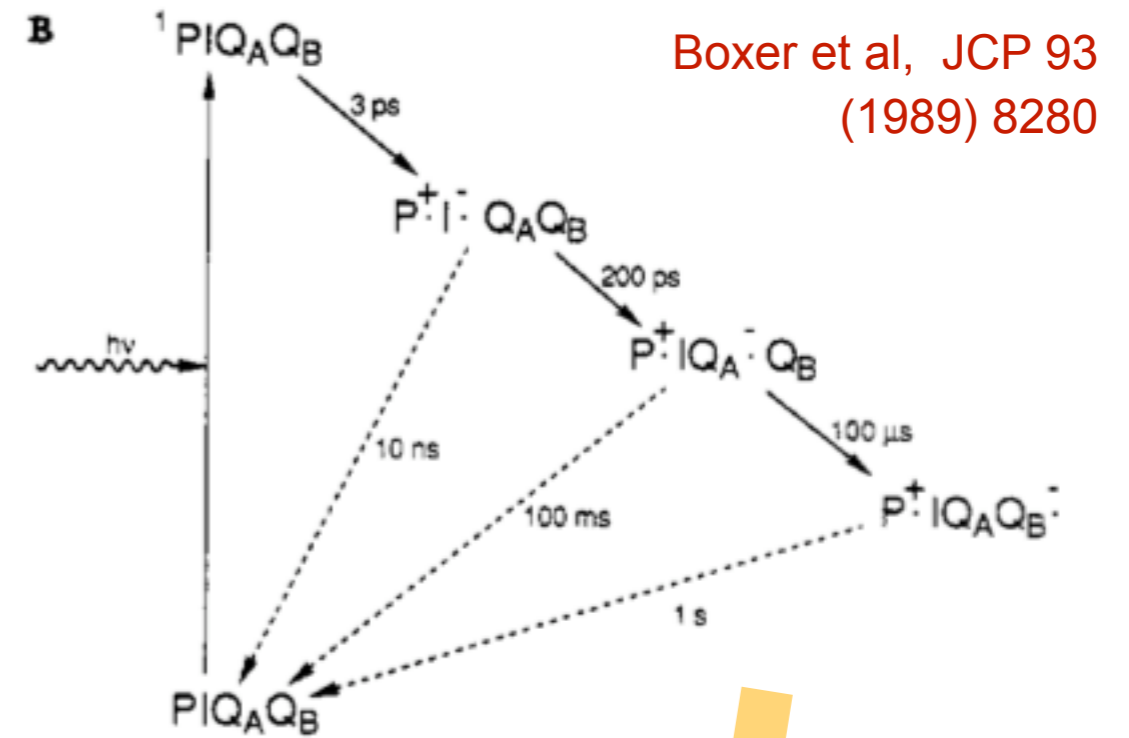
- => einfach: 4 Proteine + 2 Transporter + H⁺; Kristallstrukturen u. Reaktionen
- => klein: <30 Proteine + LHCs; alles Prozesse im Vesikel
- => abgeschlossen: definierte Randbedingungen für die Simulation
- => praktisch: Anregung mit Licht, spektroskopische Messungen

Modellierung der Proteine

RC: Photon =>
Ladungstrennung



1AIJ.pdb



Stochastische Reaktionen

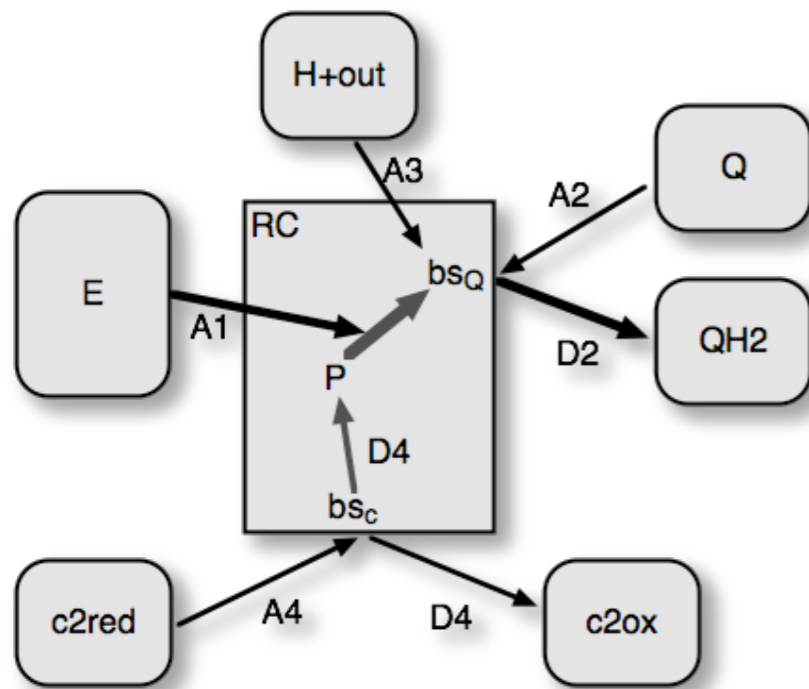
Wenn BS frei ist \Rightarrow Assoziation möglich: $BS + X \Rightarrow BS:X$

1) sind alle Bedingungen erfüllt?

2) chemische Reaktionskinetik:

Reaktionsrate:
$$\frac{d[BS:X]}{dt} = k_{on} [BS] [X]$$

Bindungs-W.keit pro BS: $P_{on} = k_{on} [X] \Delta t$



for each timestep Δt :
for each reaction:
conditions fulfilled?
determine probability:
perform reaction

Geyer, Lauck, Helms, J Biotech 129 (2007) 212

Bsp: Elektronentransfer im RC

```
// R1: transfers an electron to the Quinone
// using the energy from an exciton{
if (bs_Q && (e_P == 1)
&& (e_Q == 0) &&
((He_Q == 0) || (He_Q == 1))) {
if (LHPoolp-
>take_out(LH_kon)) {
e_P = 0; e_Q = 1;
writeInternals();
}
}
}
```

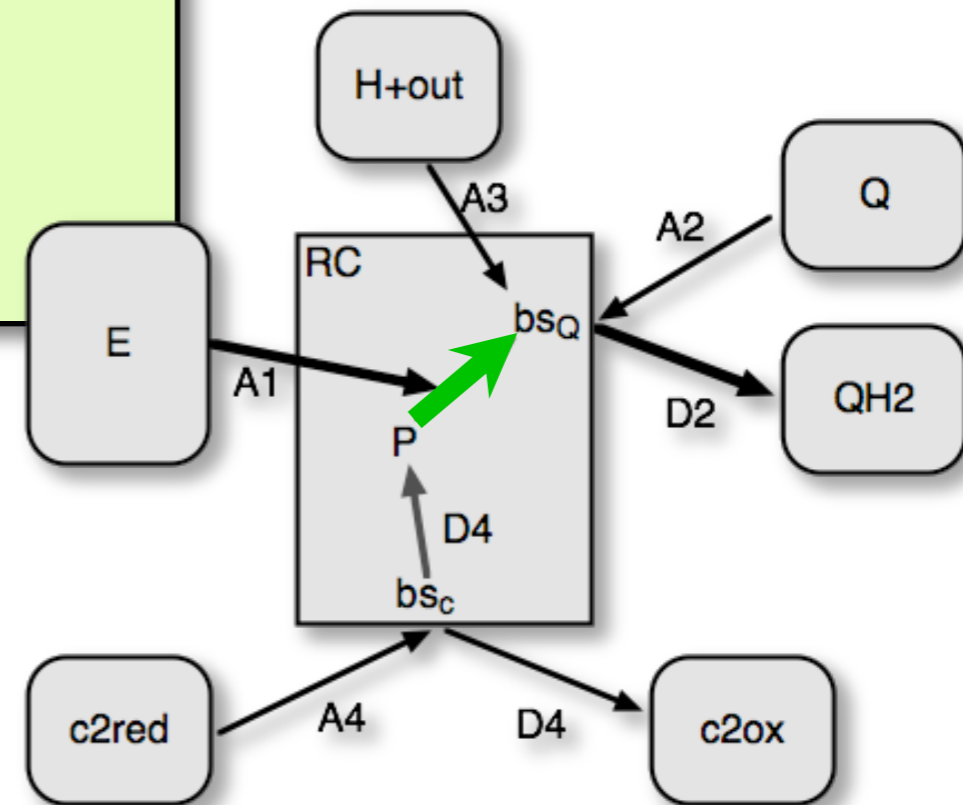
Bedingungen?

Wahrscheinlichkeit?

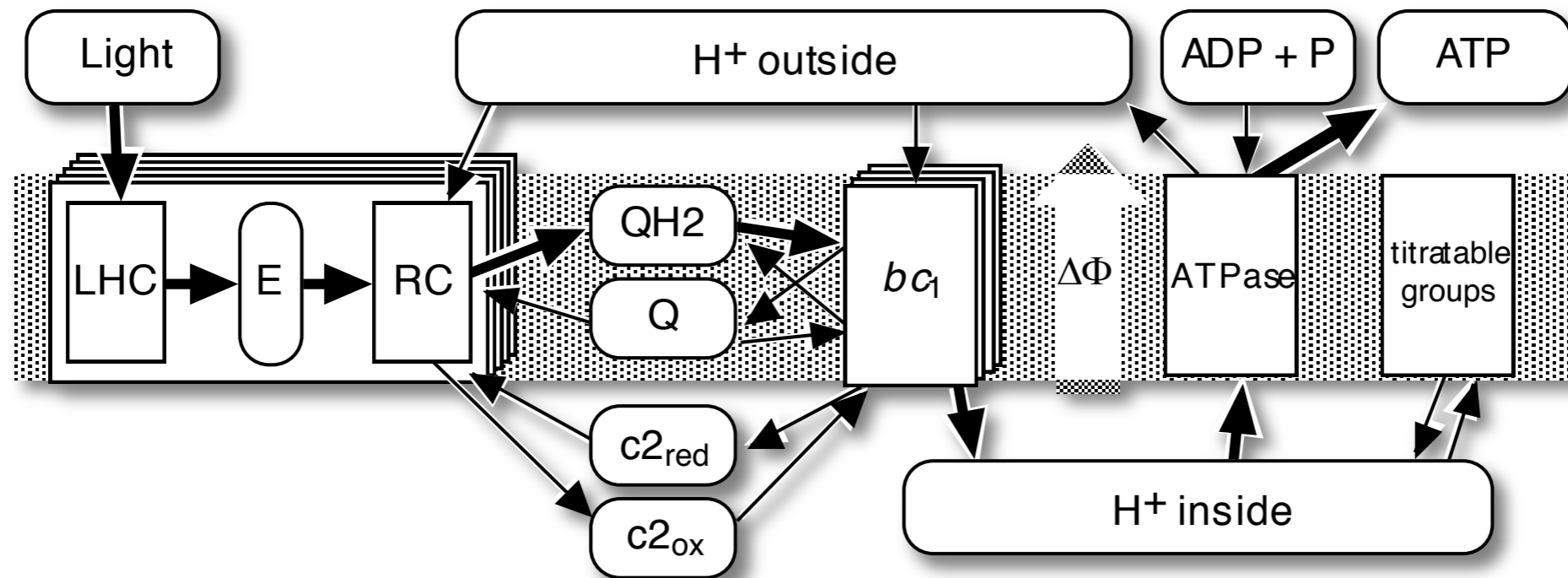
Reaktion!

Protein = {BS; Reaktionen(Zustand)}

Geyer, Lauck, Helms, J Biotech 129 (2007) 212



"Pools-and-Proteins"-Modell



40 aktive Proteine

- unabhängig voneinander
- stochastische Reaktionen mit je 1 Molekül
- Anzahl wie auf dem Vesikel

19 passive Pools

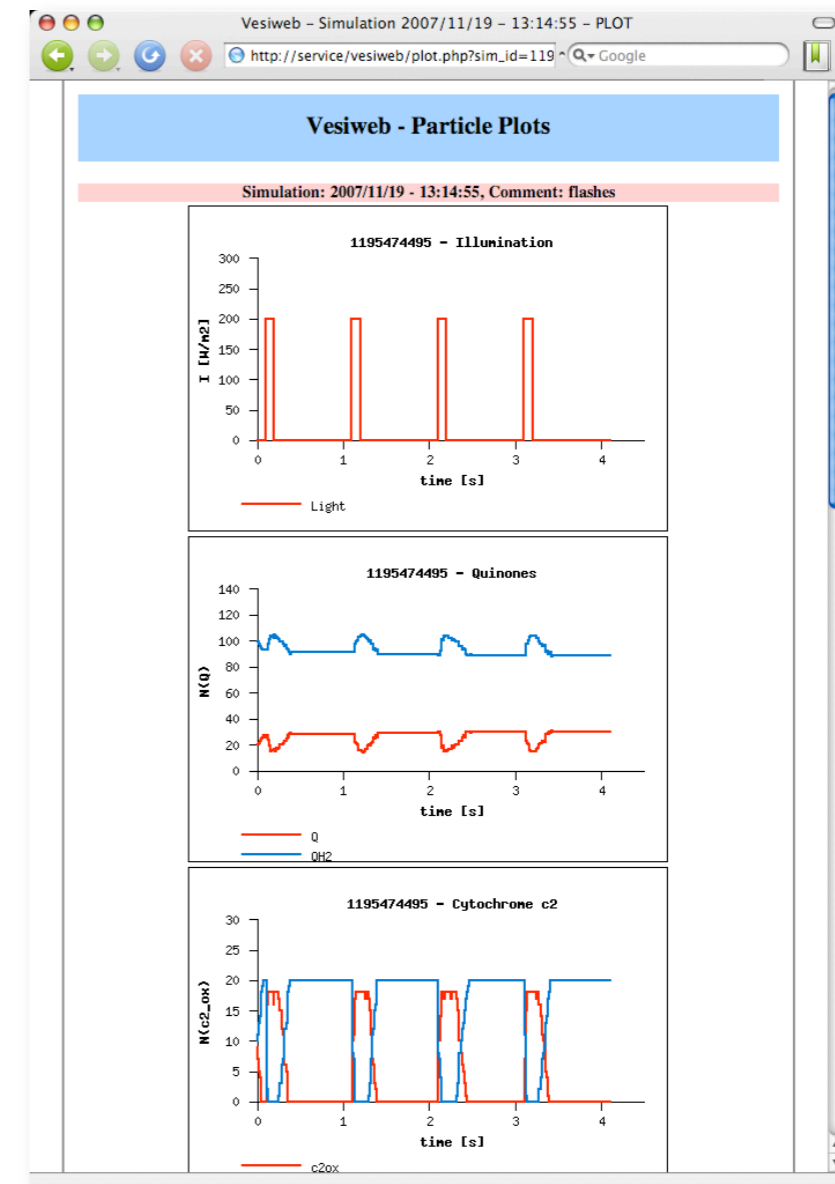
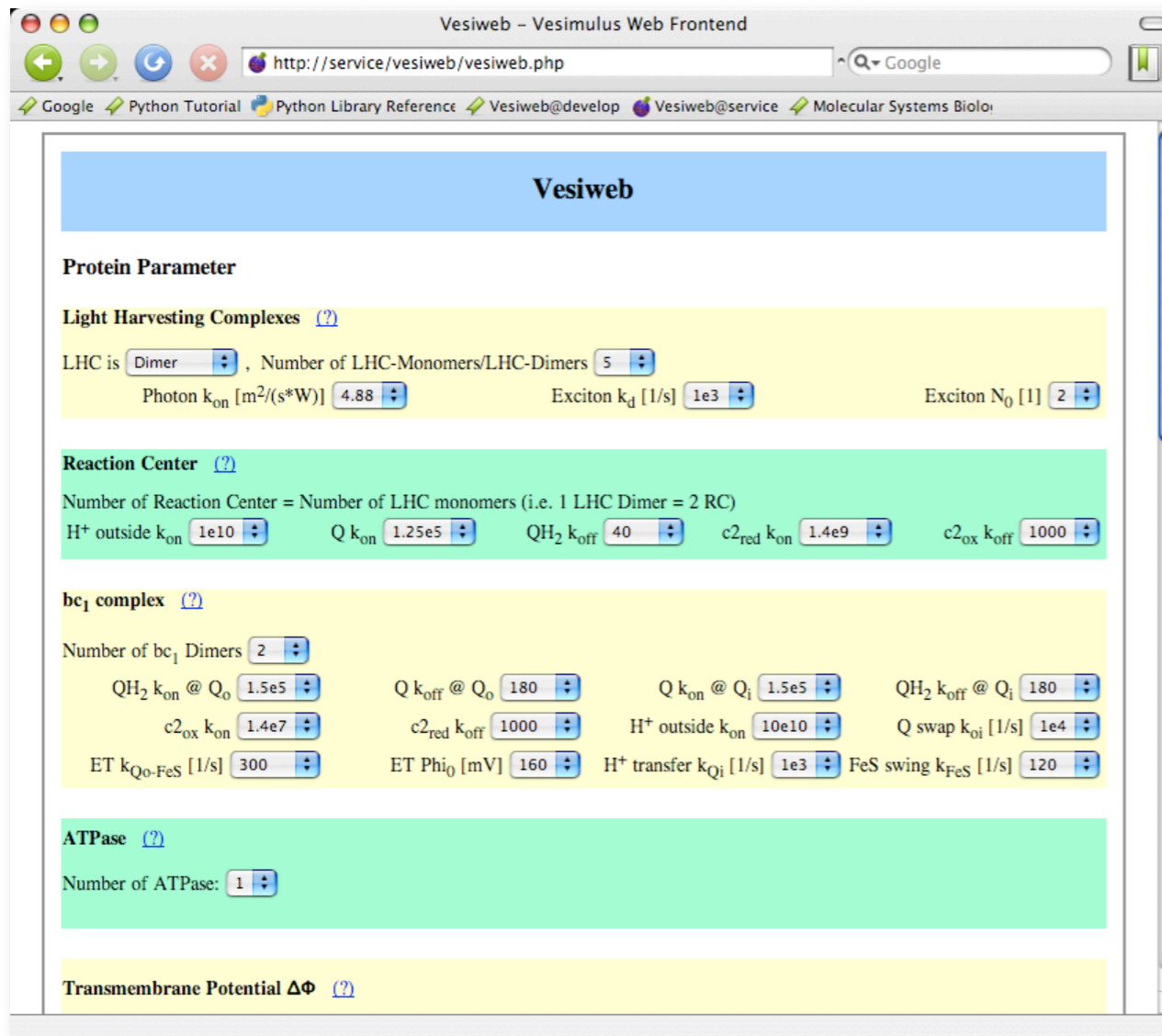
- ein Pool pro Metabolit
- hier: Diffusion ist schnell

Verbindungen definieren das biologische System
=> Pfade als "emergent behavior"

Geyer, Lauck, Helms, J Biotech 129 (2007) 212

Web Interface

Simulationen über Konfigurationsdatei oder web-interface @ service.bioinformatik.uni-saarland.de/vesiweb

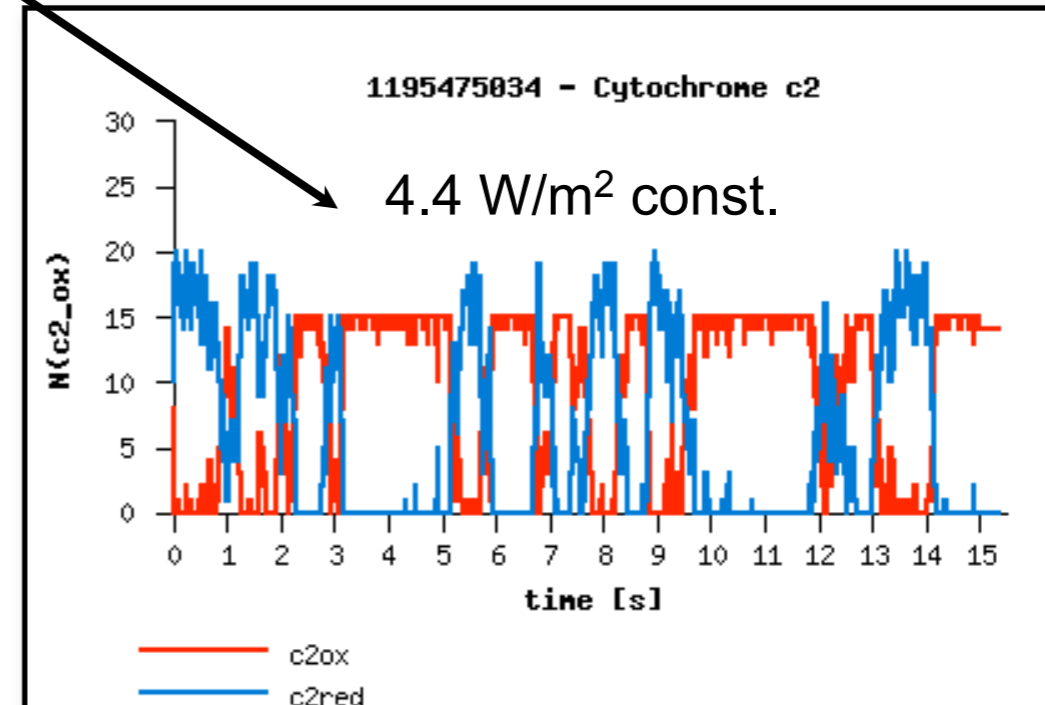
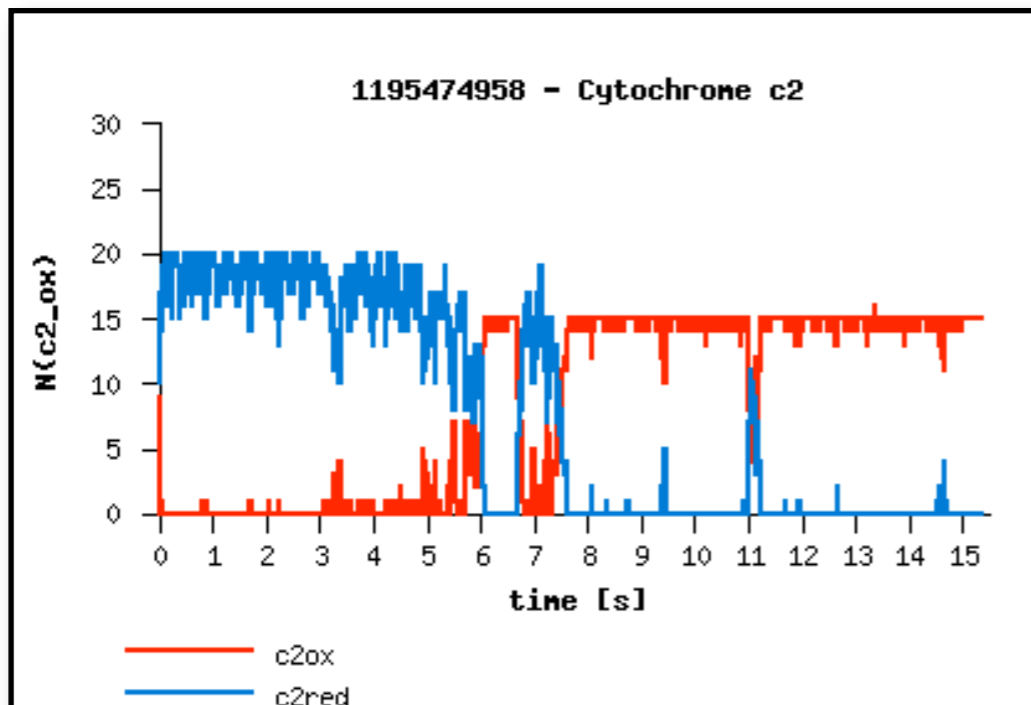
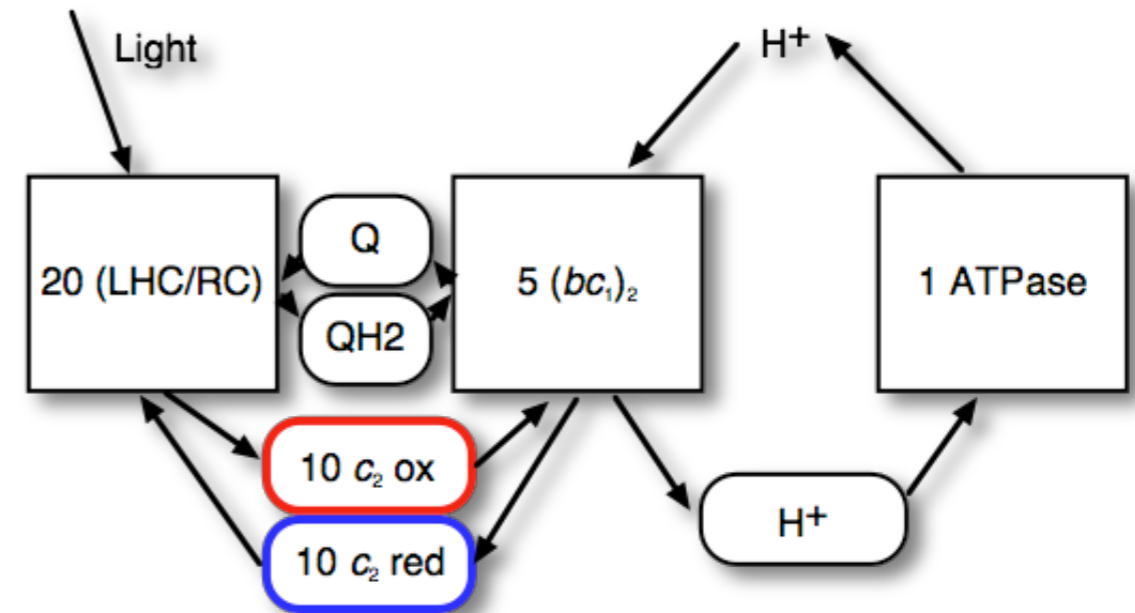
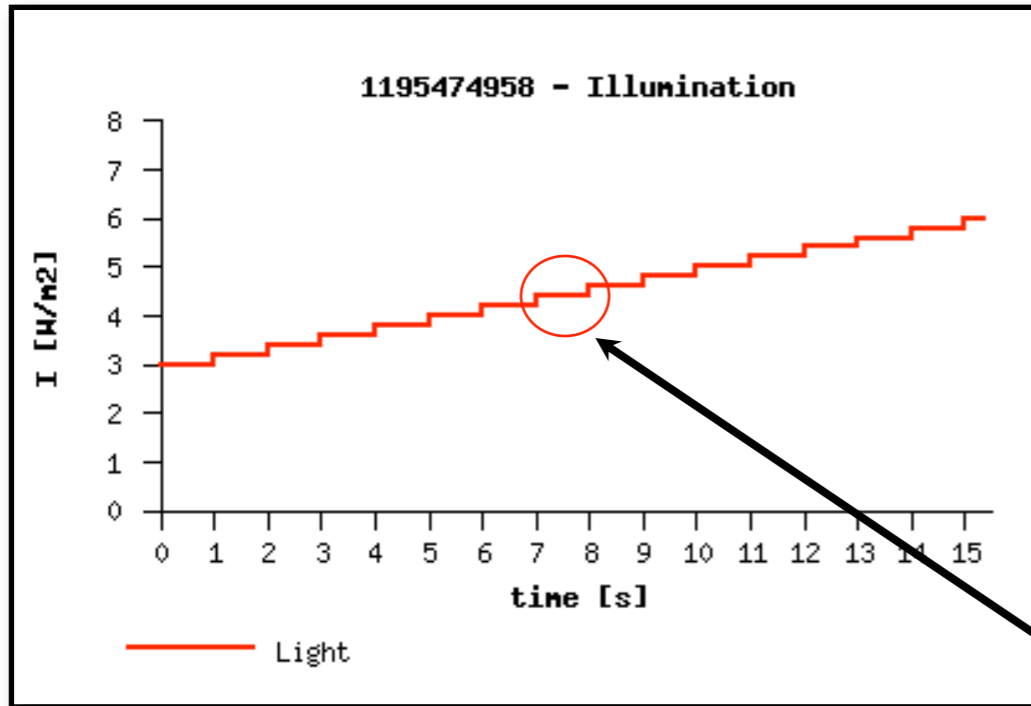


- Verstehen der Prozesse
- Modell-Verifikation + Parametrisierung gegen Experimente

[Florian Lauck. T.G., 2006]

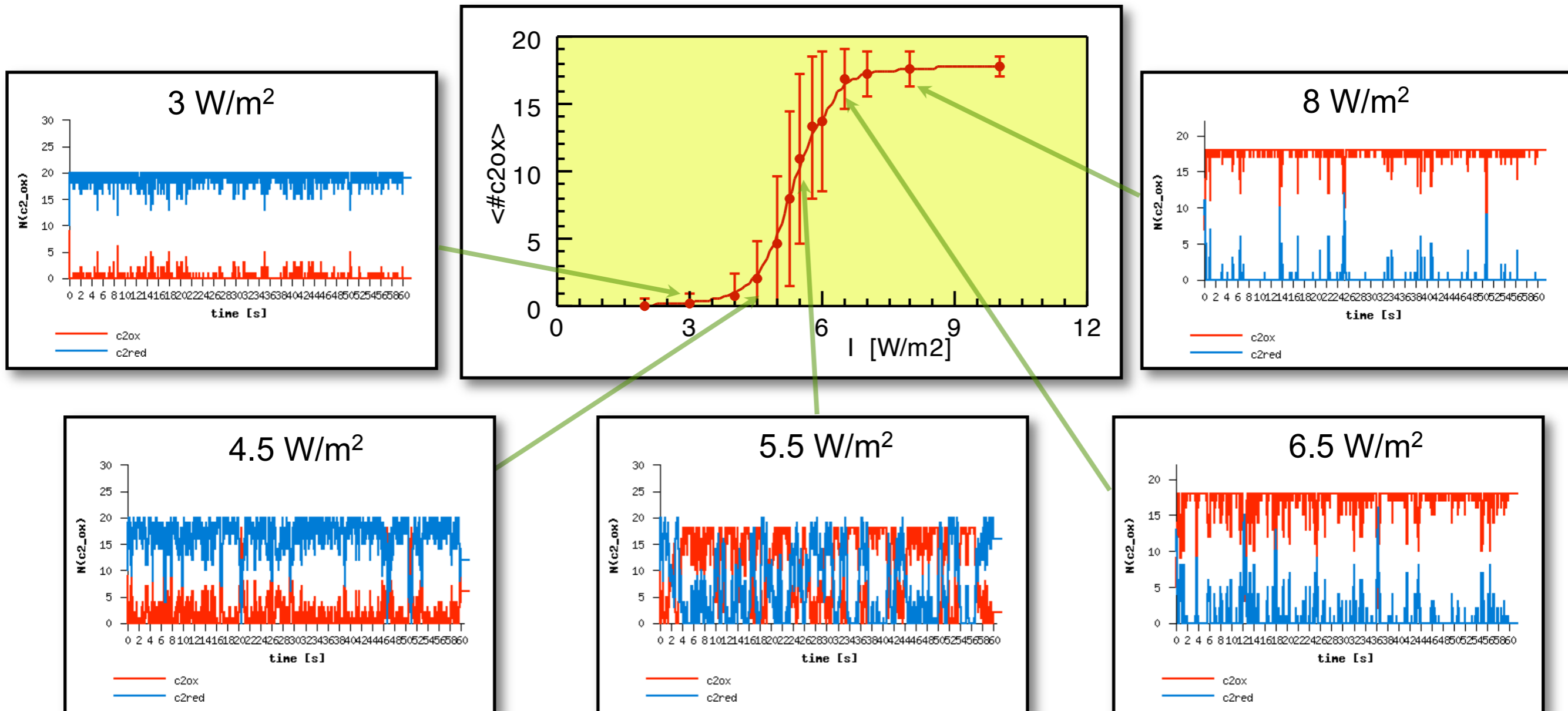
Stochastische Effekte

Oxidationszustand des Cytochrom *c*-Pools bei kontinuierlicher Beleuchtung



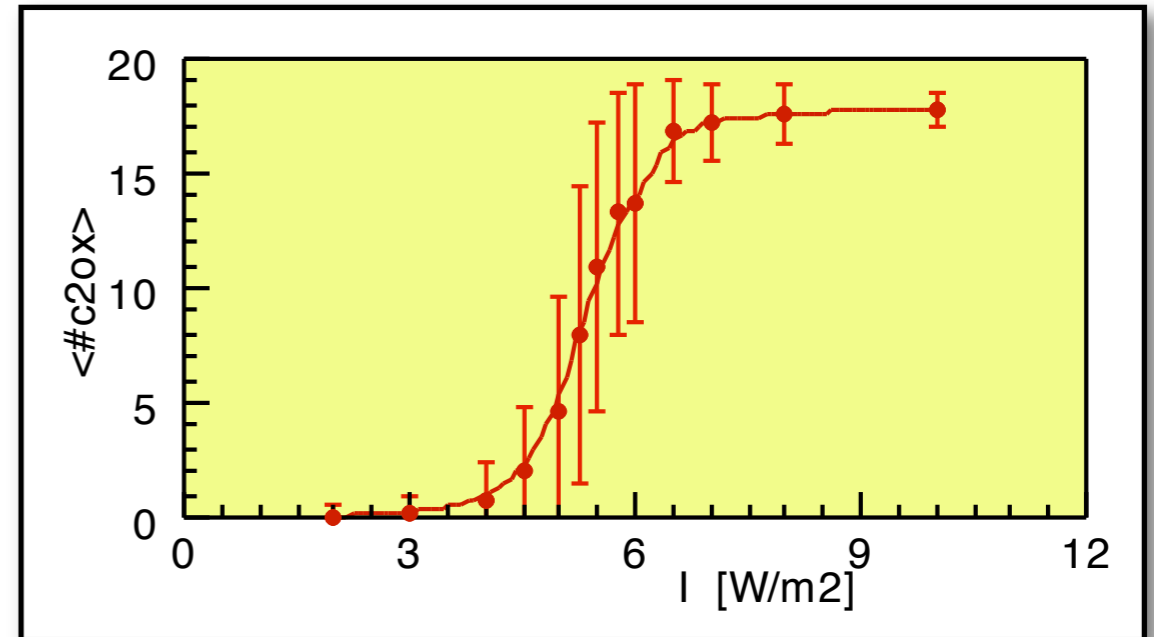
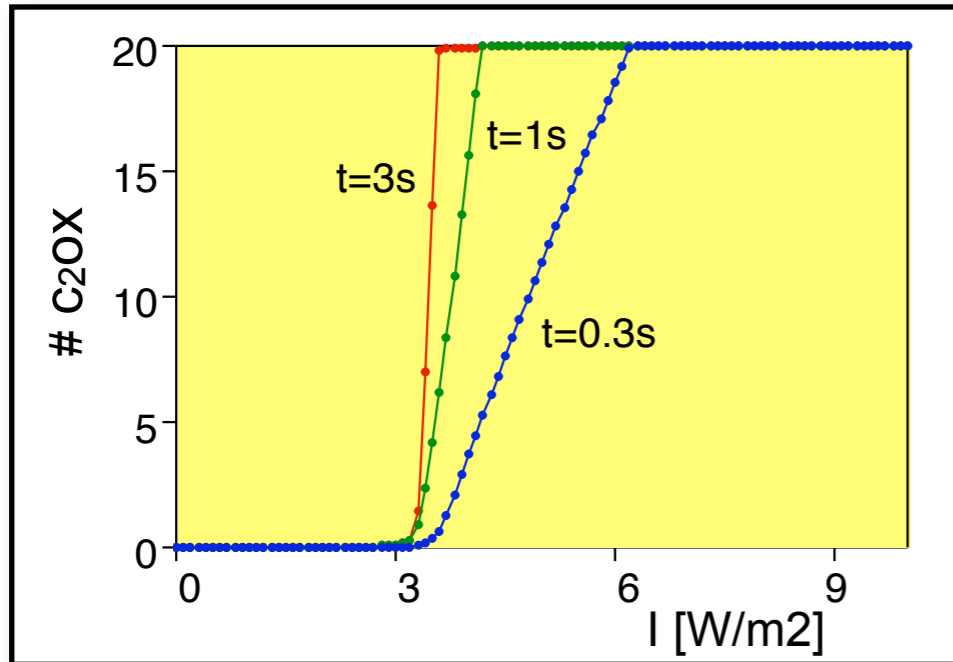
Steady State \Leftrightarrow Fluktuationen

60 Sek. bei konstanter Beleuchtung mit 10 RC/LHC-Dimeren und 4 bc1-Dimeren
=> Oxidationszustand des Cytochrom *c*-Pools



=> weicher Übergang mit starken Fluktuationen

Deterministisch vs. Stochastisch



Gleichungen mitteln, dann simulieren \Leftrightarrow Simulieren, dann Ergebnisse mitteln

scharfer Übergang

\Leftrightarrow

weicher Übergang
auch für lange Zeiten

nur numerische Unsicherheiten

\Leftrightarrow

Fluktuationen \approx Signal

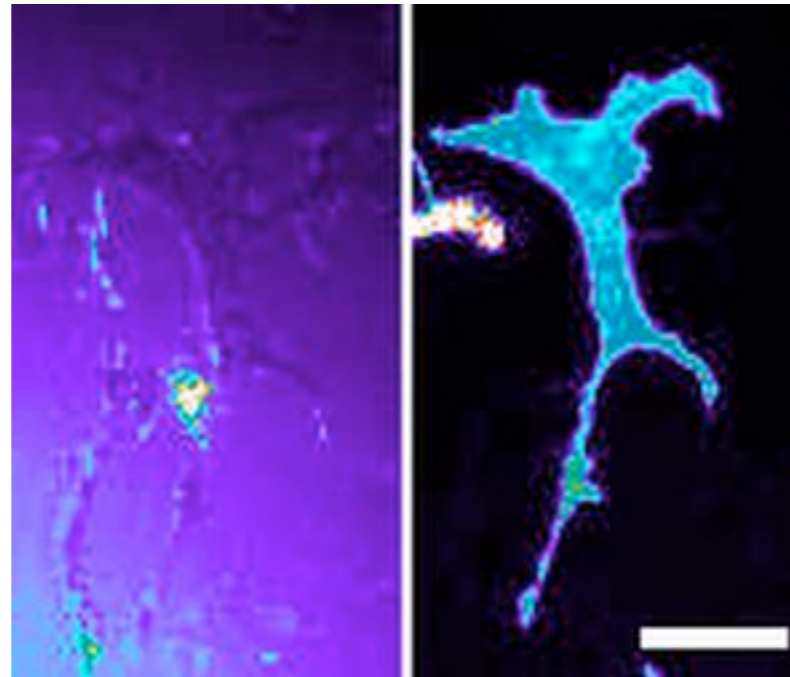
Reproduzierbare Werte

\Leftrightarrow

nur Mittelwert reproduzierbar

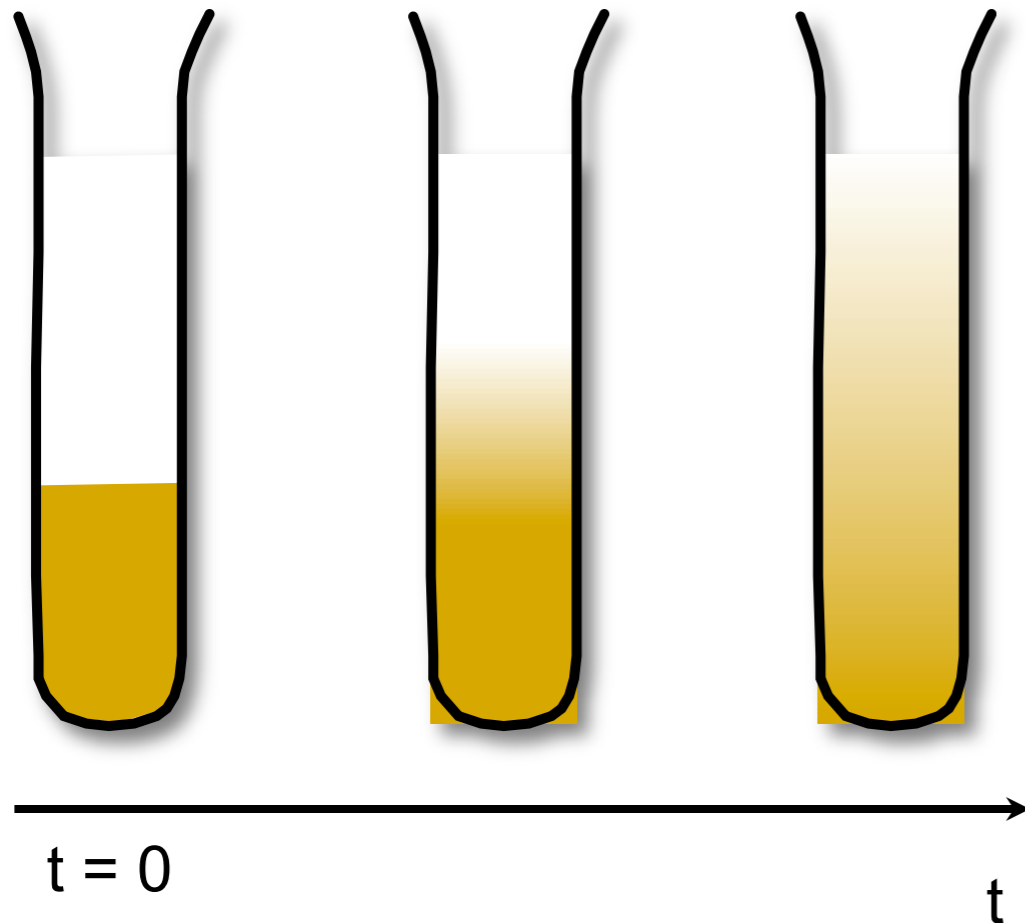
Prozesse in einer Zelle

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:

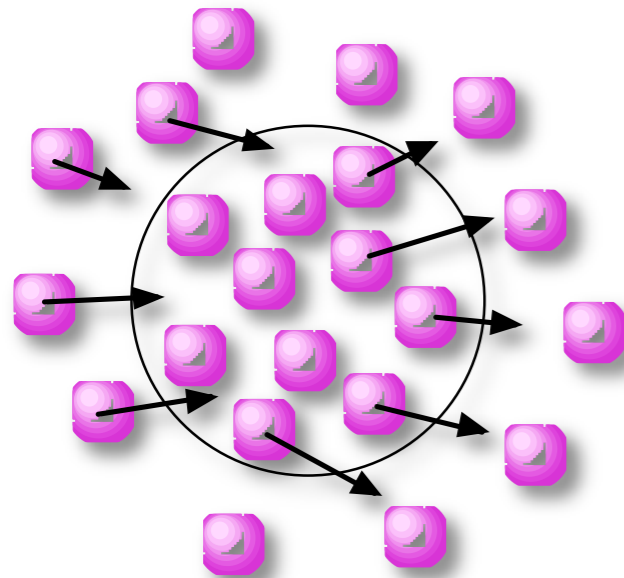
1) Kontinuitätsgleichung: wo bleibt das Material?

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

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 $r = r(t)$)

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

Diffusionsstrom

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

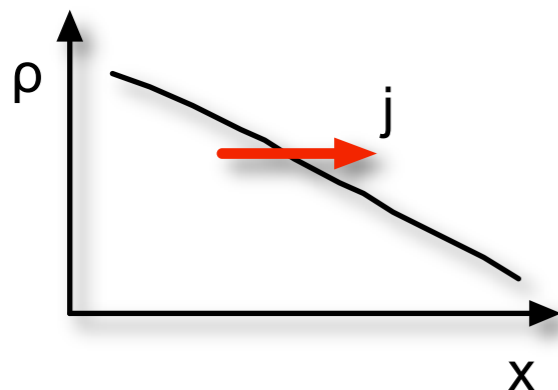
$$\vec{j}(\vec{r}, t) = -D \nabla \rho(\vec{r}, t) = -D \text{ grad } \rho(\vec{r}, t)$$

Diffusionsstrom
bei (r, t)

Strom fließt
weg von
hohen Dichten

Diffusions-
koeffizient

Dichte-
fluktuationen
(=Gradienten)

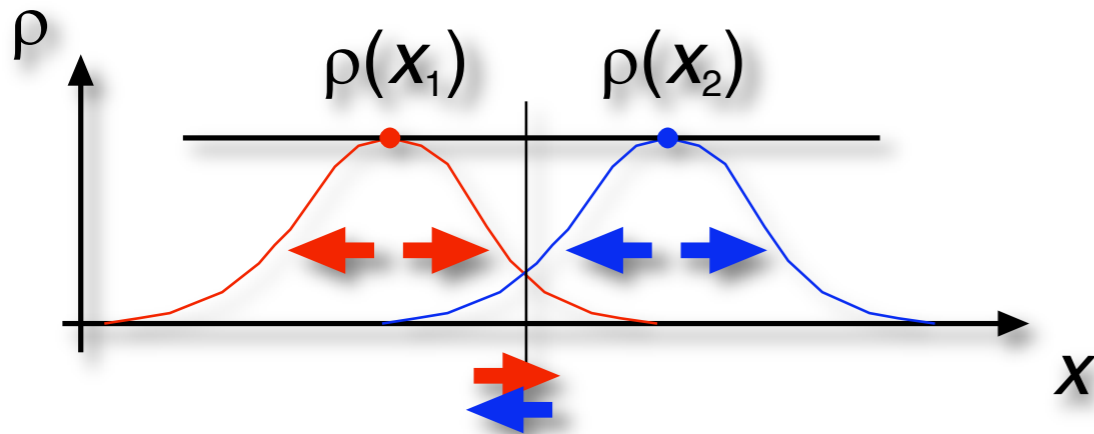


hier: phänomenologischer
Umrechnungsfaktor von
Dichteunterschieden in Teilchenströme

Diffusion mikroskopisch

Ohne externe Kräfte

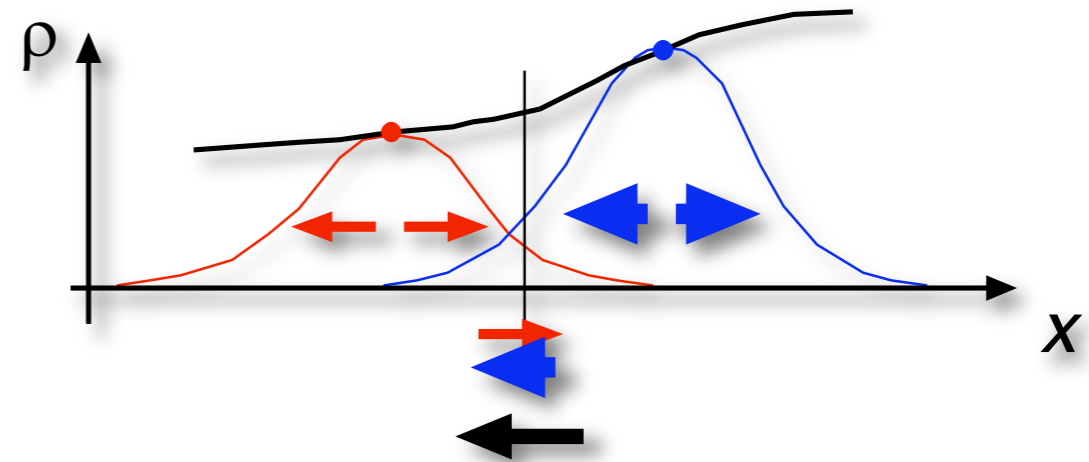
=> Teilchen bewegen sich in alle Richtungen gleich wahrscheinlich
(Gauss'sche Wahrscheinlichkeit)



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

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

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



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

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

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

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

=> Diffusionsgleichung:

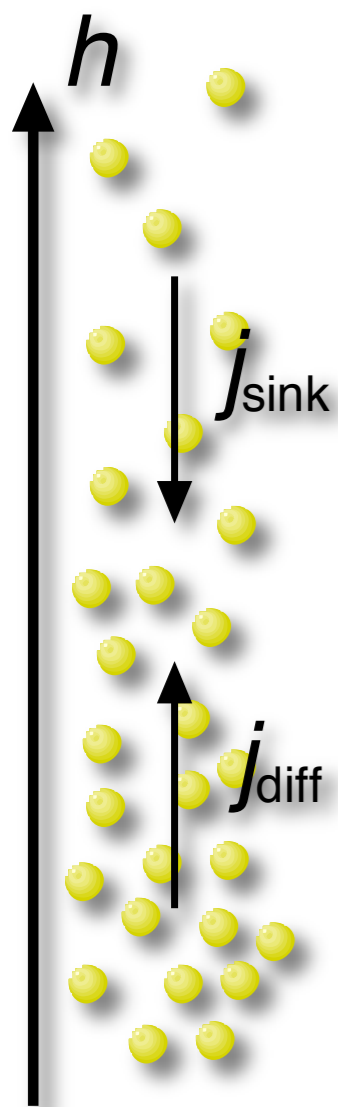
$$\frac{\partial \rho(\vec{r}, t)}{\partial t} = -\nabla \cdot (-D \nabla \rho(\vec{r}, t)) = D \Delta \rho(\vec{r}, t)$$

$D(\vec{r}, t) = \text{const}$
↓

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

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

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

stationärer Zustand ist
unabhängig von D (aber:
Relaxationszeit)

Integration

Bisher: (System von) ODEs

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

- 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 $\rho(r)$ 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 :

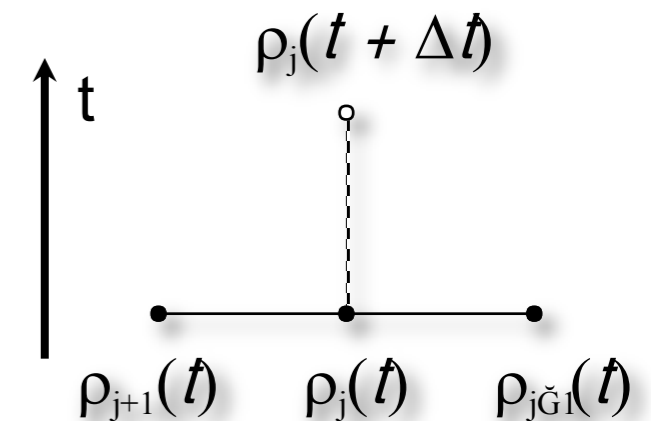
$$\frac{\rho_j(t + \Delta t) - \rho_j(t)}{\Delta t} = D \frac{\rho_{j+1}(t) - 2\rho_j(t) + \rho_{j-1}(t)}{\Delta x^2}$$

Forward in Time

Centered in Space

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:

$$\Delta t \leq \frac{\Delta x^2}{2D}$$

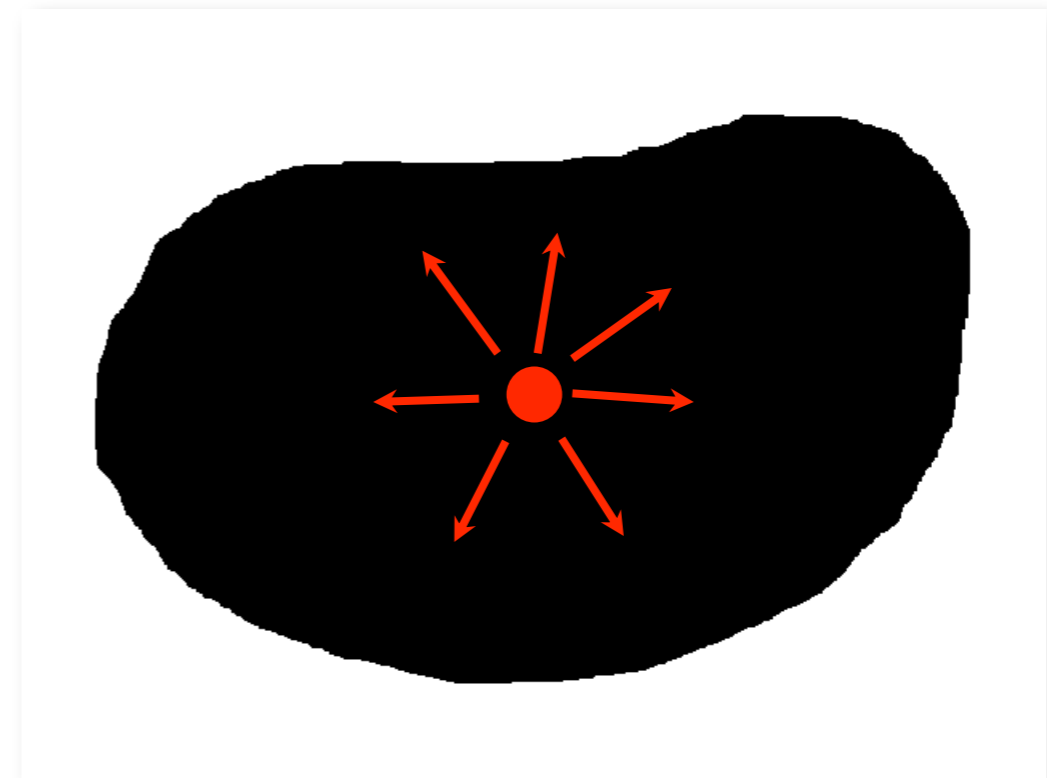
($\Delta t <$ Diffusionszeit über Abstand Δx)

Beispiel: Diffusion

Moleküle werden bei x_s produziert und in der ganzen Zelle abgebaut

Diffusion in beliebiger Geometrie:

=> Einfluß der Wände?



Simulationstool?

Do-It-Yourself

fertige SW

"The Virtual Cell":

- 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

Google Python Tutorial Python Library Reference Vesiweb@develop Vesiweb@service Molecular Systems Biolo! QTYoutube

National Resource for Cell Analysis and Modeling

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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

B

C

A

Applications

Bohndiffusion

Boten-Diffusion

Results

Results

Reactions for Innen

Innen

A

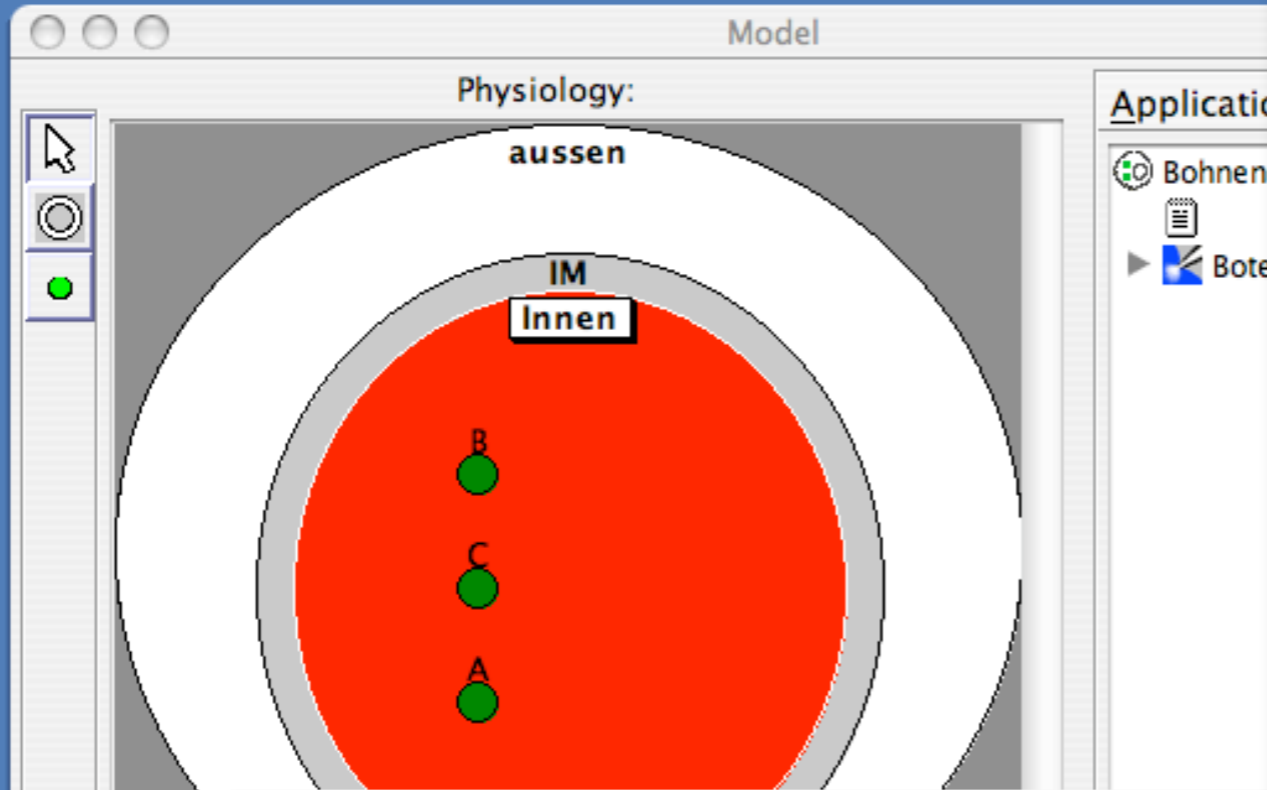
B

Abbau

C

CONNECTED Server: ms3.vcell.uhc.edu:80 User: tgeyer Java Memory Used: 62MB / 110,2MB 56%

The screenshot displays the BIOMODEL software interface. The main window, titled 'Model', shows a 'Physiology' view with three concentric regions: 'aussen' (outermost, white), 'IM' (middle, grey), and 'Innen' (innermost, red). Three green circles labeled 'A', 'B', and 'C' are positioned vertically within the 'Innen' region. To the right, an 'Applications' panel lists 'Bohndiffusion' and 'Boten-Diffusion'. Below the main window, a 'Reactions for Innen' window shows a reaction network: A (green circle) → B (green circle) → C (green circle). A yellow circle is located between A and B, and a red circle labeled 'Abbau' is located between B and C. The status bar at the bottom indicates 'CONNECTED', server information 'ms3.vcell.uhc.edu:80 User: tgeyer', and 'Java Memory Used: 62MB / 110,2MB 56%'.



Reaction Kinetics Editor

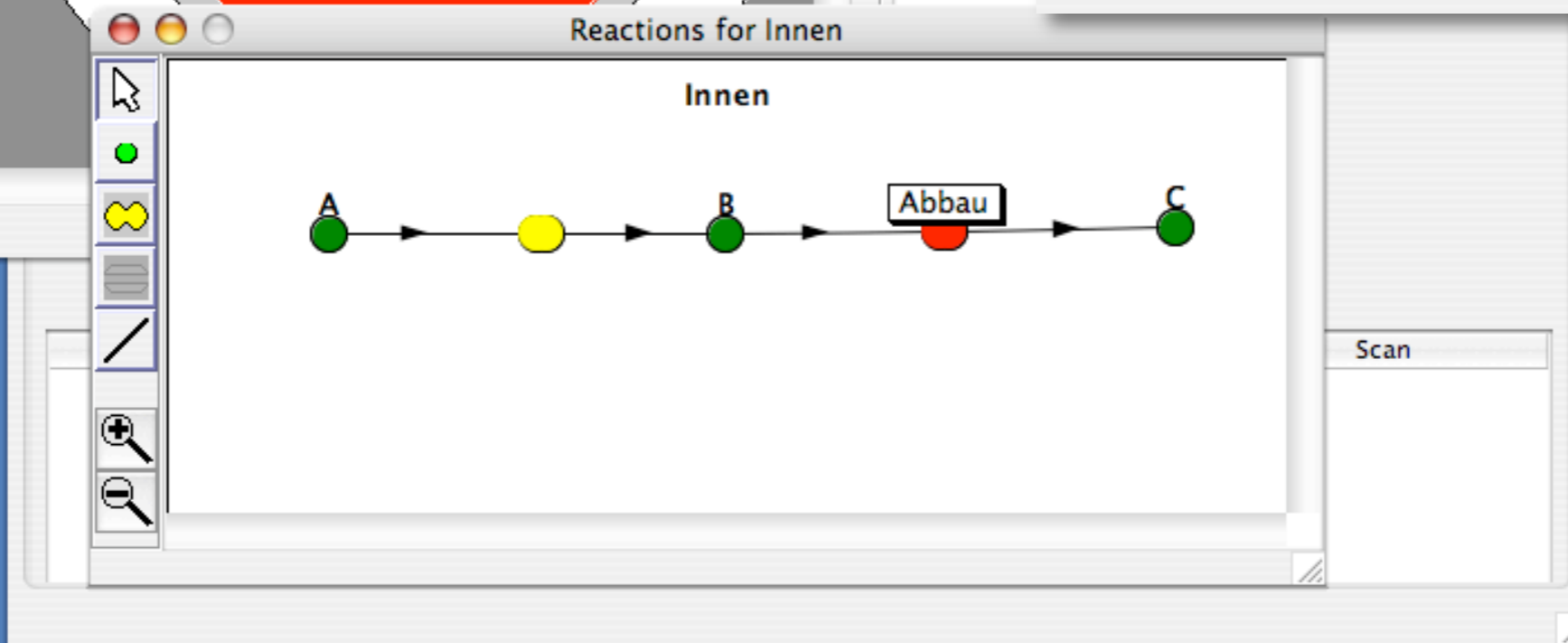
Stoichiometry

$$B_Innen \xrightleftharpoons[Kr]{Kf} C_Innen$$

Name: Abbau Rename

Kinetic type: Mass Action [$\mu\text{M/s}$] Convert to [molecules/s]

Description	Name	Expression	Ur
reaction rate	J	$(Kf \cdot B_Innen - Kr \cdot C_Innen)$	$\mu\text{M}\cdot\text{s}^{-1}$
forward rate constant	Kf	0.1	s^{-1}
reverse rate constant	Kr	0.0	s^{-1}



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...	<div style="width: 36%; background-color: #007bff; height: 10px;"></div> 36%	yes

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](#)

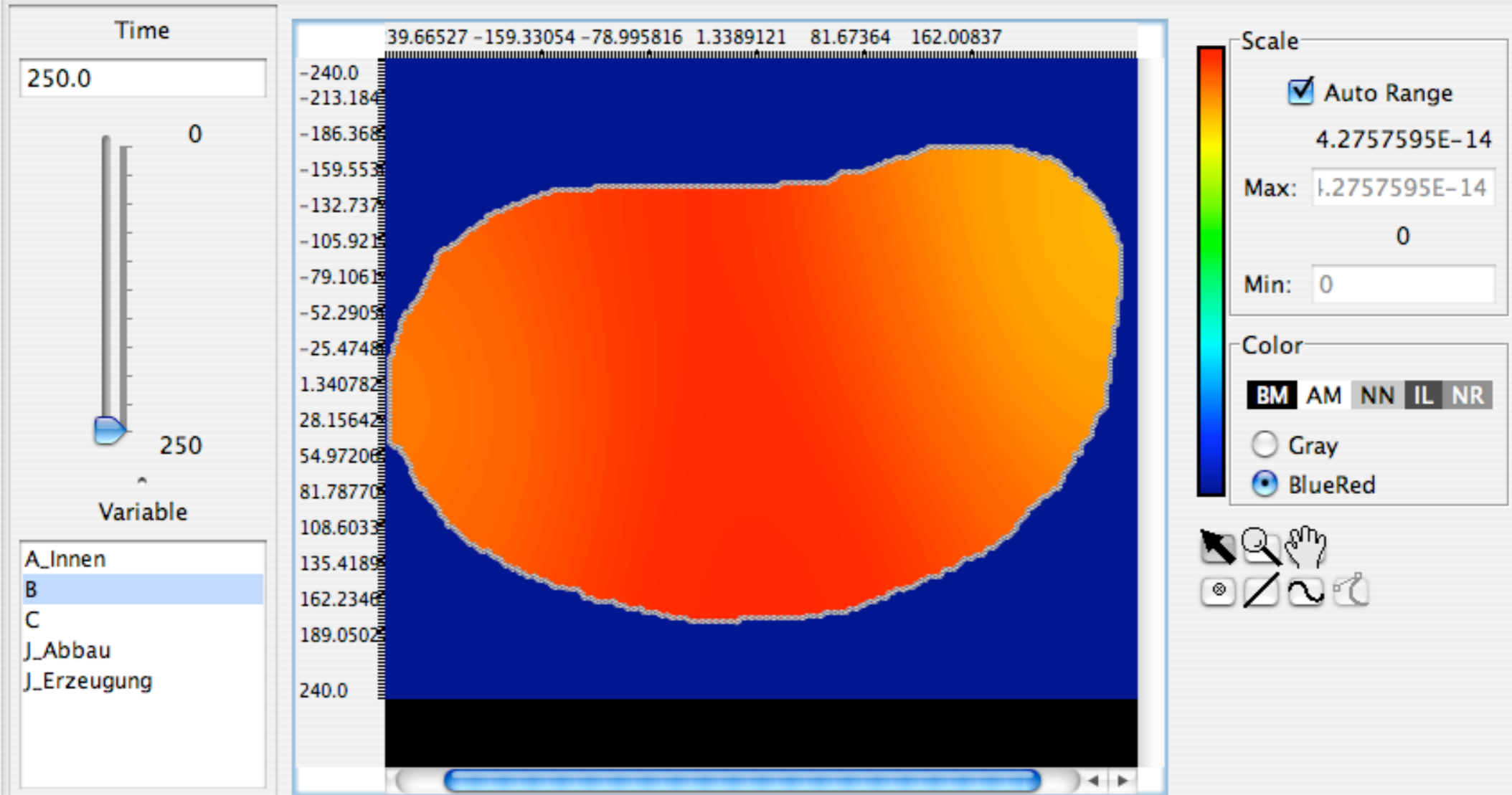
Mesh: [240 x 180 = 43200 elements](#)

Parameters with values changed from defaults:

Parameter Name	Default Value	Change Value	Scan

SIMULATION: Lauf1

View Data Export Data



Functions... (25.439331,9.3854749) [129,93] Value = 4.201516380782129E-14

Show Spatial Plot Show Time Plot Show Kymograph Statistics

CONNECTED

Server: ms3.vcell.uhc.edu:80 User: tgeyer

Java Memory Used: 50,3MB / 110,2MB

45%