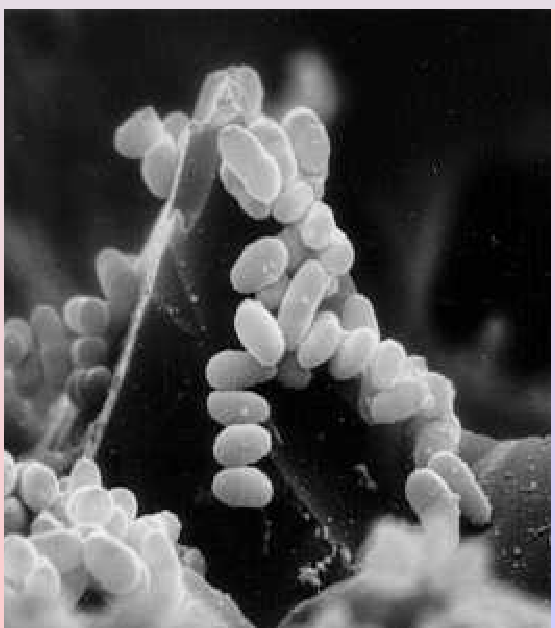
Wolfgang Wiechert
Lehrstuhl für Simulationstechnik
FB 11/12:
Maschinenbau/E-Technik/Informatik
Universität Siegen

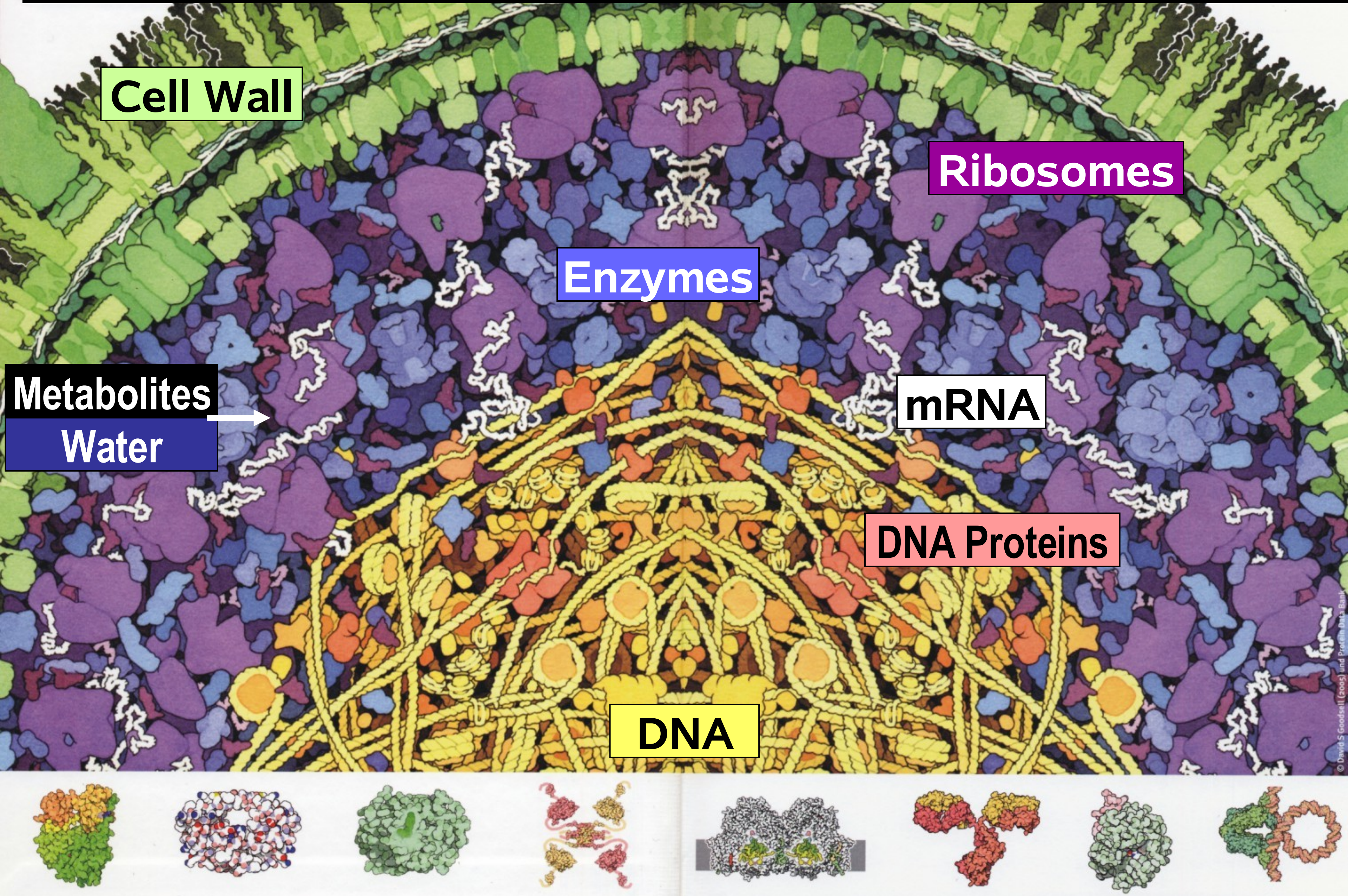
FOMAAS
ANALYSE,
SIMULATION & OPTIMIERUNG
KOMPLEXER SYSTEME

Modellierung und Simulation zellulärer Netzwerke



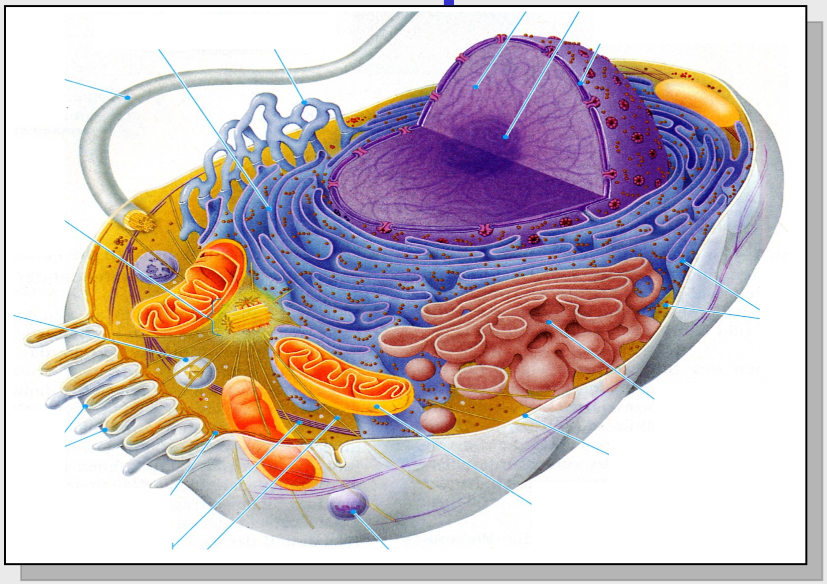
- Größenskalen
- Partikelmodelle
- Stochastische Modelle
- Räumlich verteilte Modelle
- Räumlich homogene Modelle
- Stöchiometrische Modelle

Cells are Bags of Macromolecules

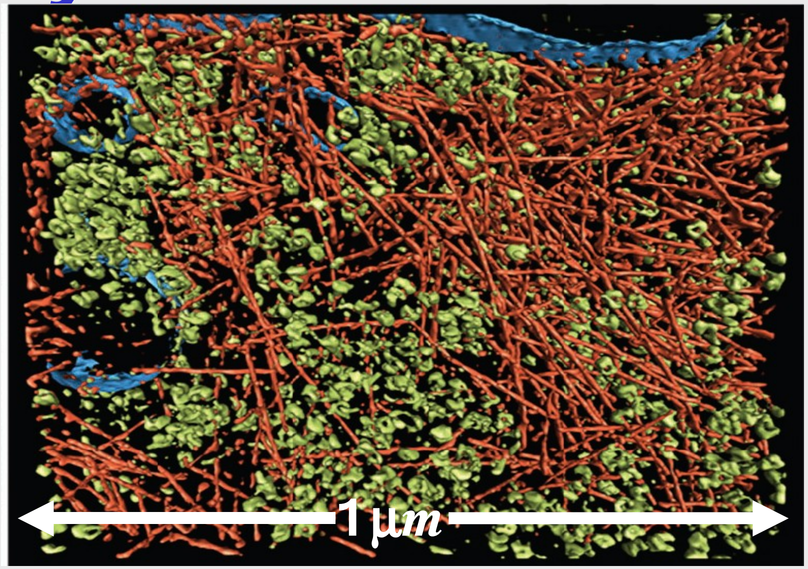


Spatial Structure of Cells

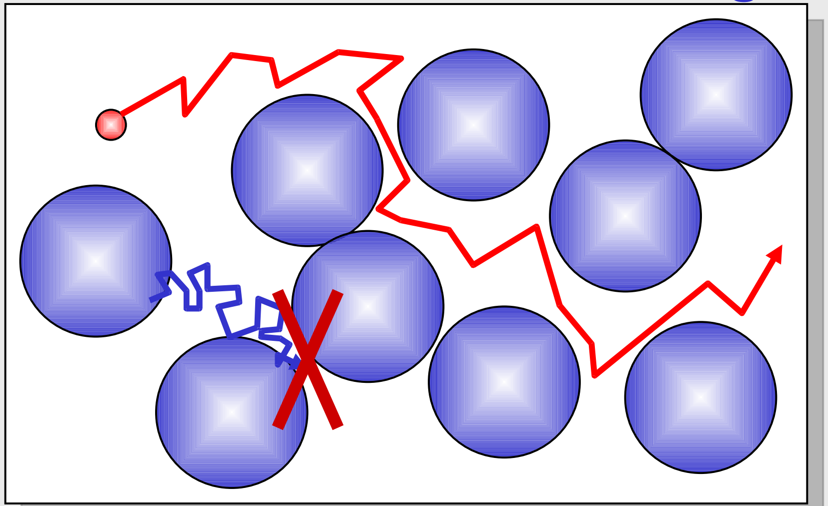
Cellular Compartments



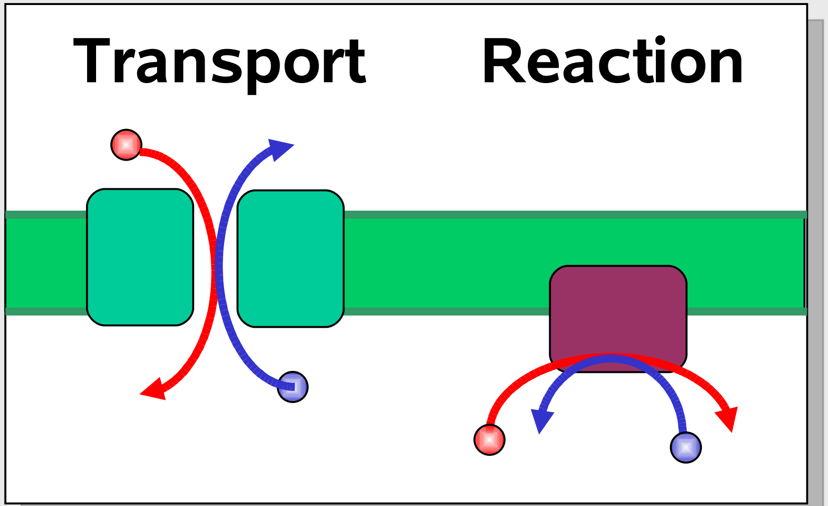
Cytosceleton



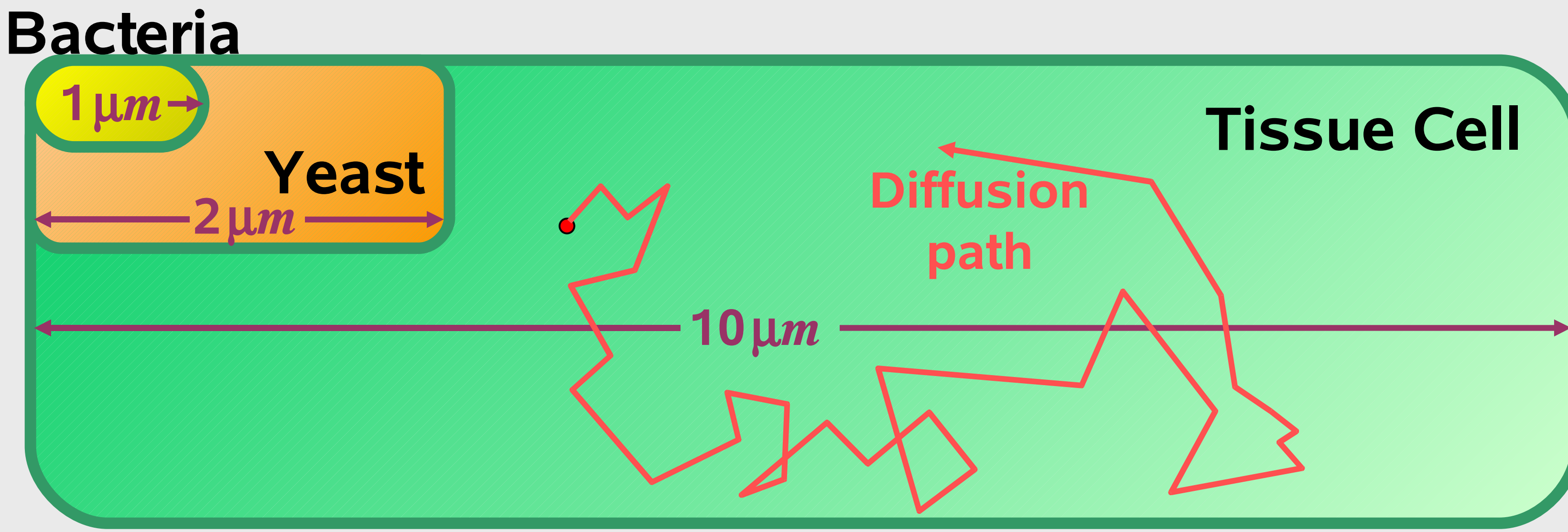
Macromolecular Crowding



Membrane Processes



Cellular Processes are driven by Molecular Motion



Diffusion time of small molecules in water: $D \sim 10^{-9}\ m^2\ s$

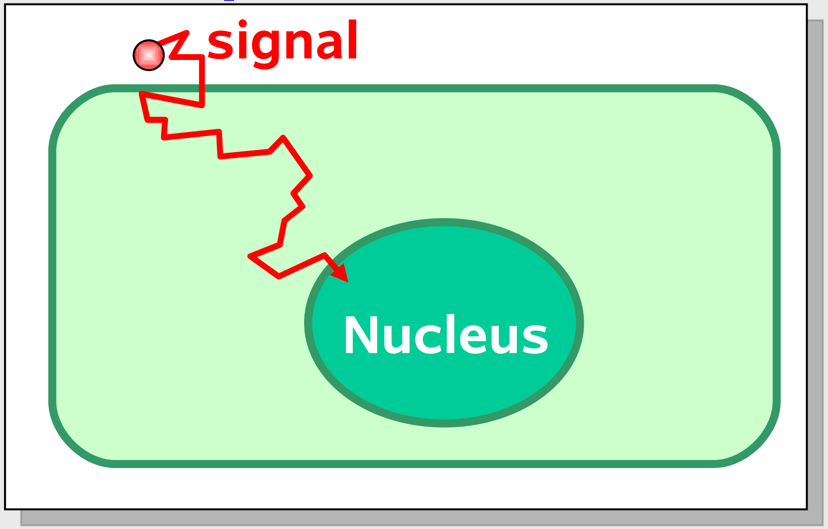
Crowded environment (hypothetical) : $D \sim 10^{-10}\ m^2\ s$

Consequences for cell modeling

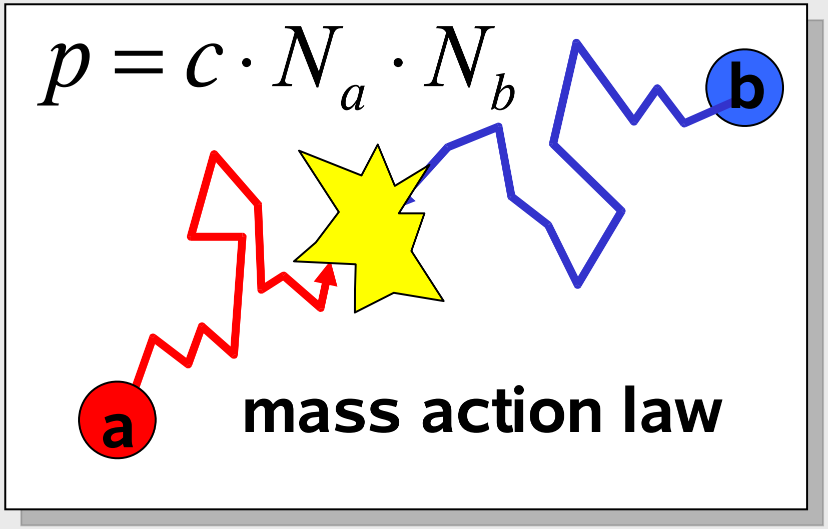
1. Space and diffusion is an issue even for tiny cells
2. Stochastic phenomena are to be expected
3. Reactions interact with diffusion processes

Stochastic Phenomena in Cells

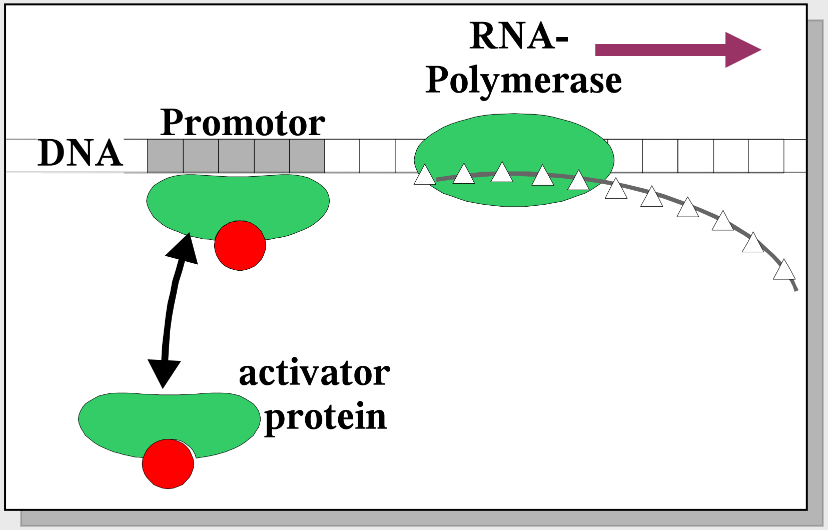
Small particle numbers



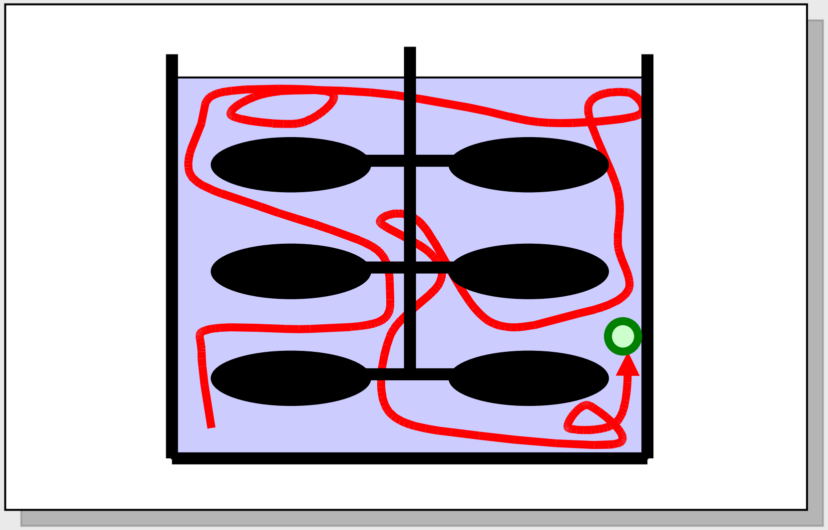
Nonlinearities



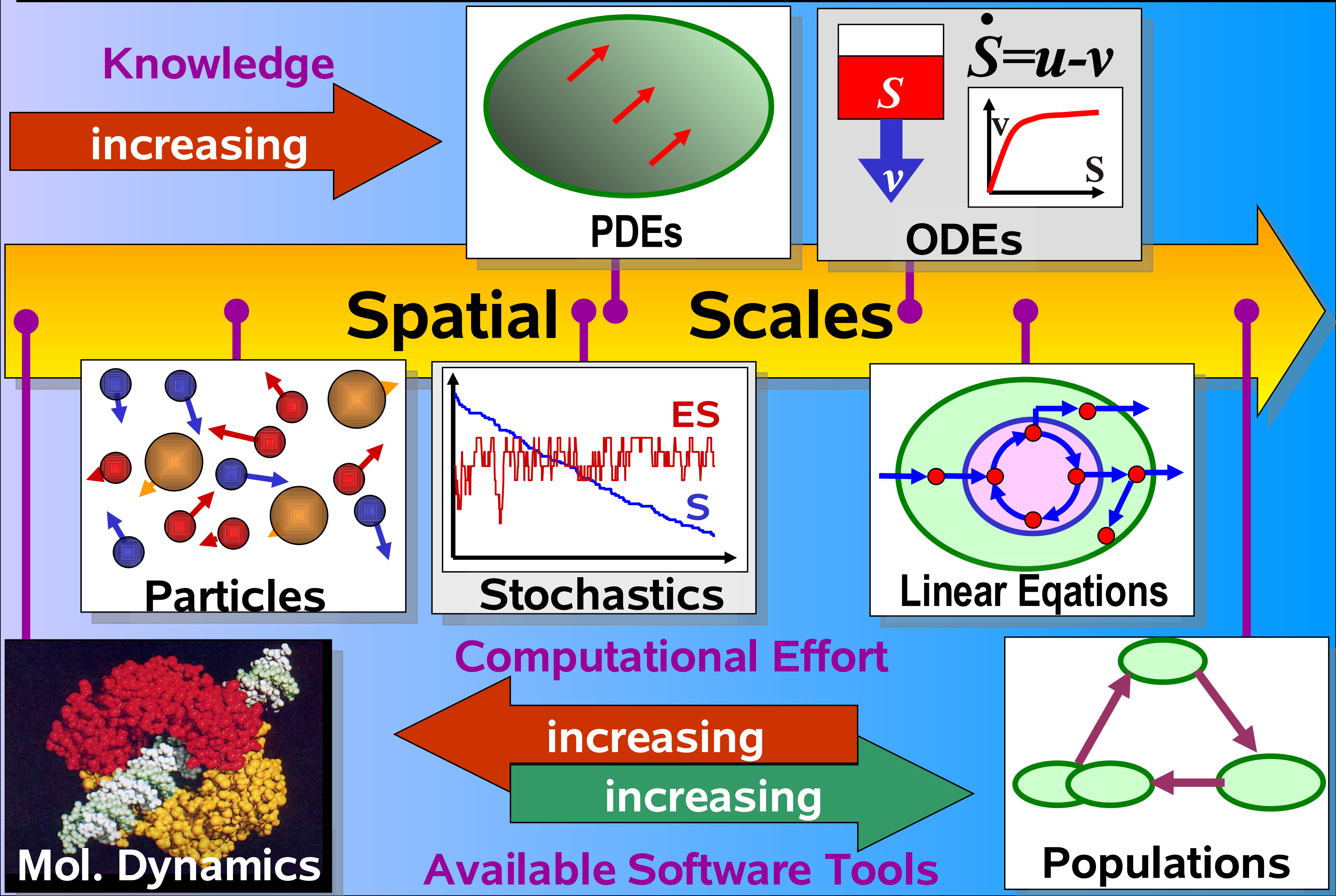
Rare molecular events



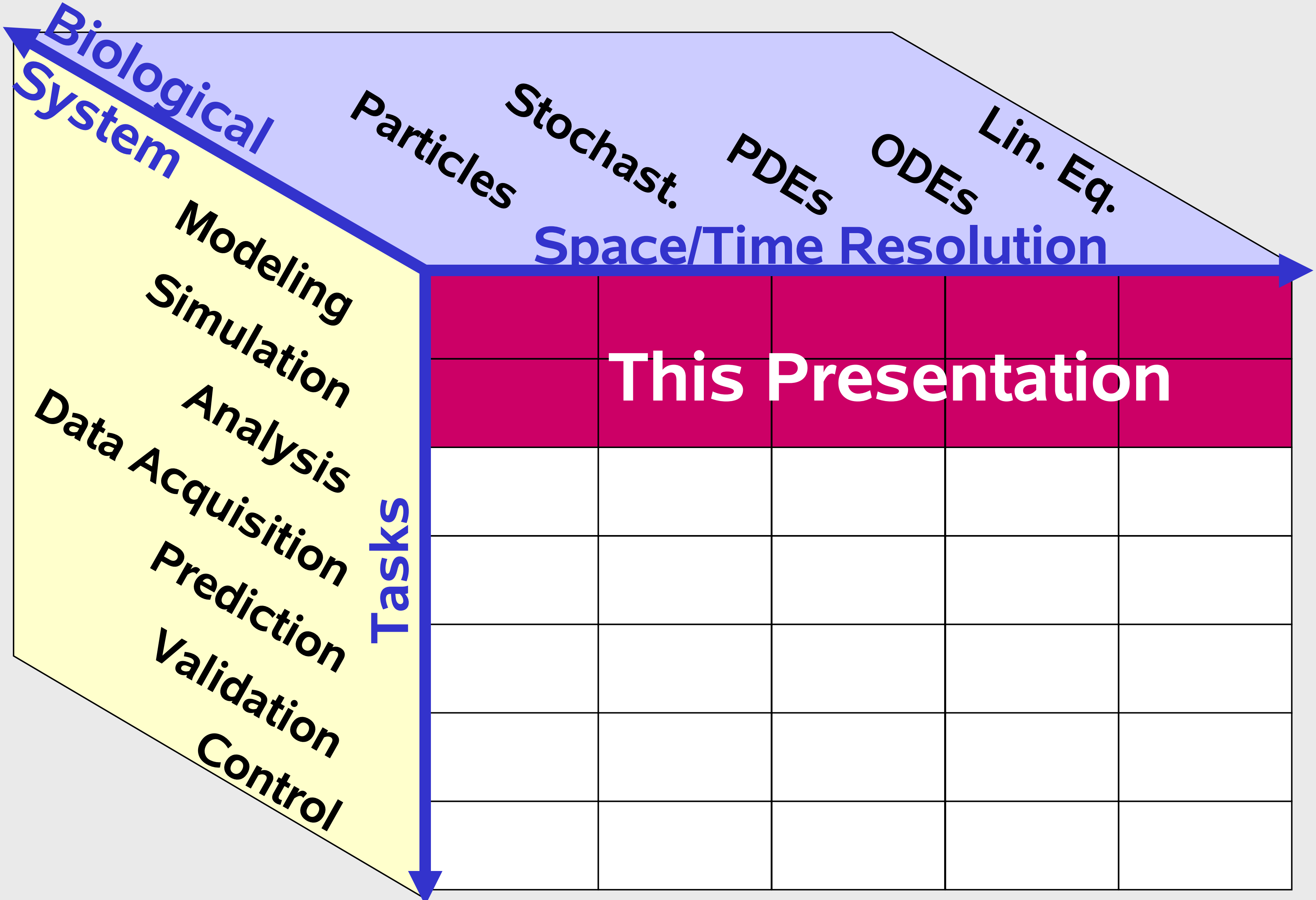
Environmental noise



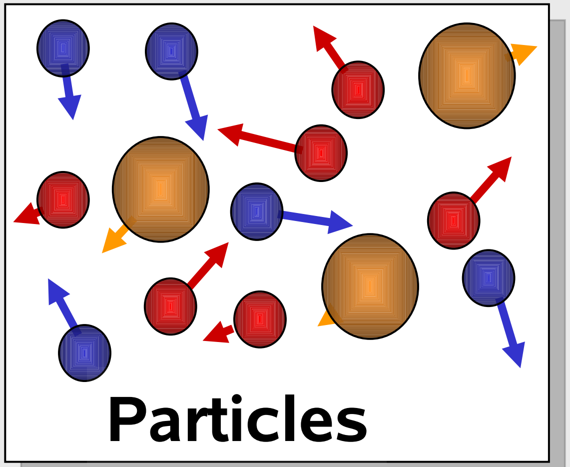
Scales of Cellular Network Modelling



Dimensions of Modeling and Simulation

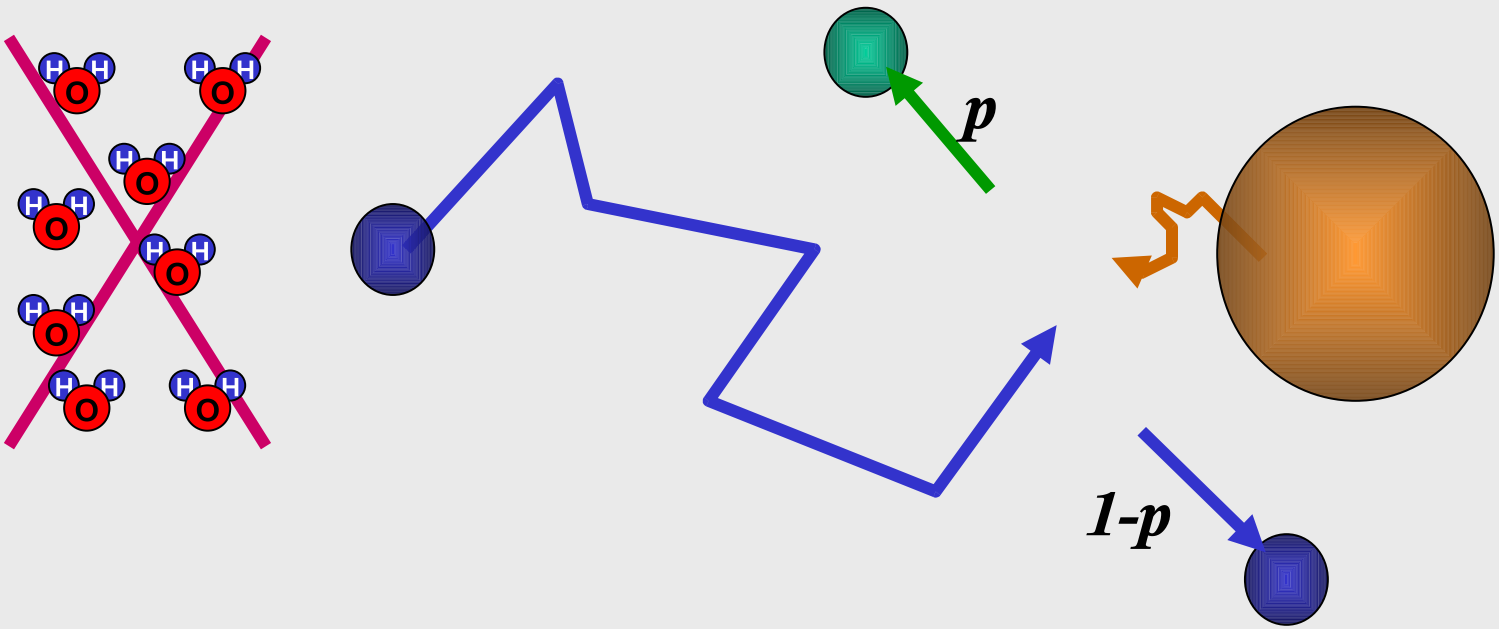


Particle Approach



Principles

- molecules are discrete particles
- water & other small molecules not considered
- stochastic particle motion
- probability laws for chemical reaction

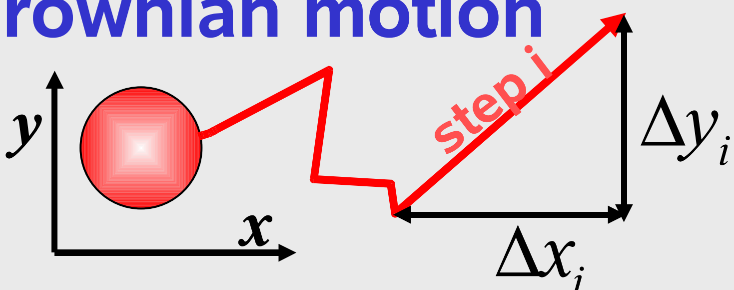


Brownian Dynamics

Principles

- Point particles
- Continuous space
- Discrete time step Δt
- Brownian motion law
- Reaction modeled

Brownian motion

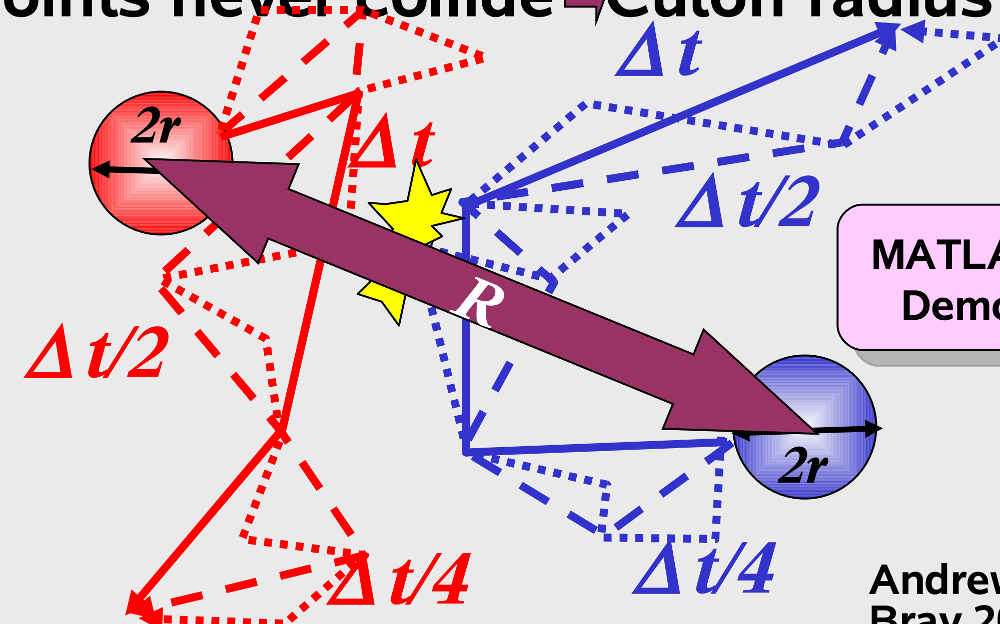


normally distributed random number

$$\Delta x_i = \sqrt{2D \cdot \Delta t} \cdot n(0,1), \quad i = 1, \ldots, t/\Delta t$$

Reaction modeling

Points never collide ⇒ Cutoff radius R



MATLAB Demo

Andrews, Bray 2004

Consistent approximation of reaction probability w.r.t. Δt possible from Fokker Planck eqn.

Consistent diffusion step size for $\Delta t \to 0$

$$\mathrm{Var}\left[\sum_i \Delta x_i\right] = \sum_i \mathrm{Var}[\Delta x_i] = \left(\sqrt{2D \cdot \Delta t}\right)^2 \cdot \sum_i 1 = 2D \cdot \Delta t \cdot t/\Delta t = 2Dt$$

Example: Intracellular Signaling

Steroid Hormones

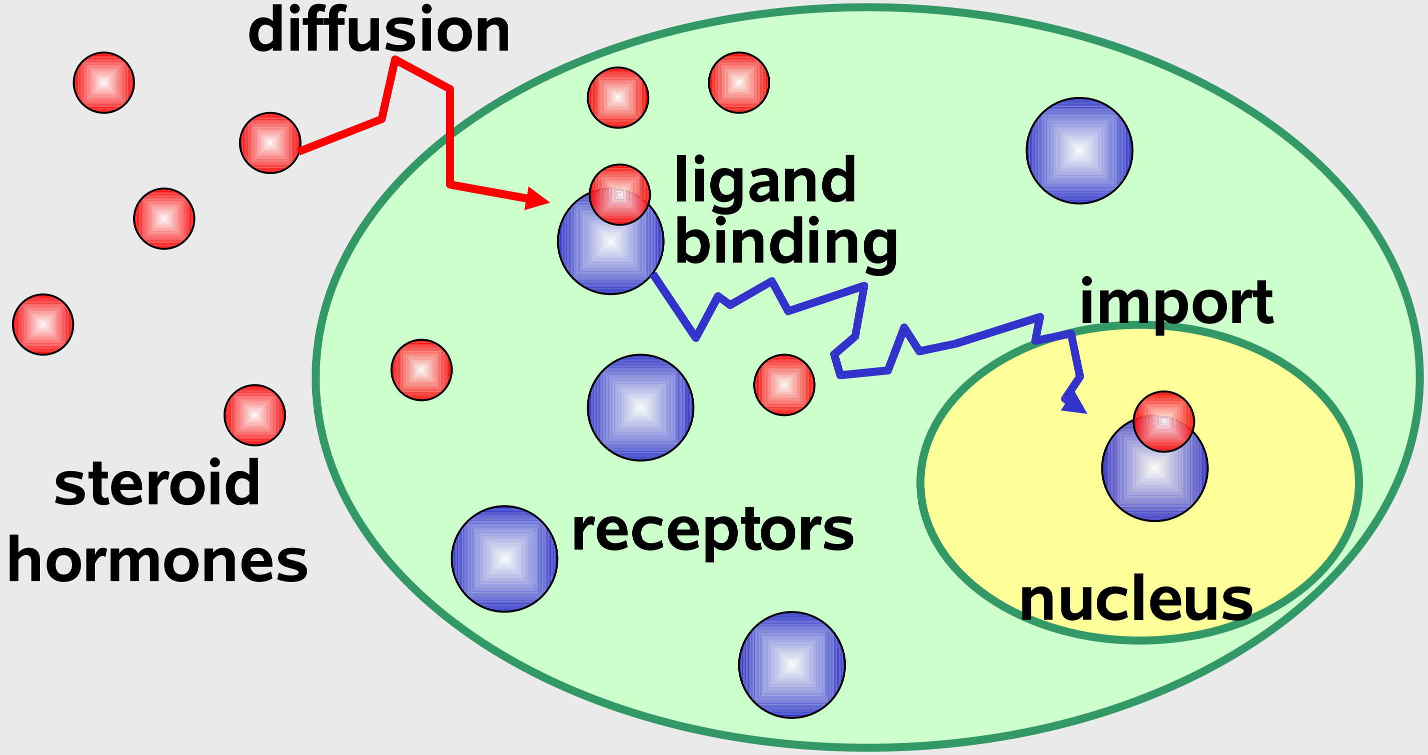
Hormones involved in male phenotype development and maintenance

Characteristics

- small molecule number
- nonlinear binding step
- long diffusion length
- first passage time important

Steroid Hormone Pathway

Lapin, Reuss 2006



Video

Example: Chemical Lotka Volterra System

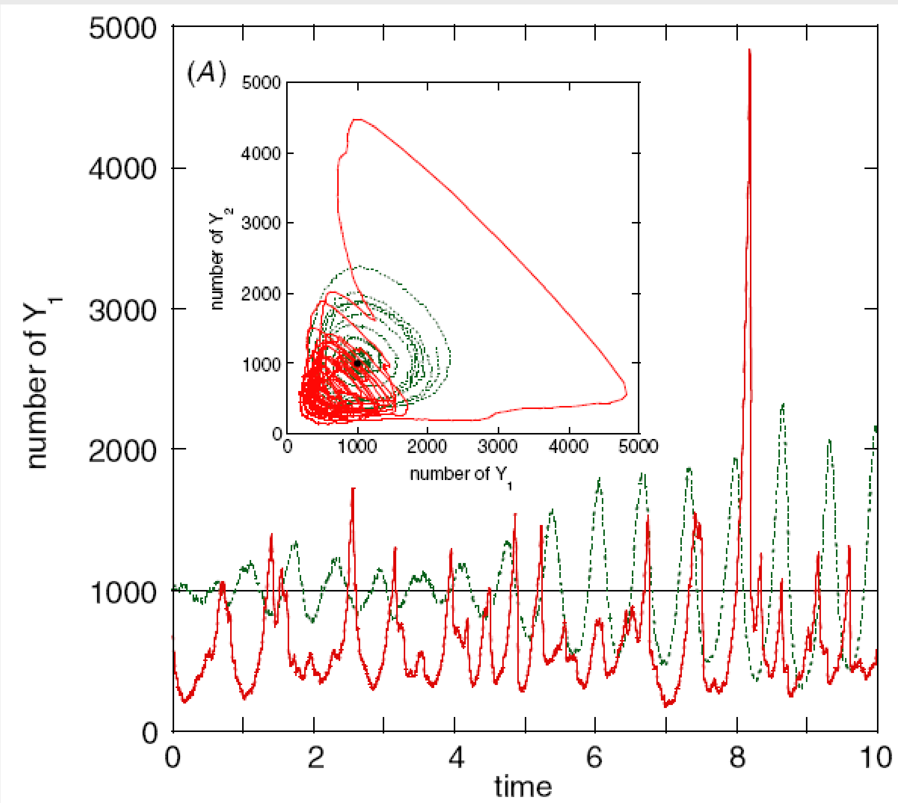
Reaction equations

$A + B \rightarrow 2B$
$B + C \rightarrow 2C$
$C \rightarrow$

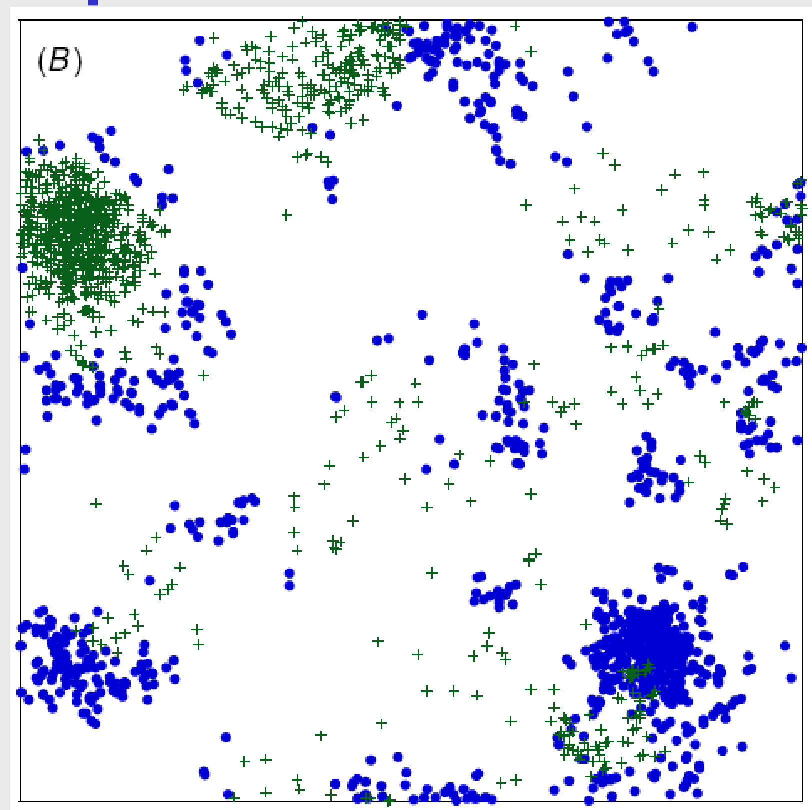
A – feed	(kept constant)	
B – prey	(growing on A)	
C – predator	(growing on B)	

Andrews, Bray 2004

Time course



Spatial distribution



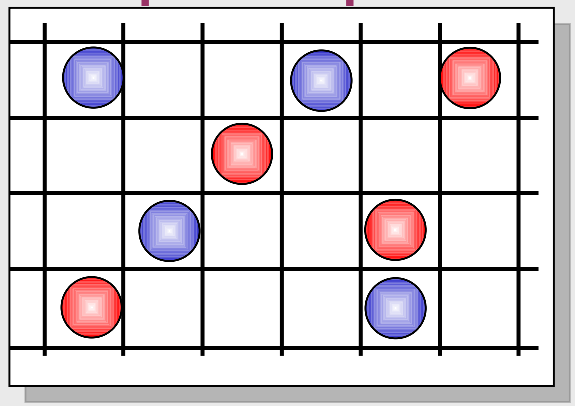
Cellular Automata Approaches

Principles

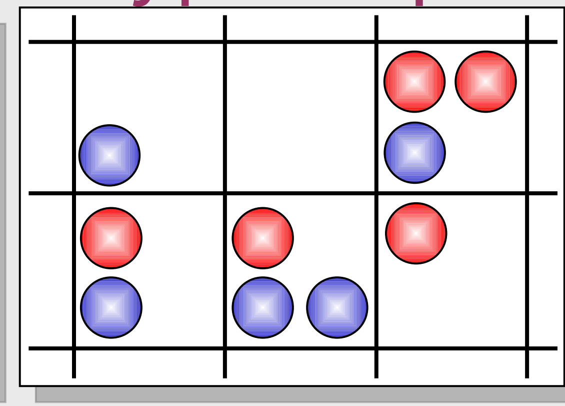
- Discrete space ΔV
- Discrete time Δt
- Particles occupy cells
- Stochastic rules for cell transitions
- Reaction modeled

Two variants

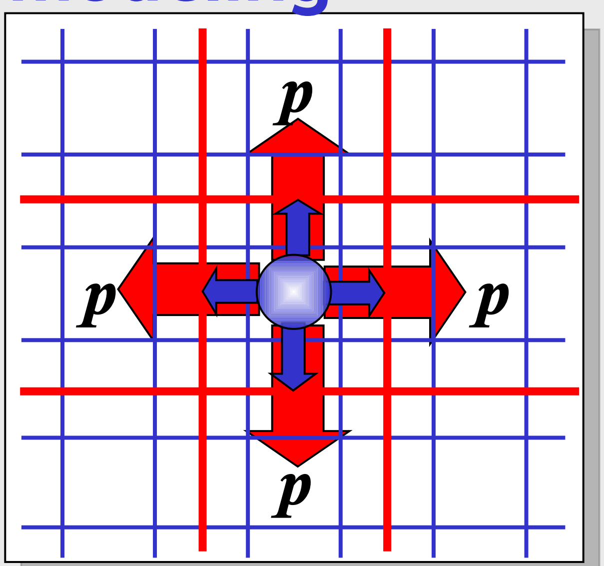
one particle per cell



many particles per cell



Consistent diffusion modeling



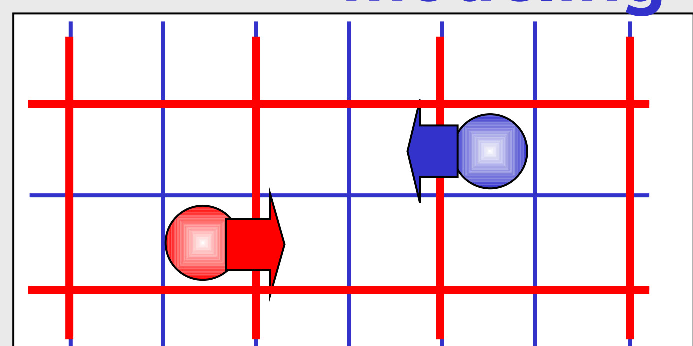
Result for 1D Lattice gas

$$p = p(\Delta t, \Delta x)$$

$$\frac{p}{1-p} = 2D \cdot \frac{\Delta t}{\Delta x^2}$$

Szopard, Drosz 1998

Consistent reaction modeling

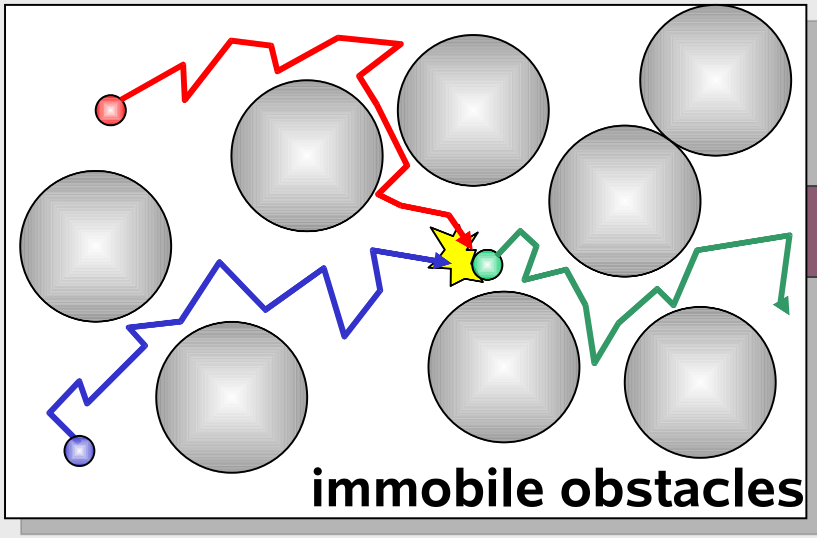


Reaction probability depends on grid size

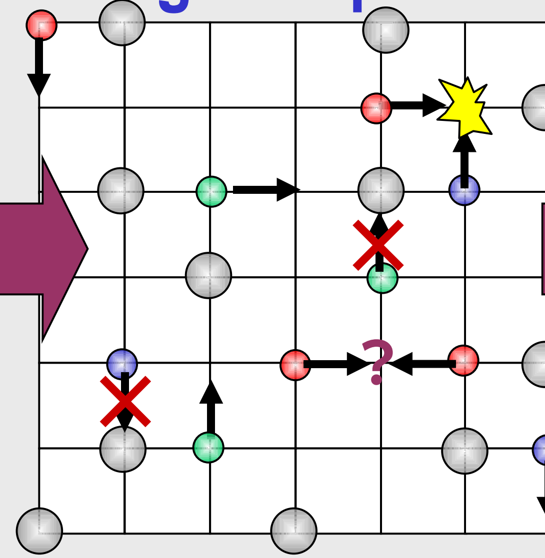
Stundzia, Lumsden 1996

Example: Macromolecular Crowding

Macromolecular Crowding



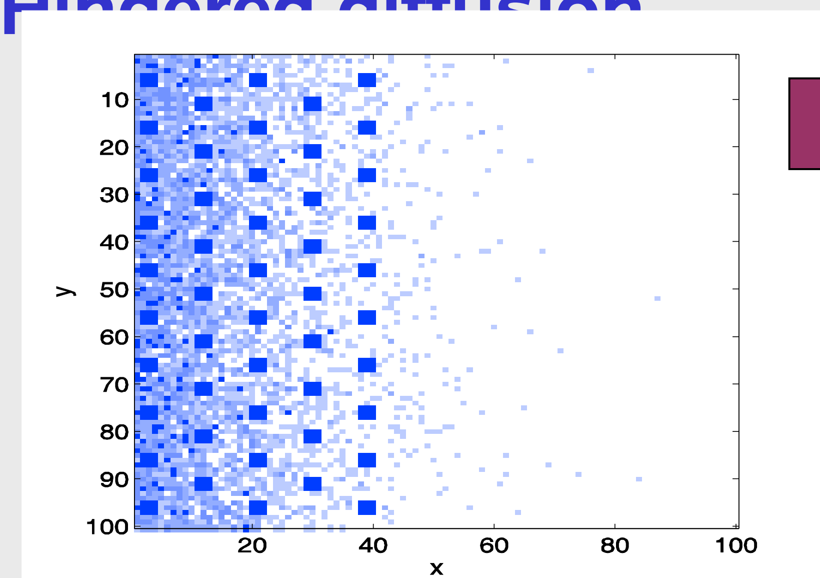
Lattice gas implementation

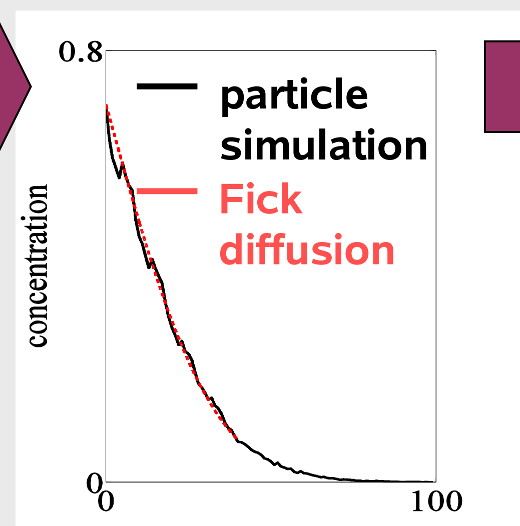


Fractal Kinetics

Schnell, Turner 2004

Hindered diffusion





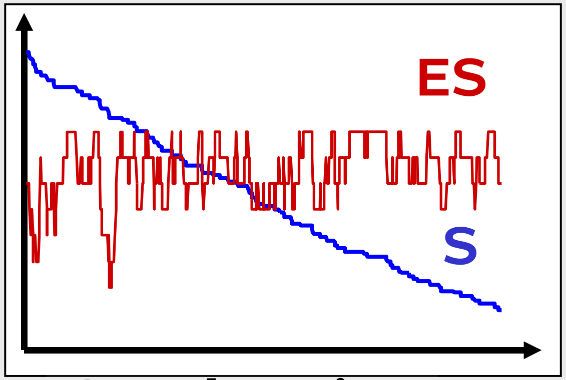
Effective Diffusion Coefficient

Buschmann 2004

Lipkow 2005

video

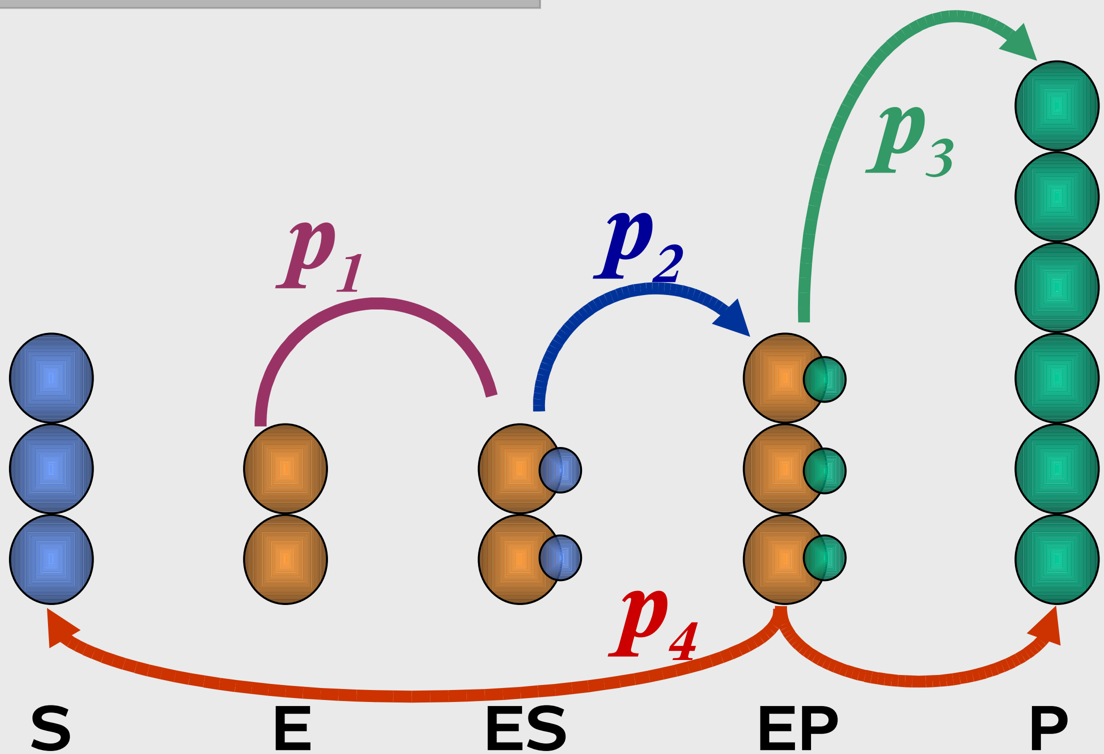
Spatially homogeneous Stochastic Models

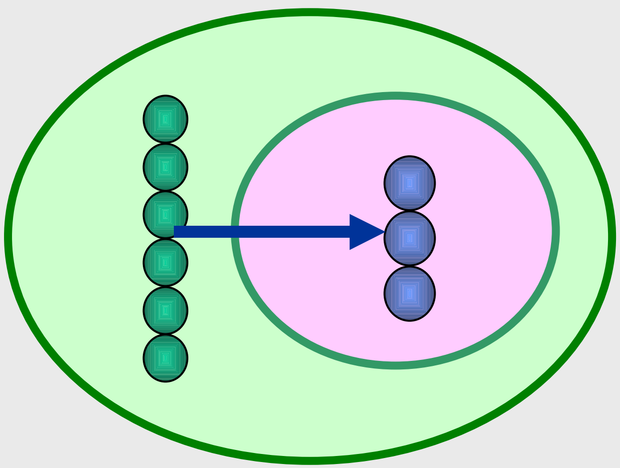


Stochastics

Principles

- integer number of molecules
- spatially homogeneous
- probability laws for chemical reaction





MATLAB demo

Gillespie‘s Stochastic Simulation Algorithm (SSA)

Principles

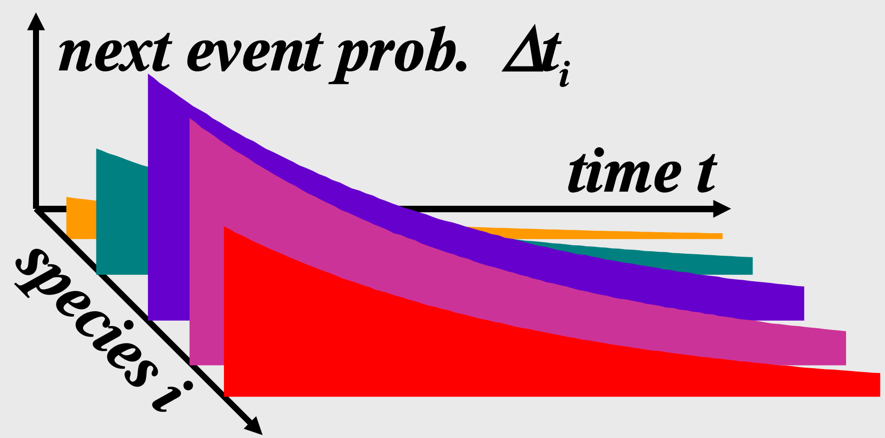
- Species $1,\ldots,N$
- Discrete state vector x
- Propensity functions $a_i(x)$:
  Reaction probability per time
- Stoichiometry vectors ν_i
- Discrete event time stepping

Next reaction event for specie i

Asuming that no other event happens until time Δt, i.e. $a_i(x)=const.$

$$\Delta t_i : \; a_i \cdot \exp(-\sum_{j=1}^{N} a_j \cdot \Delta t)$$

exponential distribution



Algorithm

Initialize $t \leftarrow t_0$ and $x \leftarrow x_0$
loop
Evaluate $a_i(x)$, $i=1,\ldots,N$
Sample from Δt_i
Compute $I = \arg\min \Delta t_i$
$t \leftarrow t+\Delta t_I$ and $x \leftarrow x + \nu_i$
end loop

Exactness property

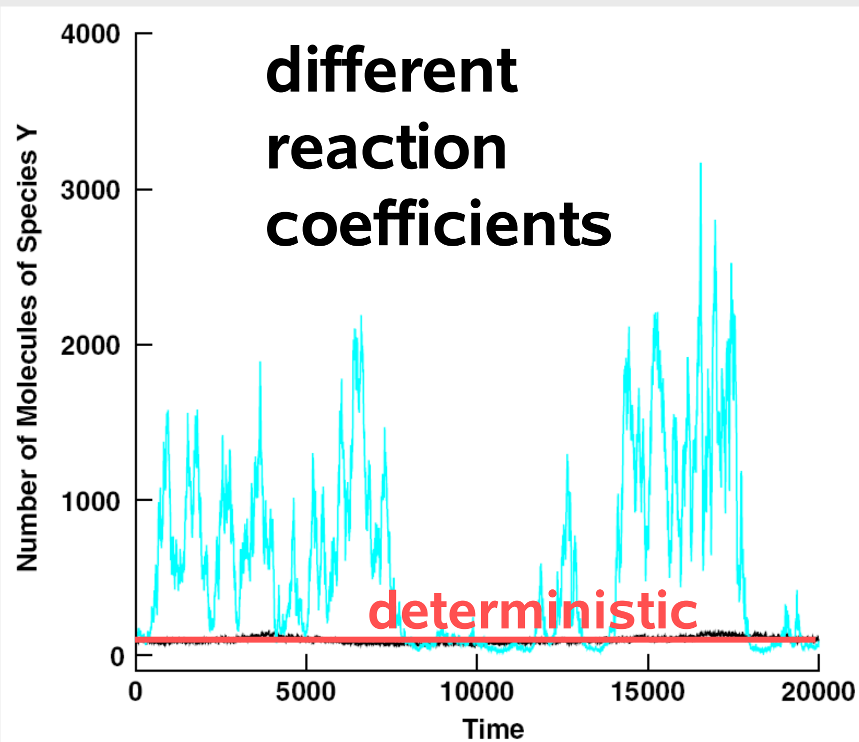
SSA computes an exact realization of the process with given propensities.

Example: Nonlinear Reactions

Monostable system

A→X→
B→Y→
X+Y→Z

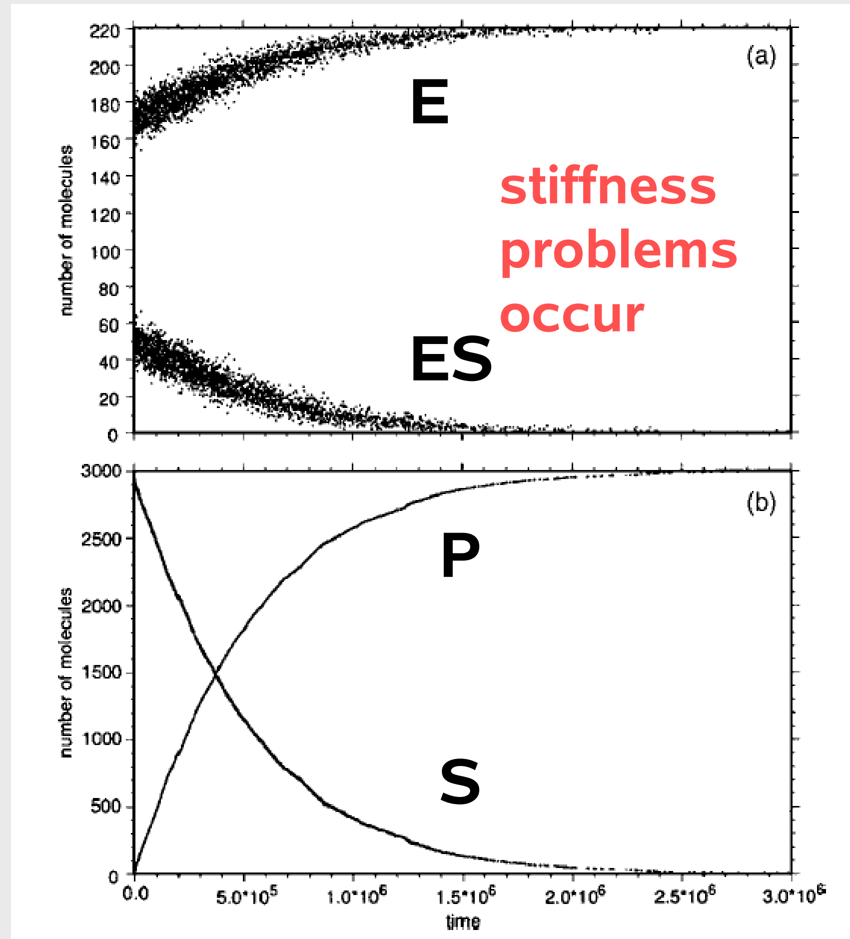
A,B – constant reservoirs
X,Y – proteins
Z – dimer



Samad, 2005

Michaelis Menten system

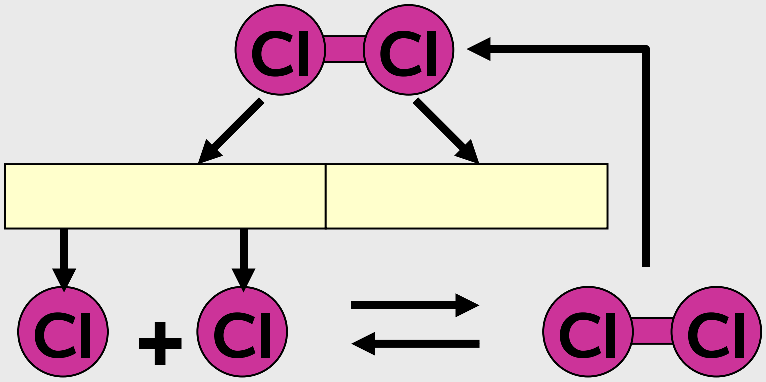
E+S→ES→P+E

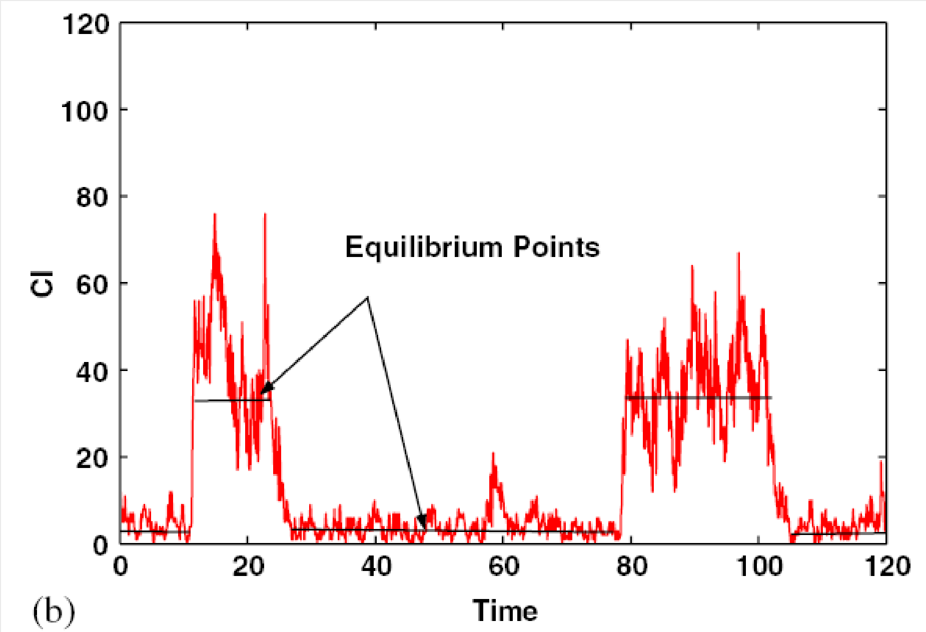


Cao, 2005

Example: Genetic Regulation

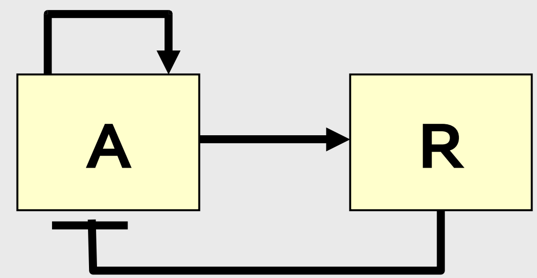
Genetic switch

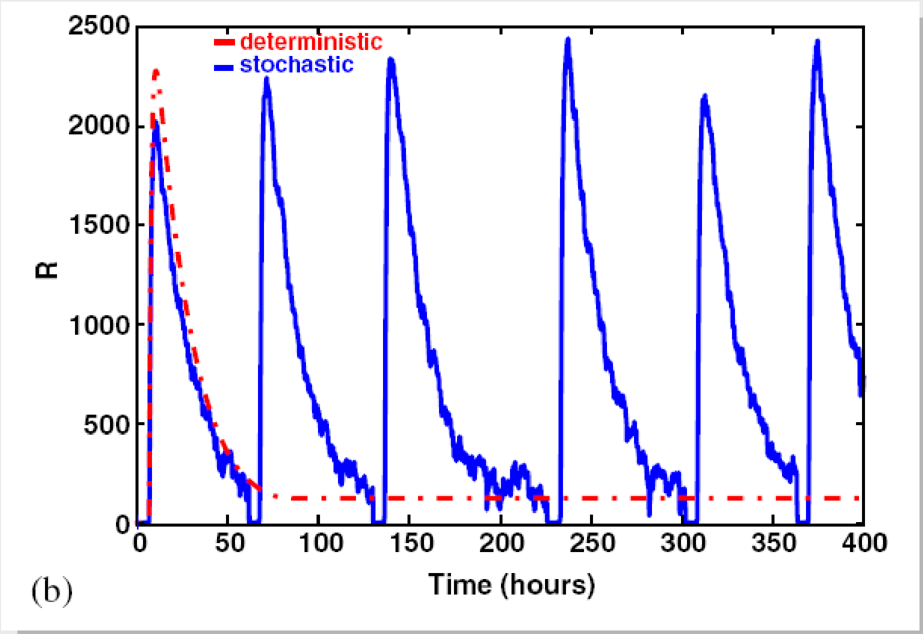




Samad, 2005

Circadian oscillator





Samad, 2005

Improvements to Gillespie's Algorithm

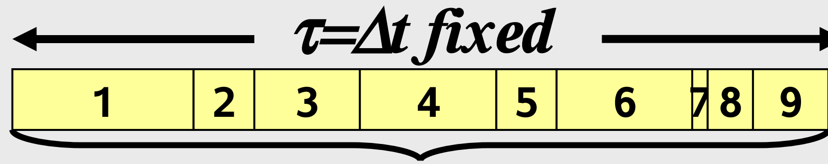
Speedup

- next reaction method
- tau leaping
- chemical Langevin SDE
- classical reaction ODE

Gibson, Bruck 2000

Gillespie 2001

Gillespie 2000



Poisson distribution (discrete)

large particle numbers

Normal distribution (continuous)

expectations + $\Delta t \rightarrow 0$

deterministic model (ODE)

Precision & Stability

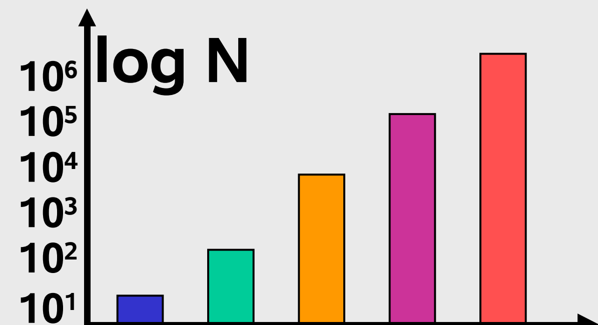
- higher order methods
- implicit tau leaping
- slow reaction method

Cao 2006

Rathinam 2003

Cao 2005

stiff sys- tems

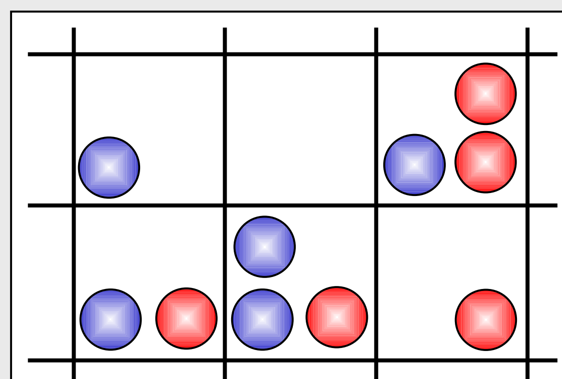


Space

- consistent spatial discretization with SSA
- classical diffusion reaction PDE

Elf, Ehrenberg 2004

Kholodenko 2006



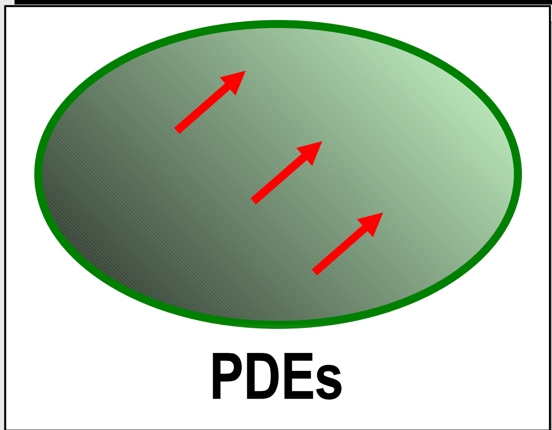
expectations

+ $\Delta T \rightarrow 0$

+ $\Delta V \rightarrow 0$

deterministic model (PDE)

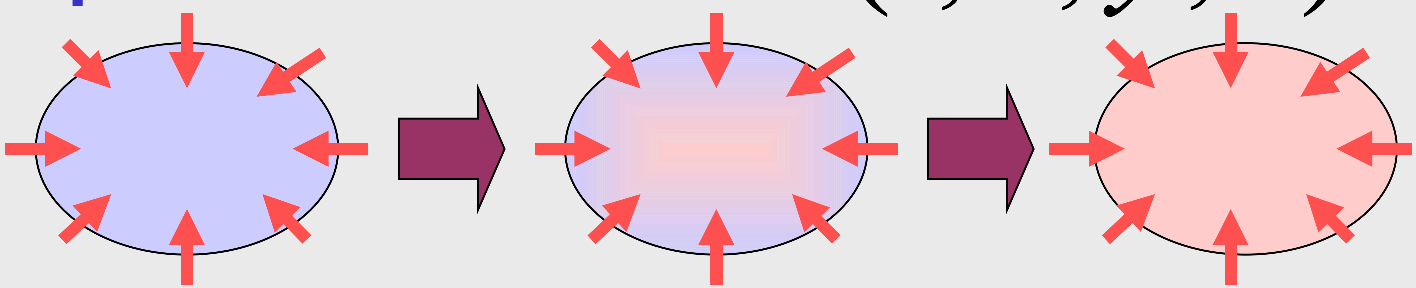
PDE Models



Principles

- species given by concentrations
- spatio-temporal distribution
- diffusion model (particle average)
- reaction model (particle average)

Spatio-temporal concentration $c(t, x, y, z)$



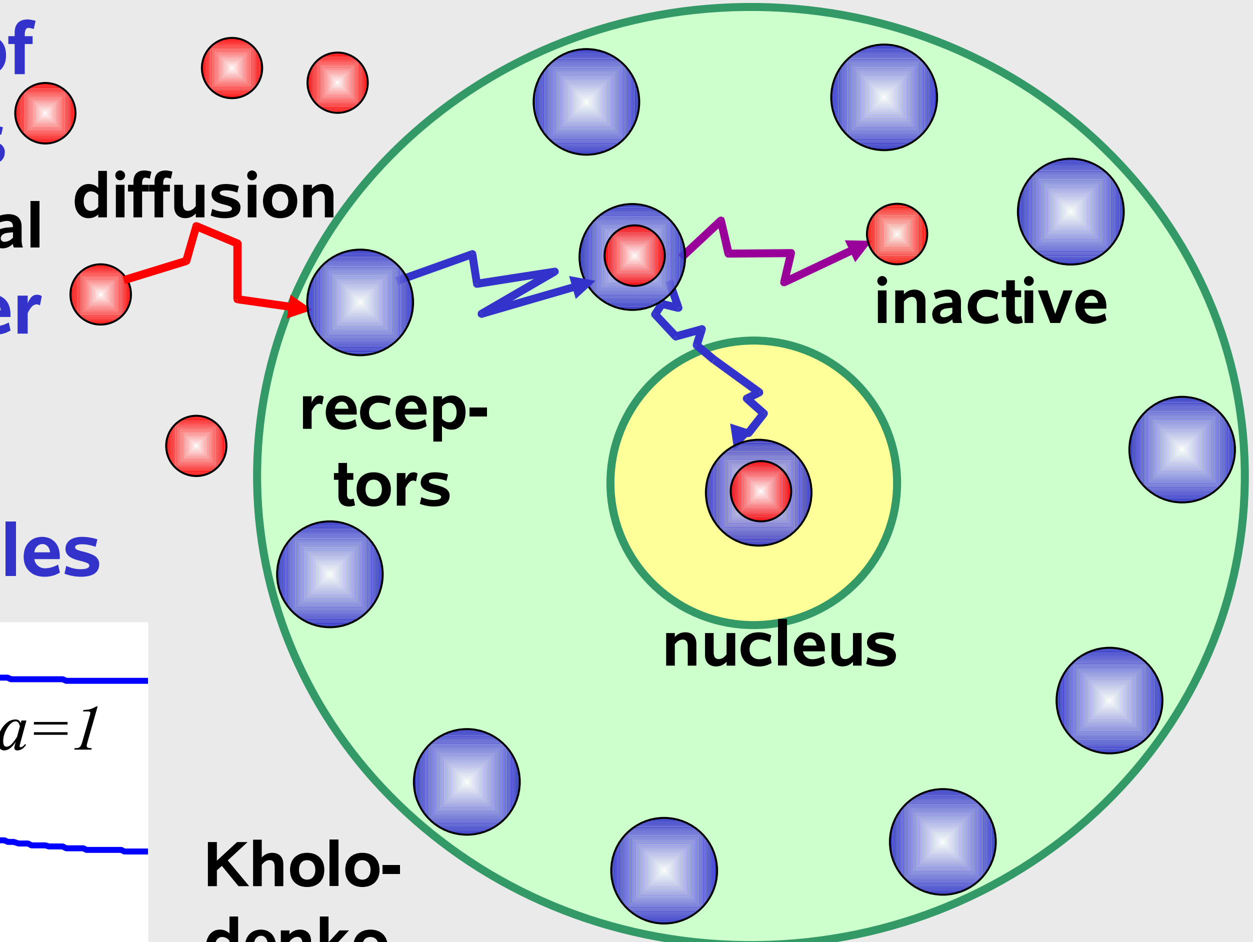
Reaction Diffusion Equation

$$\dot{c} = \nabla\left(D \cdot \nabla c\right) + r(c)$$

- $\dot{c}$: temporal change
- D: effective coefficient
- $\nabla\left(D \cdot \nabla c\right)$: diffusion flow
- $r(c)$: reaction

Example: Phosphoprotein Signals

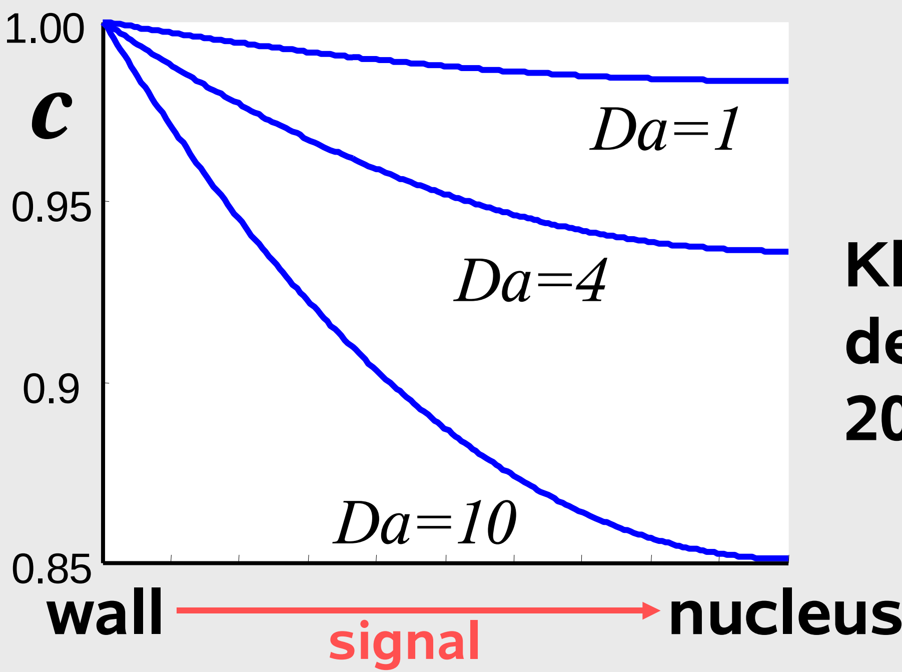
Phosphorylation of Signaling Proteins



Damköhler Number

$$Da = R^2 k / D$$

Steady State Profiles

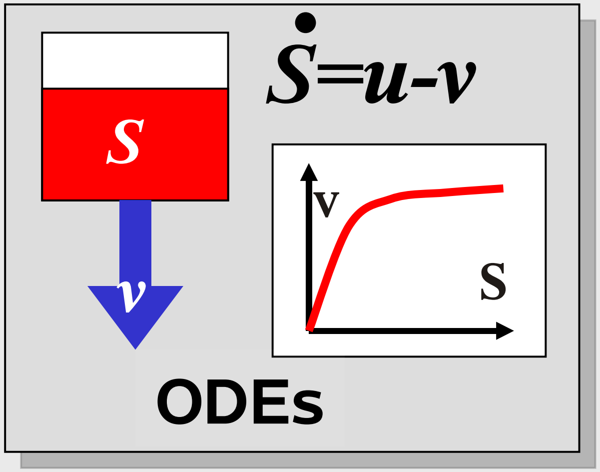


Kholo-
denko
2006

Radial RD Reaction

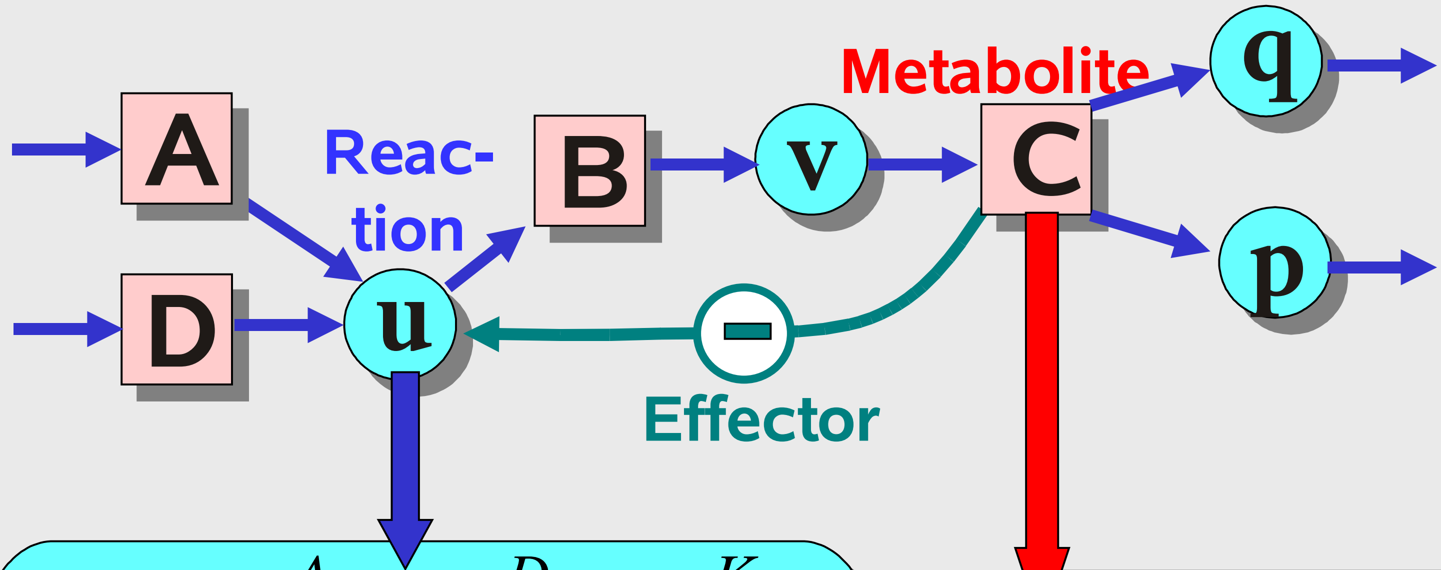
$$\frac{D}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) - kc = 0$$

ODE Models



Principles

- homogeneous concentrations
- biochemical reaction network
- enzyme kinetic reaction models
- balance equations



$$u = u_{\max} \cdot \frac{A}{A + K_A} \cdot \frac{D}{D + K_D} \cdot \frac{K_C}{C + K_C}$$

$$\dot{B} = u - v$$

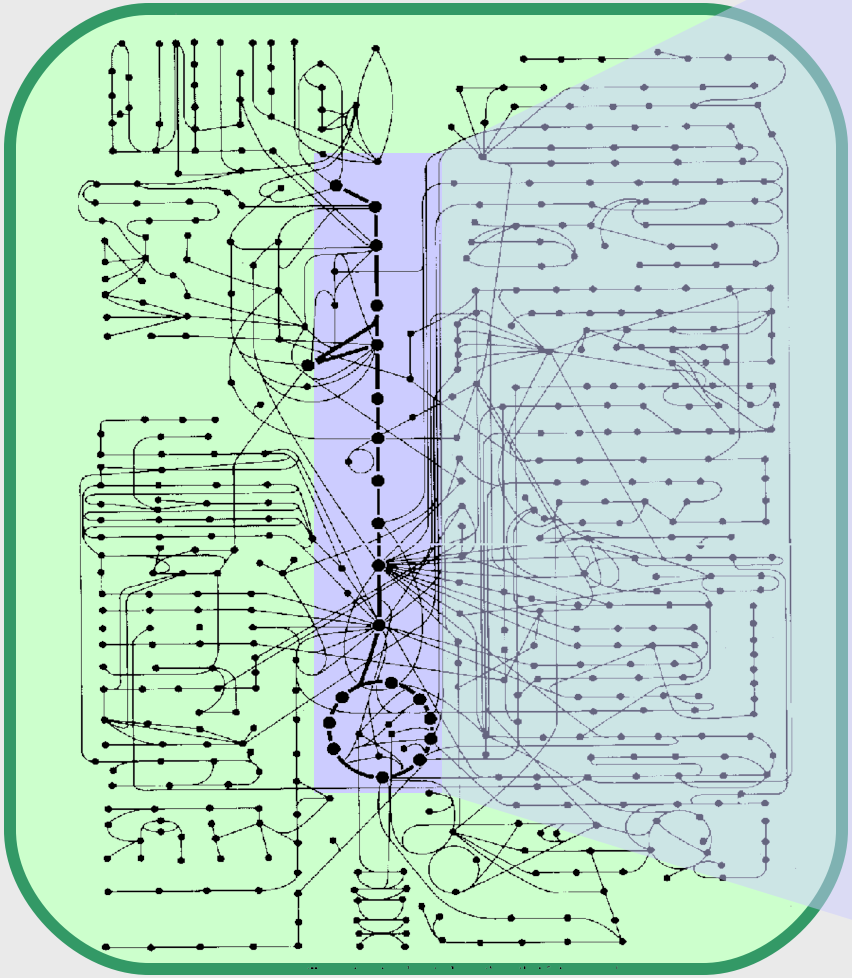
Reaction Kinetics

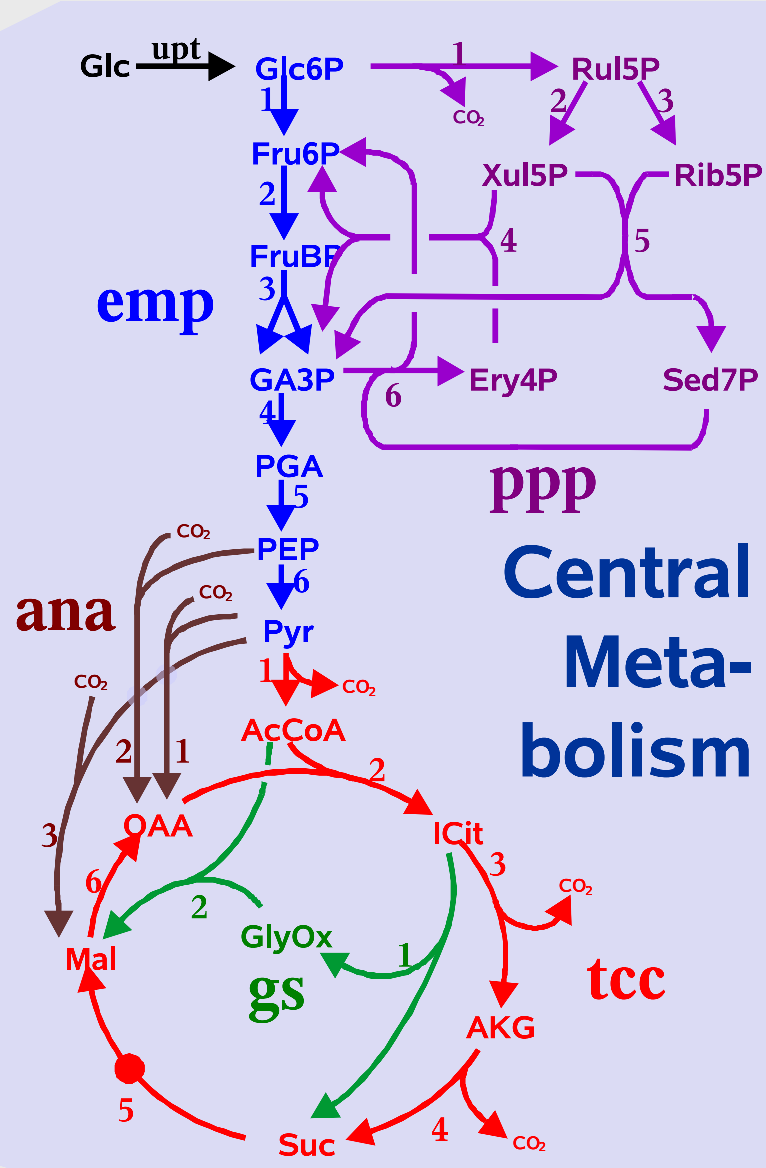
Balancing

Genome Scale Networks and Central Pathways

Total:

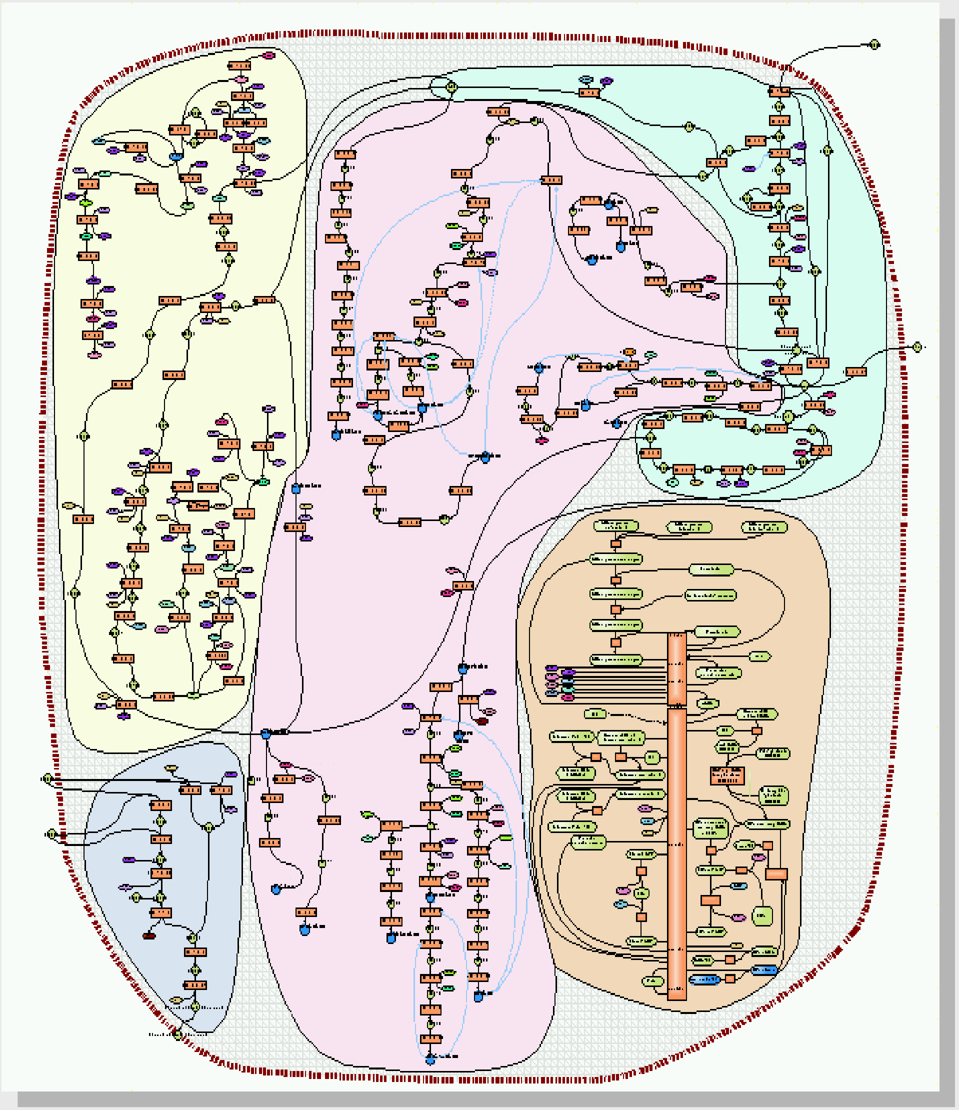
> 1000 Reactions





Tools for Network Simulation

E-Cell

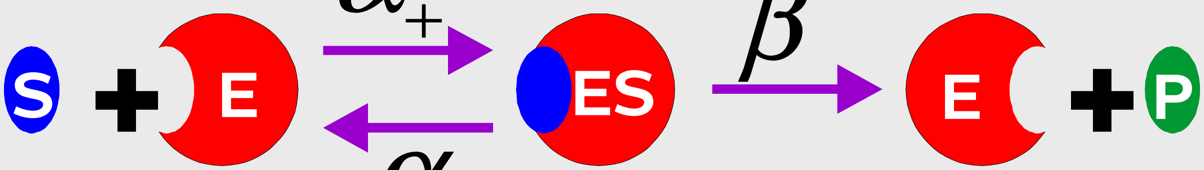


… and other tools

- BALSA
- BASIS
- BIOCHAM
- BioCharon
- ByoDyn
- BioCyc
- BioGrid
- BioModels
- BioNetGen
- BioPathwise
- Bio Sketch Pad
- BioSens
- BioSPICE
- BioSpreadsheet
- BioTapestry
- BioUML
- BSTLab
- CADLIVE
- CellDesigner
- Cellerator
- CellML2SBML
- Cellware
- CL-SBML
- CLEML
- COPASI
- Cyto-Sim
- Cytoscape
- DBsolve
- Dizzy
- E-CELL
- ecellJ
- ESS
- FluxAnalyzer
- Fluxor
- Gepasi
- Gillespie2
- HSMB
- HybridSBML
- INSILICO
- JACOBIAN
- Jarnac
- JDesigner
- JigCell
- JSim
- JWS Online
- Karyote*
- KEGG2SBML
- Kineticon
- Kinsolver*
- libSBML
- MathSBML
- MesoRD
- Meta-All
- MetaboLogica
- MetaFluxNet
- MMT2
- Modesto
- Moleculizer
- Monod
- Narrator
- NetBuilder
- Oscill8
- PANTHER
- PathArt
- PathScout
- Pathway An.
- PathwayLab
- Pathway Tools
- PathwayBuilder
- PATIKAweb
- PaVESy
- PET
- PNK
- PottersWheel
- Reactome
- ProcessDB
- PROTON
- pysbml
- PySCeS
- runSBML
- SABIO-RK
- SBML ODE
- SBML-PET
- SBMLeditor
- SBMLmerge
- SBMLR
- SBMLSim
- SBMLSim
- SBMLTB
- SBliD
- SBToolbox
- SBW
- SCIpath
- Sigmoid*
- SigPath
- SigTran
- SIMBA
- SimBiology
- Simpathica
- SimPheny*
- SimWiz
- SloppyCell
- SmartCell
- SRS P. Ed.
- StochSim
- StochKit
- STOCKS
- TERANODE
- Trelis
- Virtual Cell
- WebCell
- WinSCAMP
- XPPAUT

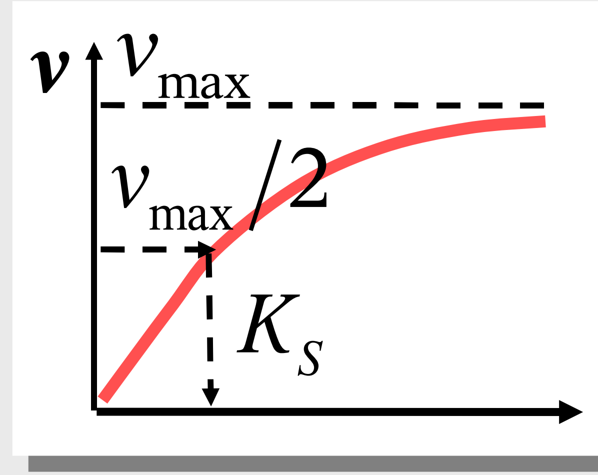
Quasi Stationary Reaction Kinetics

Michaelis Menten Model of an enzyme reaction



α_+, α_-, β

Sub-strate | Free enzyme | Enzyme-Substrate-Complex | Free enzyme | Pro-duct



Assumptions

1. Large particle number
2. Spatial homogeneity
3. Slowly changing substrate concentration
4. Substrate binding fast compared to reaction

$$\alpha_+, \alpha_- >> \beta$$

Quasi stationary rate

$$v(S) = E_0 \cdot \beta \cdot \frac{S}{S + \frac{\alpha_- + \beta}{\alpha_+}}$$

Enzyme Concentration

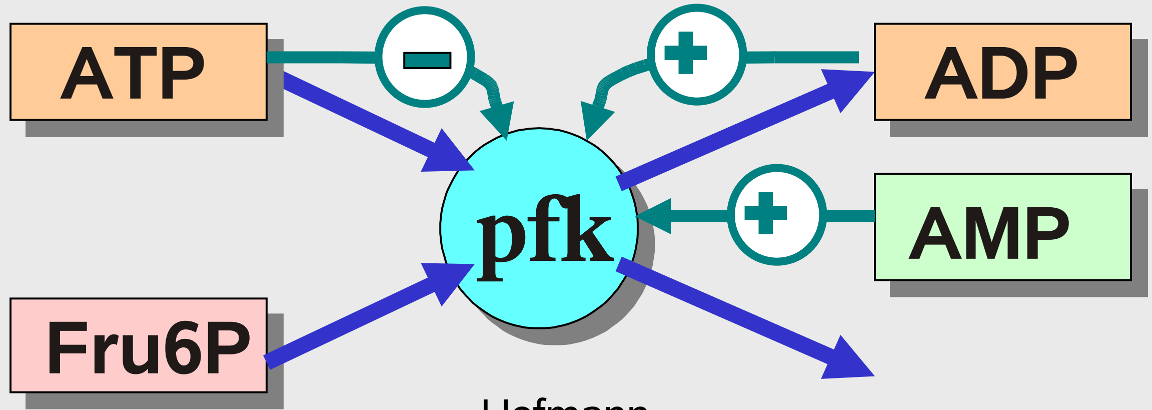
$$= v_{max} \cdot \frac{S}{S + K_S}$$

Michaelis Menten Kinetics

Many other reaction mechanisms are known.

Reaktion Kinetic Data

Simplified Phosphofructo-kinase-Model



Hofmann et al. 1982

Kinetics of PFK

$$v(F6P, ATP, ADP, AMP) = v_{\max} \cdot \cdots$$

Enzyme activity

$$\cdot \frac{ATP}{ATP + K_{ATPS}\left[1 + \frac{ADP}{K_{ADPC}}\right]} \cdot \frac{1}{1 + L_O \Big/ \left[1 + \frac{F6P}{K_{F6P}}\right]^8} \cdot \cdots$$

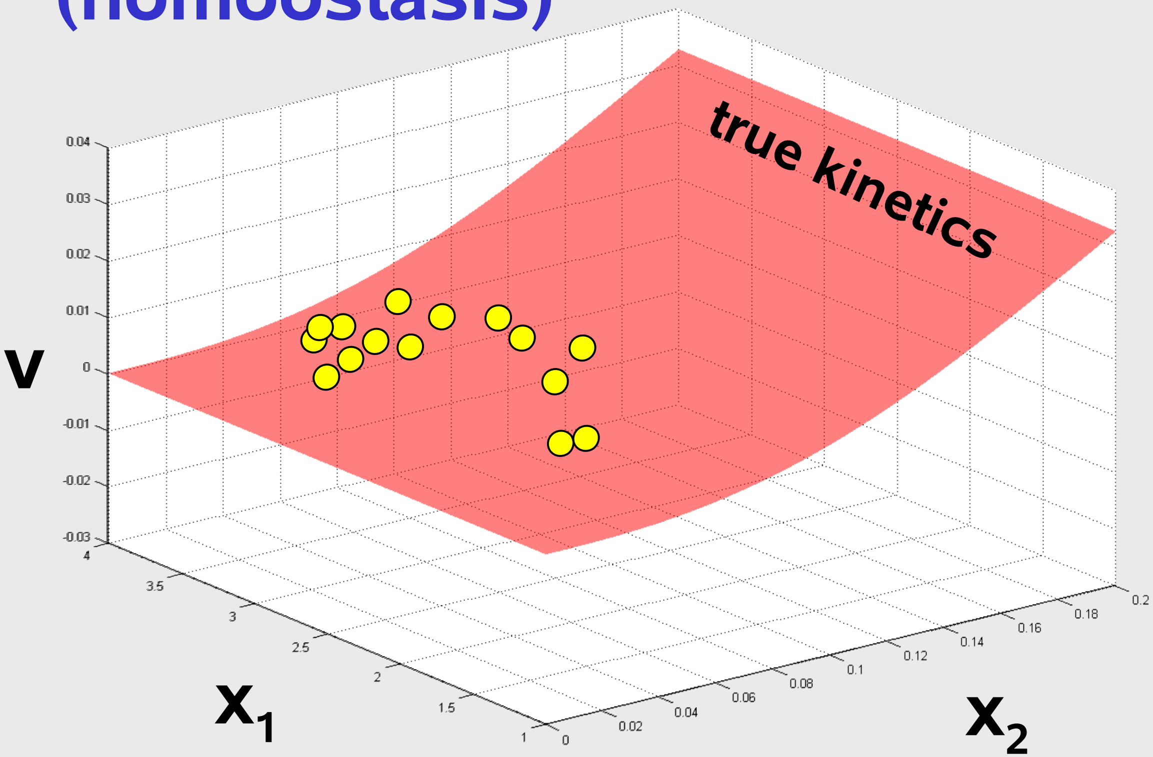
10 kinetic Parameters

$$\cdot \frac{F6P}{F6P + K_{F6PS} \cdot \left[1 + \frac{ATP}{K_{ATP1}} + \frac{ADP}{K_{ADP2}} + \frac{AMP}{K_{AMP2}}\right] \Big/ \left[1 + \frac{ADP}{K_{ADP1}} + \frac{AMP}{K_{AMP1}}\right]}$$

Number of parameters increases faster than number of reactands.

Approximate Kinetic Formats

Typical in vivo concentrations (homöostasis)



Requirements for approximations

- biologically reasonable
- nonlinear
- good approximation properties
- one parameter per reactand/effector
- good computational properties

Proposed kinetic formats

- **power laws** Savageau, Voit
- **lin-log** Heijnen
- **fuzzy** Liao

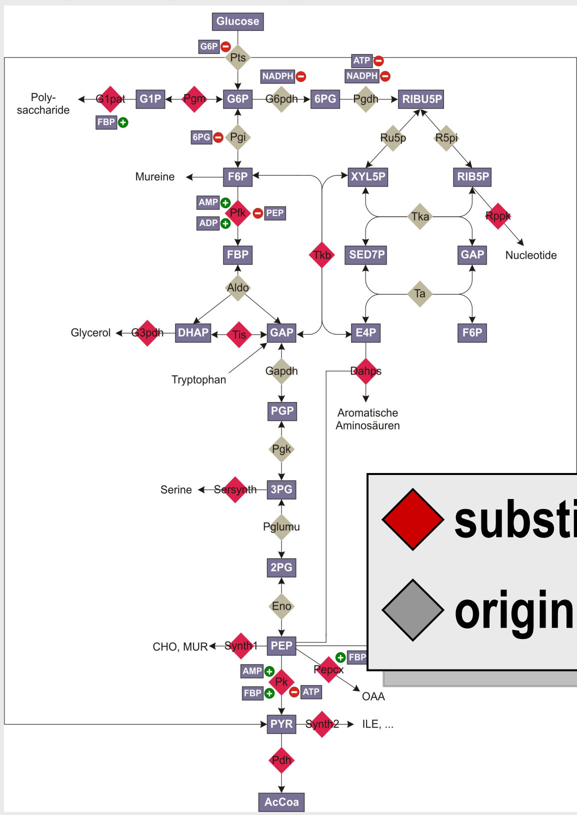
- **generic** Wiechert
- **convenience** Klipp

Example: Substitution of Kinetic Terms

Substituting kinetic terms in an E. coli model

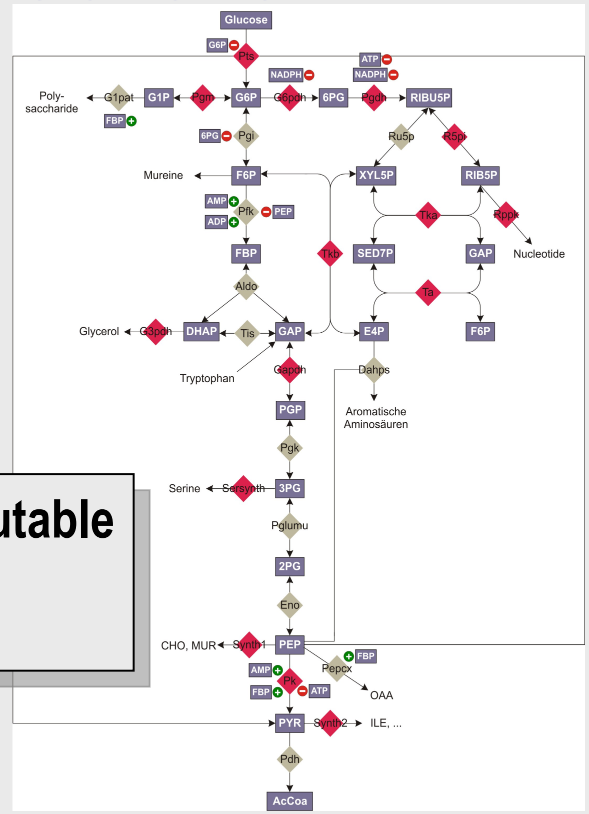
original model has 116 parameters Chassagnole 2004

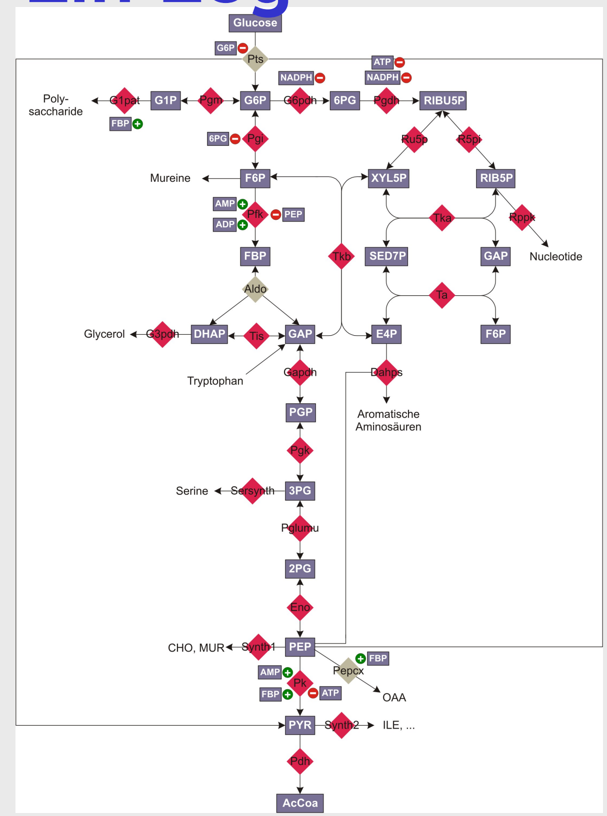
Power Law	Generic	Lin-Log



substitutable

original



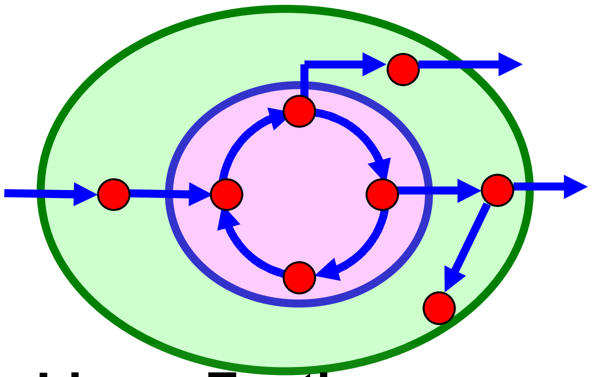


14 Substitutions (87)	15 Substitutions (93)	24 Substitutions (81)

All simplified models reproduce the same experimental data.

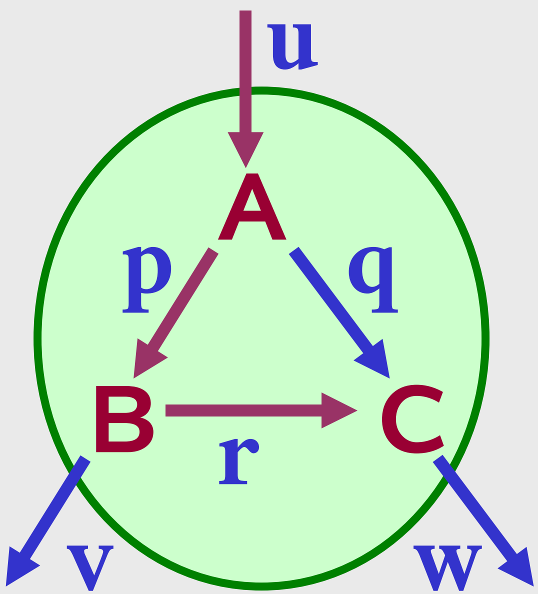
Hadlich 2007

Stoichiometric Models



Principles

- spatially homogeneous
- steady state (constant fluxes)
- reduced to metabolic fluxes

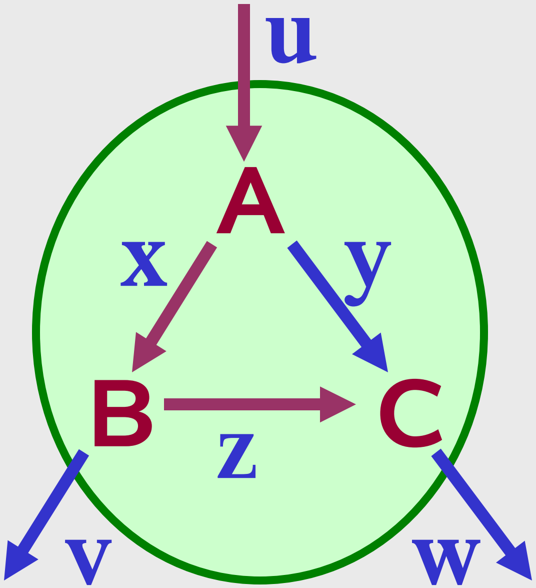


Stoichiometry

$$\begin{pmatrix} 1 & . & . & -1 & -1 & . \\ . & -1 & . & 1 & . & -1 \\ . & . & -1 & . & 1 & 1 \end{pmatrix} \cdot \begin{pmatrix} u \\ v \\ w \\ p \\ q \\ r \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

$$\mathbf{N} \cdot \mathbf{v} = \mathbf{0}$$

Stoichiometrically Feasible Fluxes



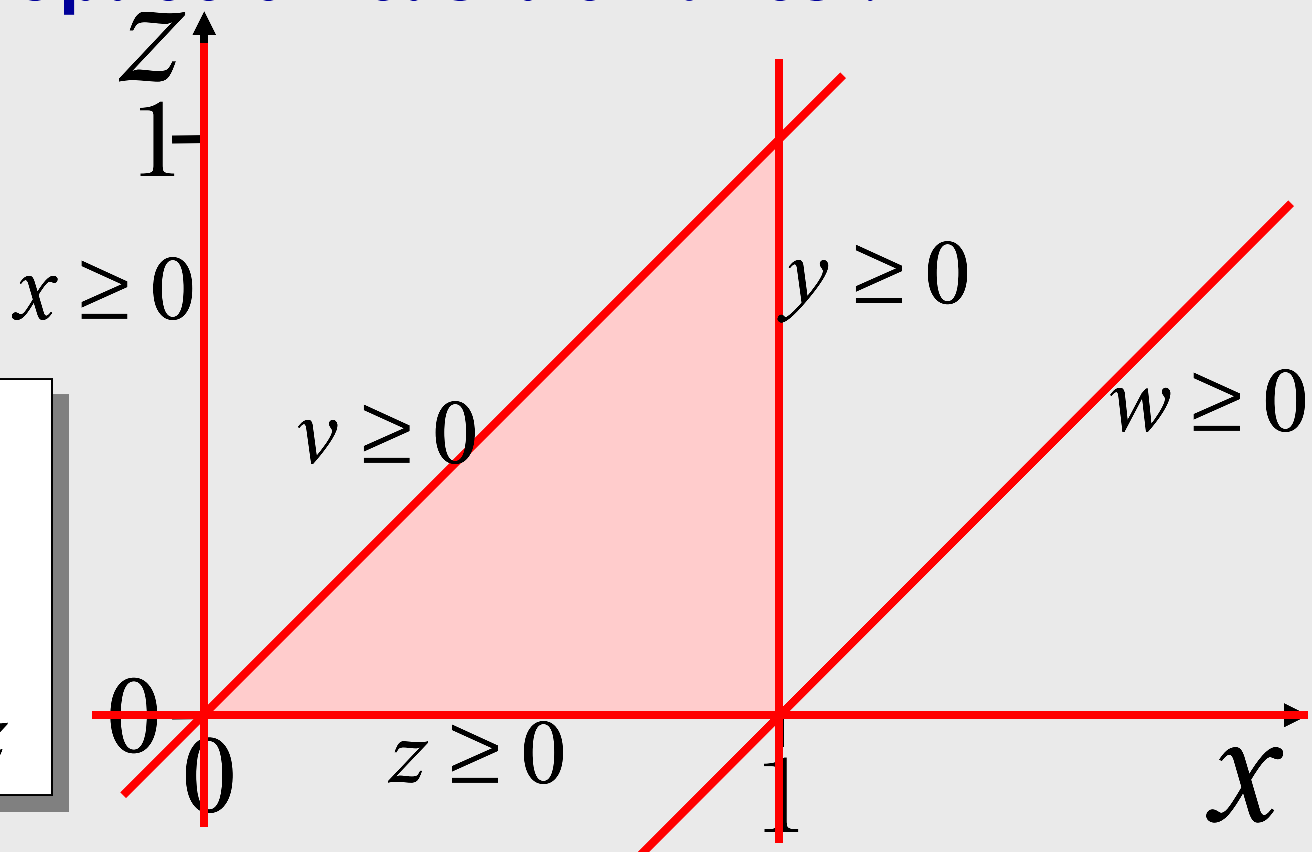
Relative fluxes:

$$u = 1$$

Unidirectionality :

$$v, w, x, y, z \geq 0$$

Space of feasible fluxes :



Stoichiometry:

$$\mathrm{A}: \; y = u - x$$

$$\mathrm{B}: \; v = x - z$$

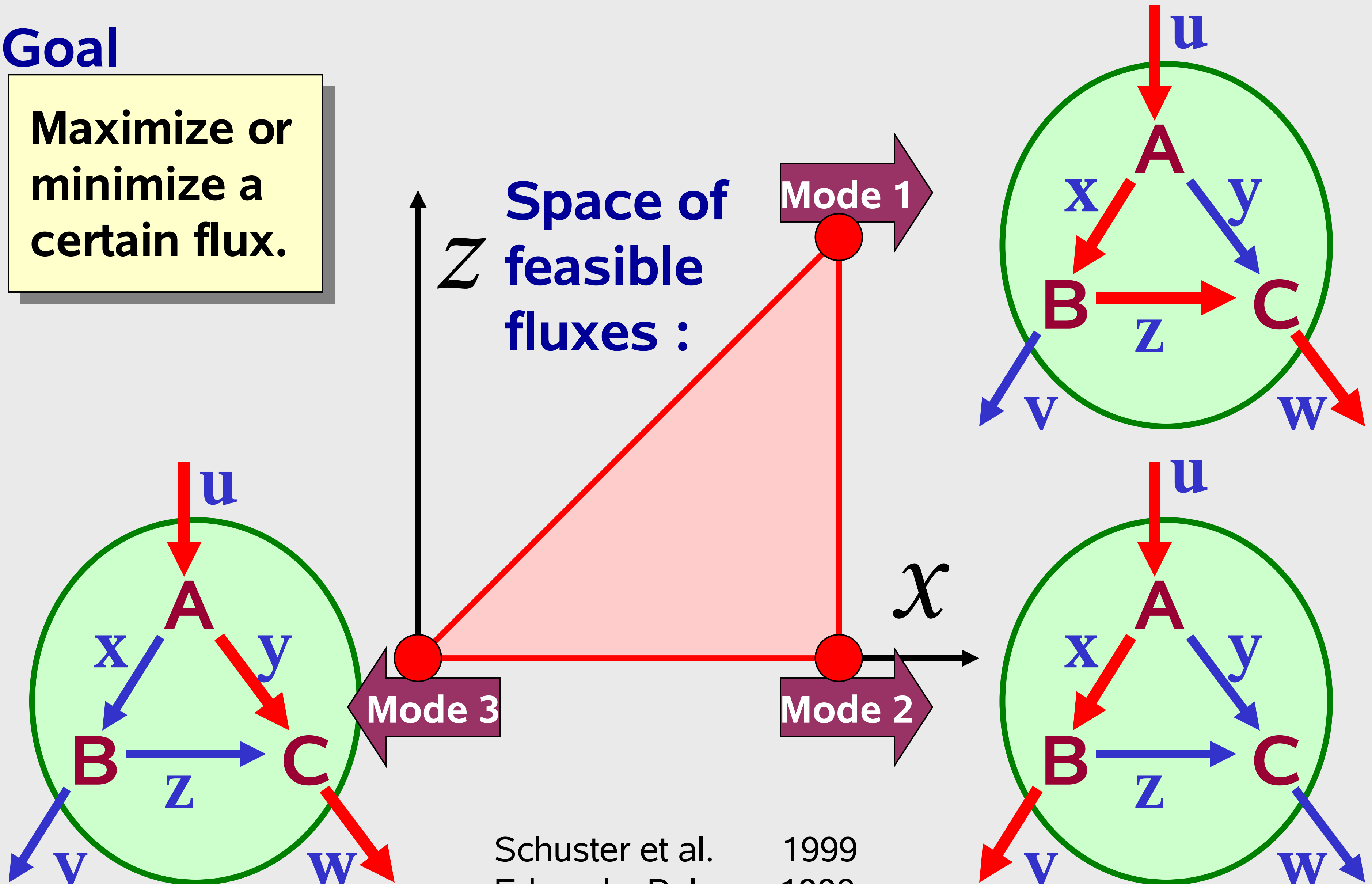
$$\mathrm{C}: \; w = y + z$$

$$= u - x + z$$

Flux Balance Analysis: Extremal Fluxes

Goal

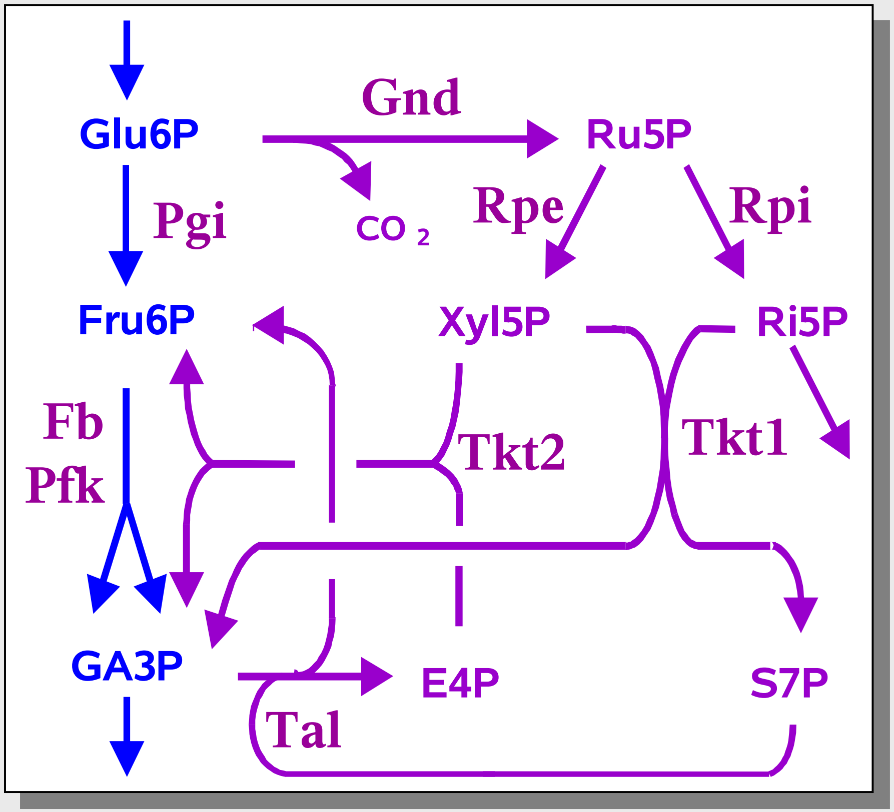
Maximize or minimize a certain flux.



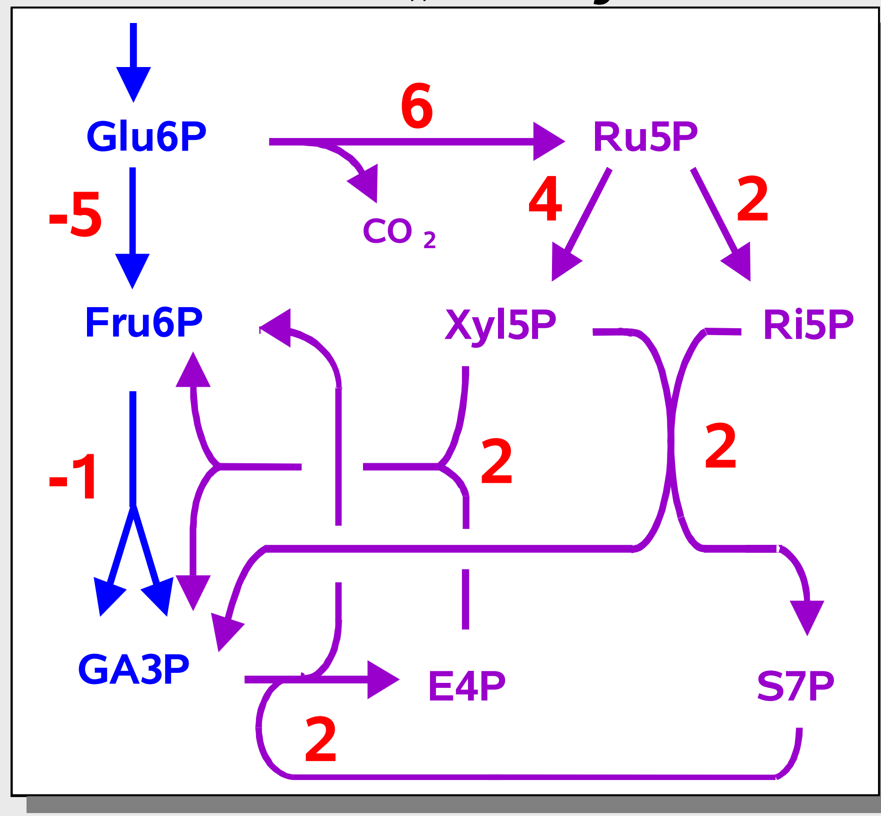
Schuster et al. 1999
Edwards, Palsson 1998

Example: Sugar Metabolism

Reactions and Pools



Mode 6: „PPP Cycle“

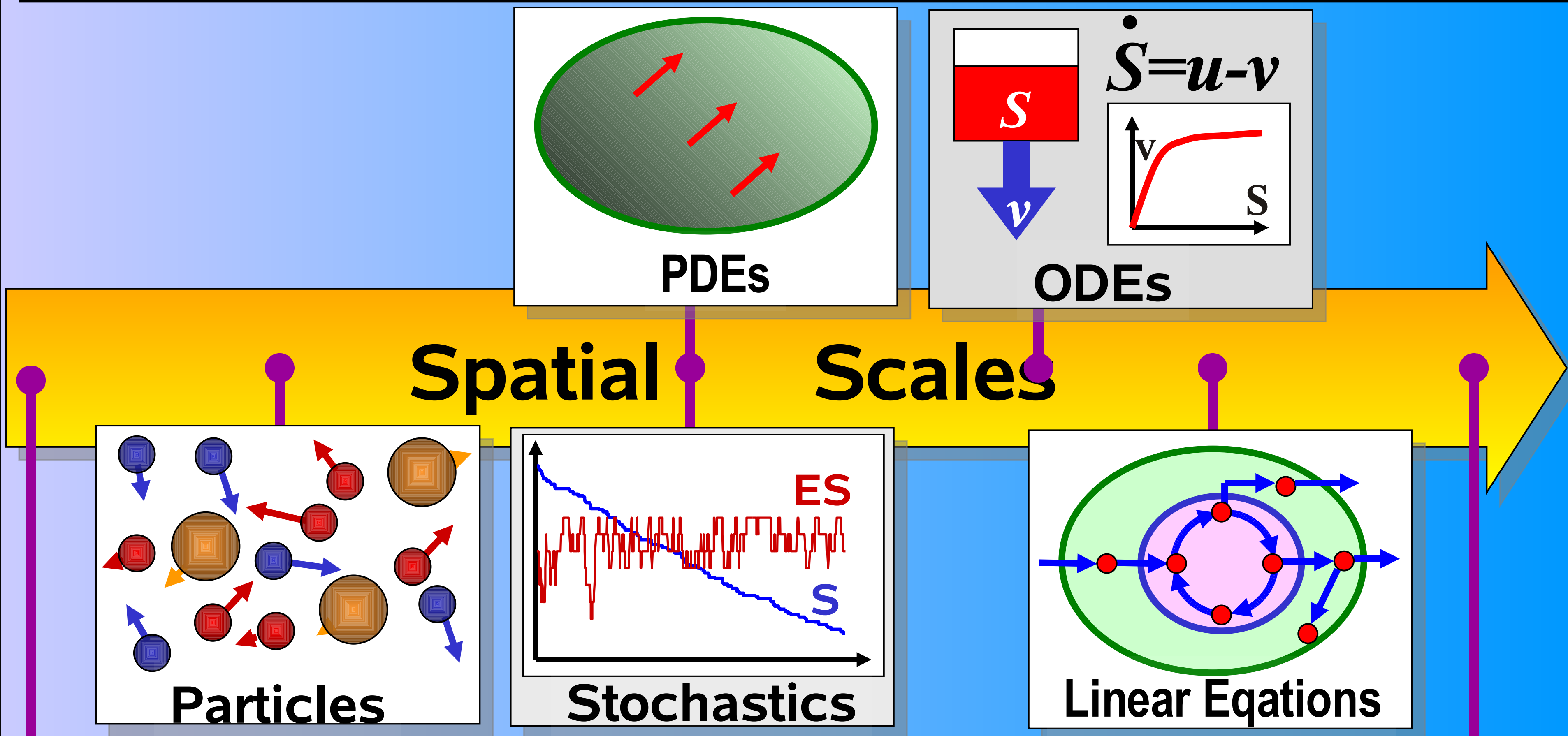


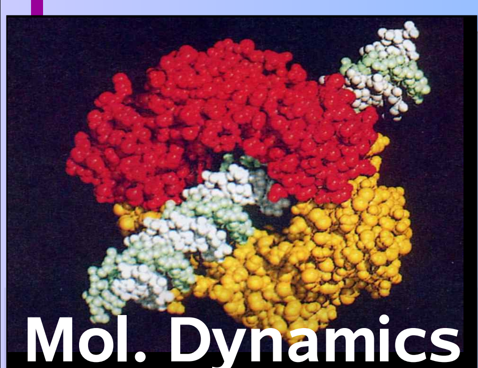
Schuster et al. 2000

Applications

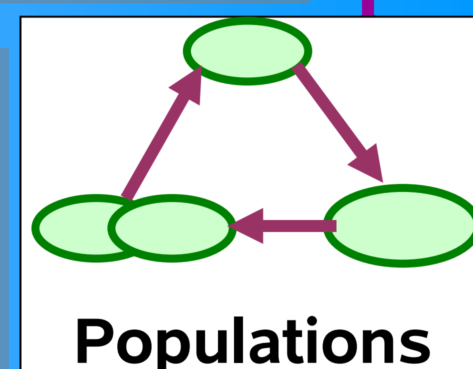
- Maximal Yields
- Screening
- Funct. Genomics
- Knockout Targets
- Drug Targets

Scales of Cellular Network Modelling





How to reduce the effort ?
How to obtain the data ?
How to validate the model ?
How to predict experiments ?



References

* K. Takahashi, S.N.V. Arjunam, M. Tomita, Space in systems biology of signalling pathways – towards intracellular molecular crowding in silico, FEBS 29342, 2005.
Cao, Y., Gillespie, D. T., Petzold, L. R.. Efficient step size selection for the tau-leaping simulation method. *Journal of Chemical Physics*, 124, 2006
Cao, Y., Petzold, L.. Accuracy limitations and the measurement of errors in the stochastic simulation of chemically reacting systems. *Journal of Computational Physics*, 212:6-24, 2006.
* El Samad, H., Khammash, M., Petzold, L., Gillespie, D.. Stochastic modelling of gene regulatory networks. *International Journal of Robust and Nonlinear Control*, 15:691-711, 2005.
Cao, Y., Gillespie, D. T., Petzold, L. R.. Accelerated stochastic simulation of the stiff enzyme-substrate reaction. *Journal of Chemical Physics*, 123, 2005.
Rathinam, M., Petzold, L. R., Cao, Y., Gillespie, D. T.. Consistency and stability of tau-leaping schemes for chemical reaction systems. *Multiscale Modeling & Simulation*, 4:867-895, 2005.
* Cao, Y., Gillespie, D. T., Petzold, L. R.. The slow-scale stochastic simulation algorithm. *Journal of Chemical Physics*, 122, 2005.
•Cao, Y., Petzold, L. R., Rathinam, M., Gillespie, D. T.. The numerical stability of leaping methods for stochastic simulation of chemically reacting systems. *Journal of Chemical Physics*, 121:12169-12178, 2004.
* Cao, Y., Li, H., Petzold, L.. Efficient formulation of the stochastic simulation algorithm for chemically reacting systems. *Journal of Chemical Physics*, 121:4059-4067, 2004.
Rathinam, M., Petzold, L. R., Cao, Y., Gillespie, D. T.. Stiffness in stochastic chemically reacting systems: The implicit tau-leaping method. *Journal of Chemical Physics*, 119:12784-12794, 2003.
Gillespie, D. T., Petzold, L. R.. Improved leap-size selection for accelerated stochastic simulation. *Journal of Chemical Physics*, 119:8229-8234, 2003.
* Medalia, Weber, Frangakis, …,Baumeister, Macromolecular architecture in eukaryotic cells…, Science 298, 1209-1213, 2002
* A. Stundzia, C.J. Lumsda, Stochastic simulation of coupled reaction-diffusion processes, J. Comput. Physics 127, 196-207 (1996)
Ander,M. et al. (2004) SmartCell: a framework to simulate cellular processes that combines stochastic approximation with diffusion and localisation: analysis of simple gene networks. Syst. Biol., 1, 129–138.
* Andrews,S.S. and Bray,D. (2004) Stochastic simulation of chemical reactions with spatial resolutionand single molecule detail. Phys. Biol., 1, 137–151.
* Gibson,M. and Bruck,J. (2000) Efficient exact stochastic simulation of chemical systems with many species and channels. J. Phys. Chem. A, 104, 1876–1889.
* Lipkow,K. et al. (2005). Simulated diffusion of phosphorylated CheY through the cytoplasm of Escherichia coli. J. Bacteriol. 187, 45–53.
Markus Ulrich, Constantin Kappel, Joël Beaudouin, Stefan Hezel, Jochen Ulrich, Roland Eils: Tropical - parameter estimation and simulation of reaction-diffusion models based on spatio-temporal microscopy images. Bioinformatics 22(21): 2709-2710 (2006)
* Gillespie, A general method for numerically simulating…, J. Comput. Physics 22, 403-434, 1976
* M.S. Apydin, C.E. Guestrin, C. Varma, D.L. Brutlag, J.-C. Latombe, Stochastic roadmap simulation for the study of ligand-protein interactions, Bioinformatics 18: S18-S26, 2002.
* H. Berry, Monte Carlo simulations of enzyme reactions in two dimensions: Fractal kinetics and spatial segregation, Biophysical Journal, 83: 1891-1901, 2002.
* B.N. Kholodenko, Cell-signalling dynamics in time and space, Nature Reviews, 7:165-176, 2006.
L. Kuepfer, U. Sauer, Modelling gene expression using stochastic simulation. Published?
* S. Schnell, T.E. Turner, Reaction kinetics in intracellular environments with macromolecular crowding: simulations and rate laws, Progr.Biophys. & Molecular Biol. 85:235-260, 2004.
* R. Grima, S. Schnell, A systematic investigation of the rate laws valid in intracellular environments, Biophys. Chemistry 124:1-10, 2006.
* A. Lapin, M. Klann, M. Reuss, Simulations of 4D-spatial-temporal dynamics in cellular signal transduction processes, Metabolic Engineering 6, Noordwijkerhoud, 2006.
J. Paulsson, J. Elf, Stochastic modelling of intracellular kinetics, Chapter 8 in: Z. Szallasi, J. Stelling, V. Periwal (eds.), System Modeling in Cellular Biology, MIT Press, 2006
K. Kruse, J. Elf, Kinetics in spatially extended systems, Chapter 9 in: Z. Szallasi, J. Stelling, V. Periwal (eds.), System Modeling in Cellular Biology, MIT Press, 2006
* D.T. Gillespie, L.R. Petzold, Numerical Simulation for biochemical kinetics, Chapter 16 in: Z. Szallasi, J. Stelling, V. Periwal (eds.), System Modeling in Cellular Biology, MIT Press, 2006