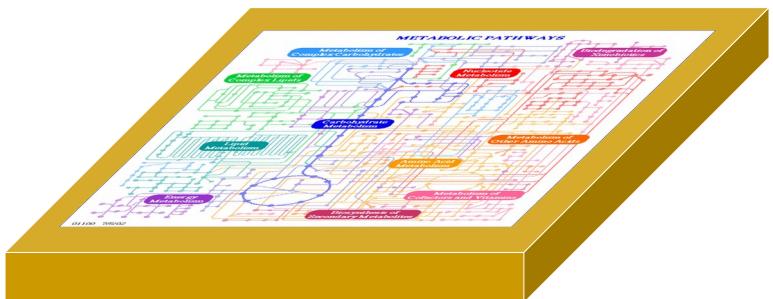


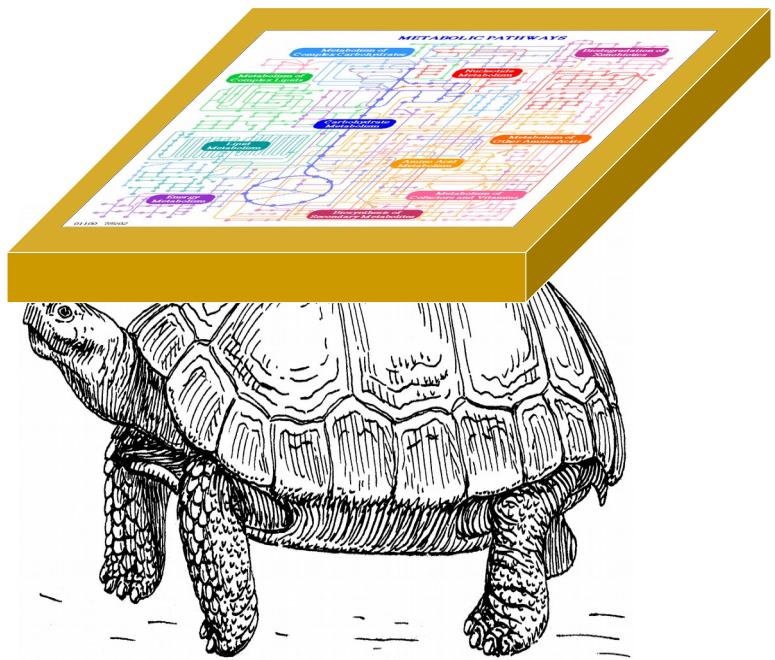


Regulatory, stochastic, spatial, and whole-cell models

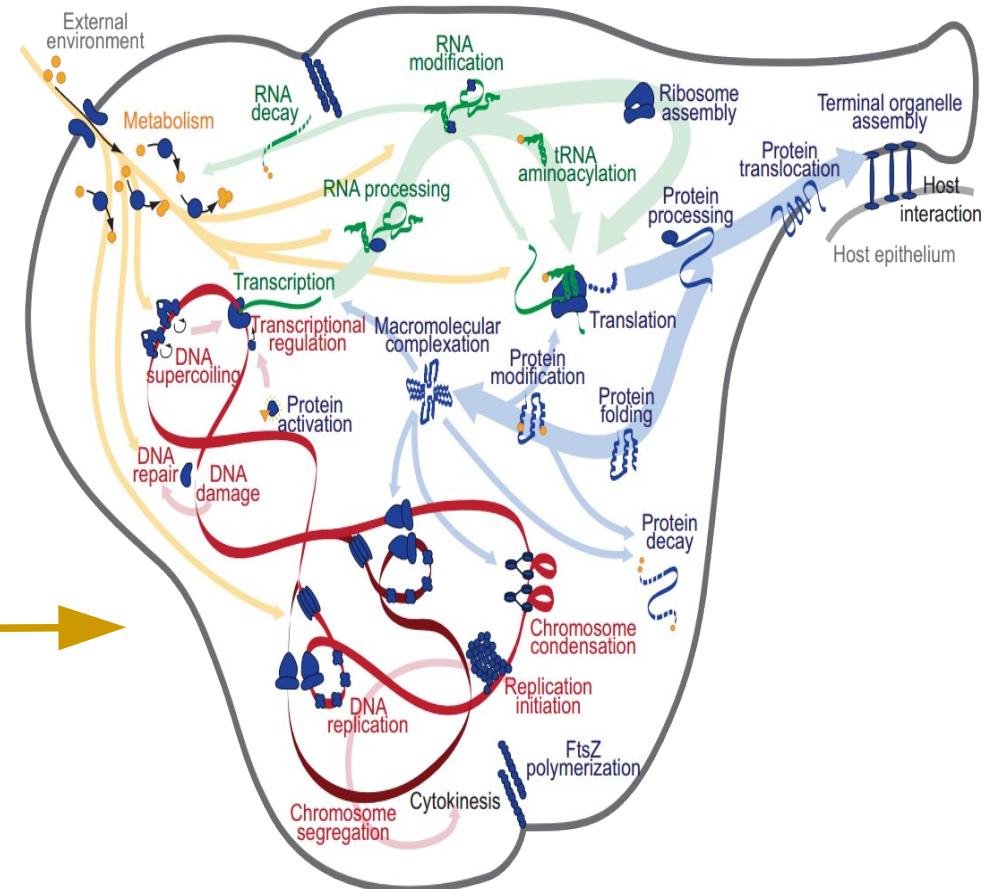
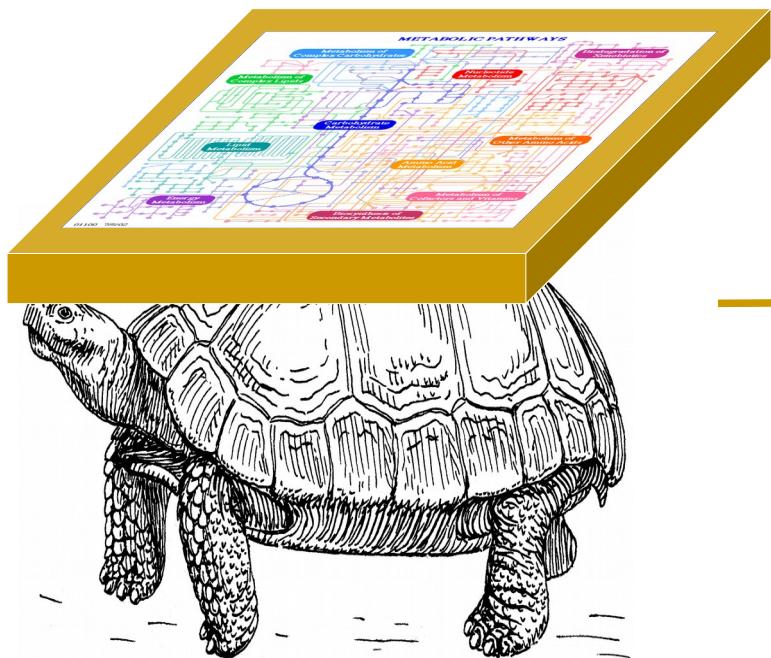
From networks to dynamic whole-cell models



From networks to dynamic whole-cell models

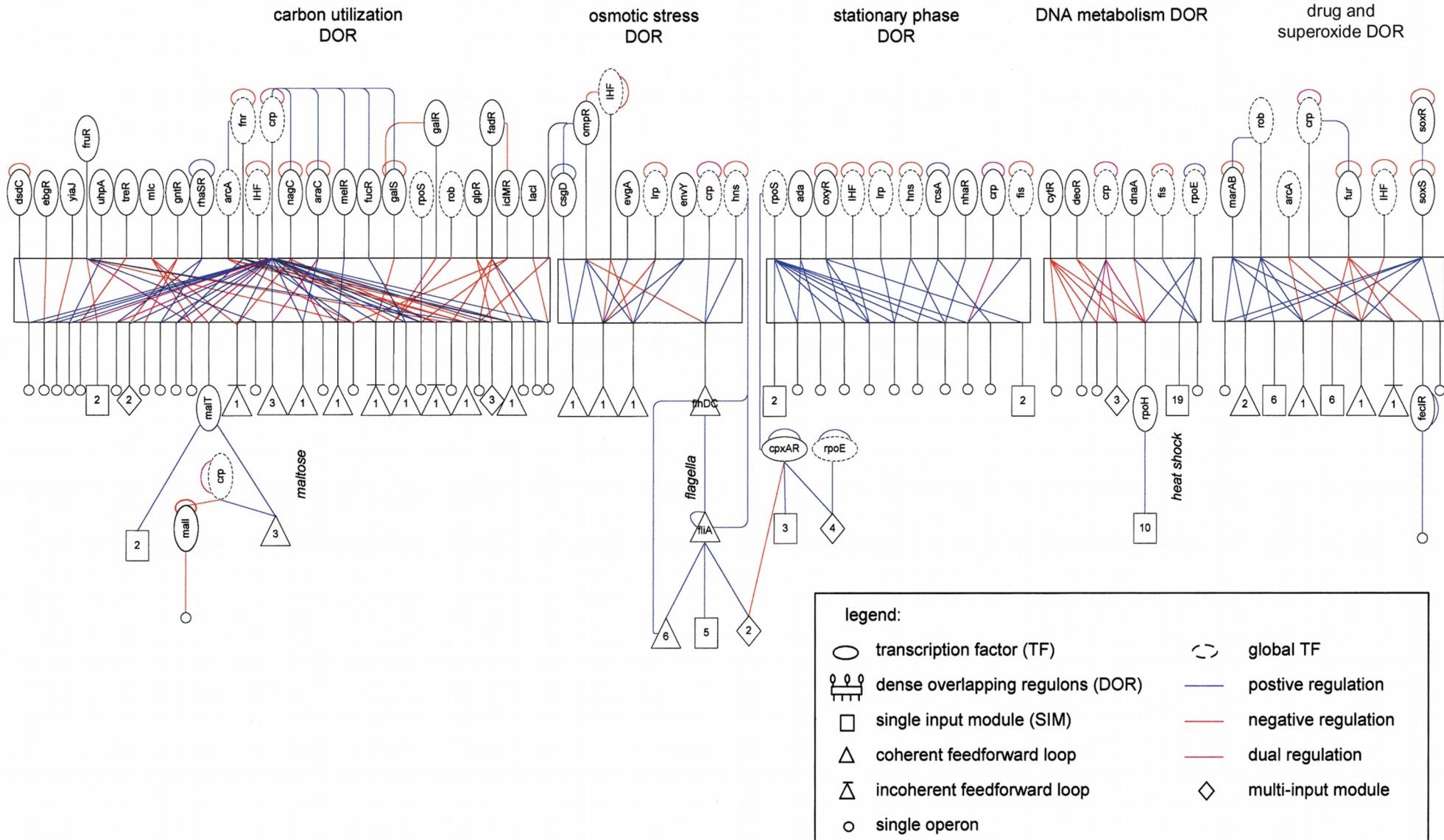


From networks to dynamic whole-cell models



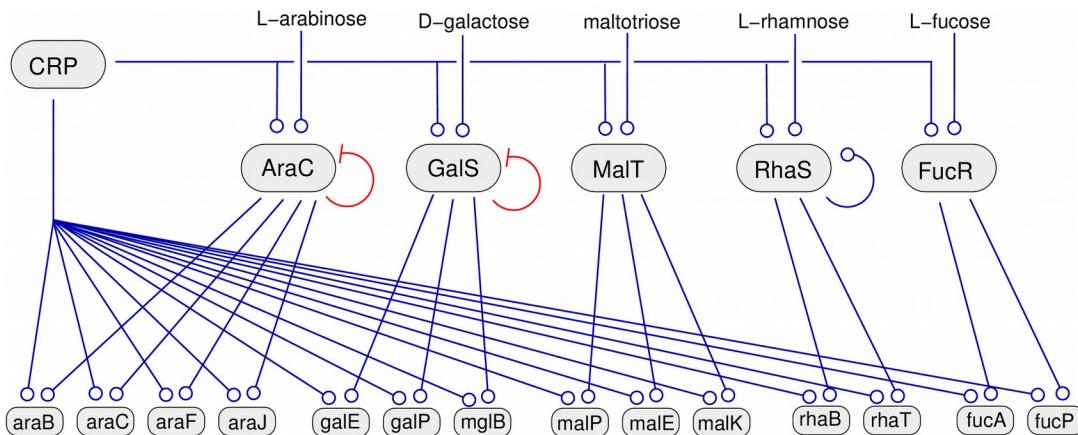
Models of gene regulation

What dynamics can emerge from gene regulatory networks?

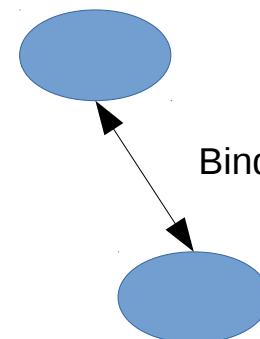


How can we obtain rate laws for mRNA production?

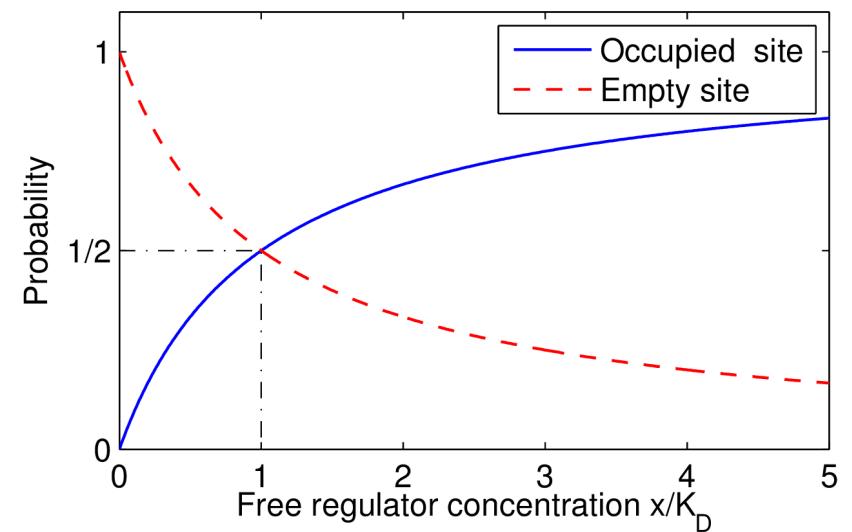
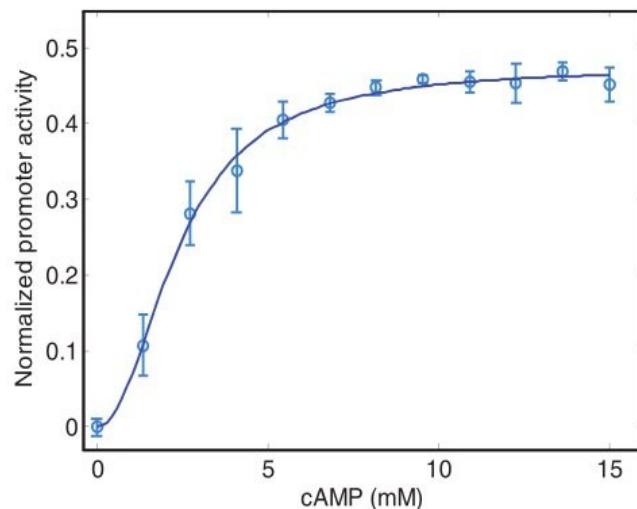
Wiring scheme of in carbon utilisation pathways in E coli



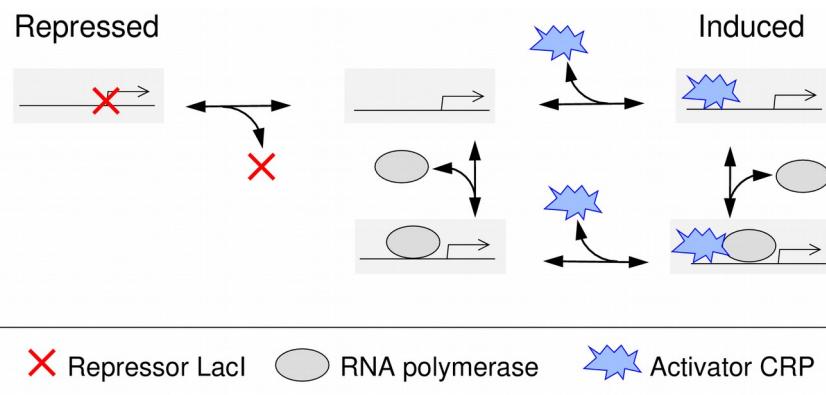
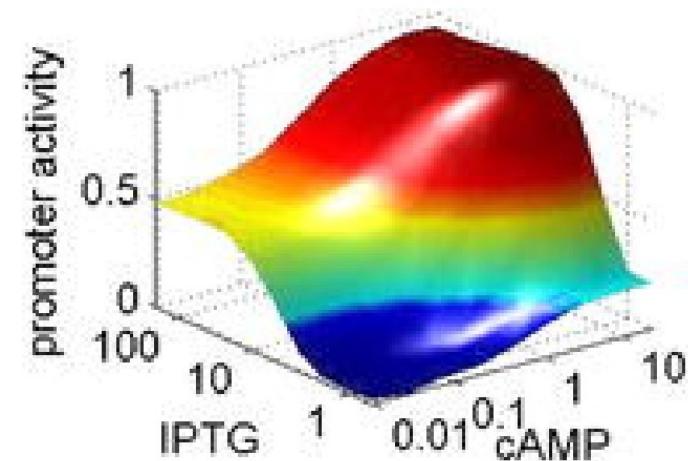
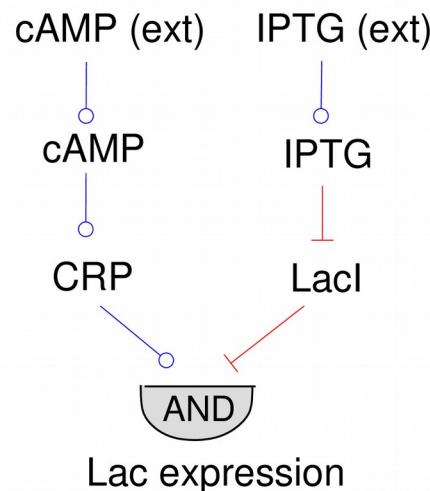
Transcription factor



Activation by transcription factor CRP in *E. coli*



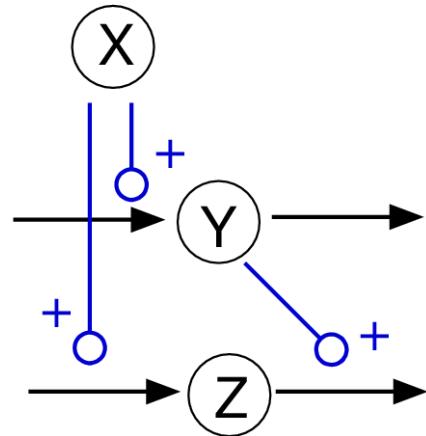
What regulation rate laws can we use for promoters with multiple inputs?



Gene regulation rate law with two inputs

$$f(x_1, x_2) = \frac{1 + a_1 x_1 + a_2 x_2}{1 + b_1 x_1 + b_2 x_2}$$

Dynamics of interacting genes: the adaptation motif

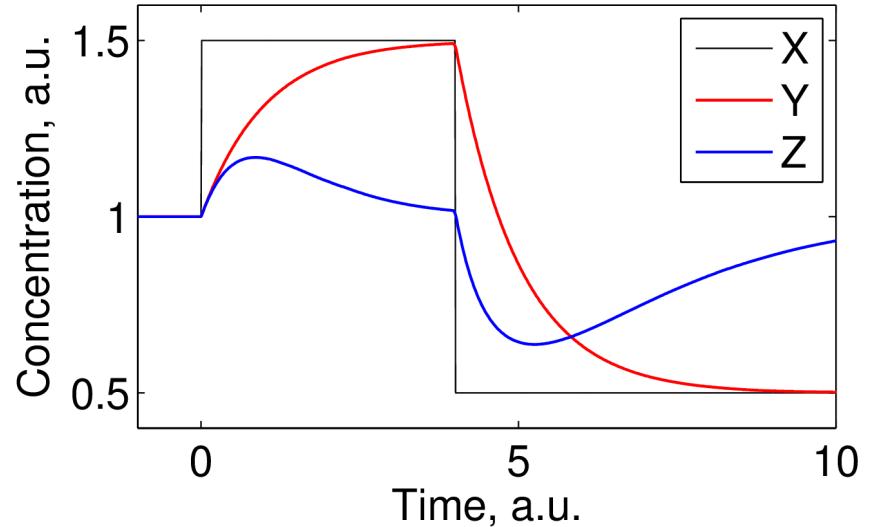
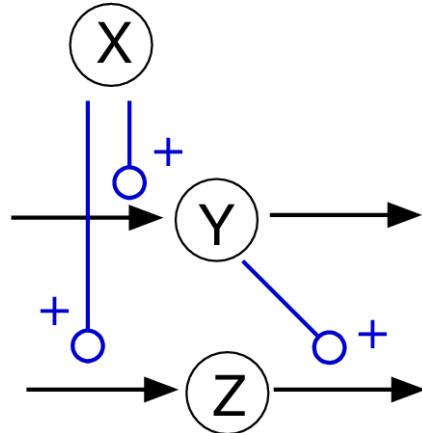


Differential equations

$$\frac{dy}{dt} = \alpha_y x - \beta_y y$$

$$\frac{dz}{dt} = \alpha_z x - \beta_z y z$$

Dynamics of interacting genes: the adaptation motif



Differential equations

$$\frac{dy}{dt} = \alpha_y x - \beta_y y$$

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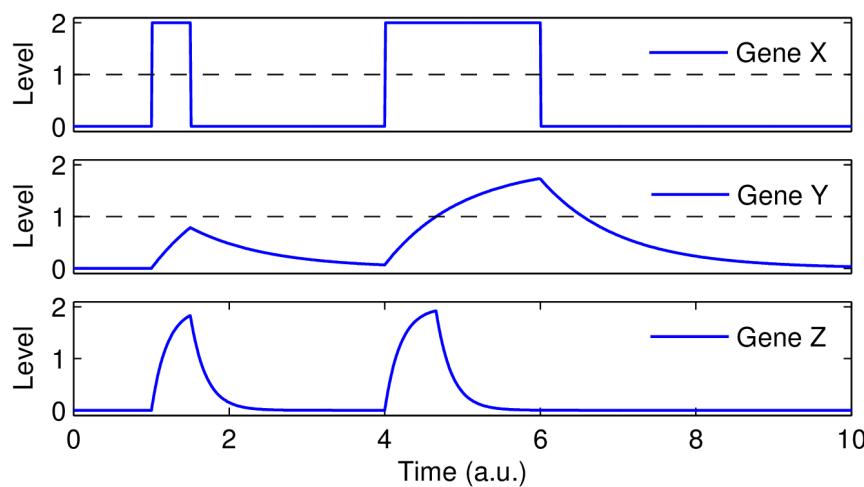
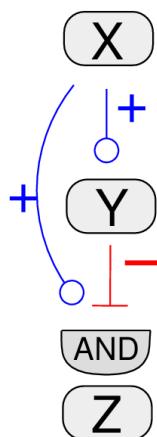
Steady state solution

$$y^{\text{steady}} = \frac{\alpha_y}{\beta_y} x$$

$$z^{\text{steady}} = \frac{\alpha_z \beta_y}{\beta_z \alpha_y}$$

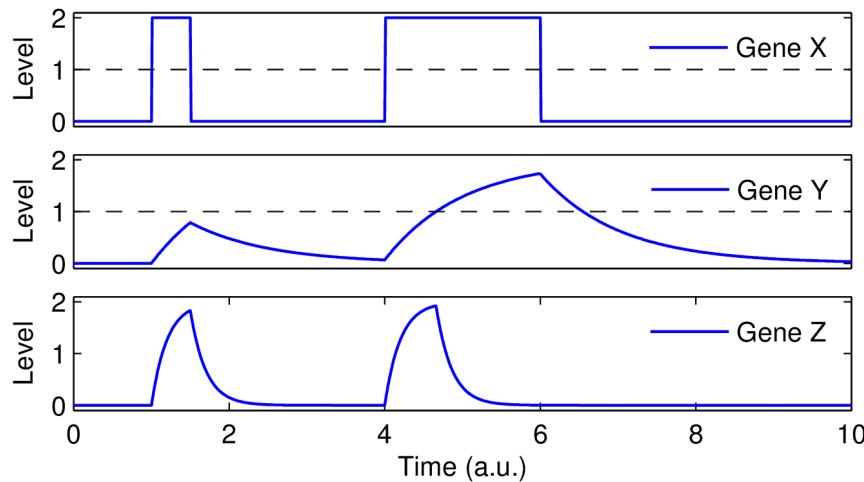
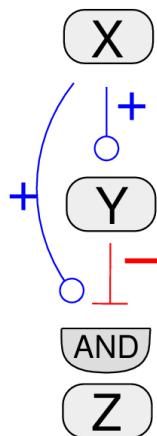
Feed-forward loops can process biochemical signals

Incoherent

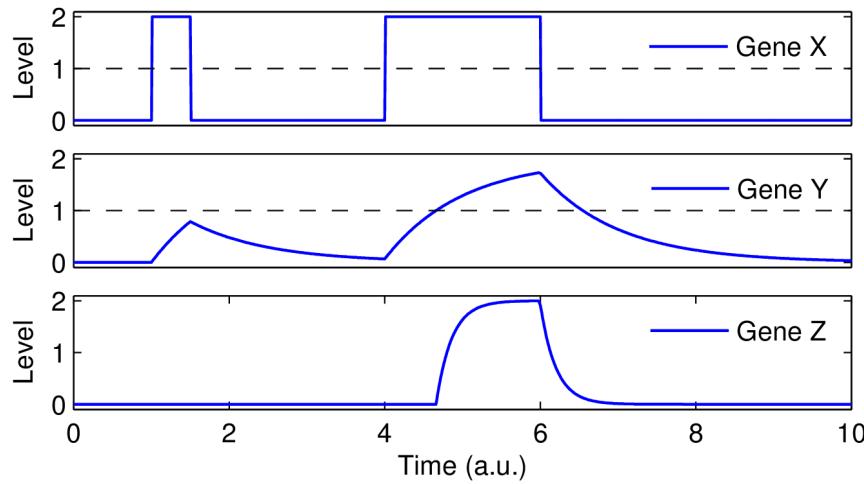
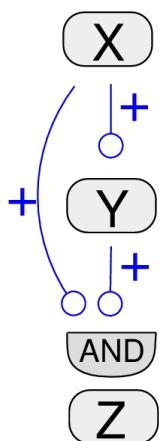


Feed-forward loops can process biochemical signals

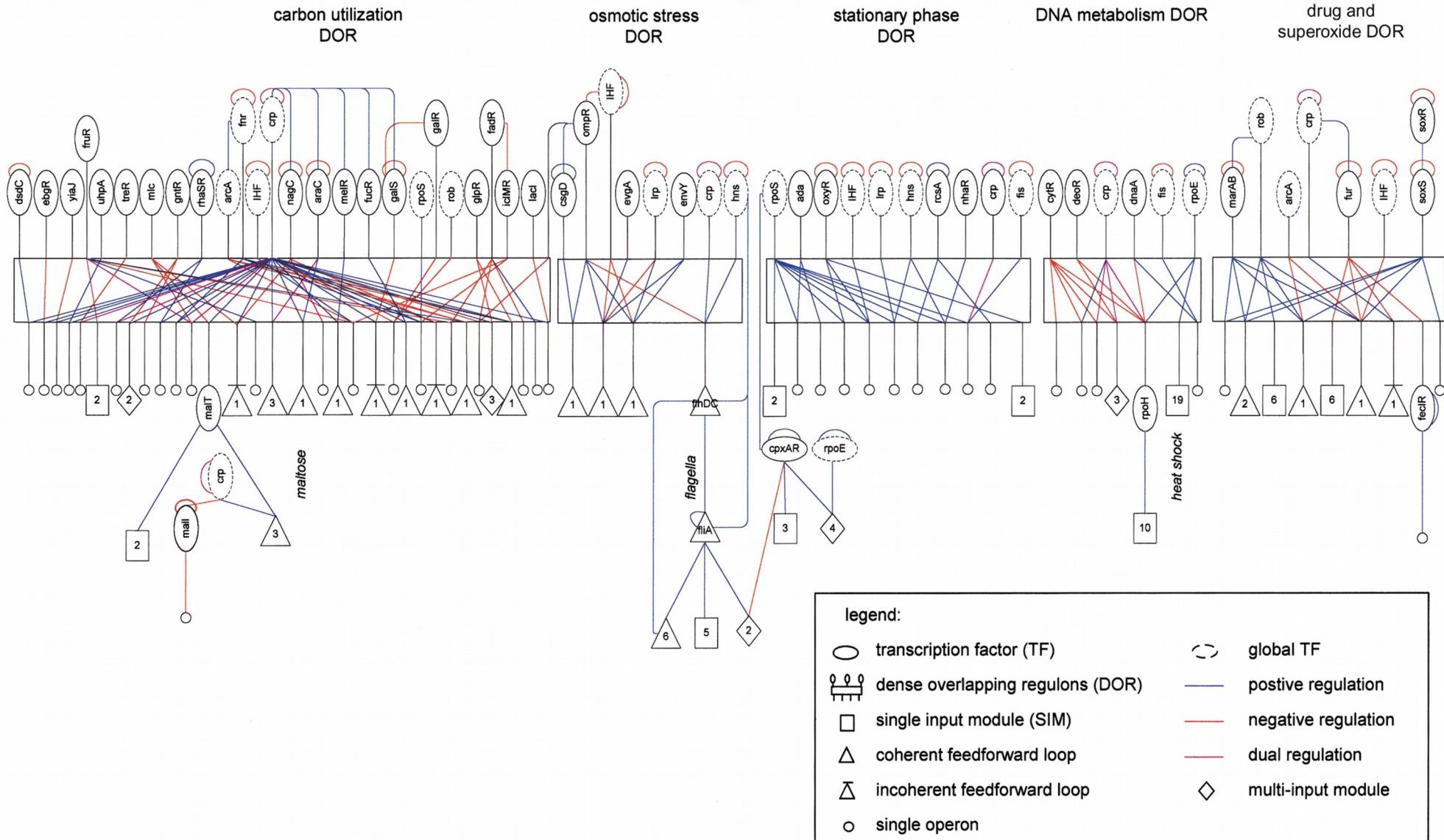
Incoherent



Coherent

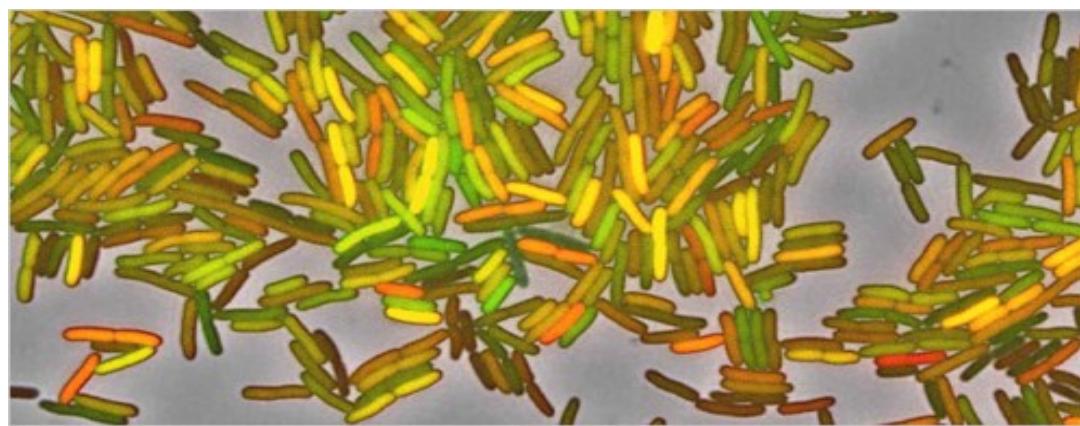


What dynamics can emerge from gene regulatory networks?

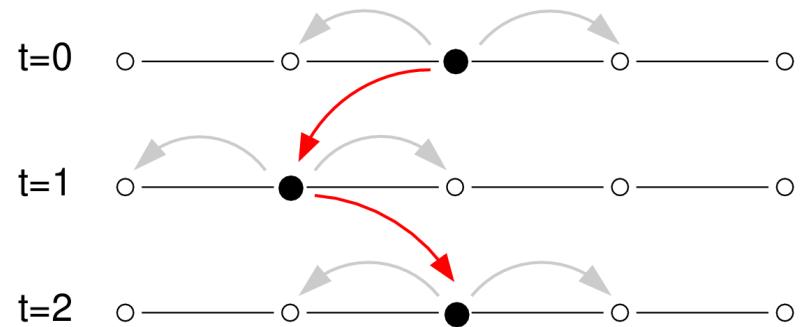
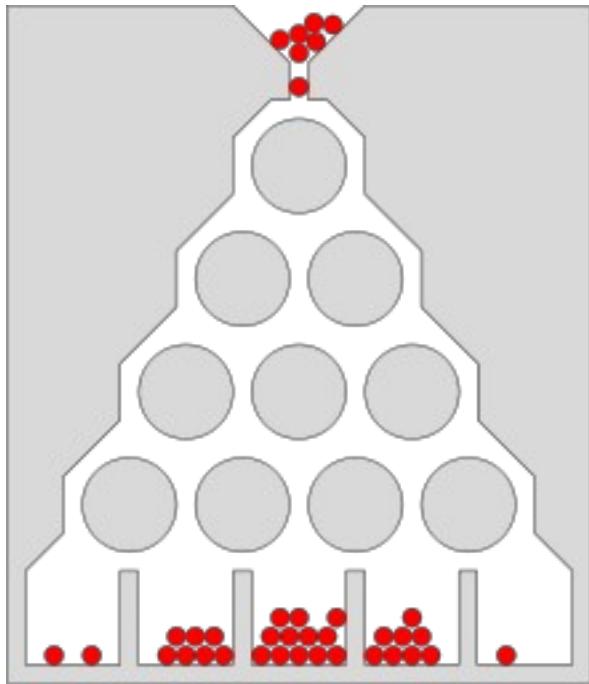


Stochastic models

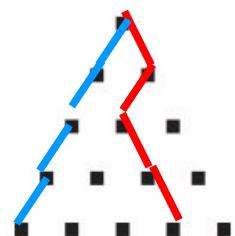
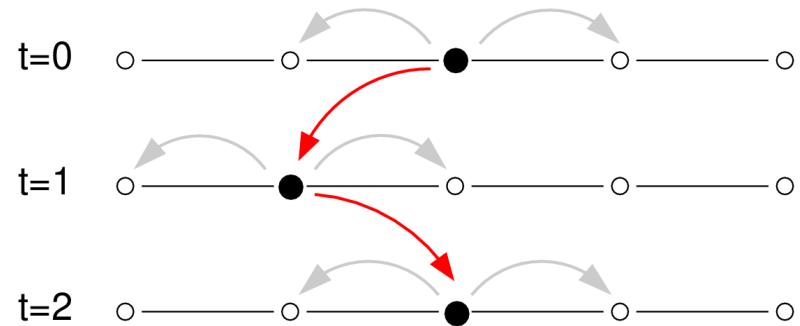
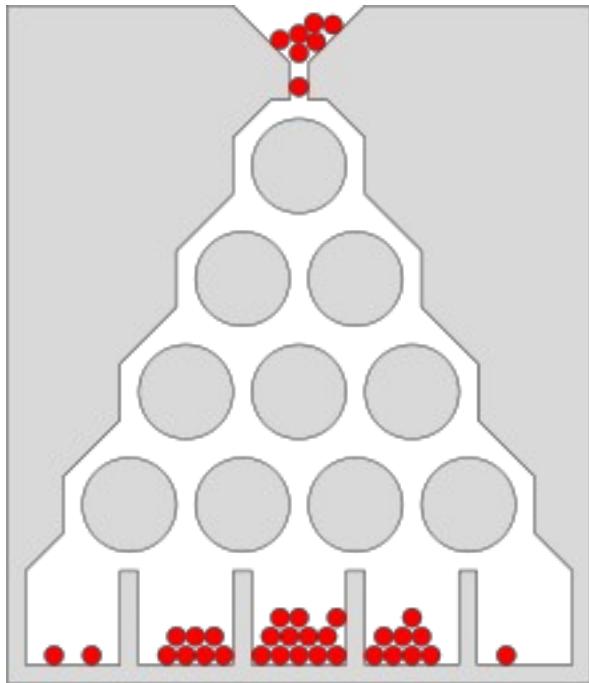
Many processes can be described as stochastic



A simple random process: the discrete random walk

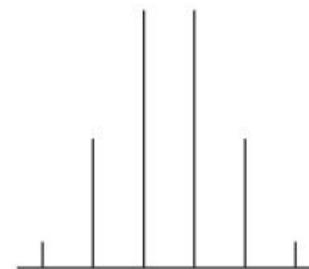


A simple random process: the discrete random walk



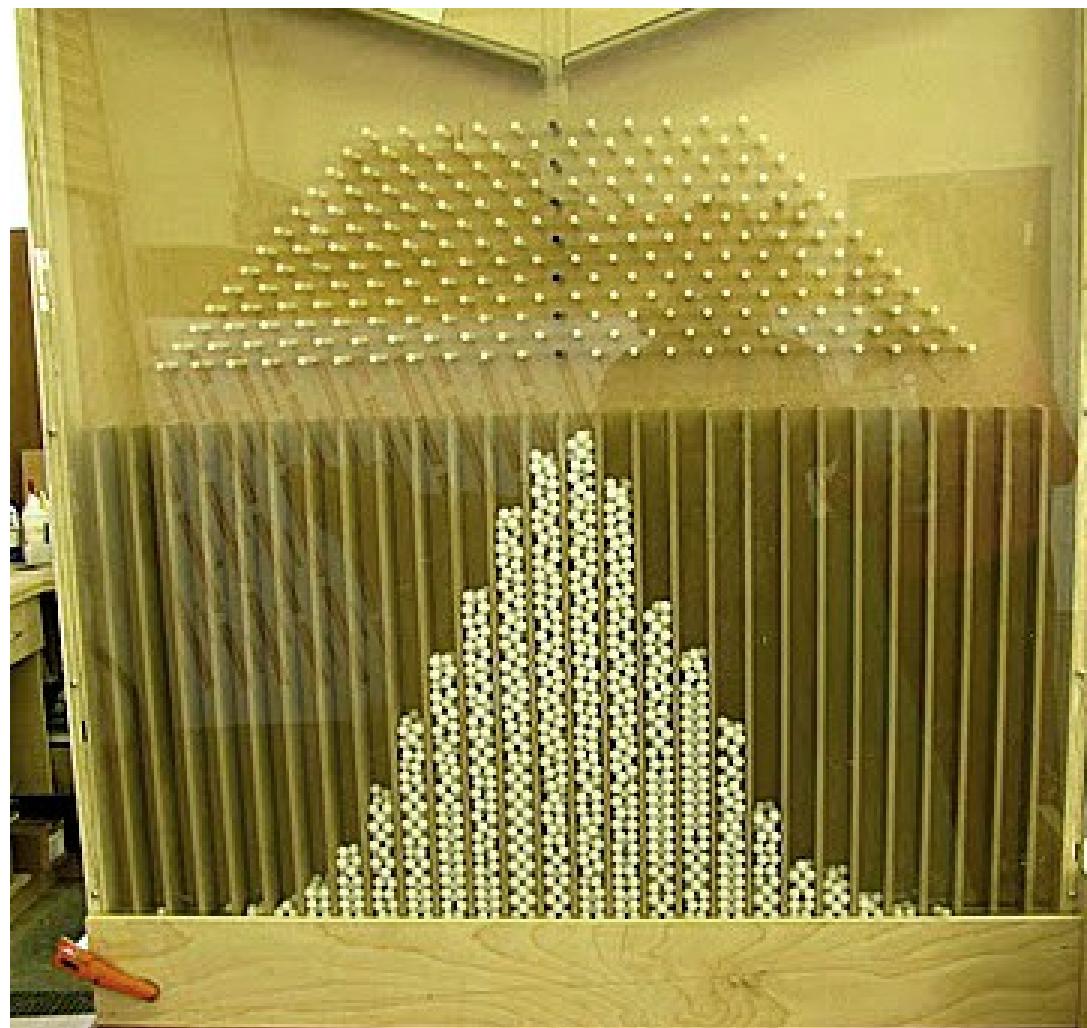
$$P_{\text{path}} = \left(\frac{1}{2}\right)^t$$

$$\begin{matrix} & & 1 \\ & & 1 & 1 \\ & & 1 & 2 & 1 \\ & & 1 & 3 & 3 & 1 \\ & & 1 & 4 & 6 & 4 & 1 \\ 1 & 5 & 10 & 10 & 5 & 1 \end{matrix}$$

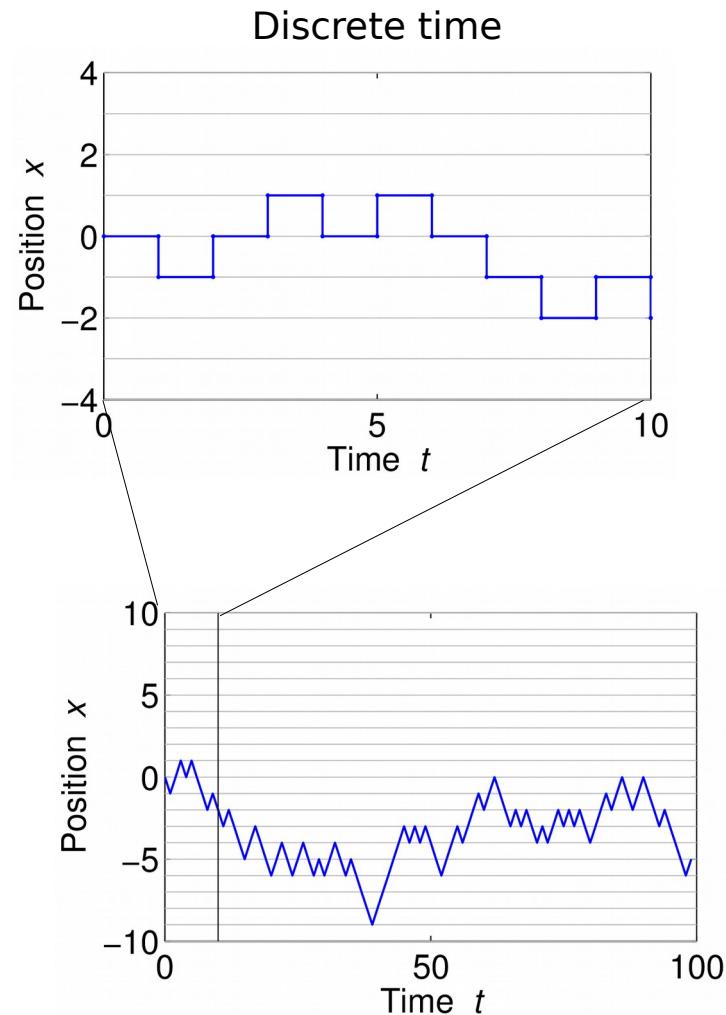


$$N = \binom{t}{x} \quad P(x, t) = \binom{t}{x} \left(\frac{1}{2}\right)^t$$

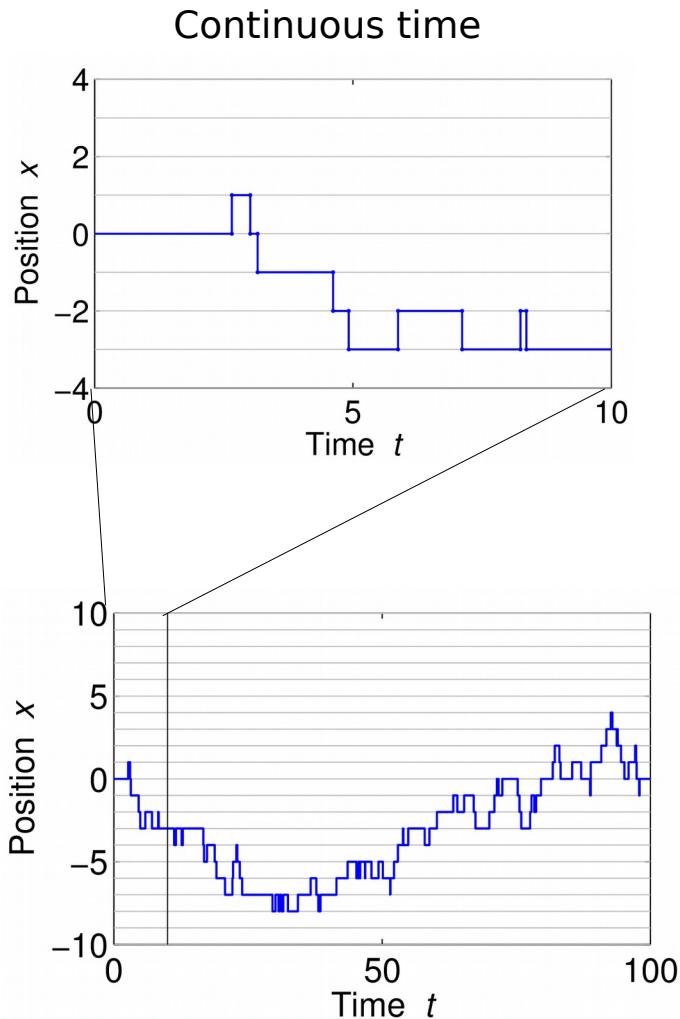
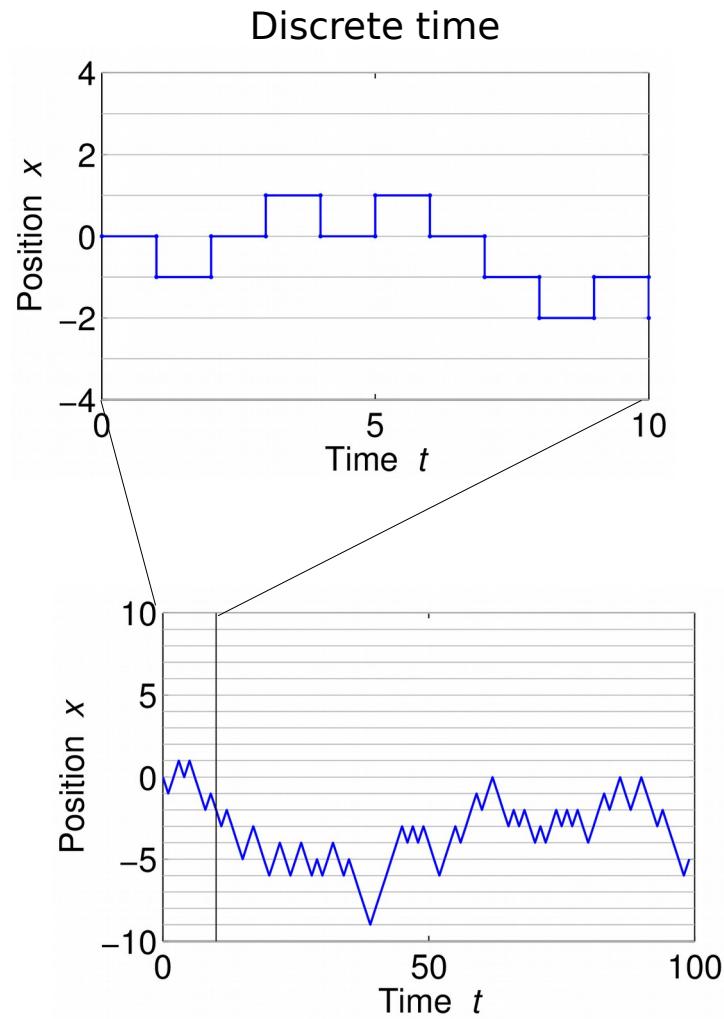
A simple random process: the discrete random walk



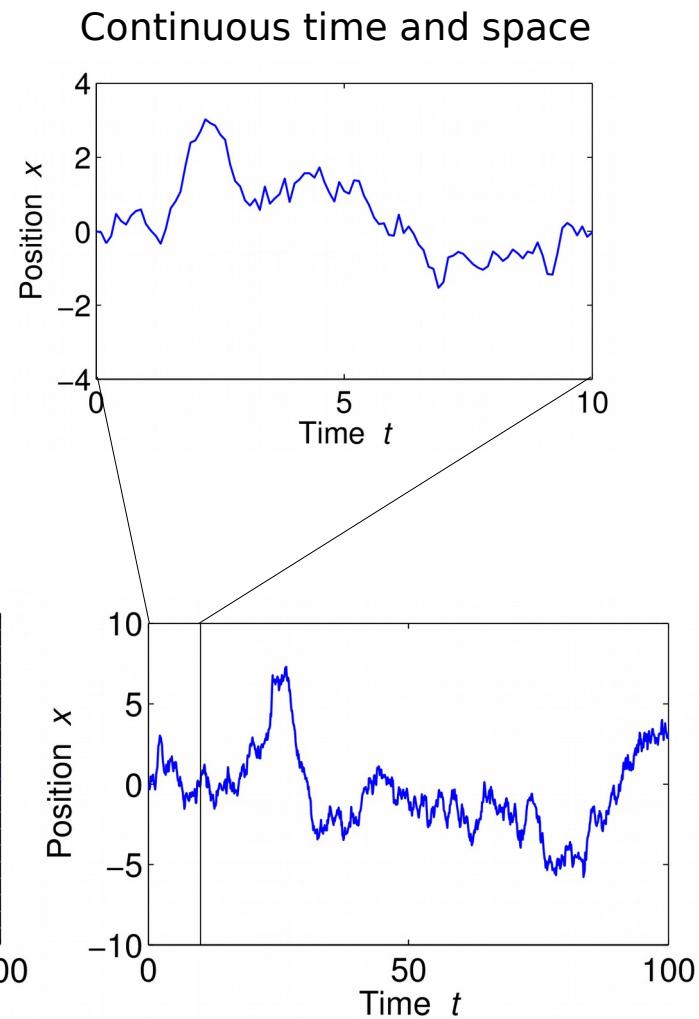
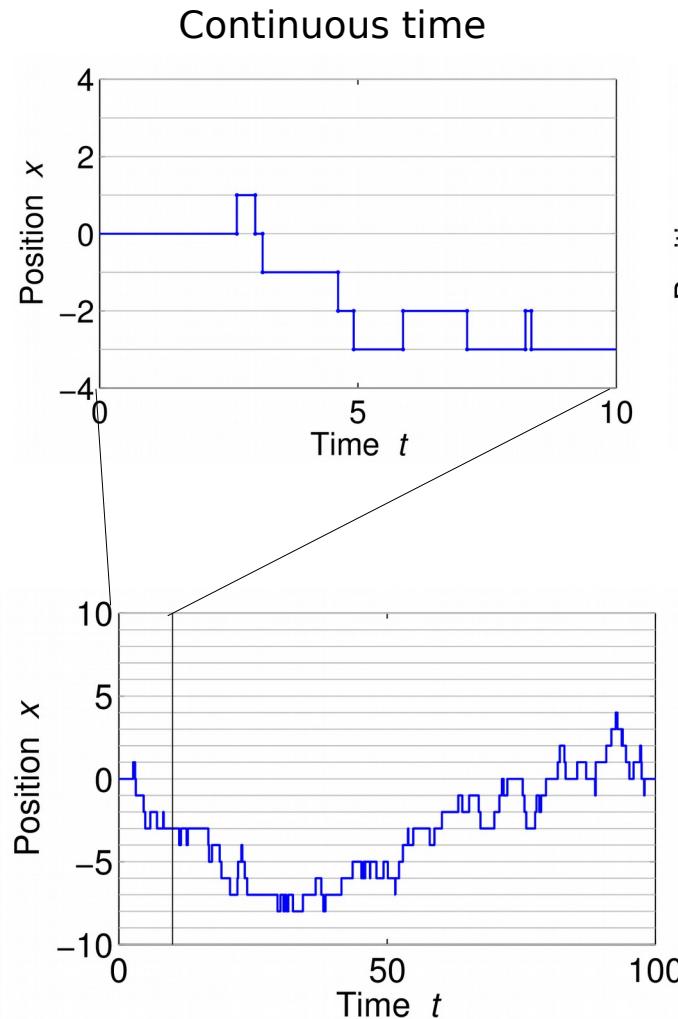
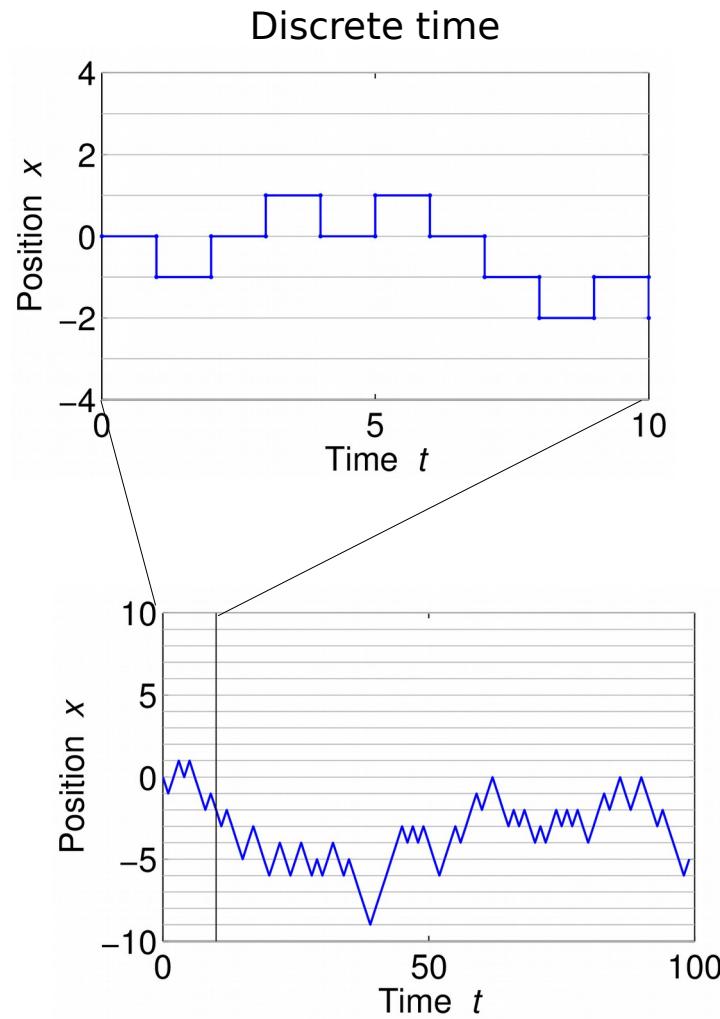
Random processes in discrete or continuous time and space



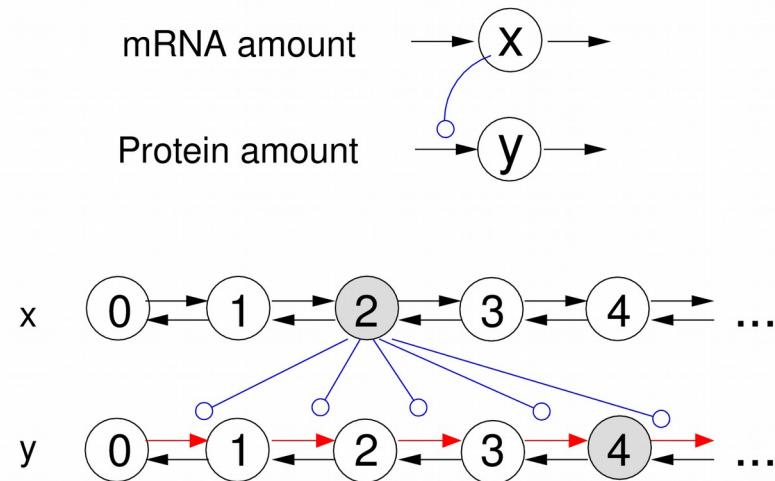
Random processes in discrete or continuous time and space



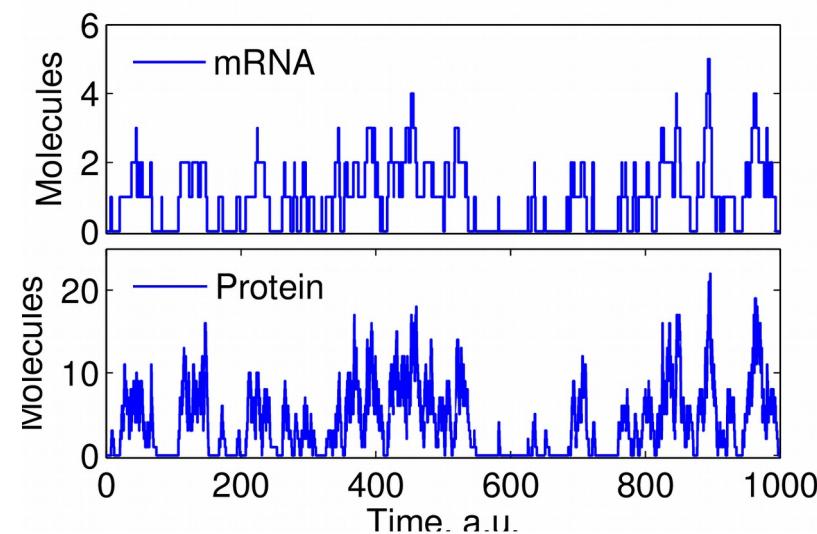
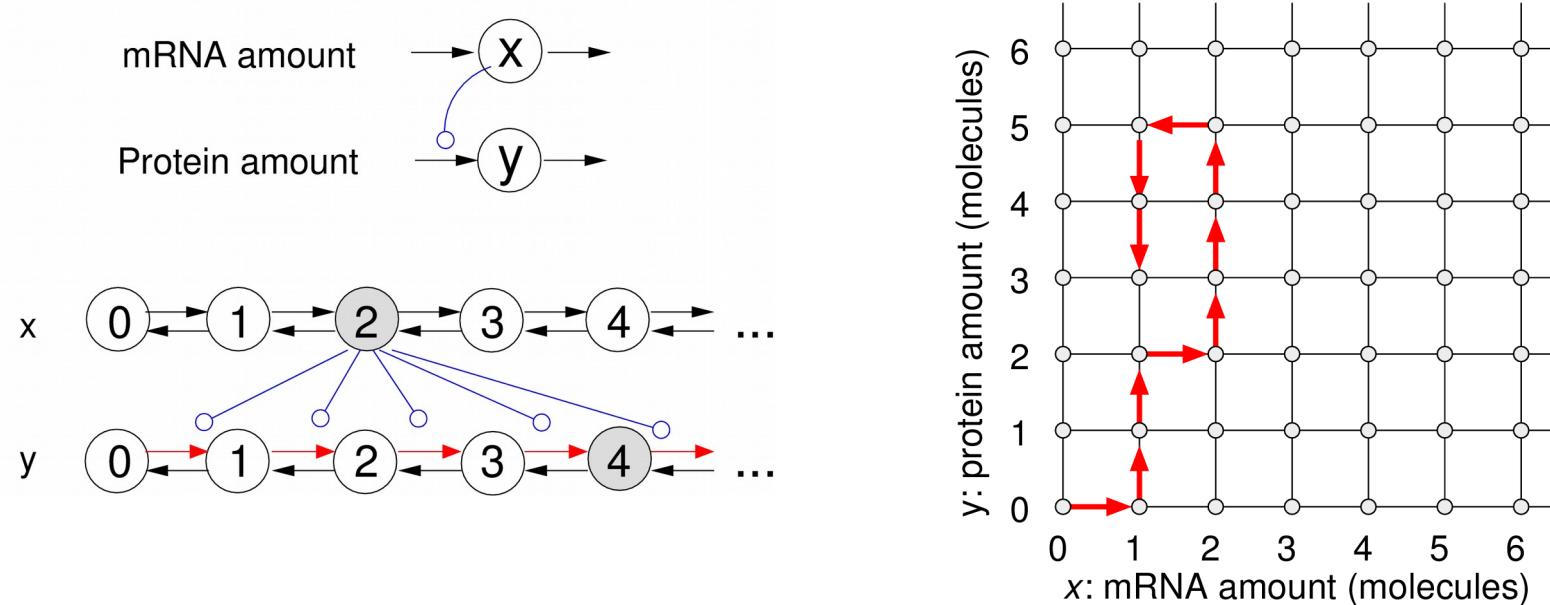
Random processes in discrete or continuous time and space



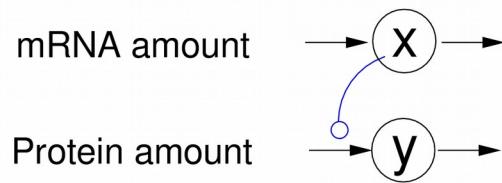
Random reaction events make particle numbers fluctuate -
a random movement in state “space”



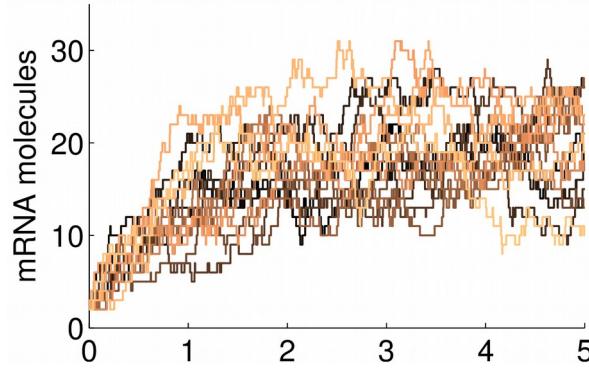
Random reaction events make particle numbers fluctuate -
a random movement in state “space”



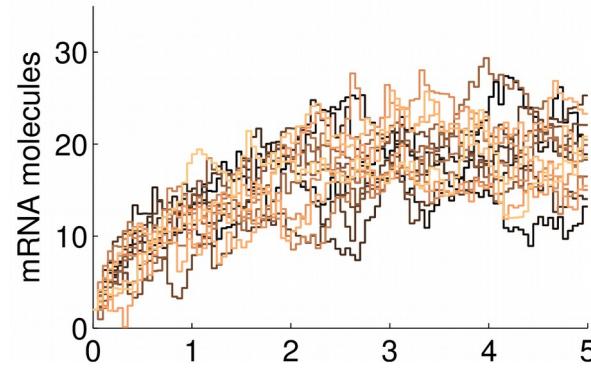
mRNA and protein amounts, simulated by different assumptions about randomness



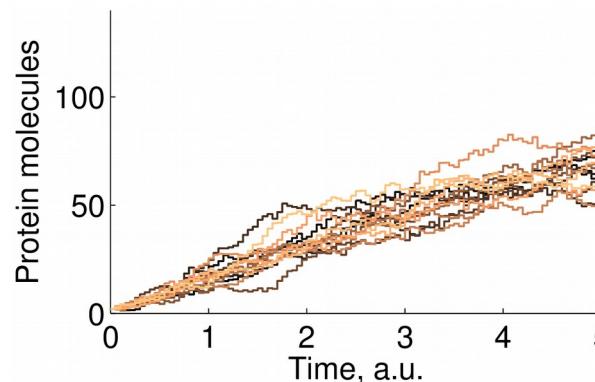
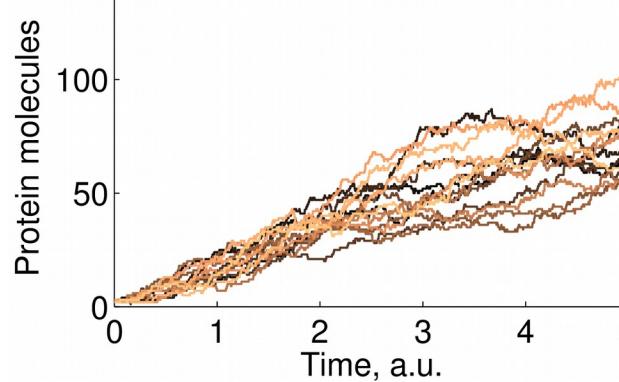
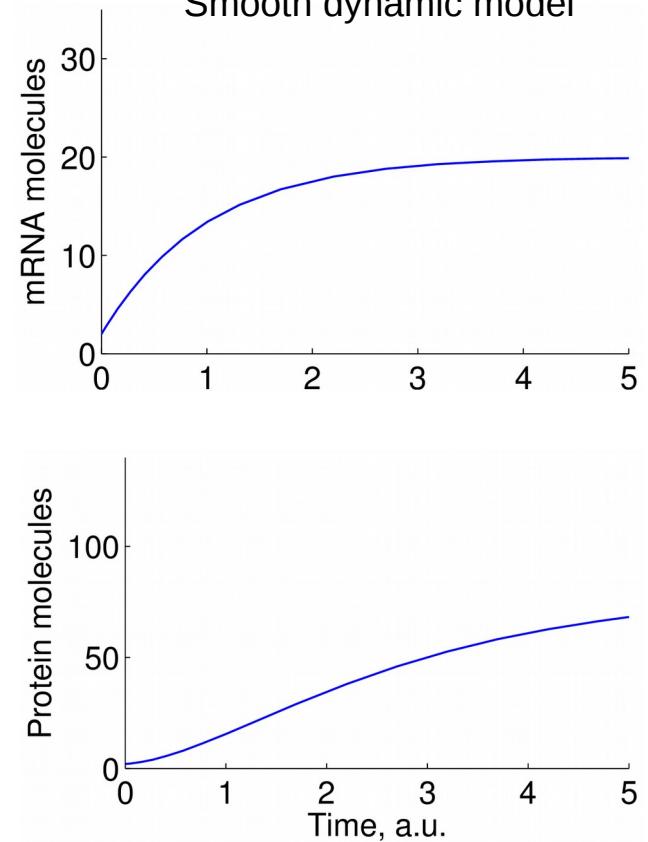
Individual random events



Random numbers of events

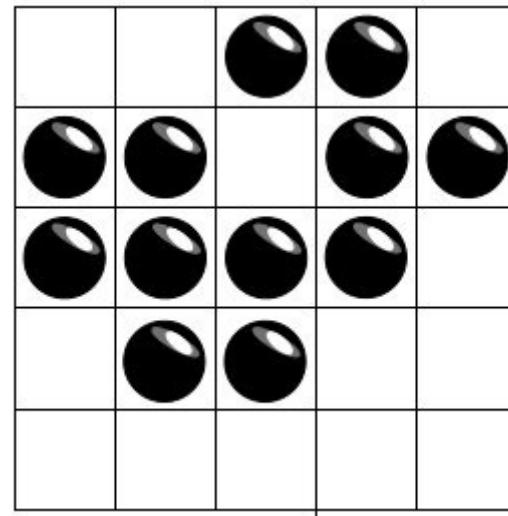
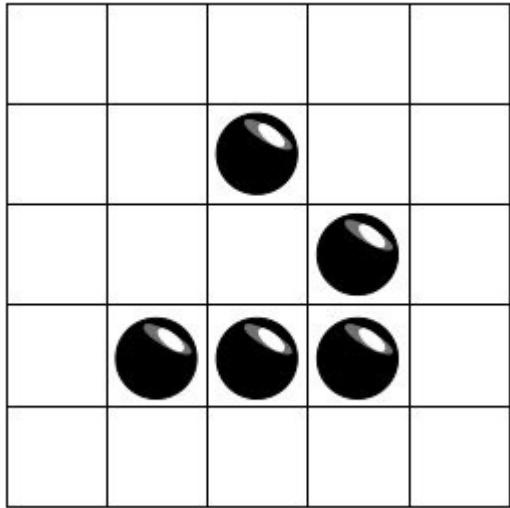


Smooth dynamic model



Dynamics in space and time

Conway's "game of life"

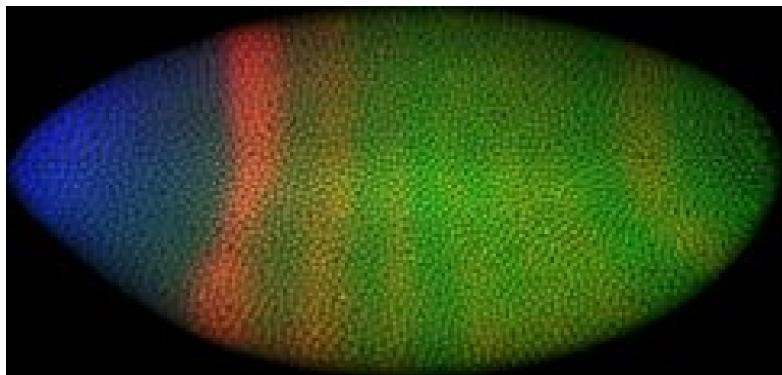


The rules are simple:

- A cell comes to life if there are exactly 3 cells on neighbouring sites.
- A cell stays alive if it has 2 or 3 neighbours

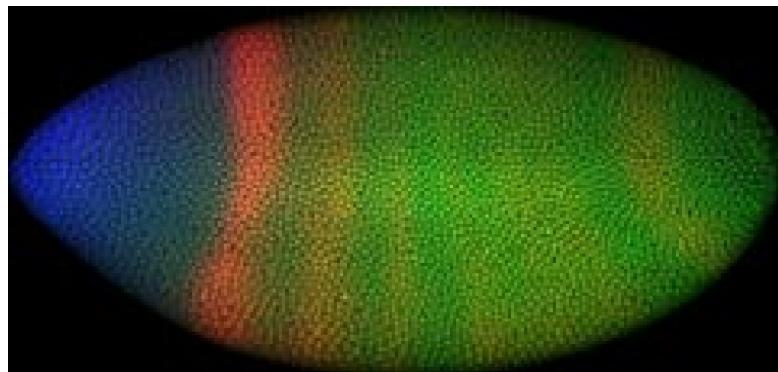
Spontaneous pattern formation can arise from reacting and diffusing signaling molecules

Gene expression in a fruit fly embryo

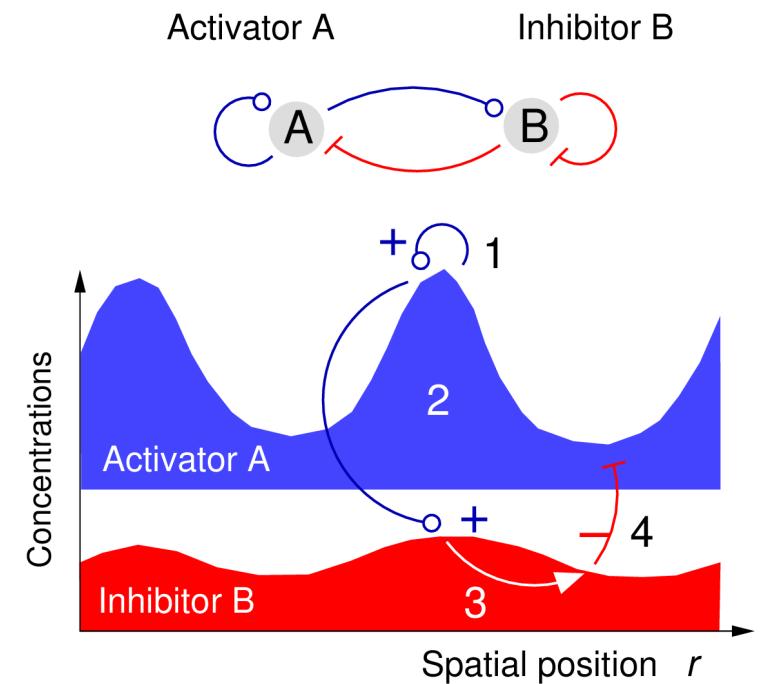


Spontaneous pattern formation can arise from reacting and diffusing signaling molecules

Gene expression in a fruit fly embryo



Activation, inhibition, and diffusion can lead to spontaneous pattern formation



Spontaneous pattern formation can arise from reacting and diffusing signaling molecules

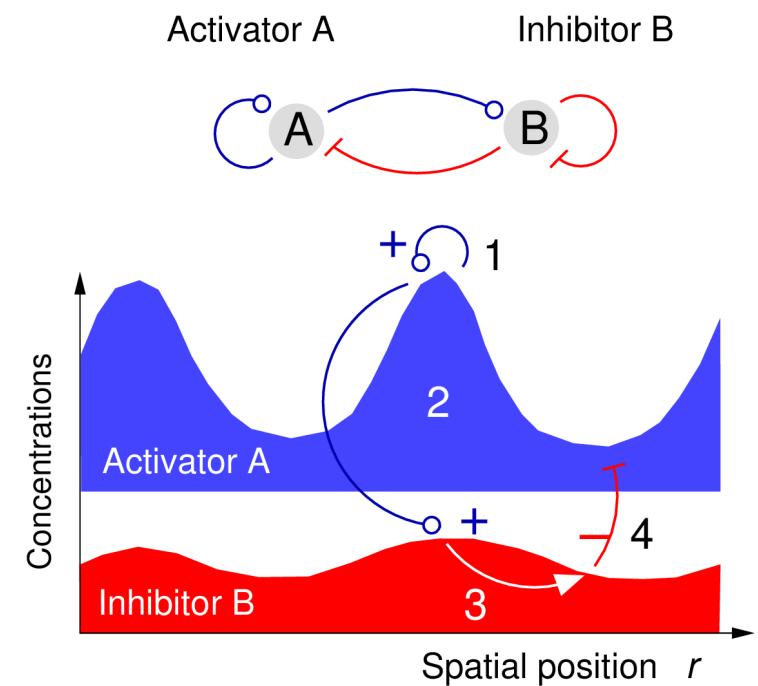
Dynamical model
("Ordinary differential equation")

$$\frac{ds(t)}{dt} = f(s(t))$$

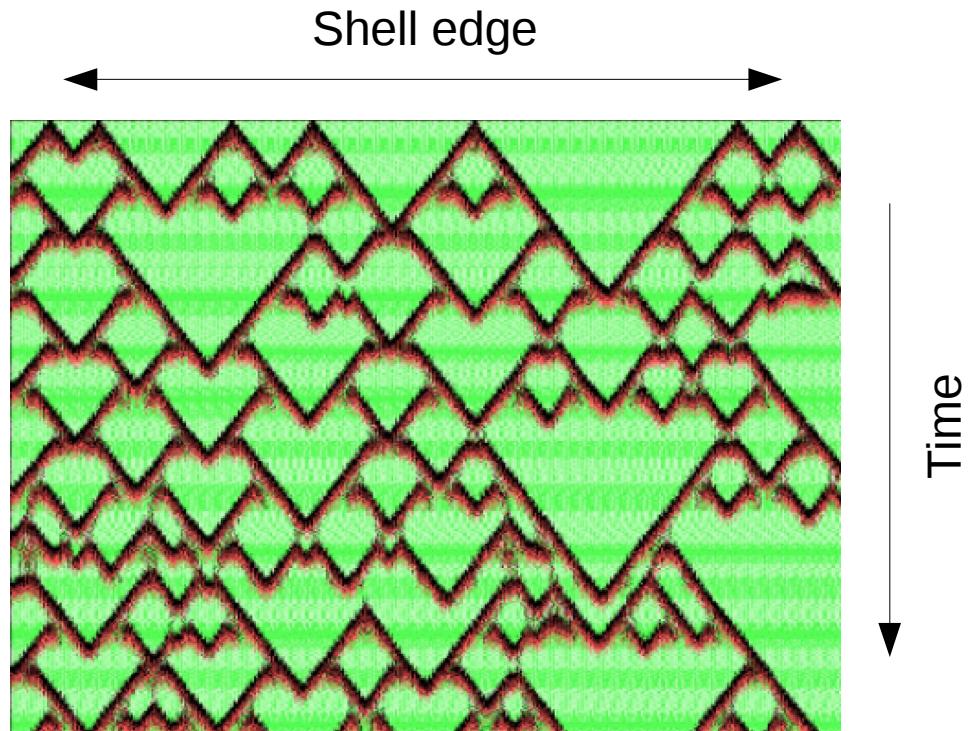
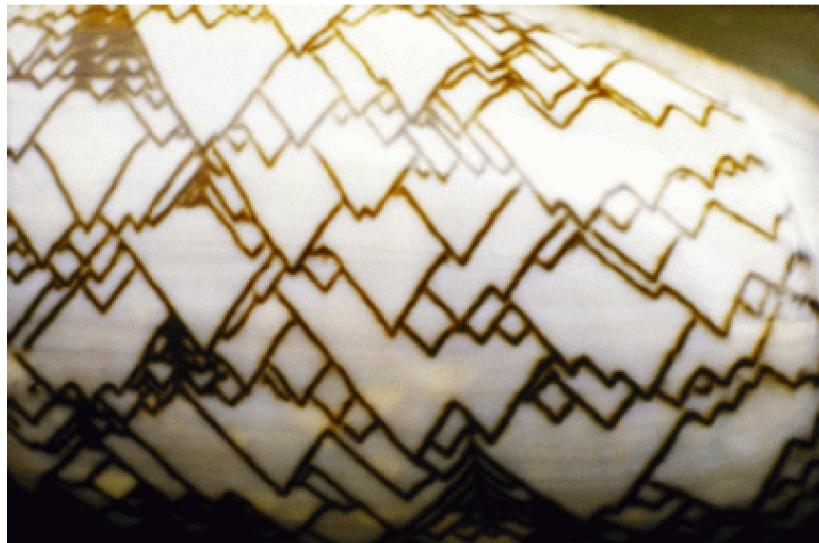
Spatial dynamic model
("Partial differential equation", with diffusion term)

$$\frac{\partial s(x, t)}{\partial t} = f(s(x, t)) + D \frac{\partial^2 s(x, t)}{\partial x^2}$$

Activation, inhibition, and diffusion
can lead to spontaneous pattern formation



Waves in spatio-temporal simulations can reproduce the (type of) patterns on seashells

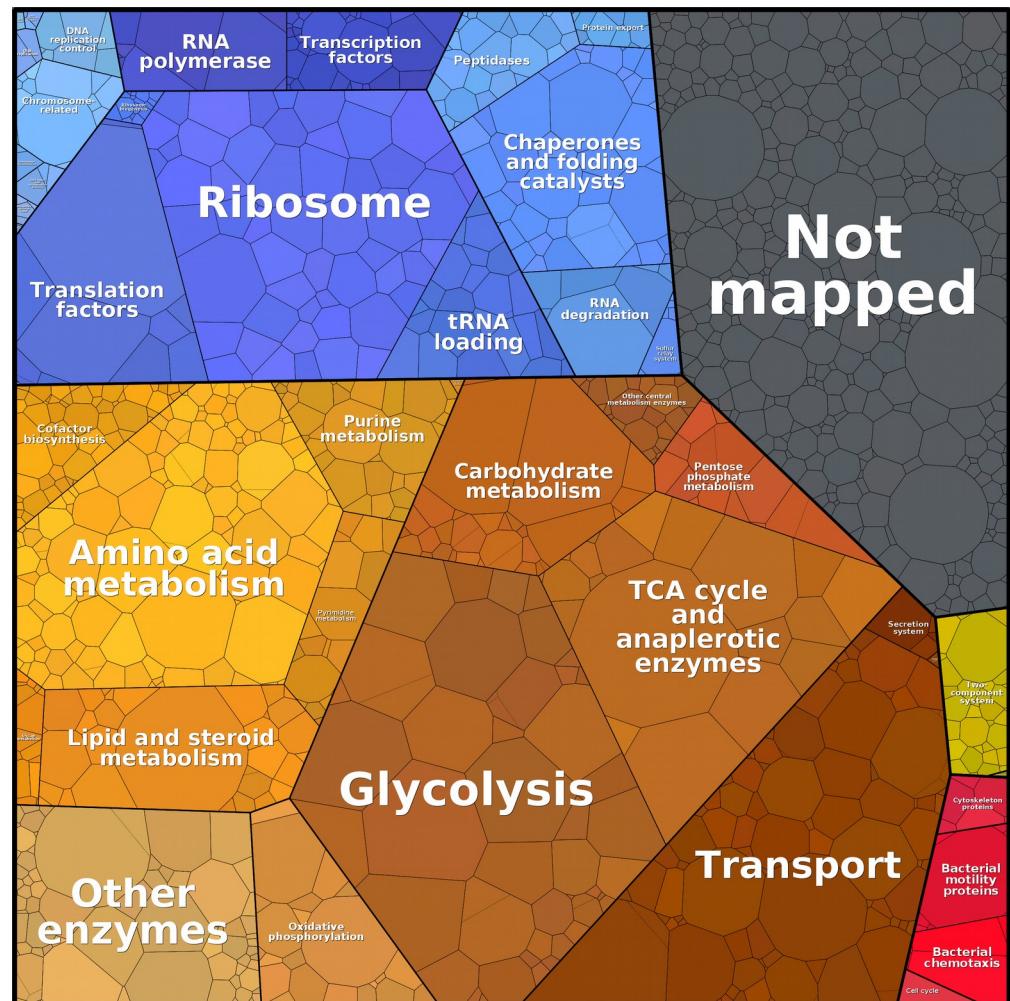
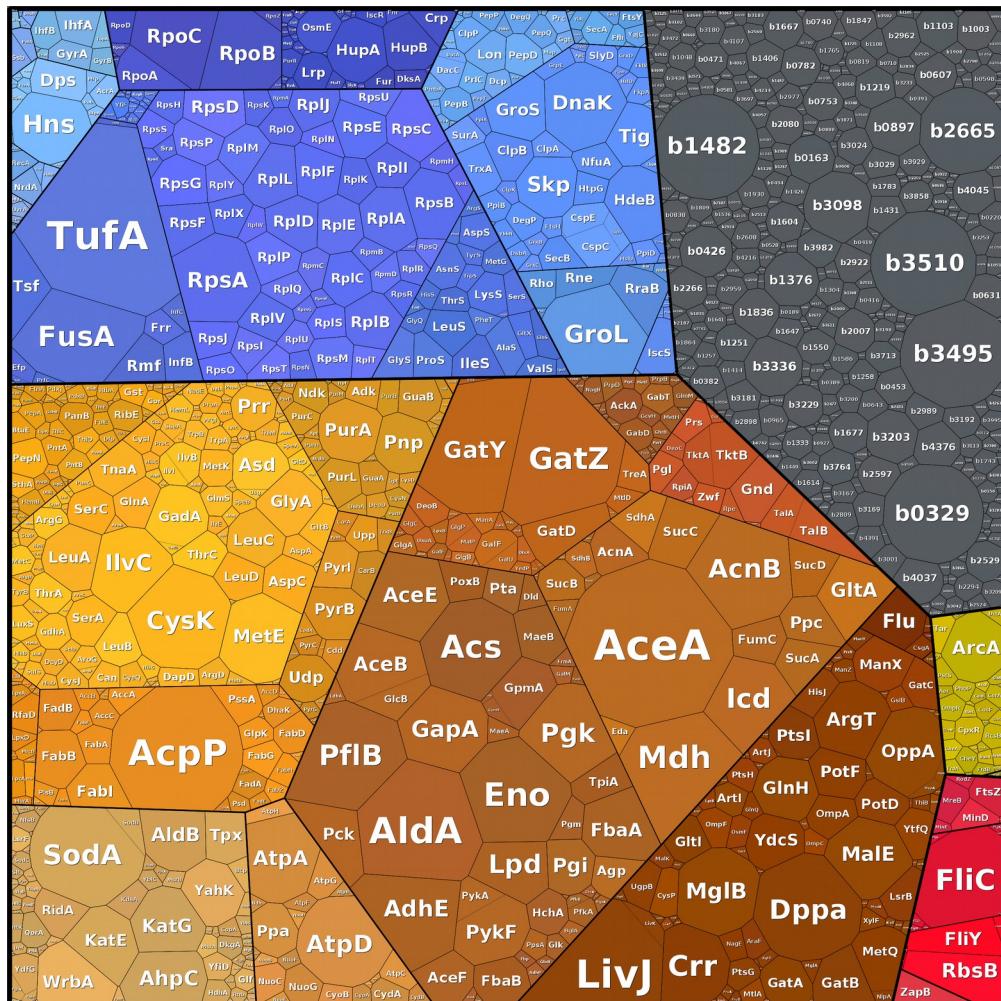


Courtesy of Hans Meinhardt

Resource allocation and whole-cell models

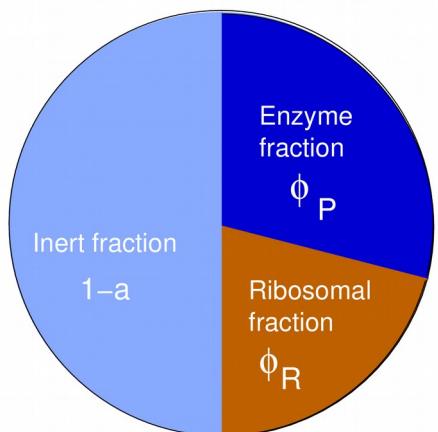
How do cells spend their protein budget?

Proteome of *E. coli* cells



The large protein fractions, described by a model

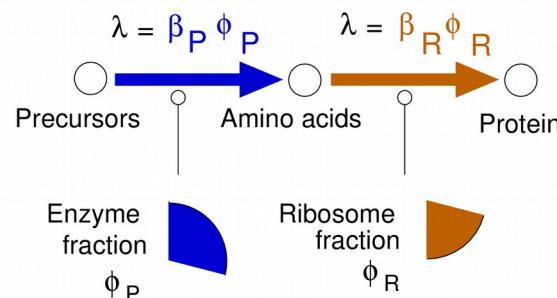
(a) Protein fractions in the sector model



Assumption 1: Enzymes and ribosomes occupy a fixed mass fraction of the proteome

$$a = \phi_P + \phi_R \quad (\text{a: Available proteome fraction})$$

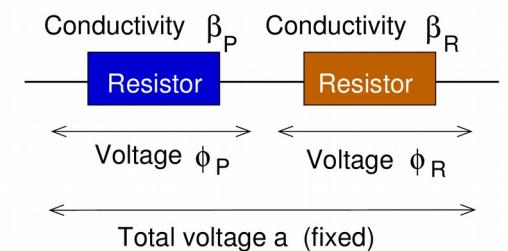
(b) Schematic model of cell growth



Assumption 2: The growth rate is proportional to each of the two proteome fractions

$$\lambda = \beta_P \phi_P = \beta_R \phi_R \quad \begin{matrix} \beta_P & \text{Nutrient capacity} \\ \beta_R & \text{Translation capacity} \end{matrix}$$

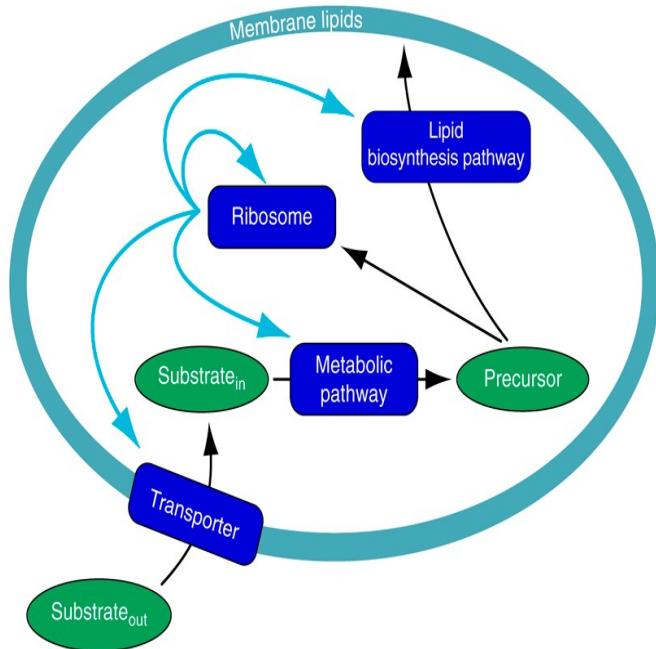
(c) Analogy to electric circuit



$$\phi_P = \frac{\beta_R}{\beta_P + \beta_R} a \quad \phi_R = \frac{\beta_P}{\beta_P + \beta_R} a$$

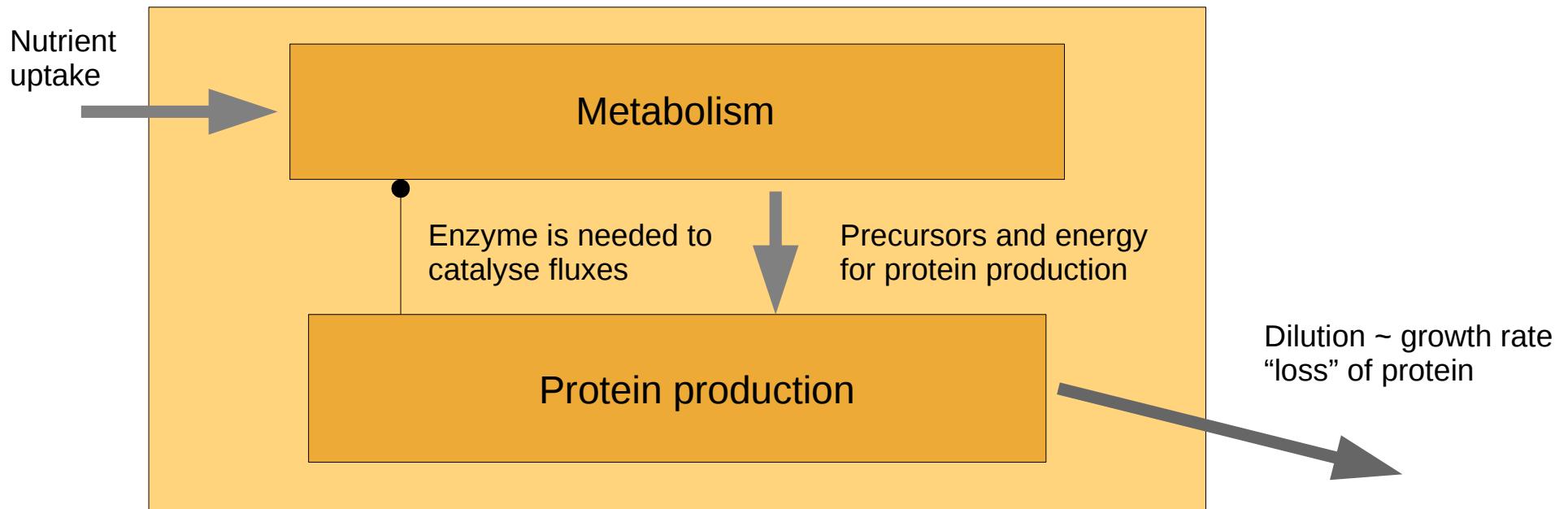
$$\lambda = \frac{\beta_P \beta_R}{\beta_P + \beta_R} a$$

Simple model of a self-replicating cell



- A “minimal self-replicator” that includes metabolism and enzyme production
- Optimizing resource allocation can explain why cells shift from efficient to inefficient catabolism at high growth rates

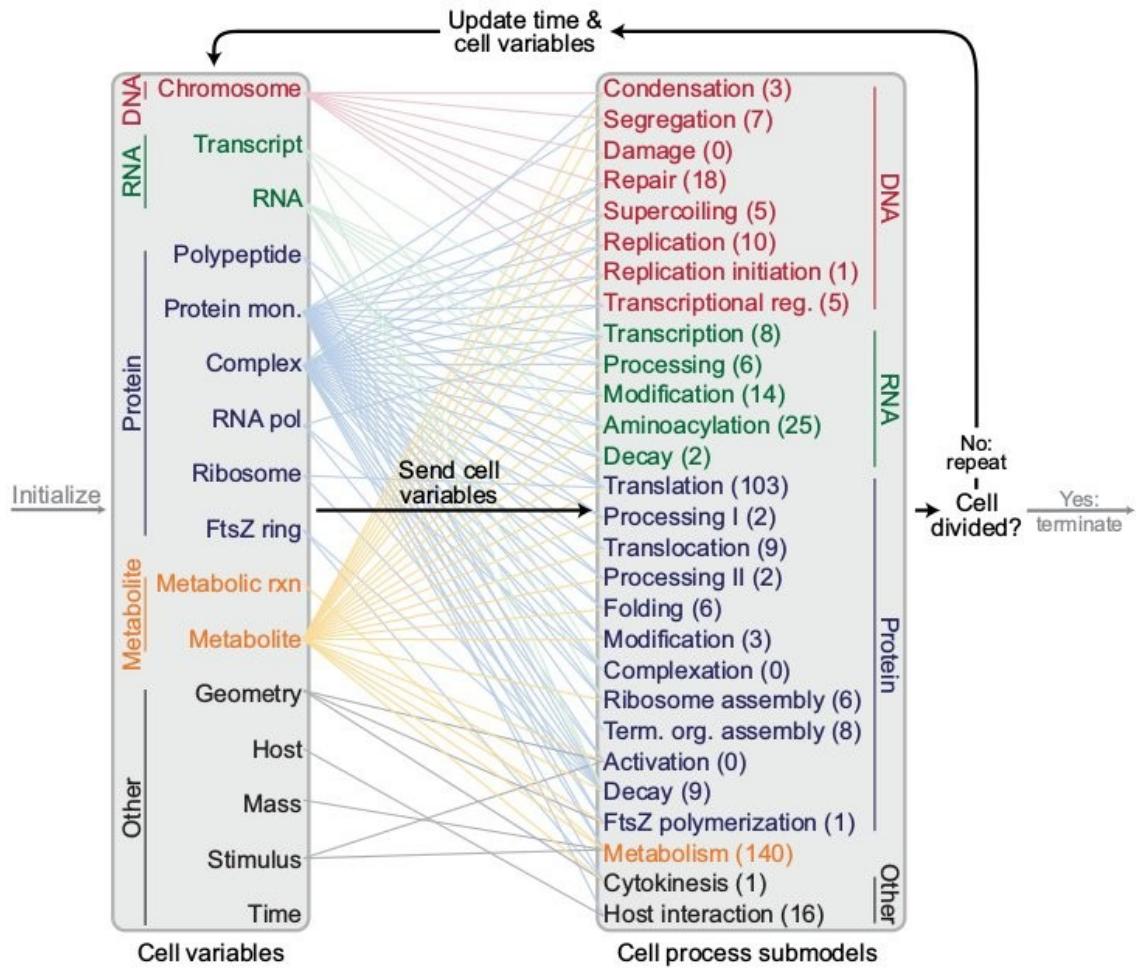
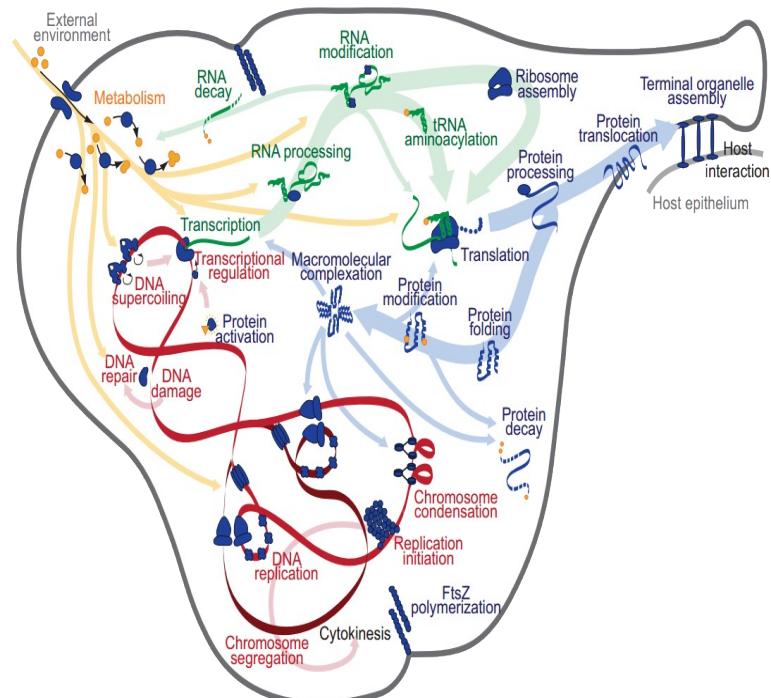
Resource balance analysis: Flux balance analysis, applied to the entire cell



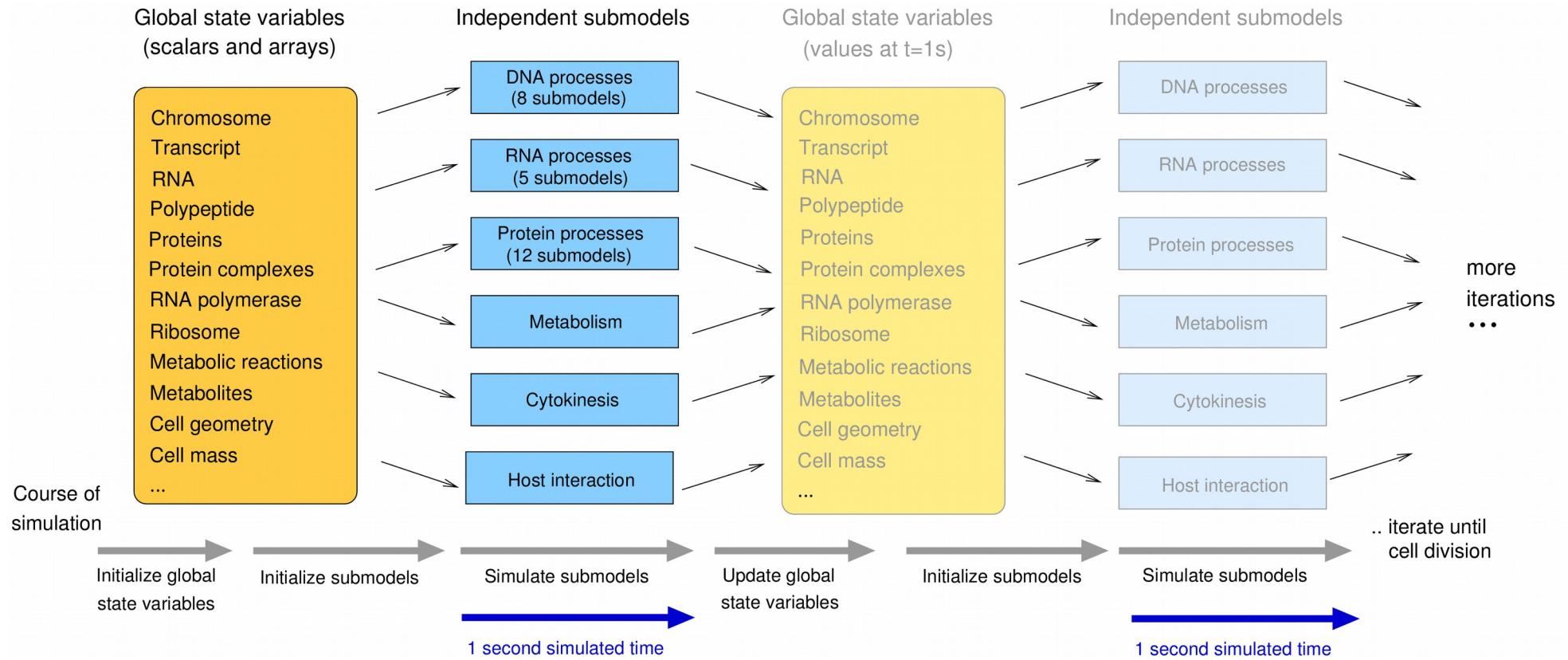
- Fix a growth rate;
Can a steady (growth) state be maintained? → linear (i.e., FBA-like) problem P
- Repeat this many times; find the maximal growth rate at which P can be solved

A whole-cell model for *Mycoplasma pneumoniae*

Whole-cell model overview

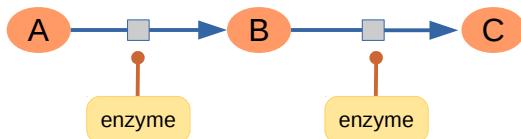


How the modular whole-cell model is simulated



Modelling formalisms for biochemical systems

Kinetic models

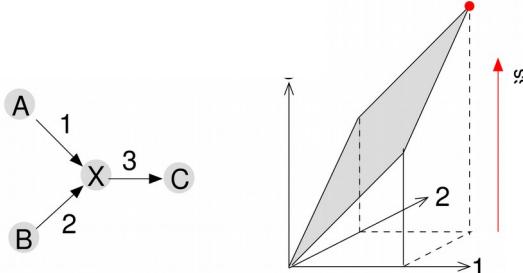


concentration stoichiometry reaction rate

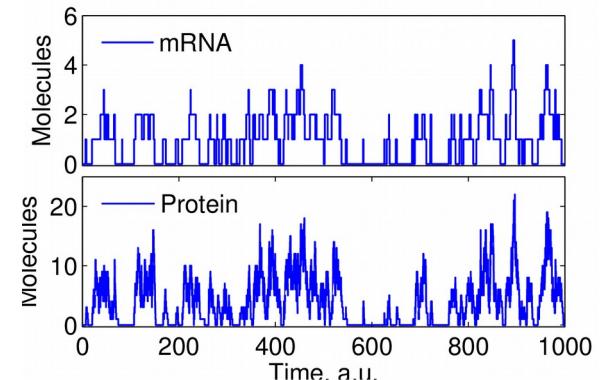
$$\frac{dx_i}{dt} = \sum_l n_{il} v_l(x, p)$$

parameters

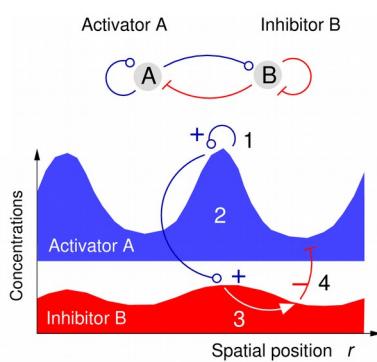
Stationary fluxes ("constraint-based models")



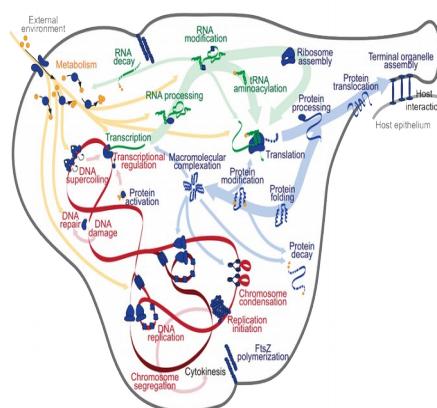
Stochastic models



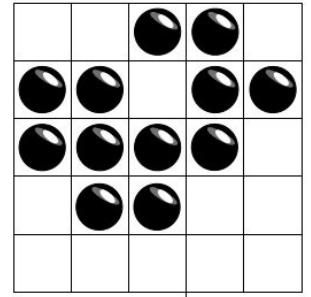
Spatial models



Whole-cell models



... and many more!



Thank you !



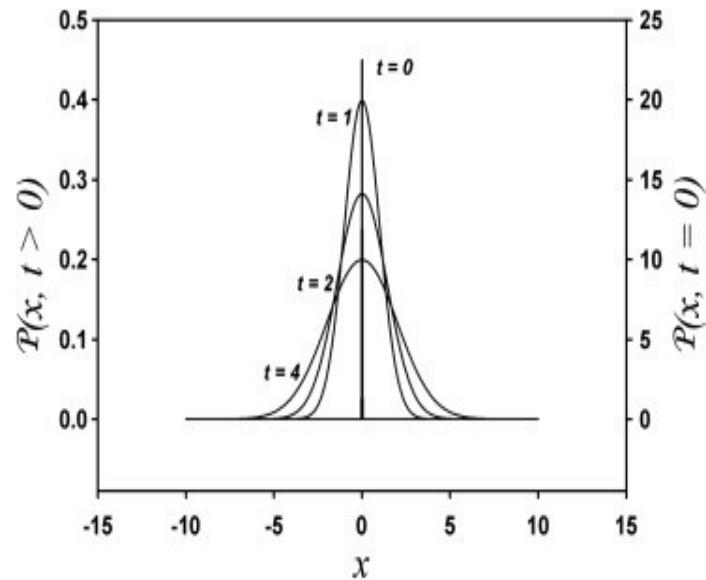
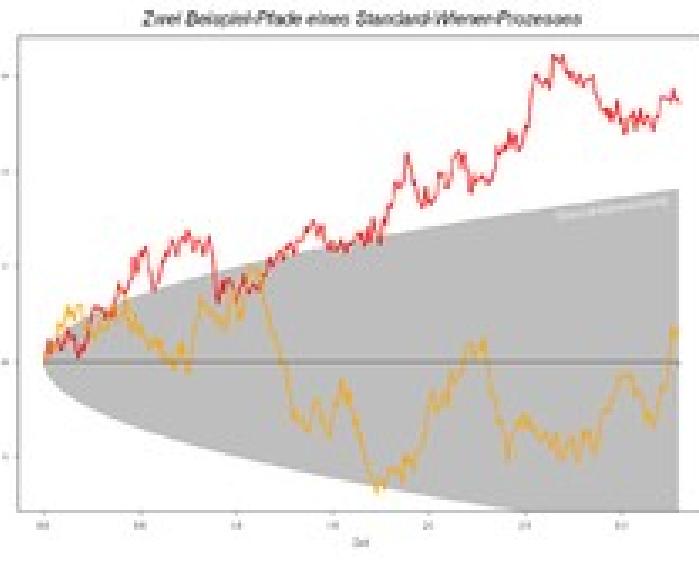
Brownian motion in continuous time and space is described by the Wiener process



Albert Einstein
(1879-1955)



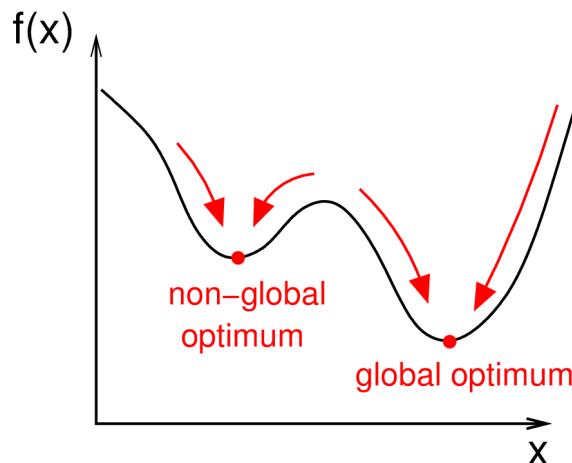
Norbert Wiener
(1894-1964)



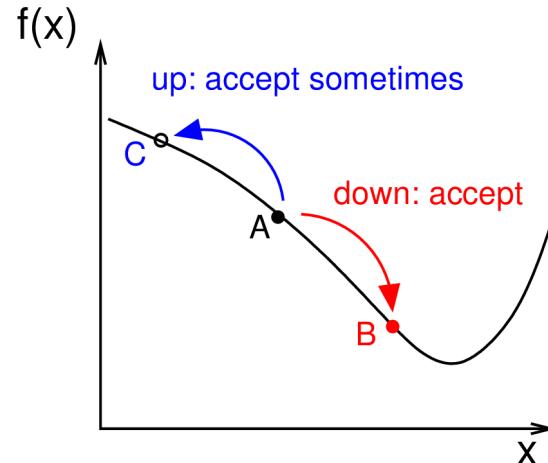
Optimisation and evolution

Numerical optimisation - and optimisation by evolution

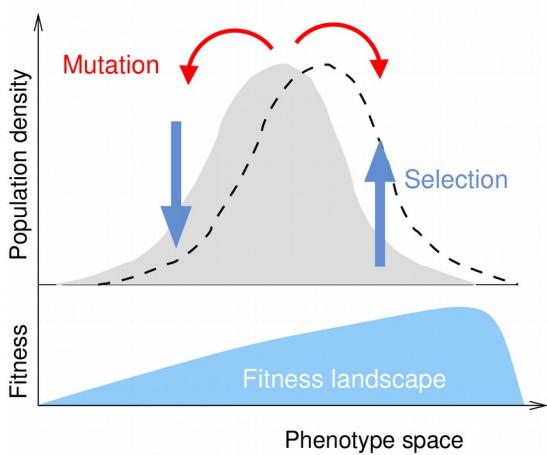
(a) Optimization



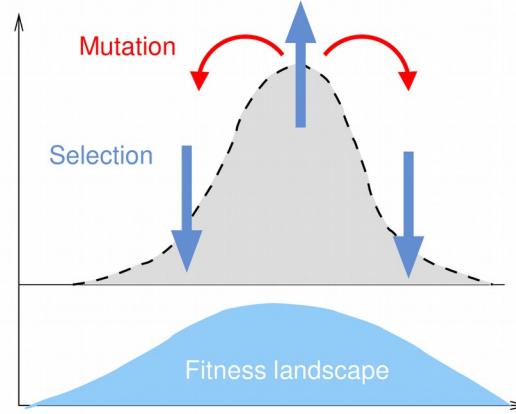
(b) Metropolis algorithm



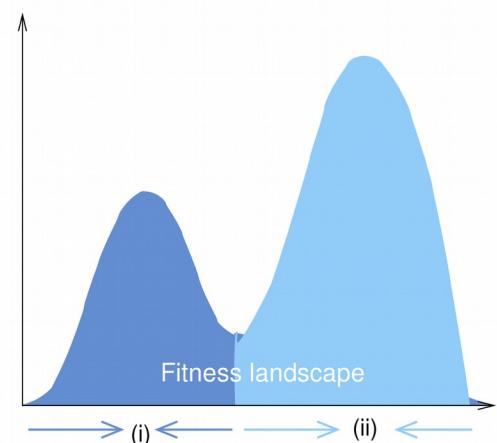
(a)



(b)

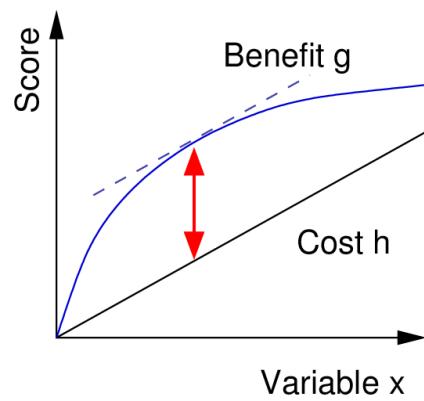


(c)

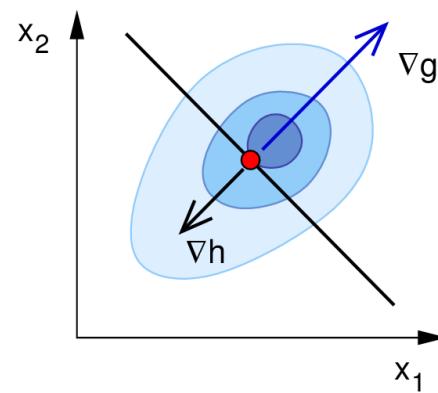


Different approaches to describing optimality

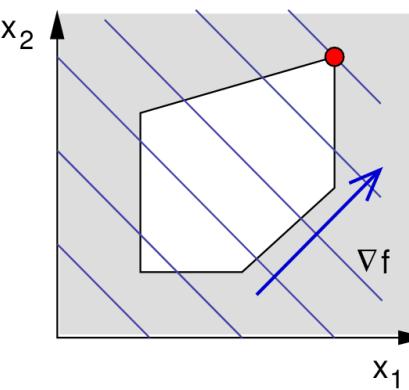
(a) Cost–benefit optimization



(b) Constrained optimization



(c) Linear programming



(d) Pareto optimization

