IV121: Computer science applications in biology

Quantitative Models in Biology

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Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.

EVROPSKÁ UNIE

INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Obsah

Continuous mass action

Stochastic mass action

Beyond elementary reaction kinetics

What is continous? What does continuous mean?

- think of physical motion
    - by means of classical mechanics
    - by means of classical electrodynamics
    - all are models...
    - compare with quantum mechanics – the scale of $10^{-8}m$ makes the barrier between views...
- think of a crowd of thousand people
    - what you observe when someone disappears?
    - what you observe when someone new appears?
- think of molecules in a solution or in a cell ...

Continuous model of reaction kinetics

- assume well-stirred solution
- high amounts of all substances
- fixed thermodynamics conditions (temperature, pressure, . . .)
- fixed volume of the solution

Continuous model of reaction kinetics

$$A \xrightarrow{k}$$

- consider a barrel with a substance A of molar volume $[A]$ $[M]$
- how much of substance A "flows out" per a single time unit?
  - value proportional to $[A](t)$ in a given time t

$$-\frac{d[A](t)}{dt} = k \cdot [A](t)$$

  - coefficient of proporcionality is denoted k $[s^{-1}]$
    so-called *kinetic constant (coefficient)*
    - determines the speed of mass decay ("outflow")

Continuous model of reaction kinetics

$$\frac{[A](t)}{dt} = k \cdot [A](t)$$

- which functions has the same form as its derivation?
    - $f(t) = 1 + t + t^2/2! + t^3/3! + t^4/4! + \ldots$

$$f(t) = e^t$$

    - platí

$$\frac{de^t}{dt} = e^t$$

Continuous model of reaction kinetics

$$A \xrightarrow{k}$$

$$-\frac{d[A](t)}{dt} = k \cdot [A](t)$$

Continuous model of reaction kinetics

$$A \xrightarrow{k}$$

$$-\frac{d[A](t)}{dt} = k \cdot [A](t) \Leftrightarrow [A](t) = [A](0) \cdot e^{-kt}$$

- so-called first-order kinetics (a special case of mass action)
- linear autonomous differential equation
- unique solution
- can be either analytically solved or numerically approximated

Continuous model of reaction kinetics

- state is a vector of actual amounts of all susbtances in the system
- continuous-time dynamics: the state change $X(t) \rightarrow X(t + dt)$ updates all components of X (continuous concurrent flow of all reactions)
- we consider **reaction rate** as a function of time: for a reaction R in time t we denote the actual rate $v_R(t)$

reaction type	rate function v_R	state update
$\rightarrow A$	$v_R(t) = k$	$\frac{dA}{dt} = -v_R$
$A \rightarrow B$	$v_R(t) = k \cdot [A](t)$	$\frac{dA}{dt} = -v_R$, $\frac{dB}{dt} = v_R$
$A + B \rightarrow AB$	$v_R(t) = k \cdot [A](t) \cdot [B](t)$	$\frac{dA}{dt} = \frac{dB}{dt} = -v_R$, $\frac{dAB}{dt} = v_R$
$2A \rightarrow AA$	$v_R(t) = k \cdot [A]^2$	$\frac{dA}{dt} = -2v_R$, $\frac{dAA}{dt} = v_R$

General Mass Action Kinetics

$$\sum_{i=1}^{k} s_i \cdot A_i \rightarrow \sum_{j=1}^{l} p_j \cdot B_j$$

$$v = \prod_{i=1}^{k} {A_i}^{s_i}$$

$$\forall 1 \leq i \leq k.\, \frac{dA_i}{dt} = -s_i \cdot v$$
$$\forall 1 \leq j \leq l.\, \frac{dB_j}{dt} = p_j \cdot v$$

Example: Michaelis-Menten

$$S + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} P + E$$

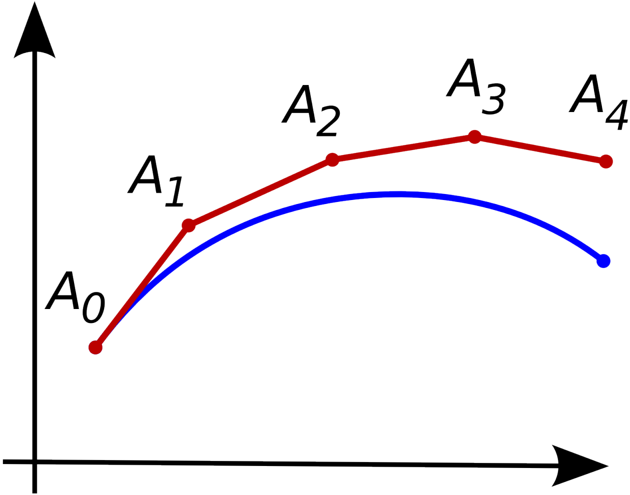
$$\frac{d[S]}{dt} = -k_1[E][S] + k_2[ES]$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_2[ES] + k_3[ES]$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_2[ES] - k_3[ES]$$

$$\frac{d[P]}{dt} = k_3[ES]$$

Euler method



Euler method

- approximate solution $y(t)$ (Euler):

$$\begin{aligned} y'(t) &= f(t, y(t)) \\ y(0) &= y_0 \end{aligned}$$

- exact solution $\varphi(t)$:

$$\begin{aligned} \varphi'(t) &= f(t, \varphi(t)) \\ \varphi(0) &= y_0 \end{aligned}$$

- for each $n \geq 0$, $t_n = n\Delta t$:

$$y_n \approx \varphi(t_n)$$

Euler method

Exact solution $\varphi(t)$ satisfies:

$$\begin{aligned} \varphi(t_{n+1}) &= \varphi(t_n) + \int_{t_n}^{t_{n+1}} \varphi'(t)dt \\ &= \varphi(t_n) + \int_{t_n}^{t_{n+1}} f(t,\varphi(t))dt \end{aligned}$$

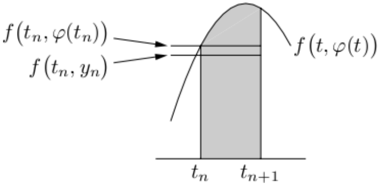
Numerical approximation:

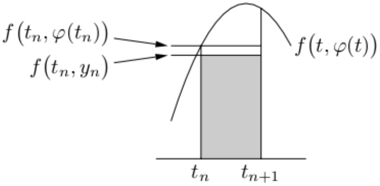
$$y_{n+1} = y_n + \sigma$$

where

$$\sigma \approx \int_{t_n}^{t_{n+1}} f(t,\varphi(t))dt$$

Euler method I



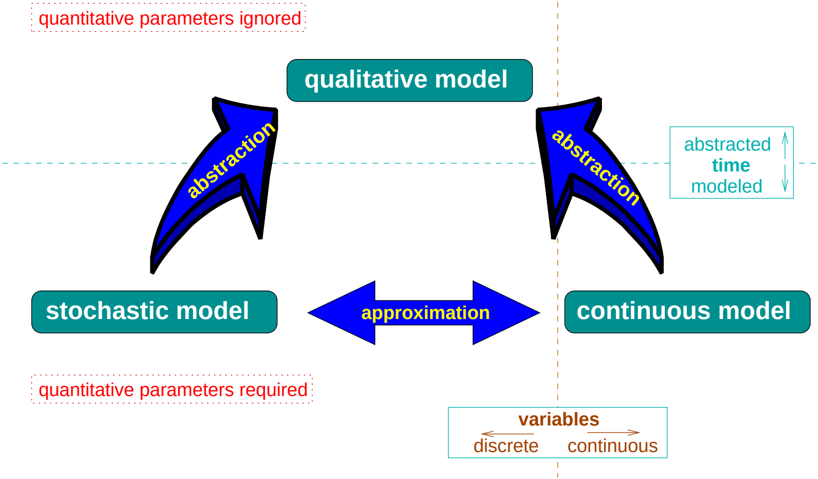


$$\frac{dy}{dt} = f(t, y)$$

$$y_{n+1} = y_n + \Delta t \cdot f(t_n, y_n)$$

```
1. init $t_0$, $y_0$, $\Delta t$, $n$;
2. for j from 1 to n do
    2.1 $m := f(t_0, y_0)$;
    2.2 $y_1 := y_0 + \Delta t m$;
    2.3 $t_1 := t_0 + \Delta t$;
    2.4 $t_0 := t_1$;
    2.5 $y_0 := y_1$;
3. end
```

Petri Net Analysis Framework



quantitative parameters ignored

qualitative model

abstraction

abstraction

abstracted
time
modeled

stochastic model

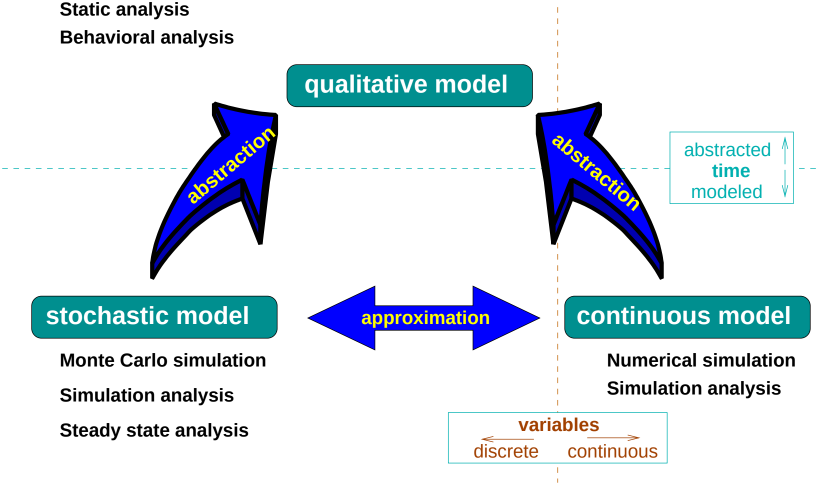
approximation

continuous model

quantitative parameters required

variables
discrete ← → continuous

Petri Net Analysis Framework



Static analysis

Behavioral analysis

qualitative model

abstraction

abstraction

abstracted
time
modeled

stochastic model

approximation

continuous model

Monte Carlo simulation

Simulation analysis

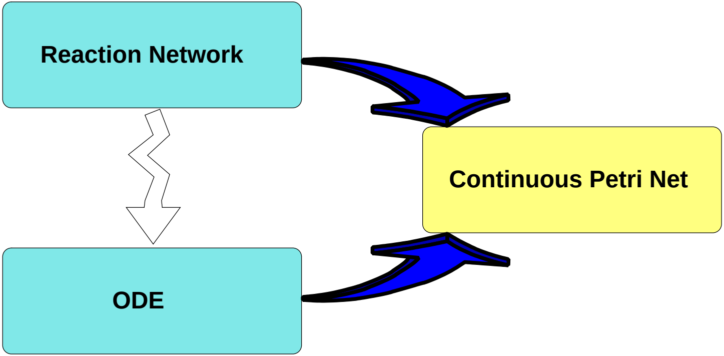
Steady state analysis

Numerical simulation

Simulation analysis

variables
discrete ← → continuous

Petri Net Representation of Models



Reaction Network

Continuous Petri Net

ODE

- for mass action kinetics both transformations are direct
- unique Petri net representation of ODEs always achievable

S. Soliman, M. Heiner (2010) "A Unique Transformation from Ordinary Differential Equations to Reaction Networks." PLoS ONE 5(12): e14284. doi:10.1371/journal.pone.0014284

Continuous Petri Nets

Structure

Continuous Petri net is a quadruple $\mathcal{N} = \langle S, R, f, v, m(0) \rangle$ where

- S finite set of *places* (substances),
- T finite set of *transitions* (reactions),
- $f : ((P \times T) \cup (T \times P)) \rightarrow \mathbb{N}_0$ set of weighted edges,
    - $x\bullet = \{y \in S \cup R \mid f(x, y) \neq 0\}$ denotes target of x
    - $\bullet x = \{y \in S \cup R \mid f(y, x) \neq 0\}$ denotes source of x
    - weight represents stoichiometric coefficients
- v is mapping which assigns each transition $r \in R$ a function $h_r : \mathbb{R}^{|\bullet r|} \rightarrow \mathbb{R}$
    - v represents transition (reaction) rate
- $m(0) : S \rightarrow \mathbb{R}_0^+$ is *initial marking* (initial condition).

Continuous Petri Nets

Dynamics

Number of places denotes the dimension of the system, $n = |S|$.

Each place $s \in S$ is marked by a value in $\mathbb{R}_0^+$ (representing concentration of the respective species):

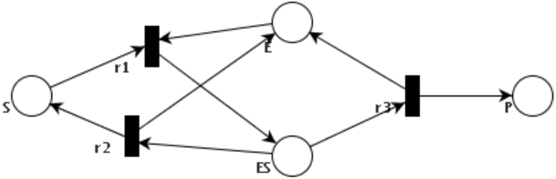
- in Petri net terminology evaluation of places is called *marking* and represented as an n-dimensional vector $m \in \mathbb{R}^n$
- marking evolves in time: $m(t)$

Dynamics of each place $s \in S$ is defined by an ODE:

$$\frac{dm_s(t)}{dt} = \sum_{r \in \bullet s} f(r,s)v(r) - \sum_{r \in s \bullet} f(s,r)v(r)$$

Continuous Petri Nets

Michaelis-Menten Mass Action Kinetics Example



$$r_1:\ E+S\rightarrow ES,\ r_2:\ ES\rightarrow E+S,\ r_3:\ ES\rightarrow P+E$$

$$\frac{dm_S}{dt}=v(r_2)-v(r_1)$$

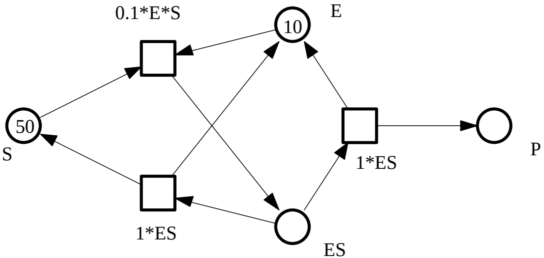
$$\frac{dm_E}{dt}=v(r_2)+v(r_3)-v(r_1)$$

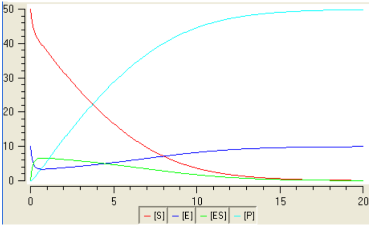
$$\frac{dm_{ES}}{dt}=v(r_1)-v(r_2)-v(r_3)$$

$$\frac{dm_P}{dt}=v(r_3)$$

Continuous Petri Nets

Michaelis-Menten Mass Action Kinetics Example





$$\frac{dm_S}{dt} = k_2 m_{ES} - k_1 m_E m_S$$

$$\frac{dm_E}{dt} = k_2 m_{ES} + k_3 m_{ES} - k_1 m_E m_S$$

$$\frac{dm_{ES}}{dt} = k_1 m_E m_S - k_2 m_{ES} - k_3 m_{ES}$$

$$\frac{dm_P}{dt} = k_3 m_{ES}$$

$$k_1 = 0.1\ [M^{-1}s^{-1}]$$

$$k_2 = 1\ [s^{-1}]$$

$$k_3 = 1\ [s^{-1}]$$

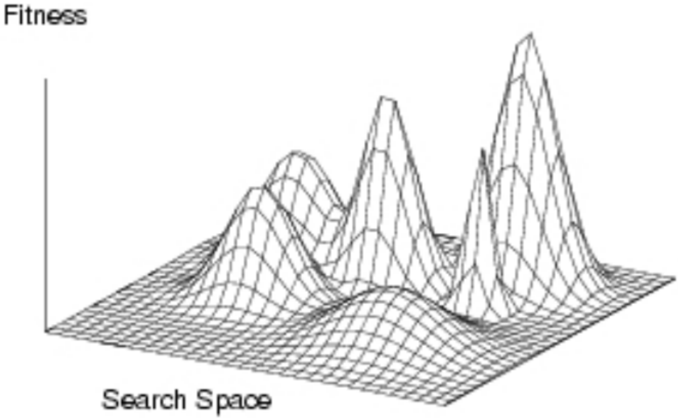
Parameter Estimation Problem

- inverse problems – determine the model from measured data
- quite easy for linear systems, but what for non-linear?
- general steps in inverse problem solution:
  1. identify relations among variables
  2. identify functions describing relations (e.g., mass action)
  3. estimate constants appearing in the functions – **parameter estimation**

Parameter Estimation Problem

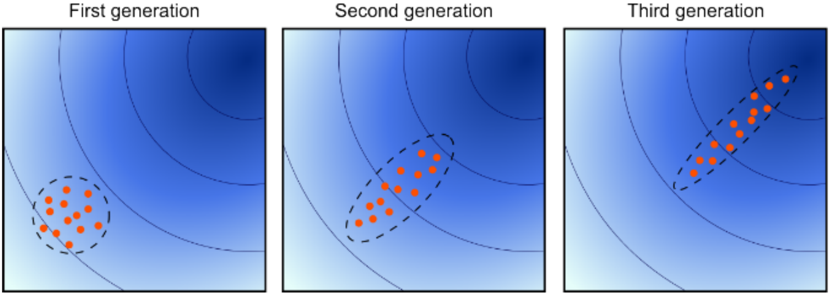
- parameter estimation is solved as optimization problem w.r.t. measured data
- the goal is to minimize average deviation of model from data
- so-called least squares method
- we seek for global minima
- many heuristics for optimization procedure, many algorithms

Parameter Landscape



Parameter Landscape

Walking the landscape to find the global minimum



Tool Support for Continuous Models

- format transformation and models editing
    - Snoopy – Petri nets representation visual editing, SBML export/import, Petri net variants transformation
    - CellDesigner – SBGN visual editing, SBML export/import
    - CellIllustartor – visual editing, hybrid Petri nets simulation
- analysis
    - Octave, Matlab (simulation and SBML: SBMLToolBox, SimBiology ToolBox)
    - COPASI (simulation, SBML export/import, other analysis tasks)
    - BioCHAM (robustness analysis, model checking)

Literature

- M. Feinberg. *Lectures on Chemical Reaction Networks.* `http://www.che.eng.ohio-state.edu/~FEINBERG/LecturesOnReactionNetworks/`
- M. Heiner, D. Gilbert & R. Donaldson. *Petri Nets for Systems and Synthetic Biology.* SFM 2008: 215-264
- Hoops S. et al. *COPASI – a COmplex PAthway SImulator.*, Bioinformatics 22, 3067-74
- T. Vejpustek. *Parameter estimation v COPASI – tutotial.* `http://anna.fi.muni.cz/~xsafran1/PV225/parameter_estimation/copasi.html`.

Obsah

Continuous mass action

Stochastic mass action

Beyond elementary reaction kinetics

Stochastic model of reaction kinetics

- assume well-stirred solution
    - uniform distribution of molecules in solution
- low amounts of substances
- fixed thermodynamics conditions (temperature, pressure, . . .)
- fixed volume of the solution
- reactions (molecule collisions) viewed as discrete events

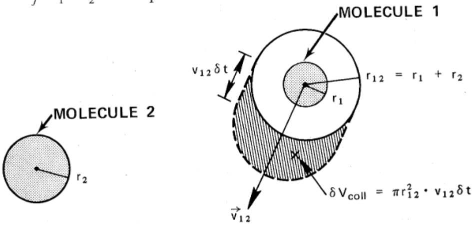
Stochastic model of reaction kinetics

- discrete events happen in continuous time
- time between two events is a stochastic quantity
  - average probability (over the whole solution) of reaction realization in given time
  - some reactions faster (more probable), some slower (less probable)
  - probability depends on amounts of reactant molecules
- stochasticity is a measure of uncertainty caused by other (non-reactive) events happening in solution
  $\Rightarrow$ approximation of the following aspects:
  - molecule position and rotation
  - molecule motion (speed)

Stochastic model of reaction kinetics

Gillespie's Hypothesis

R_j: $S_1 + S_2 \xrightarrow{c_j}$ products



$$\text{Prob}\{v_{12}\text{-collision in } dt\} = \frac{(\pi r_{12}^2)(v_{12}dt)}{\Omega}. \quad \text{Prob}\{R_j \,|\, v_{12}\text{-collision}\} \triangleq p_j(v_{12}).$$

$$\underbrace{\left\langle \left(\frac{(\pi r_{12}^2)(v_{12}dt)}{\Omega}\right) \times p_j(v_{12}) \right\rangle_{v_{12}}}_{\substack{\text{Prob that a randomly chosen} \\ S_1\text{-}S_2 \text{ pair does an } R_j \text{ in next } dt}} \times x_1 x_2 = \underbrace{\left(\frac{\pi r_{12}^2}{\Omega} \left\langle v_{12}\, p_j(v_{12}) \right\rangle_{v_{12}}\right)}_{c_j} x_1 x_2\, dt = \underbrace{c_j x_1 x_2}_{a_j(\mathbf{x})}\, dt$$

$$R_j \text{ iff "}\textit{collisional K.E.}\text{"} > E_j \quad \Rightarrow \quad \left\langle v_{12}\, p_j(v_{12}) \right\rangle_{v_{12}} = \underbrace{\sqrt{\frac{8k_BT}{\pi m_{12}}}}_{\langle v_{12}\rangle} \underbrace{\exp\left(-\frac{E_j}{k_BT}\right)}_{\text{Arrhenius}}$$

D. T. Gillespie. Exact Stochastic Simulation of Coupled Chemical Reactions. In Journal of Physical Chemistry, volume 81, No. 25, pages 2340-2381. 1977.

Stochastic model of reaction kinetics

Gillespie's Hypothesis

- basic Newtonian physics and thermodynamics is assumed
- realization probability for reaction R_j globally characterized by the rate constant c_j
  - depends on radii of colliding molecules and their average relative velocities (considerred relatively to the solution volume)
  - direct function of temperature and molecular structure
- if a pair of two molecules has kinetic energy higher than reaction energy then the reaction is realized

Stochastic model of reaction kinetics

Comparison of models

- continuous kinetics provides a **macro-scale view**
    - systems view abstracting from location (space)
    - continuous dynamics of large quantities – quantitity as a population
    - single average evolution of averaged (well-stirred) events
- stochastic kinetics provides a **meso-scale view**
    - systems view still abstracting from location (space)
    - discrete dynamics of low quantities
    - all possible evolutions of averaged (well-stirred) events

Stochastic model of reaction kinetics

Grand probability function

- Gillespie's hypothesis enables stochastic formulation of molecular (low population) dynamics
- for time t the grand probability function $Pr(X;t)$ characterizes the probability that there will be present X_i molecules of species S_i, $X = \langle X_1, ..., X_n \rangle$ is a vector quantity denoting configuration of the population

Stochastic model of reaction kinetics

Grand probability function

- Gillespie's hypothesis enables stochastic formulation of molecular (low population) dynamics
- for time t the grand probability function $Pr(X;t)$ characterizes the probability that there will be present X_i molecules of species S_i, $X = \langle X_1, \ldots, X_n \rangle$ is a vector quantity denoting configuration of the population
- how to compute?

Stochastic model of reaction kinetics

Grand probability function

- considering reactions as discrete events leads to:

$$\begin{aligned} Pr(X;t+dt) &= Pr(X;t)\cdot Pr(\text{no state change}) \\ &+\textstyle\sum_{i=1}^{m} Pr(X-u_i;t)\cdot Pr(\text{state changed to X}) \end{aligned}$$

where

- dt is a small time step in which at most 1 reaction occurs
- u_i is **update** caused by the effect of reaction R_i ($X \rightarrow X + u_i$)

Stochastic model of reaction kinetics

Grand probability function

- considering reactions as discrete events leads to:

$$\begin{aligned} Pr(X;t+dt) &= Pr(X;t)\cdot(1-\textstyle\sum_{i=1}^{m}\chi_i(X)dt) \\ &+ \textstyle\sum_{i=1}^{m} Pr(X-u_i;t)\chi_i(X-u_i)dt \end{aligned}$$

where

- dt is a small time step in which at most 1 reaction occurs
- u_i is **update** caused by the effect of reaction R_i ($X \rightarrow X + u_i$)
- χ_i is hazard function characterizing the probability of exactly one occurrence of R_i in time interval dt

Stochastic model of reaction kinetics

Hazard function

In a particular configuration, probability of reaction realization in given time is characterized by **hazard function**.

Hazard function for reaction R is denoted $\chi_R(X)$ where X is a current state (configuration, marking). Assume R is assigned a stochastic rate constant c_R. The table below shows the hazard function for all forms of elementary reactions:

$\rightarrow *$	$\chi_R(X) = c_R$
$A \rightarrow *$	$\chi_R(X) = c_R \cdot X_A$
$A + B \rightarrow *$	$\chi_R(X) = c_R \cdot X_A \cdot X_B$
$2A \rightarrow *$	$\chi_R(X) = c_R \cdot \frac{X_A \cdot (X_A - 1)}{2}$

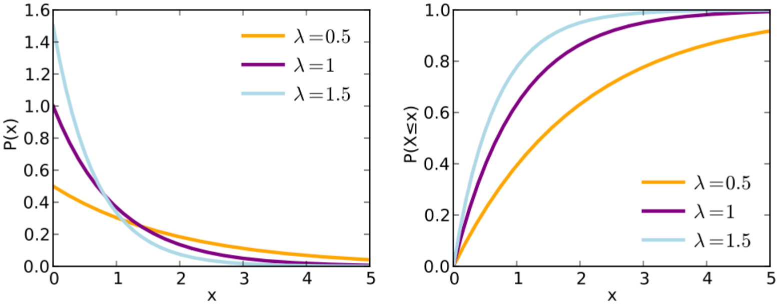
stochastic mass action

Stochastic model of reaction kinetics

Stochastic Simulation Algorithm – SSA

- single transition $X(t) \rightarrow X(t + dt)$ updates just one component of X
- realization of just one reaction R
- reaction realization does not take time
- in a state $X(t)$, the time to next realization of reaction R_i is characterized by distribution $Exp(\chi_{R_i}(X))$

Exponential distribution



$$E(X) = \frac{1}{\lambda}$$

Stochastic model of reaction kinetics

- for transition $X(t) \rightarrow X(t + dt)$, dt is the time to earliest reaction event
- dt is sampled as minimal time over all n reactions:

$$dt \sim Exp(\chi(X)) \qquad \chi(m) = \sum_{i=1}^{n} \chi_{R_i}(X)$$

- reaction R_i is chosen with probability: $P(R_i) = \frac{\chi_{R_i}(X)}{\chi(X)}$
- formally this comes from the property of exponential distribution
- the model behind is continuous-time Markov process

Gillespie direct method (SSA)

Output: a single trajectory realizing the grand probability distribution

1. initialize $t = 0$, $X(0)$
2. compute $\chi_{R_i}(X)\ \forall i \in \{1, ..., n\}$
3. compute $\chi(X) \equiv \sum_{i=1}^{n} \chi_{R_i}(X)$
4. sample $\tau \in Exp(\chi(X))$
5. $t := t + \tau$
6. choose reaction R_i with probability $\frac{\chi_{R_i}(X)}{\chi(X)}$
7. update: $X(t) = X(t - \tau) + u_{R_i}$
8. while $t < T_{max}$ go to (2)

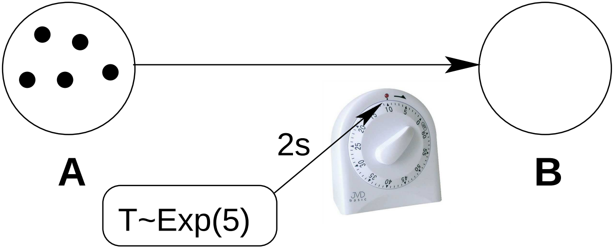
Example

Consider reaction: $A \rightarrow B$

$$\begin{pmatrix}5\\0\end{pmatrix}$$

Example

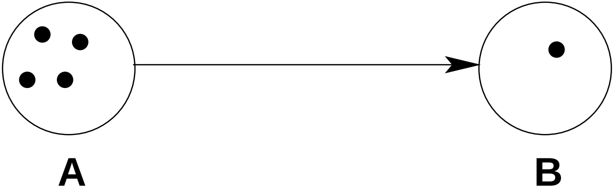
Consider reaction: $A \rightarrow B$



$$\begin{pmatrix} 5 \\ 0 \end{pmatrix} \rightarrow$$

Example

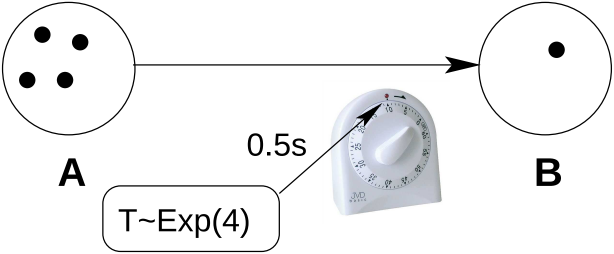
Consider reaction: $A \rightarrow B$



$$\begin{pmatrix}5\\0\end{pmatrix} \rightarrow (2s) \rightarrow \begin{pmatrix}4\\1\end{pmatrix}$$

Example

Consider reaction: $A \rightarrow B$



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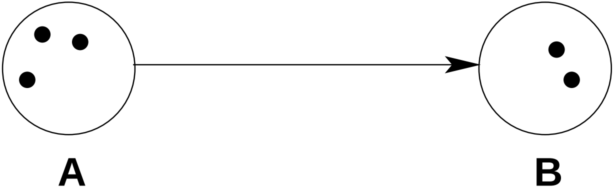
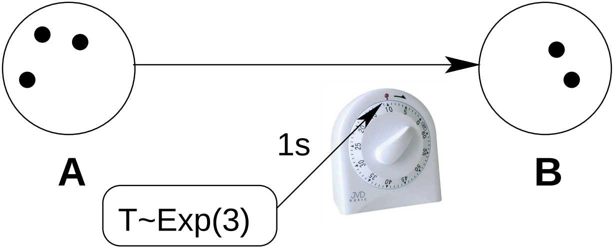


$$\begin{pmatrix}5\\0\end{pmatrix} \rightarrow (2s) \rightarrow \begin{pmatrix}4\\1\end{pmatrix} \rightarrow (0.5s) \rightarrow \begin{pmatrix}3\\2\end{pmatrix}$$

Example

Consider reaction: $A \rightarrow B$



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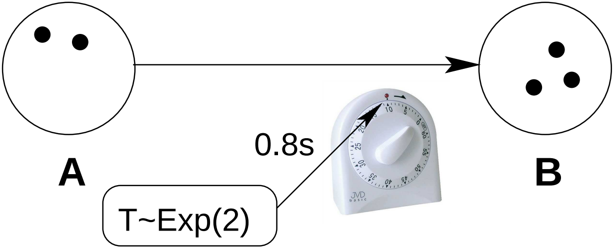
Example

Consider reaction: $A \rightarrow B$



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Example

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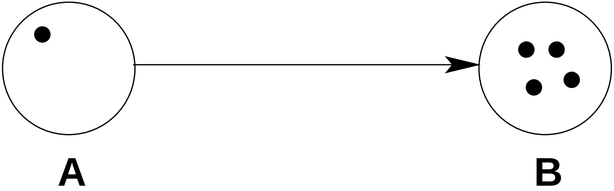
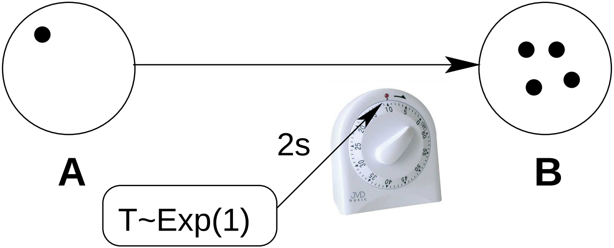


$$\begin{pmatrix}5\\0\end{pmatrix} \rightarrow (2s) \rightarrow \begin{pmatrix}4\\1\end{pmatrix} \rightarrow (0.5s) \rightarrow \begin{pmatrix}3\\2\end{pmatrix} \rightarrow (1s) \rightarrow \begin{pmatrix}2\\3\end{pmatrix} \rightarrow (0.8s) \rightarrow \begin{pmatrix}1\\4\end{pmatrix}$$

Example

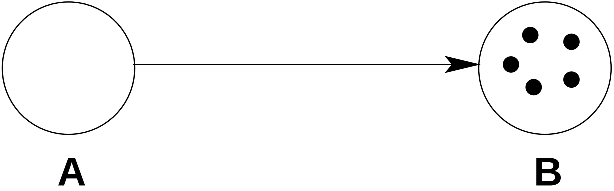
Consider reaction: $A \to B$



$$\begin{pmatrix}5\\0\end{pmatrix} \to (2s) \to \begin{pmatrix}4\\1\end{pmatrix} \to (0.5s) \to \begin{pmatrix}3\\2\end{pmatrix} \to (1s) \to \begin{pmatrix}2\\3\end{pmatrix} \to (0.8s) \to \begin{pmatrix}1\\4\end{pmatrix} \to$$

Example

Consider reaction: $A \rightarrow B$



$$\begin{pmatrix}5\\0\end{pmatrix} \rightarrow (2s) \rightarrow \begin{pmatrix}4\\1\end{pmatrix} \rightarrow (0.5s) \rightarrow \begin{pmatrix}3\\2\end{pmatrix} \rightarrow (1s) \rightarrow \begin{pmatrix}2\\3\end{pmatrix} \rightarrow$$

$$(0.8s) \rightarrow \begin{pmatrix}1\\4\end{pmatrix} \rightarrow (2s) \rightarrow \begin{pmatrix}0\\5\end{pmatrix}$$

Example

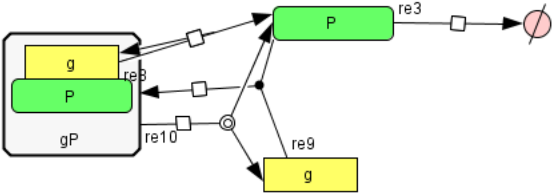
Consider reaction: $A \rightarrow B$

$$\begin{pmatrix}5\\0\end{pmatrix} \rightarrow (2s) \rightarrow \begin{pmatrix}4\\1\end{pmatrix} \rightarrow (0.5s) \rightarrow \begin{pmatrix}3\\2\end{pmatrix} \rightarrow (1s) \rightarrow \begin{pmatrix}2\\3\end{pmatrix} \rightarrow$$

$$(0.8s) \rightarrow \begin{pmatrix}1\\4\end{pmatrix} \rightarrow (2s) \rightarrow \begin{pmatrix}0\\5\end{pmatrix}$$

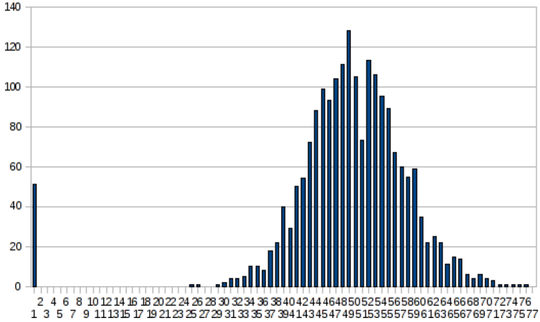
- hazard function considered: $\chi(X) = 1 \cdot X_A$

Example – positive autoregulation of gene expression



$$
\begin{aligned}
R_1 &: \ P + g \longrightarrow gP \\
R_2 &: \ gP \longrightarrow g + P \\
R_3 &: \ gP \longrightarrow gP + P \\
R_4 &: \ P \longrightarrow
\end{aligned}
$$

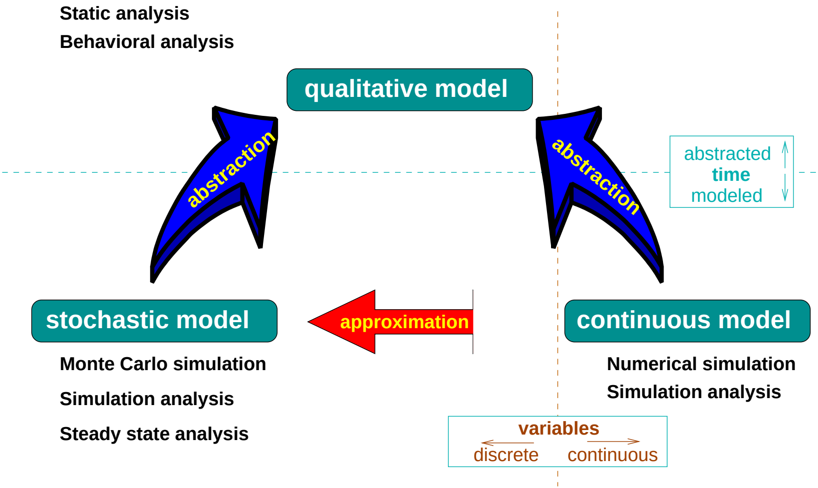
Example – positive autoregulation of gene expression



- initial settings: $g(0) = 5, P(0) = 2, gP(0) = 0;$ $c_1 = c_2 = 1, c_3 = 0.1, c_4 = 0.01$
- distribution in $t = 1000$ for 2000 simulations

Petri Net Analysis Framework

Stochastic Model



Static analysis

Behavioral analysis

qualitative model

stochastic model

continuous model

Monte Carlo simulation

Simulation analysis

Steady state analysis

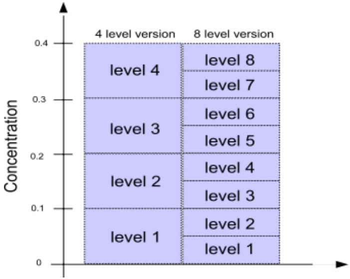
Numerical simulation

Simulation analysis

Discrete Approximation

- notion of Petri Net token
- token represent molecule or a certain concentration level
    - suppose bounded concentration for all substrates: $\langle 0, max) \subset \mathbb{R}$
    - uniform partitioning into N intervals:

$$0, (0, 1 \cdot \frac{max}{N}\rangle, (1 \cdot \frac{max}{N}, 2 \cdot \frac{max}{N}\rangle, \ldots, (N - 1 \cdot \frac{max}{N}, N \cdot \frac{max}{N}\rangle$$



Discrete Approximation

Stochastic vs. continuous model

- substance concentration $[M]$:

  $$c = \frac{n}{V}$$

  where n substance quantity $[mol]$, V solution volume $[l]$

- expressed in terms of Avogadro constant (number of particles in 1 mol):

  $$c = \frac{N}{N_A \cdot V}$$

  where N_A Avogadro constant $[mol^{-1}]$, V solution volume $[l]$ and N number of molecules.

- transformation factor:

  $$\gamma = N_A \cdot V \; [mol^{-1} l] \Rightarrow N = c \cdot \gamma, \; c = \frac{N}{\gamma}$$

Discrete Approximation

Stochastic vs. continuous model

A continuous Petri net $\mathcal{N} = \langle S, R, f, v, m(0) \rangle$ can be transformed to a stochastic Petri net $\mathcal{N} = \langle S, R, f, v', m(0) \rangle$:

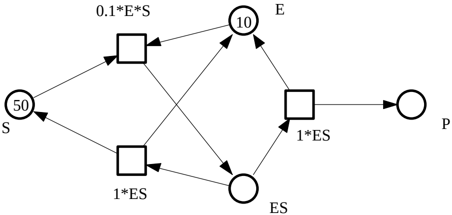
- $m(0) : S \rightarrow \mathbb{N}_0$ is *initial marking*
- v' assigns each transition a *hazard*:

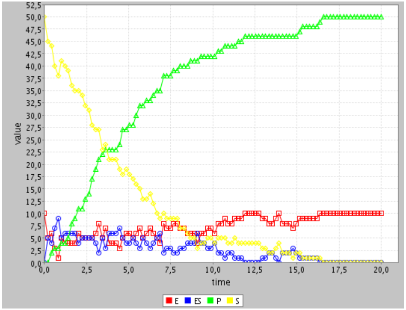
reaction type $r \in R$	$v(r) \rightarrow v'(r)$ transformation
$\rightarrow A$	$v'(r) = v(r)$
$A \rightarrow B$	$v'(r) = v(r)$
$A + B \rightarrow AB$	$v'(r) = \frac{v(r)}{\gamma}$
$A + A \rightarrow AA$	$v'(r) = \frac{2v(r)}{\gamma}$

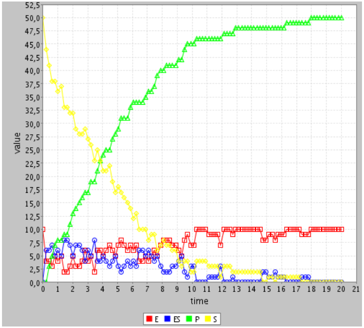
L. Cardelli (2008), "From Processes to ODEs by Chemistry". In 5th International Conference on Theoretical Computer Science, pages 261-281. DOI:10.1007/978-0-387-09680-3_18

Stochastic Petri Nets

Michaelis-Menten Stochastic Mass Action Kinetics Example





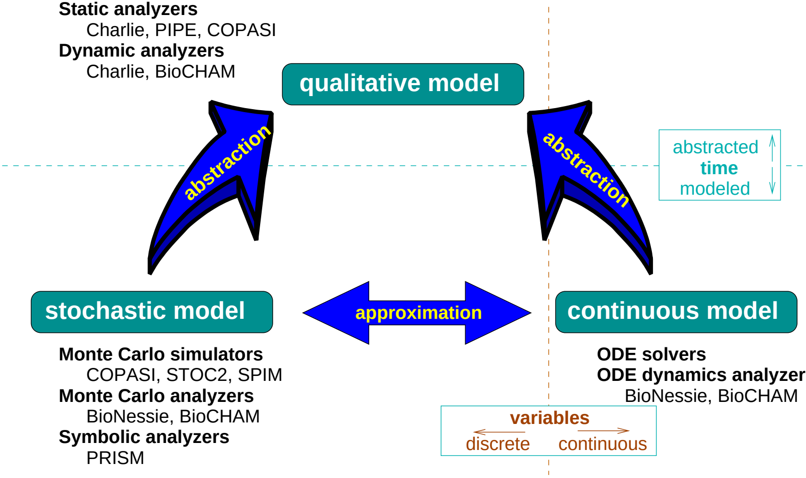


Tool Support

- Monte Carlo simulation
  - Dizzy, COPASI, SPiM
- simulation analysis
  - BioNessie (statistical model checking)
  - BioCHAM
- symbolic analysis
  - PRISM (strong transient and steady state analysis)

Petri Net Analysis Framework

Tool Support Overview



Static analyzers
Charlie, PIPE, COPASI
Dynamic analyzers
Charlie, BioCHAM

qualitative model

stochastic model

Monte Carlo simulators
COPASI, STOC2, SPIM
Monte Carlo analyzers
BioNessie, BioCHAM
Symbolic analyzers
PRISM

continuous model

ODE solvers
ODE dynamics analyzers
BioNessie, BioCHAM

Literature

- M. Heiner, D. Gilbert & R. Donaldson. *Petri Nets for Systems and Synthetic Biology.* SFM 2008: 215-264
- D. Wilkinson. *Stochastic Modelling for Systems Biology, second edition.*, Chapman & Hall/CRC, 2011.
- D. T. Gillespie. Exact Stochastic Simulation of Coupled Chemical Reactions. In Journal of Physical Chemistry, volume 81, No. 25, pages 2340-2381. 1977

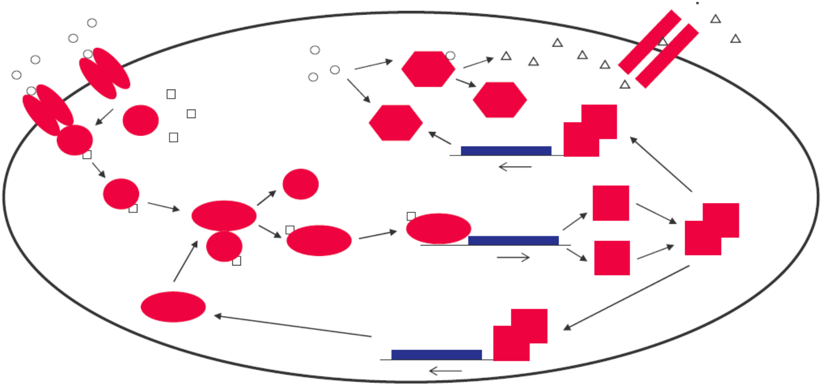
Obsah

Continuous mass action

Stochastic mass action

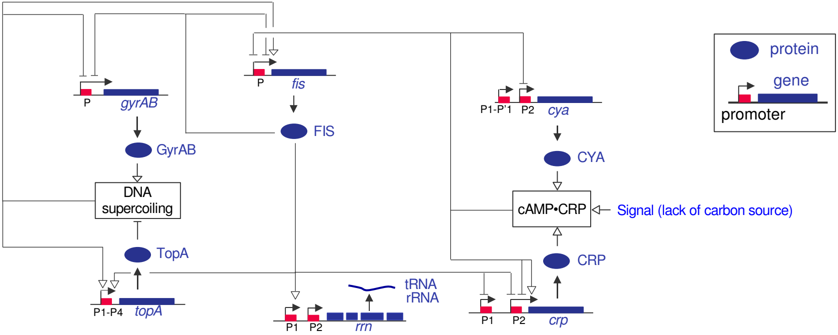
Beyond elementary reaction kinetics

Regulatory Networks of Cellular Processes

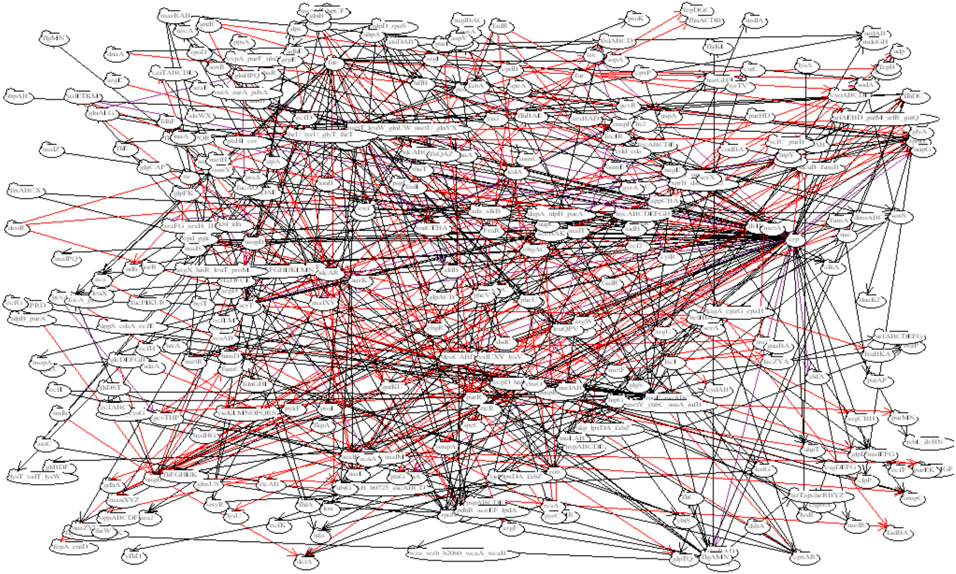


- identify substances (proteins, genes)
- identify interactions (transcriptory activation, repression – do we know reactions behind?)

Example of a gene regulatory network



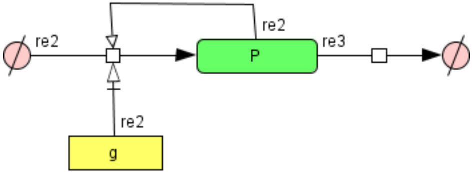
Gene regulatory network of E. Coli



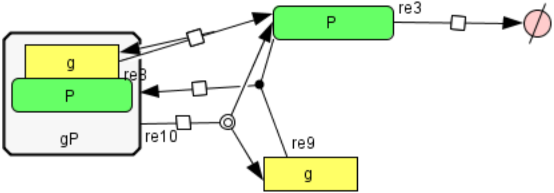
Rational Kinetics

- in continuous framework the regulatory interactions are modeled by specific rate functions
- approximation makes several limiting assumptions
- enzyme kinetics
    - Michaelis-Menten rate function
    - substrate concentration must be higher then enzyme concentration
- Hill kinetics
    - gene regulatory interactions
    - S-functions for activation/repression
    - cooperativity of transcription factors increases steepness
    - can be rigorously abstracted in discrete domain

Example – positive autoregulation of gene expression

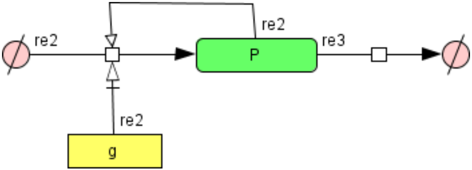


$$\rightarrow P; P$$
$$P \rightarrow$$



$$P + g \rightarrow gP$$
$$gP \rightarrow g + P$$
$$gP \rightarrow gP + P$$
$$P \rightarrow$$

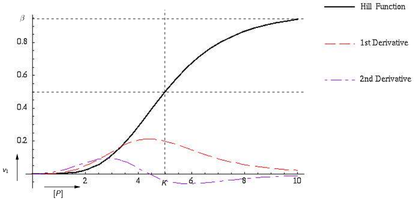
Example – positive autoregulation of gene expression



$$\to P; P$$
$$P \to$$

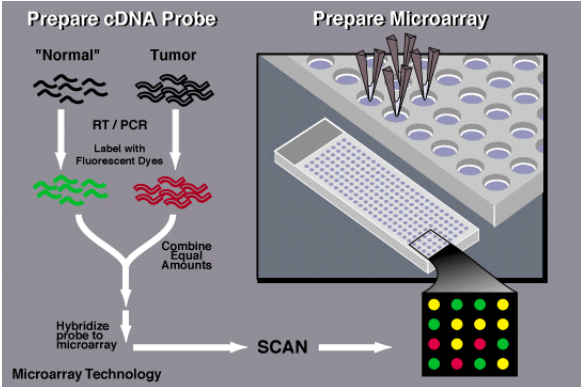
$$v_1 = \beta \cdot \frac{P^n}{K^n + P^n}$$
$$v_2 = \gamma \cdot P$$

$$\frac{dP}{dt} = v_1 - v_2$$

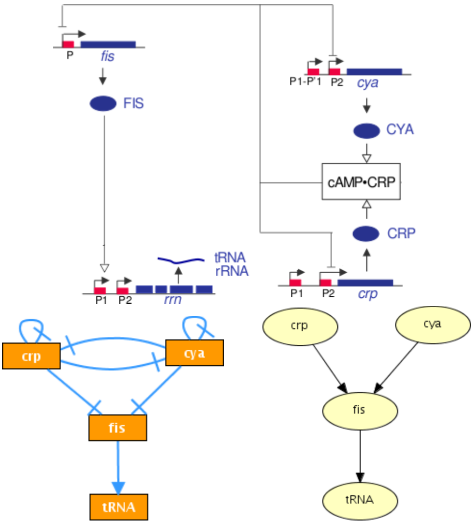


Identification of regulatory dynamics

- systems measurement of transcriptome (mRNA concentration) is imprecise and discrete!
- interactions can be partially identified by analysis of transcriptor factor binding sites (e.g., TRANSFAC)
- microarray experiments can be reversed engineered

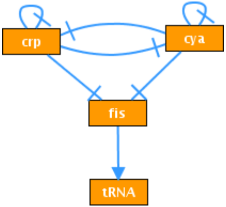


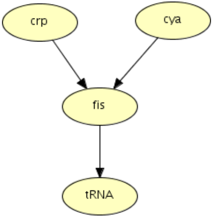
Identification of regulatory dynamics



Identification of regulatory dynamics

Boolean and Bayesian networks

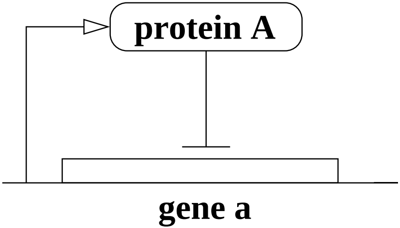




$$\begin{aligned} crp(t+1) &= \neg crp(t) \wedge \neg cya(t) \\ cya(t+1) &= \neg cya(t) \wedge \neg crp(t) \\ fis(t+1) &= \neg crp(t) \wedge \neg cya(t) \\ tRNA(t+1) &= fis(t) \end{aligned}$$

$$\begin{gathered} P(X_{crp}) \\ P(X_{cya}) \\ P(X_{fis} | X_{crp}, X_{cya}) \\ P(X_{tRNA} | X_{fis}) \end{gathered}$$

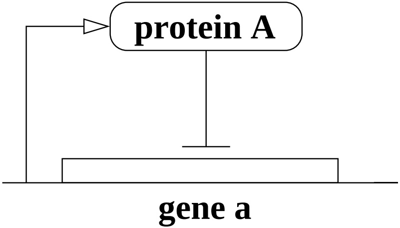
Model example – autoregulation

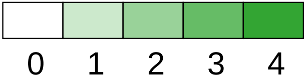


protein A

gene a

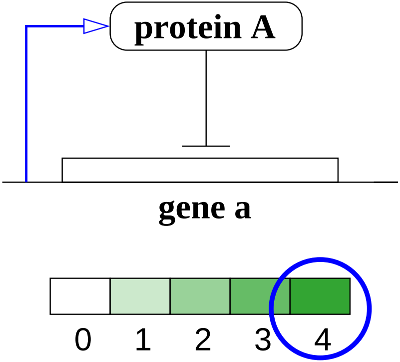
Model example – autoregulation





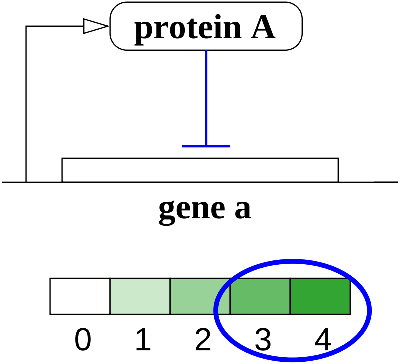
- identification of discrete expression levels

Model example – autoregulation



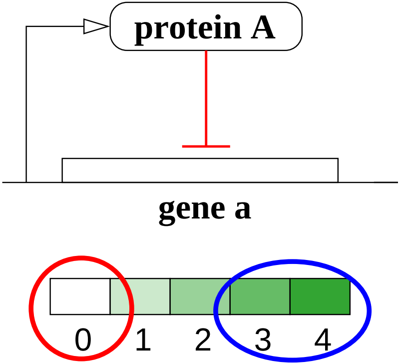
- spontaneous (basal) transcription: $A \longrightarrow 4$

Model example – autoregulation



- range of regulatory activity ($A \in \{3, 4\} \Rightarrow$ regulation active)

Model example – autoregulation



- target level $(A \in \{3,4\} \Rightarrow A \to 0)$

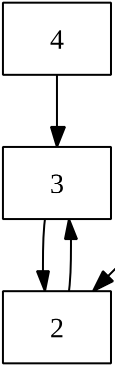
State space – autoregulation

- state transition system $\langle S, T, S_0 \rangle$
  - S state set, $S \equiv \{0, 1, 2, 3, 4\}$
  - $S_0 \subseteq S$ initial state set
  - $T \subseteq S \times S$ transition function:

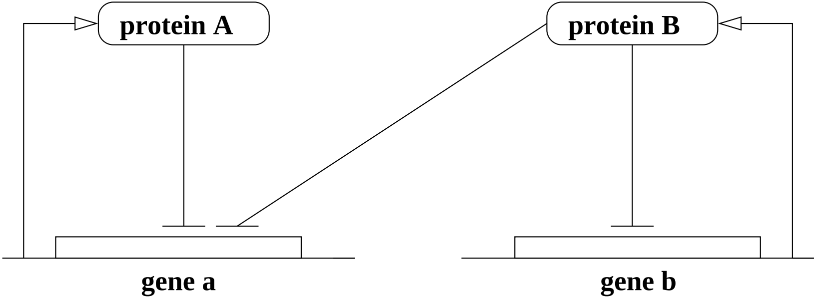
source state	active regulation	target state
0	$\emptyset; [A \rightarrow 4]$	1
1	$\emptyset; [A \rightarrow 4]$	2
2	$\emptyset; [A \rightarrow 4]$	3
3	$A \rightarrow^{-} A; [A \rightarrow 0]$	2
4	$A \rightarrow^{-} A; [A \rightarrow 0]$	3

State space – autoregulation

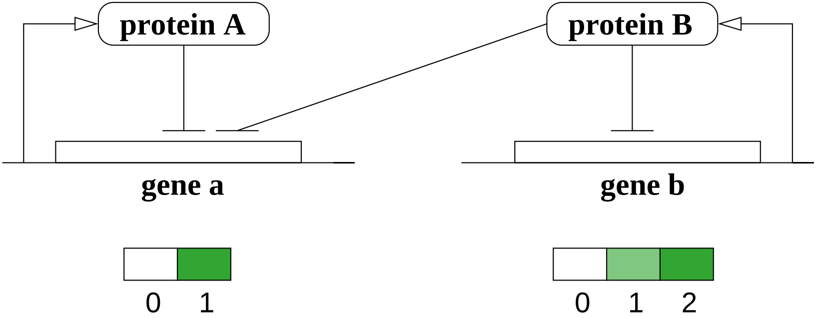
state transition system for negative autoregulation $\langle S, T, S_0 = S \rangle$:



Combined regulation

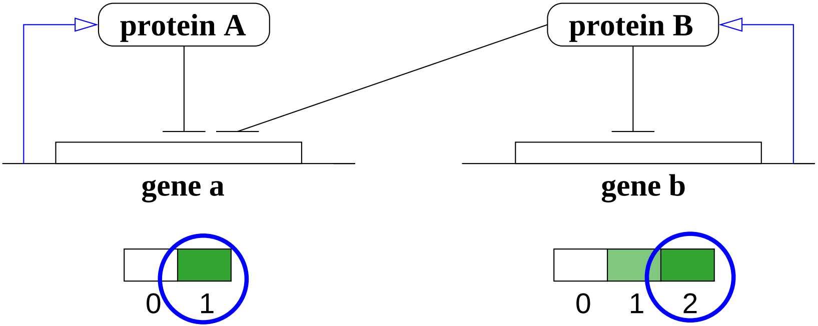


Discrete characteristics of dynamics



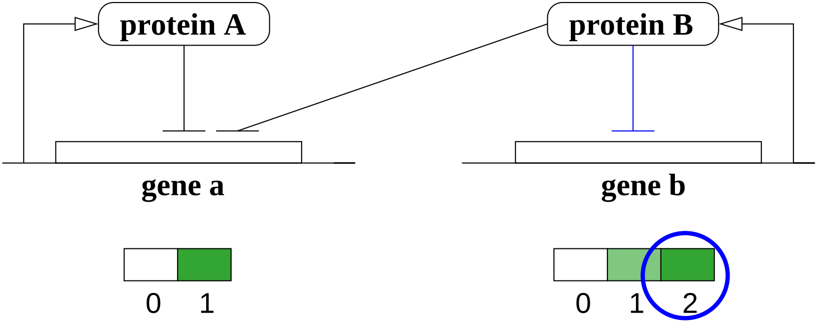
- identification of dicrete levels of expression

Discrete characteristics of dynamics



- spontaneous (basal) transcription: $A \rightarrow 1$, $B \rightarrow 2$

Characteristics of regulation



protein A

protein B

gene a

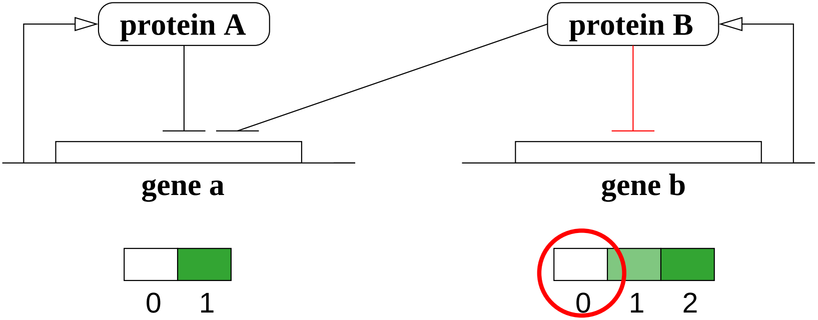
gene b

0 1

0 1 2

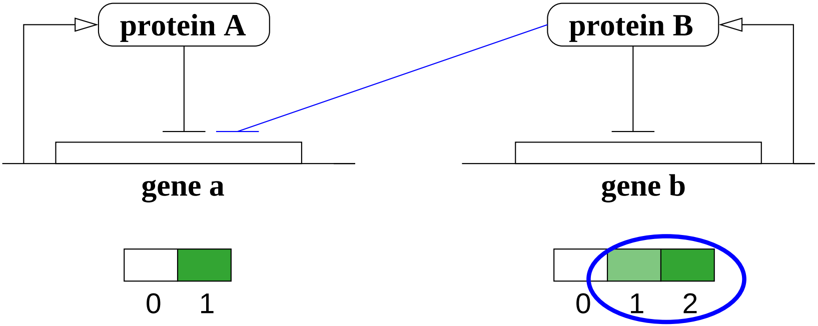
- range of regulatory activity $B \rightarrow^{-} B$ ($B = 2 \Rightarrow$ regulation active)

Characteristics of regulation



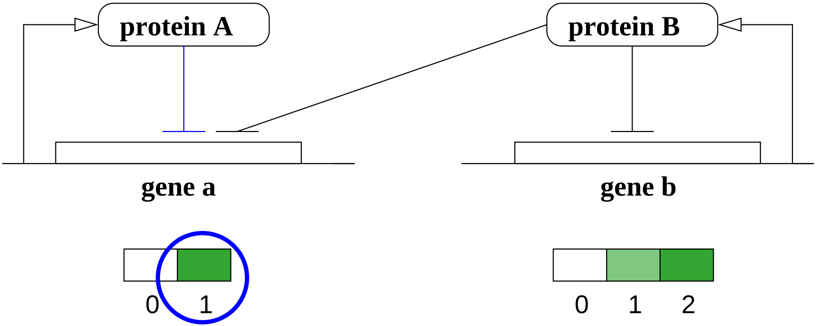
- target level $B \rightarrow^{-} B$ $(B = 2 \Rightarrow B \rightarrow 0)$

Characteristics of regulation – input function



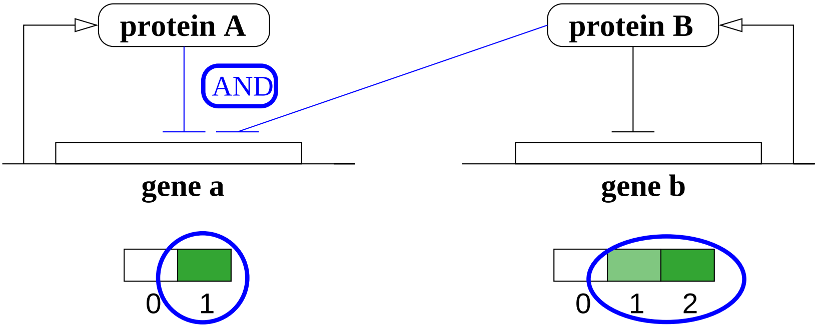
- range of regulatory activity $B \rightarrow^{-} A$ ($B \in \{1, 2\} \Rightarrow$ reg. active)

Characteristics of regulation – input function



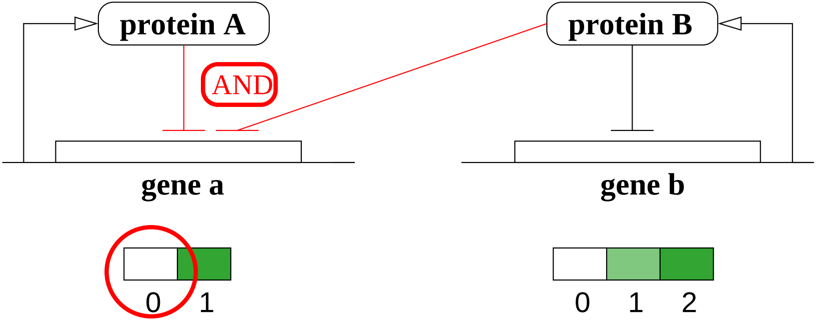
- range of regulatory activity $A \rightarrow^{-} A$ $(A = 1 \Rightarrow$ reg. active)

Characteristics of regulation – input function



- AND-combined regulation $A \rightarrow^- A \wedge B \rightarrow^- A$:
  $A = 1 \wedge B \in \{1, 2\} \Rightarrow$ regulation active

Characteristics of regulation – input function



- target levels of combined regulation $A \rightarrow^{-} A \wedge B \rightarrow^{-} A$: $A = 1 \wedge B \in \{1, 2\} \Rightarrow A \rightarrow 0$

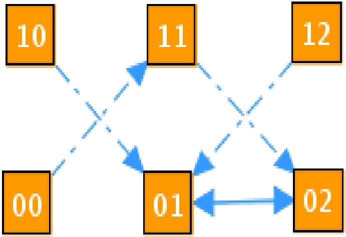
State space – synchronnous semantics

- state transition system $\langle S, T, S_0 \rangle$
  - $S \equiv \{0,1\} \times \{0,1,2\}$
  - $S_0 \subseteq S$, we consider $S_0 = S$
  - $T \subseteq S \times S$ transition function:

source state	active regulation	target state
$[0,0]$	$\emptyset$; $[A \rightarrow 1, B \rightarrow 2]$	$[1,1]$
$[0,1]$	$B \rightarrow^{-} A$; $[A \rightarrow 0, B \rightarrow 2]$	$[0,2]$
$[0,2]$	$B \rightarrow^{-} B \wedge B \rightarrow^{-} A$; $[A \rightarrow 0, B \rightarrow 0]$	$[0,1]$
$[1,0]$	$A \rightarrow^{-} A$; $[A \rightarrow 0, B \rightarrow 2]$	$[0,1]$
$[1,1]$	$A \rightarrow^{-} A \wedge B \rightarrow^{-} A$; $[A \rightarrow 0, B \rightarrow 2]$	$[0,2]$
$[1,2]$	$A \rightarrow^{-} A \wedge B \rightarrow^{-} A \wedge B \rightarrow^{-} B$; $[A \rightarrow 0, B \rightarrow 0]$	$[0,1]$

State space – synchronnous semantics

state transition system $\langle S, T, S_0 = S \rangle$:



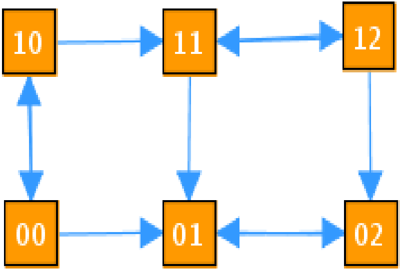
State space – asynchronnous semantics

- state transition system $\langle S, T, S_0 \rangle$
    - $S \equiv \{0,1\} \times \{0,1,2\}$
    - $S_0 \subseteq S$, we consider $S_0 = S$
    - $T \subseteq S \times S$ transition function:

source state	active regulation	target states
$[0,0]$	$\emptyset$; $[A \to 1, B \to 2]$	$[1,0]$, $[0,1]$
$[0,1]$	$B \to^{-} A$; $[A \to 0, B \to 2]$	$[0,2]$
$[0,2]$	$B \to^{-} B \wedge B \to^{-} A$; $[A \to 0, B \to 0]$	$[0,1]$
$[1,0]$	$A \to^{-} A$; $[A \to 0, B \to 2]$	$[0,0]$, $[1,1]$
$[1,1]$	$A \to^{-} A \wedge B \to^{-} A$; $[A \to 0, B \to 2]$	$[0,1]$, $[1,2]$
$[1,2]$	$A \to^{-} A \wedge B \to^{-} A \wedge B \to^{-} B$; $[A \to 0, B \to 0]$	$[0,2]$, $[1,1]$

State space – asynchronnous semantics

state transition system $\langle S, T, S_0 = S \rangle$:



Properties of discrete semantics

- synchronous semantics
    - effect of active regulations is realized in terms of a single event
    - strong approximation leading to deterministic state transition system
- asynchronnous semantics
    - effect of active regulations is realized for each gene/protein individually in terms of single events
    - nondeterminism models all possible serializations (so called interleaving)
    - approximation is rather conservative

Free Tool Support

- Gene Interaction Network simulation (GINsim)
  `http://gin.univ-mrs.fr/GINsim/accueil.html`
- asynchronous and synchronous simulation
  - allows to get rough understanding of regulatory logic
  - allows to identify potential steady states of regulation
  - purely qualitative modelling and analysis
- directly allow application of a large set of computer scientific tools
  - graph algorithms for state space graph analysis
  - model checking
- Genetic Network Analyzer (GNA)
  http://www.genostar.com/en/genostar-software/gnasim.html
  - rigorous relation to continuous model

Literature

- Thomas, R. *Regulatory networks seen as asynchronous automata : a logical description.* J. Theor. Biol. 153 ,(1991) 1-23.
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