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.

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 $X(t) \to X(t+dt)$ 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
$\to A$	$v_R(t) = k$	$\frac{dA}{dt} = -v_R$
$A \to B$	$v_R(t) = k \cdot [A](t)$	$\frac{dA}{dt} = -v_R,\ \frac{dB}{dt} = v_R$
$A + B \to AB$	$v_R(t) = k \cdot [A](t) \cdot [B](t)$	$\frac{dA}{dt} = \frac{dB}{dt} = -v_R,\ \frac{dAB}{dt} = v_R$
$2A \to AA$	$v_R(t) = k \cdot [A]^2$	$\frac{dA}{dt} = -2v_R,\ \frac{dAA}{dt} = v_R$

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

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

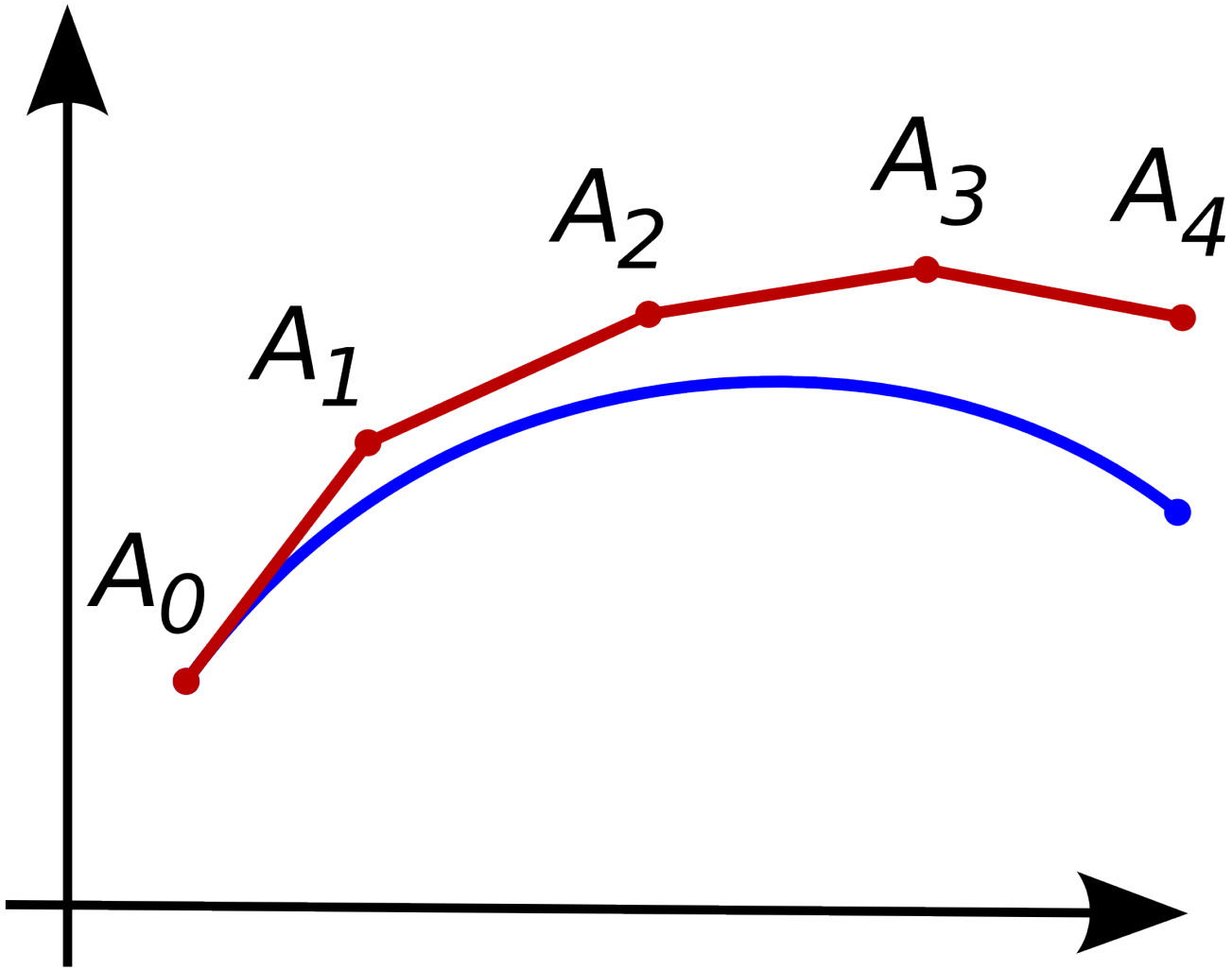
$$\frac{d[S]}{dt} = -k_1[E][S] + k_2[ES]$$

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

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

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

Euler method



Euler method

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

$$y'(t) = f(t, y(t))$$
$$y(0) = y_0$$

- exact solution $\varphi(t)$:

$$\varphi'(t) = f(t, \varphi(t))$$
$$\varphi(0) = y_0$$

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

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

Euler method

Exact solution $\varphi(t)$ satisfies:

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

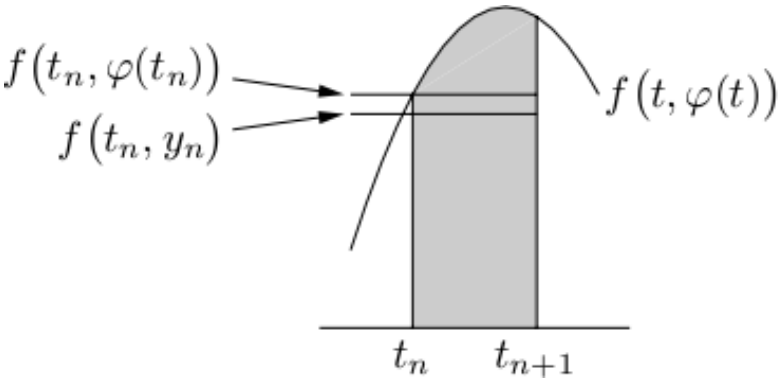
Numerical approximation:

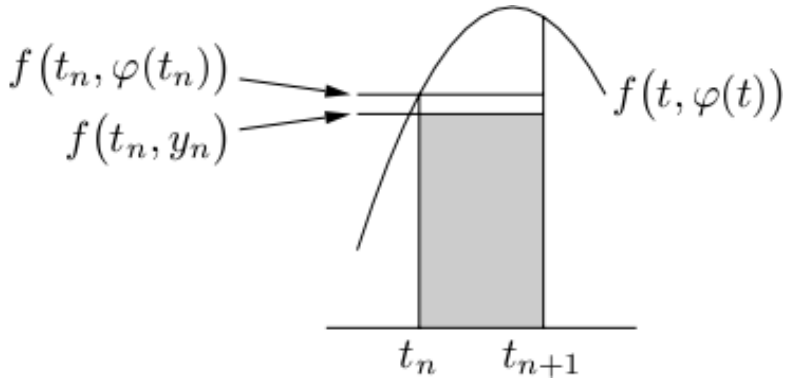
$$y_{n+1} = y_n + \sigma$$

where

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

Euler method I



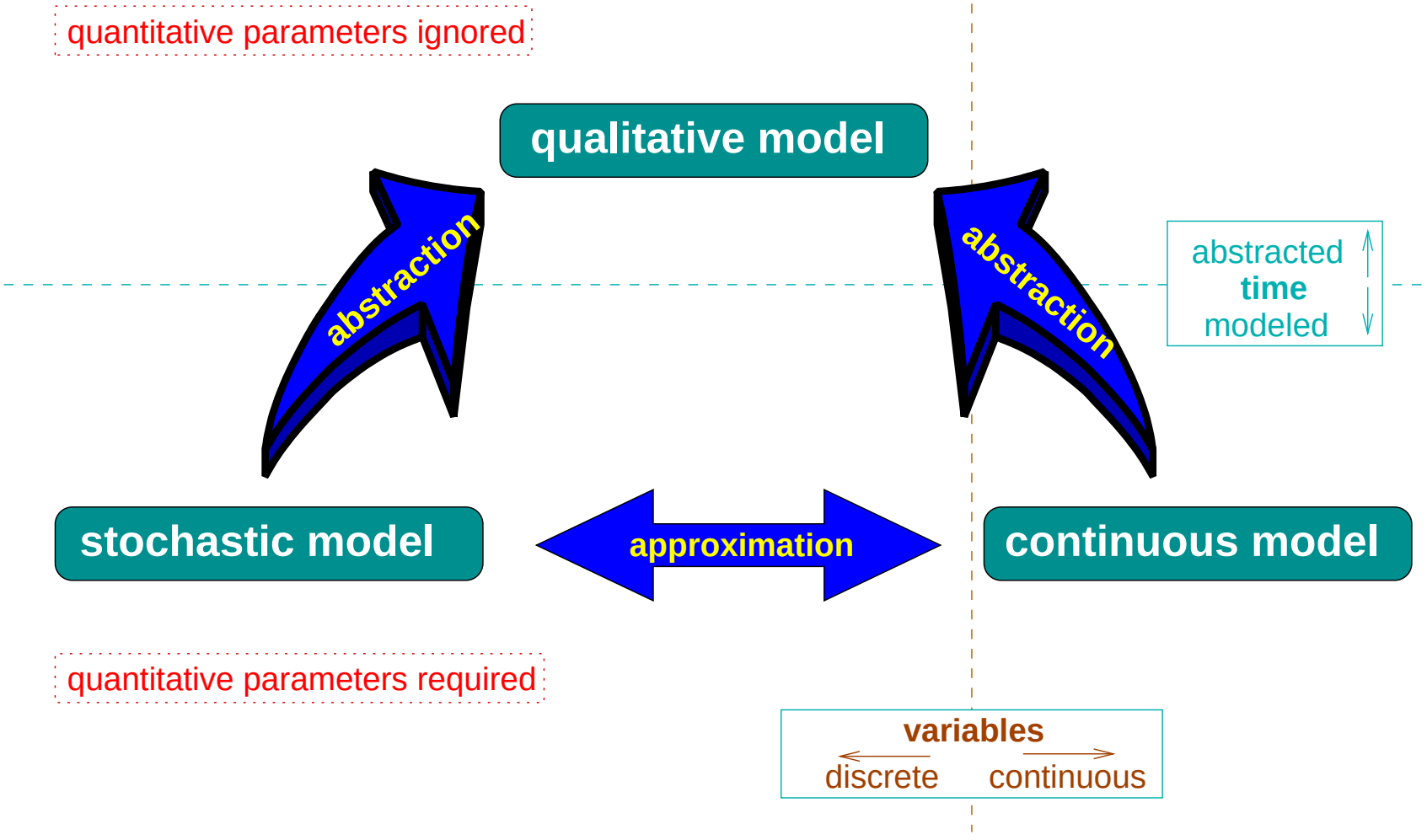


$$\frac{dy}{dt} = f(t, y)$$

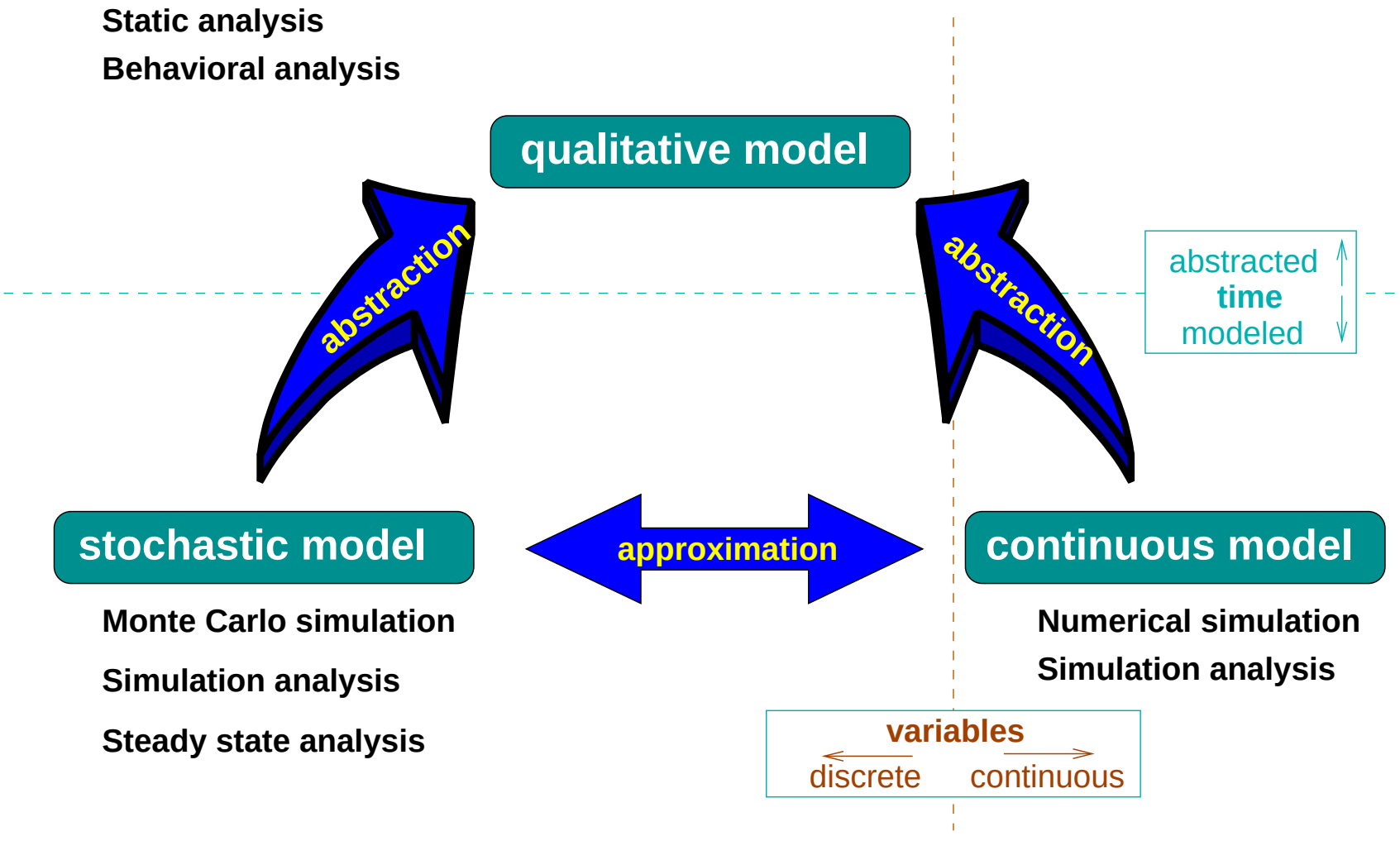
$$y_{n+1} = y_n + \Delta t \cdot f(t_n, y_n)$$

1. `init` t_0, y_0, Δt, 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`

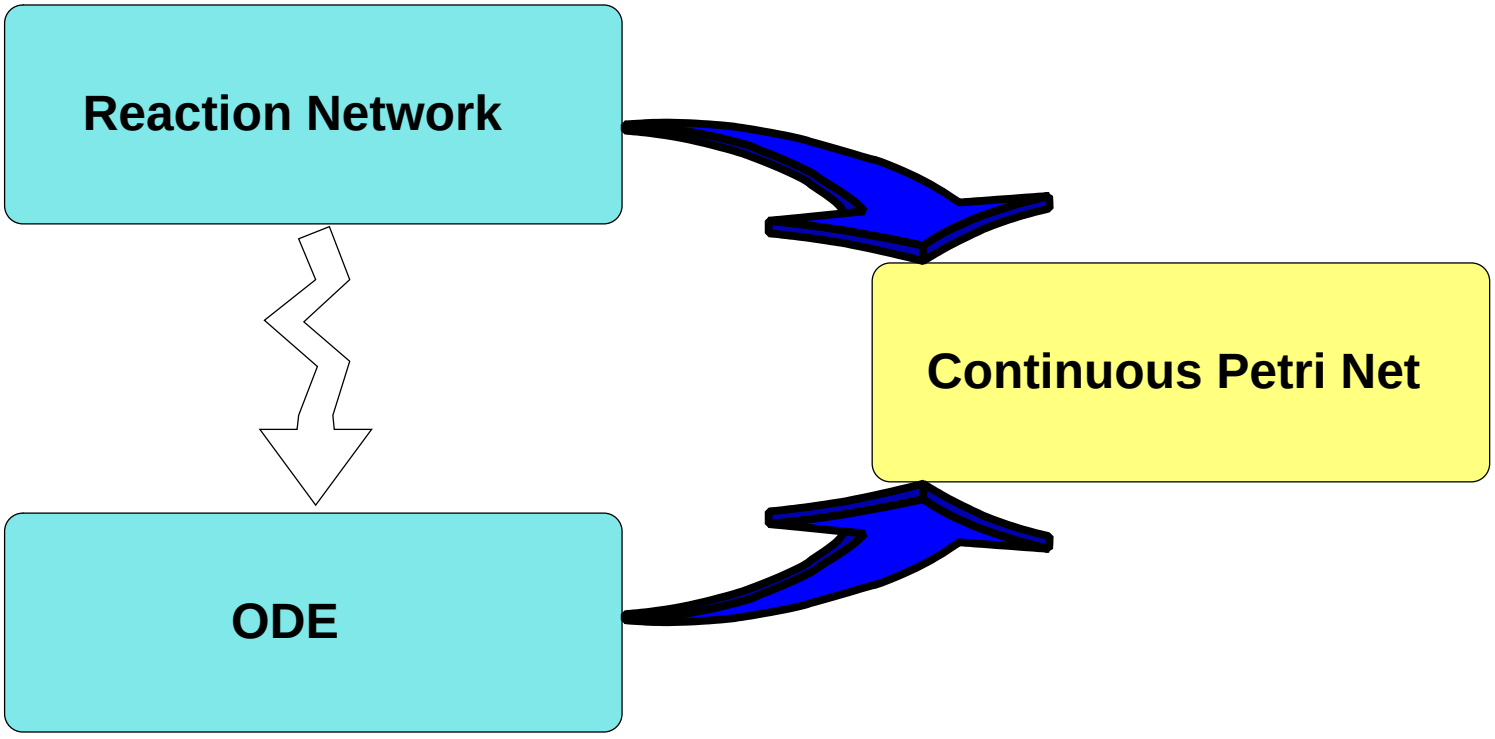
Petri Net Analysis Framework



Petri Net Analysis Framework



Petri Net Representation of Models



- 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),
- $f : ((P \times T) \cup (T \times P)) \to \mathbb{N}_0$ 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 $h_r : \mathbb{R}^{|\bullet r|} \to \mathbb{R}$
  - v represents transition (reaction) rate
- $m(0) : S \to \mathbb{R}_0^+$ 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):

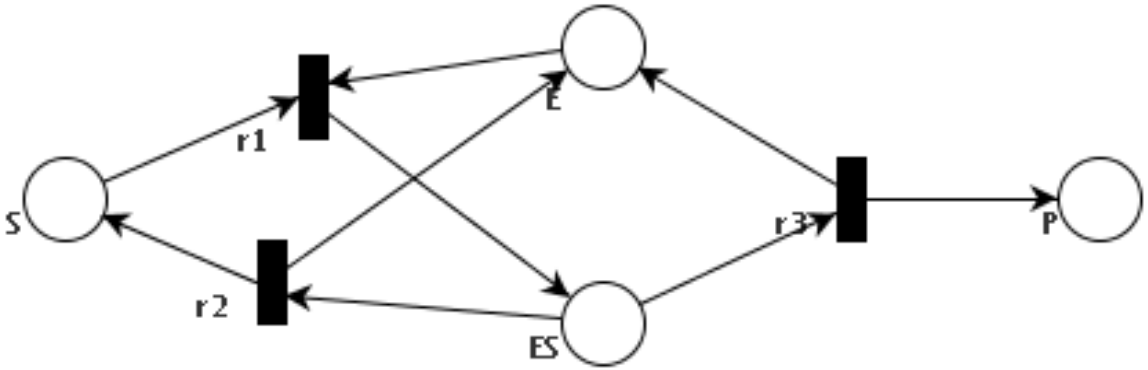
- in Petri net terminology evaluation of places is called *marking* and represented as an n-dimensional vector $m \in \mathbb{R}^n$
- marking evolves in time: $m(t)$

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



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

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

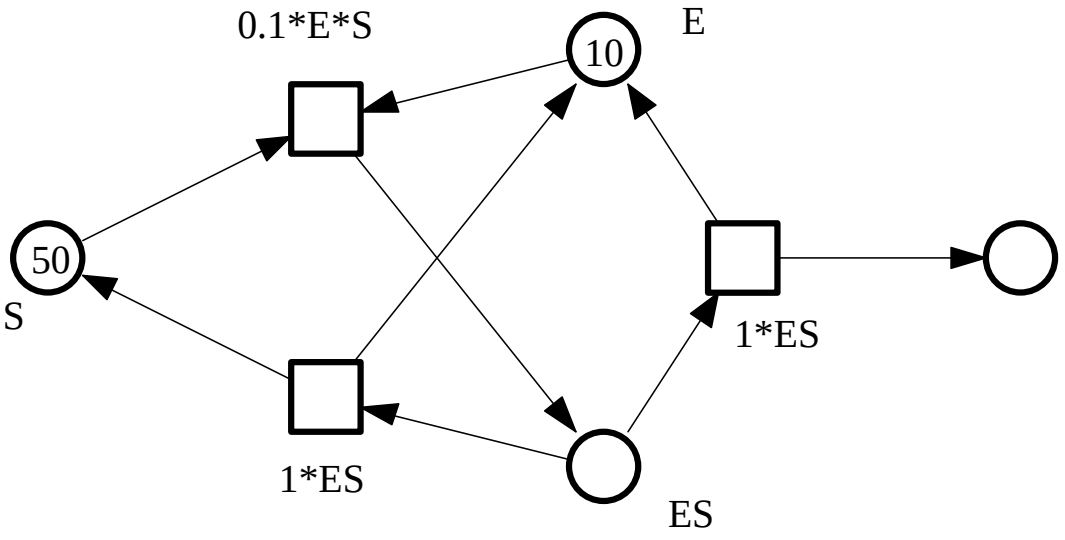
$$\frac{dm_E}{dt} = v(r_2) + v(r_3) - v(r_1)$$

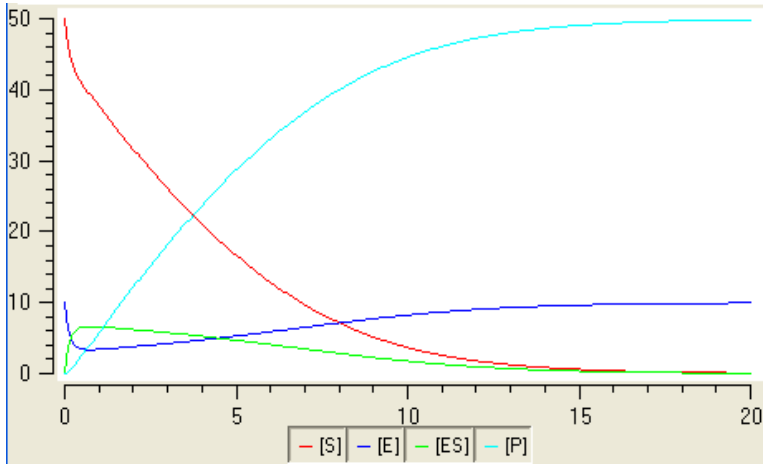
$$\frac{dm_{ES}}{dt} = v(r_1) - v(r_2) - v(r_3)$$

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

Continuous Petri Nets

Michaelis-Menten Mass Action Kinetics Example





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

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

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

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

$$k_1 = 0.1\,[M^{-1}s^{-1}]$$
$$k_2 = 1\,[s^{-1}]$$
$$k_3 = 1\,[s^{-1}]$$

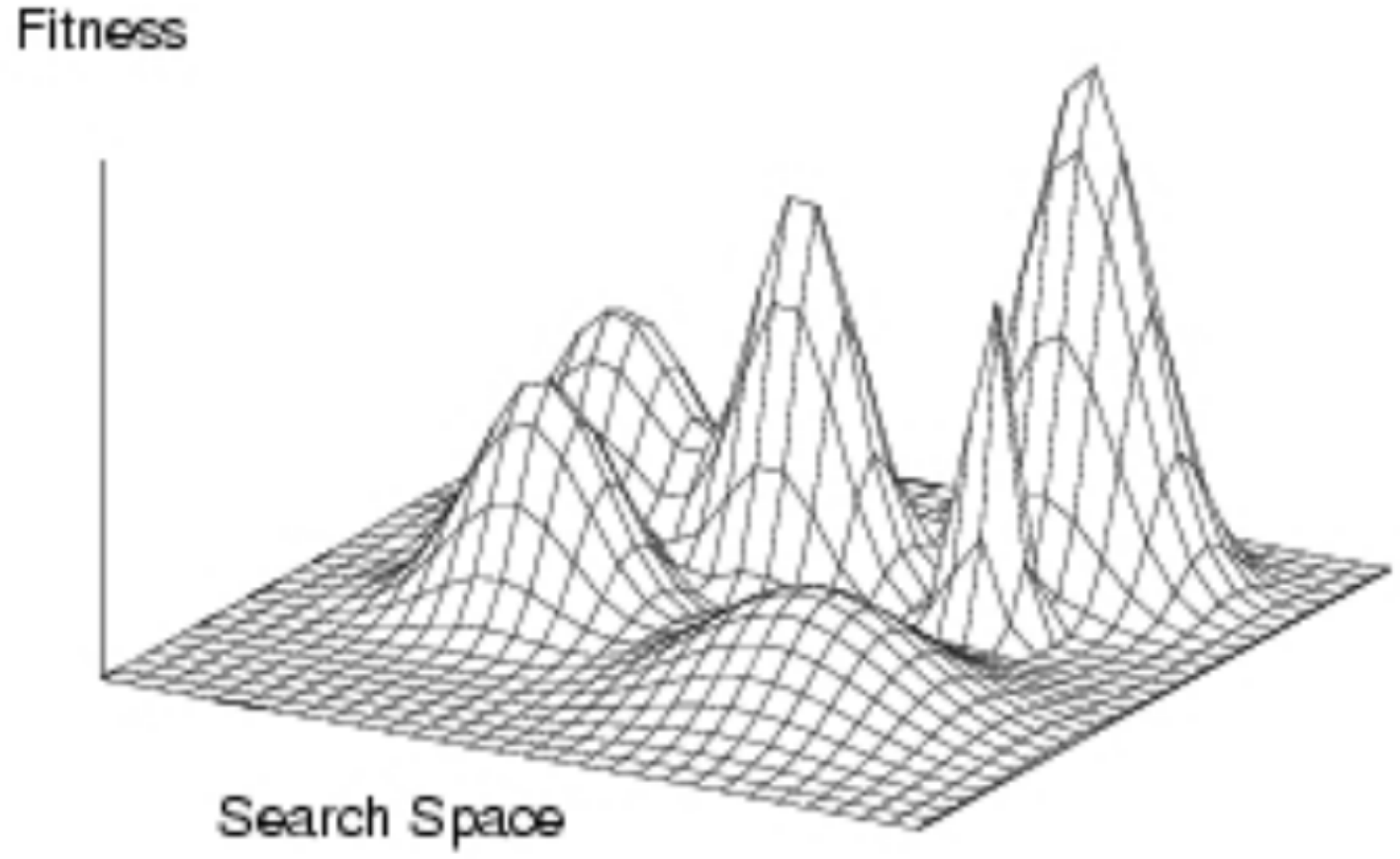
Parameter Estimation Problem

- 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

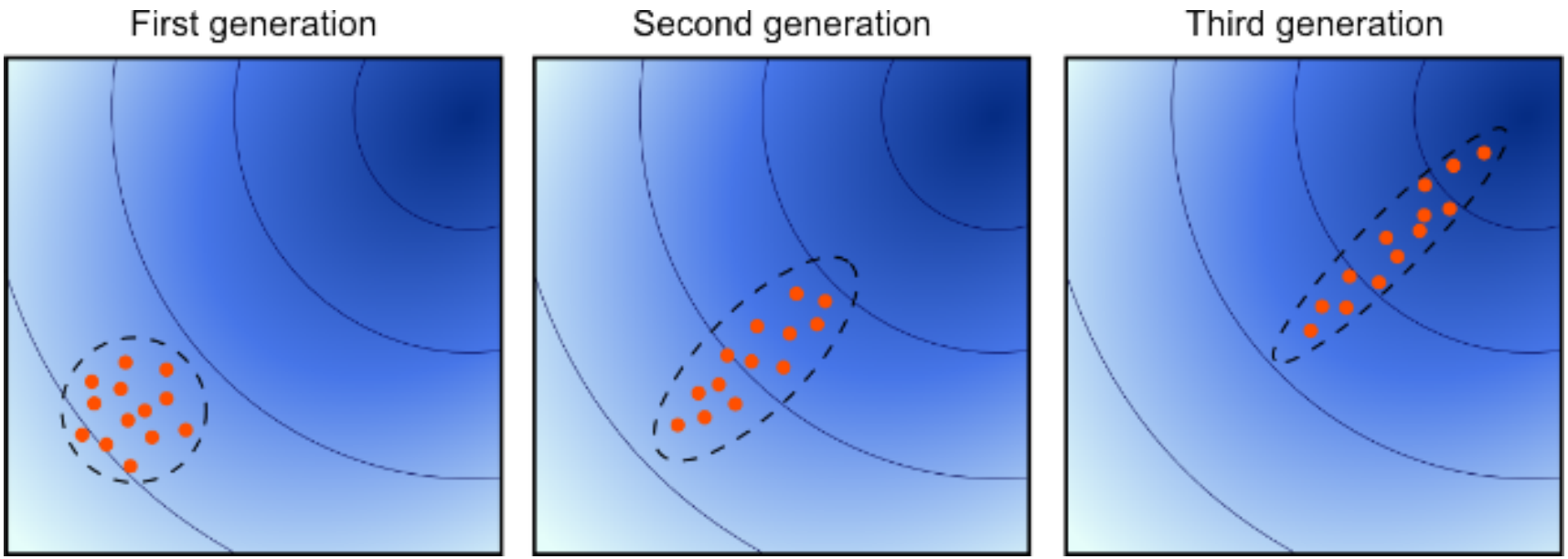
- parameter estimation is solved as optimization problem w.r.t. measured data
- the goal is to minimize average deviation of model from data
- so-called least squares method
- we seek for global minima
- many heuristics for optimization procedure, many algorithms

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
  - CellIIIustartor – 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

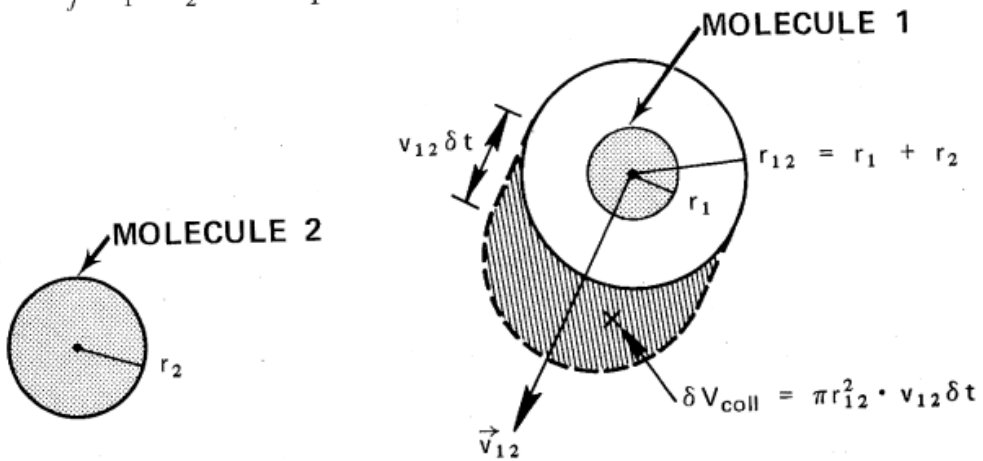
Stochastic model of reaction kinetics

- 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, $X = \langle X_1, ..., X_n \rangle$ 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:

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

  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:

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

  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:

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

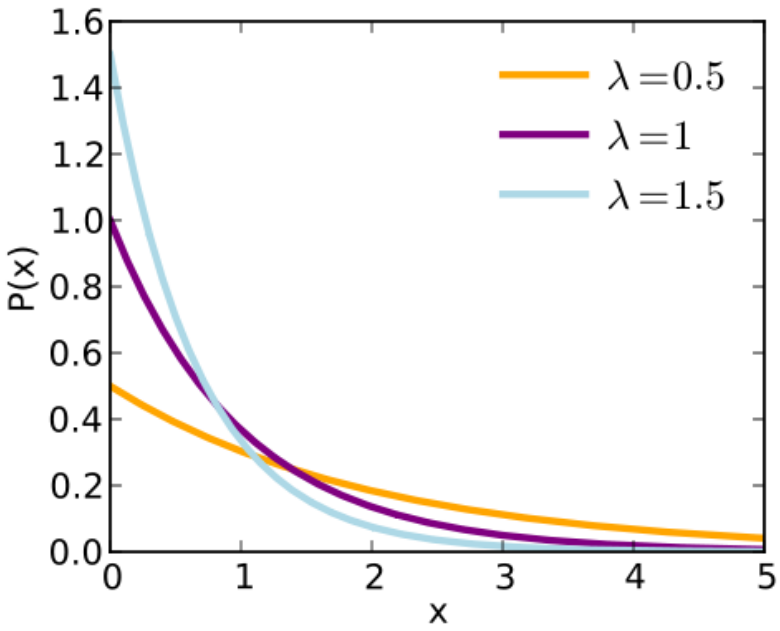
stochastic mass action

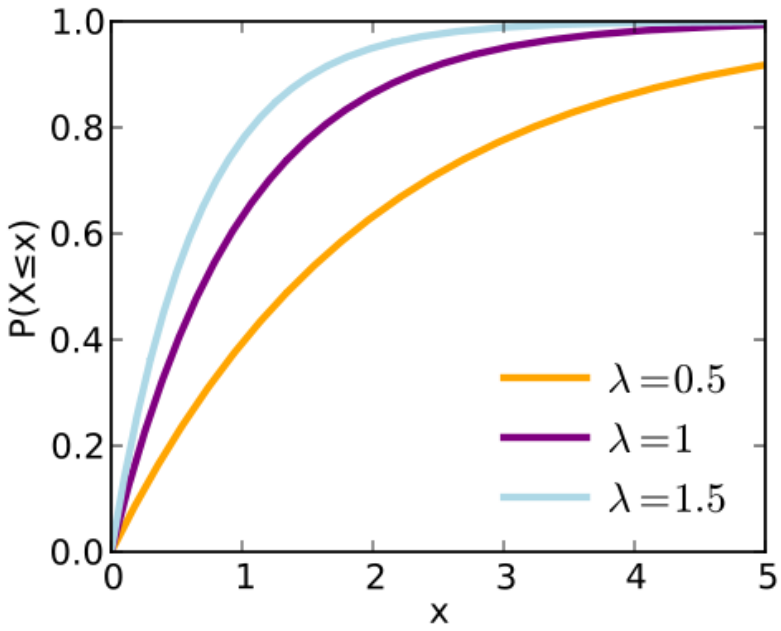
Stochastic model of reaction kinetics

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 $X(t) \to X(t+dt)$, 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)

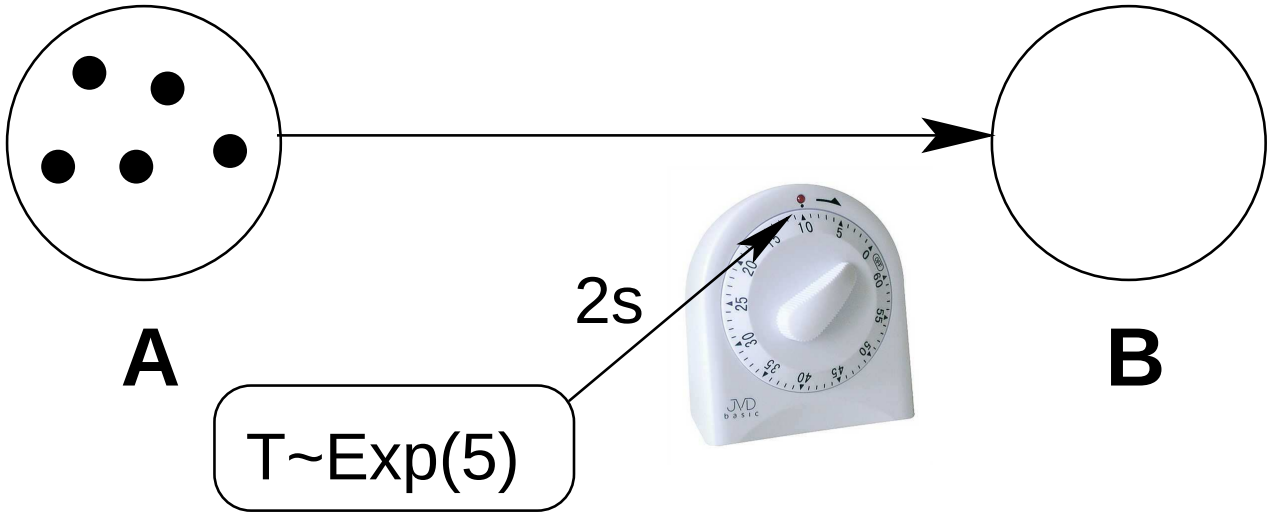
Example

Consider reaction: $A \rightarrow B$

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

Example

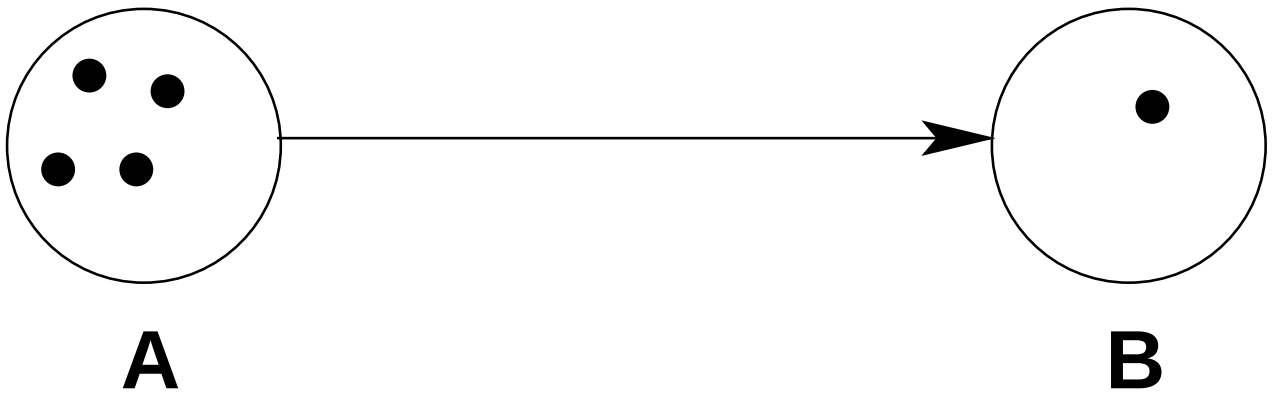
Consider reaction: $A \to B$



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

Example

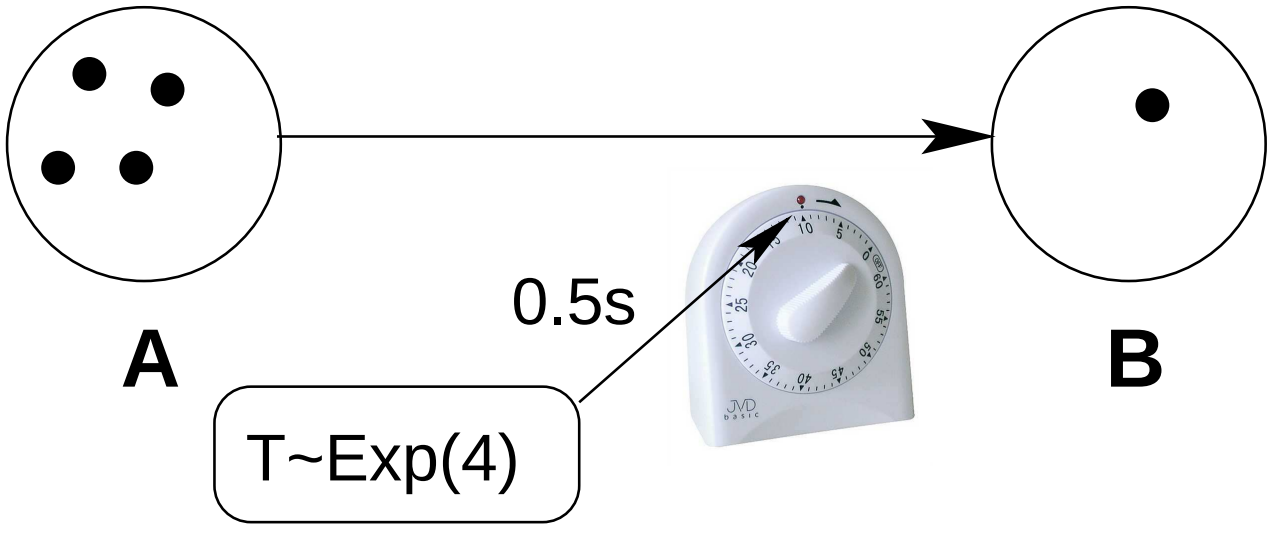
Consider reaction: $A \rightarrow B$



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

Example

Consider reaction: $A \to B$



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

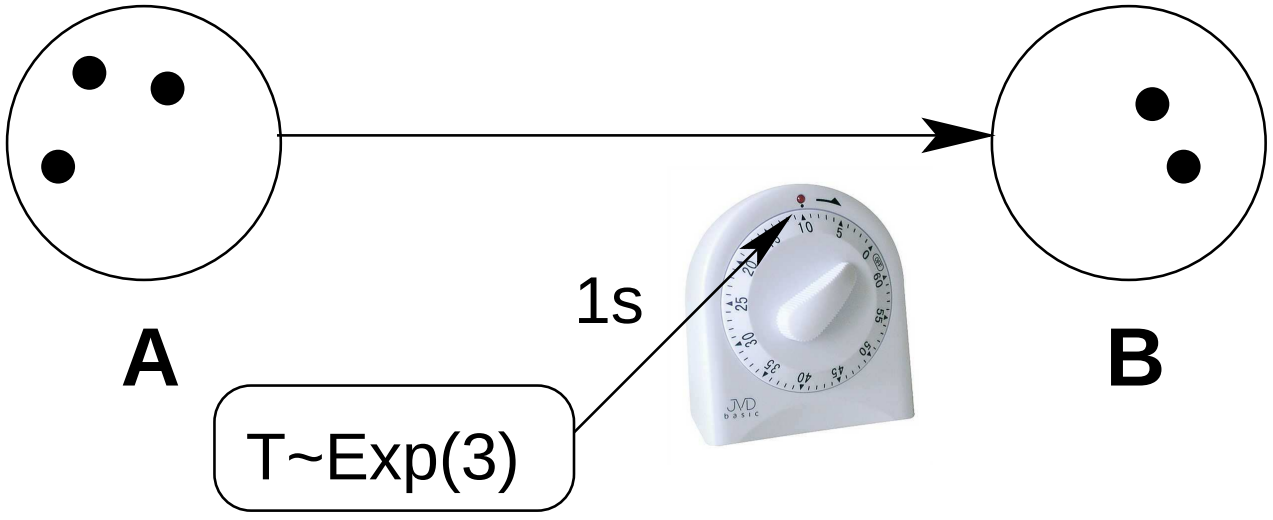
Example

Consider reaction: $A \rightarrow B$

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

Example

Consider reaction: $A \to B$



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

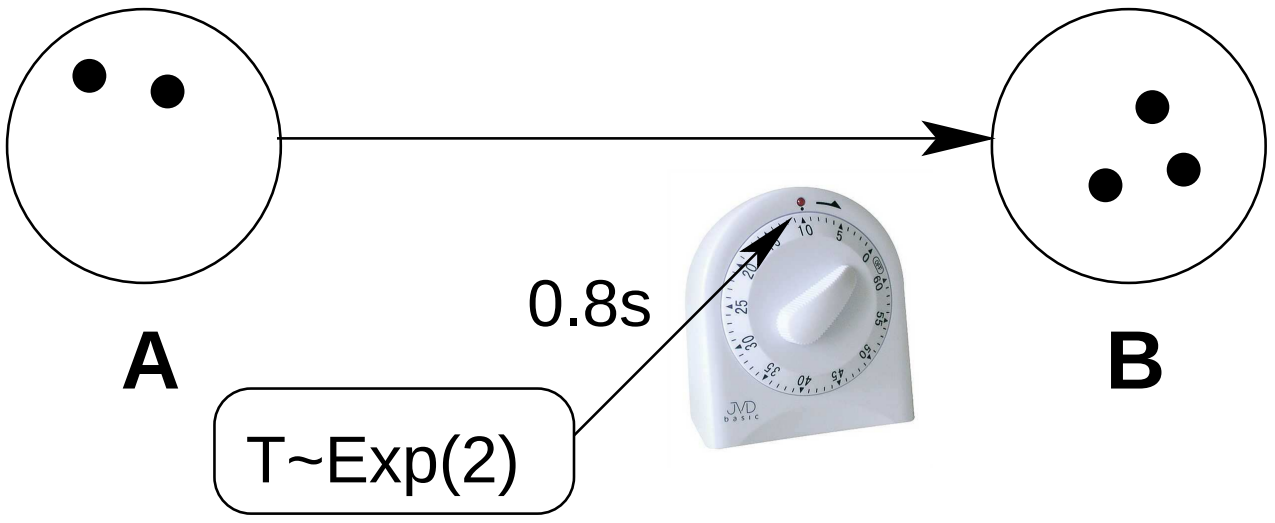
Example

Consider reaction: $A \rightarrow B$

$$\binom{5}{0} \rightarrow (2s) \rightarrow \binom{4}{1} \rightarrow (0.5s) \rightarrow \binom{3}{2} \rightarrow (1s) \rightarrow \binom{2}{3}$$

Example

Consider reaction: $A \to B$



$$\binom{5}{0} \to (2s) \to \binom{4}{1} \to (0.5s) \to \binom{3}{2} \to (1s) \to \binom{2}{3} \to$$

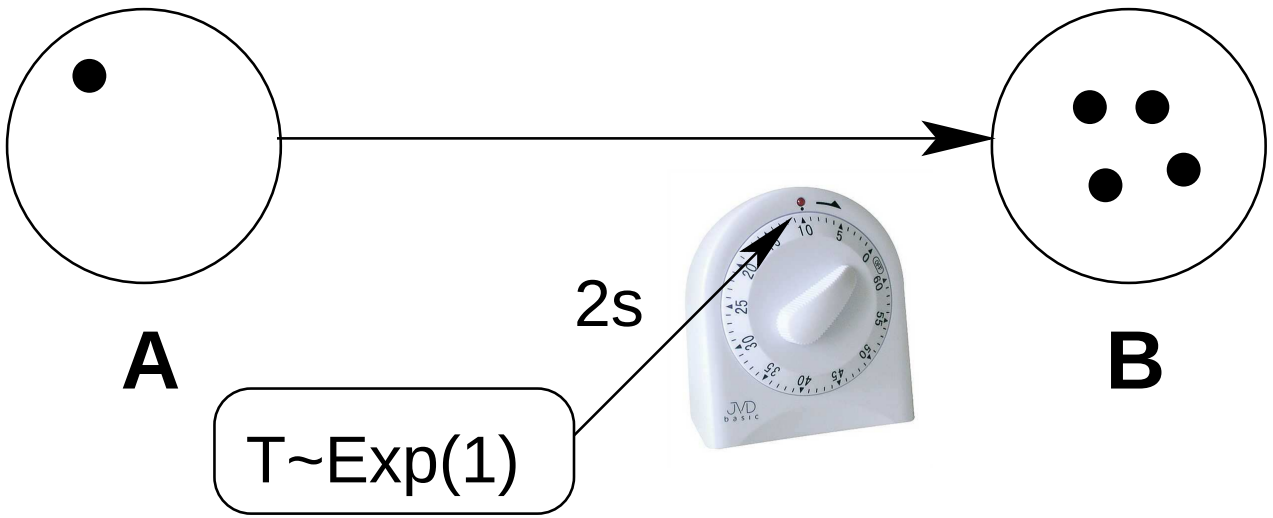
Example

Consider reaction: $A \rightarrow B$

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

Example

Consider reaction: $A \to B$



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

Example

Consider reaction: $A \rightarrow B$

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

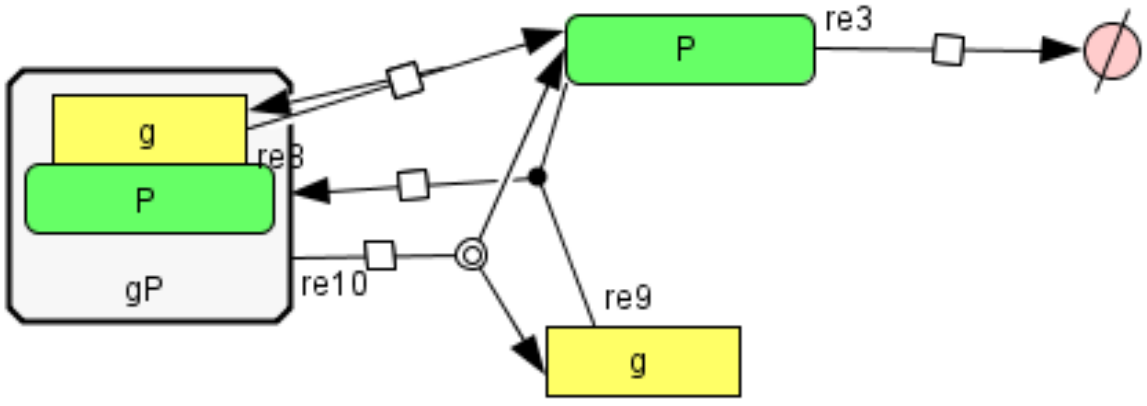
Example

Consider reaction: $A \to B$

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

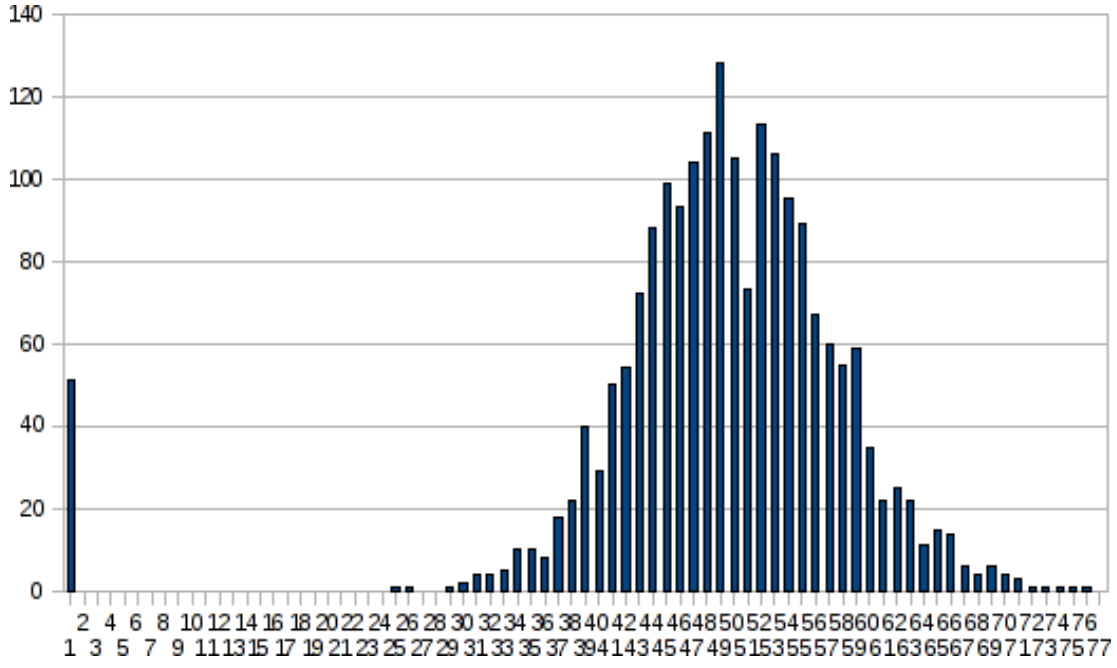
- hazard function considered: $\chi(X) = 1 \cdot X_A$

Example – positive autoregulation of gene expression



$$R_1 : \; P + g \rightarrow gP$$
$$R_2 : \; gP \rightarrow g + P$$
$$R_3 : \; gP \rightarrow gP + P$$
$$R_4 : \; P \rightarrow$$

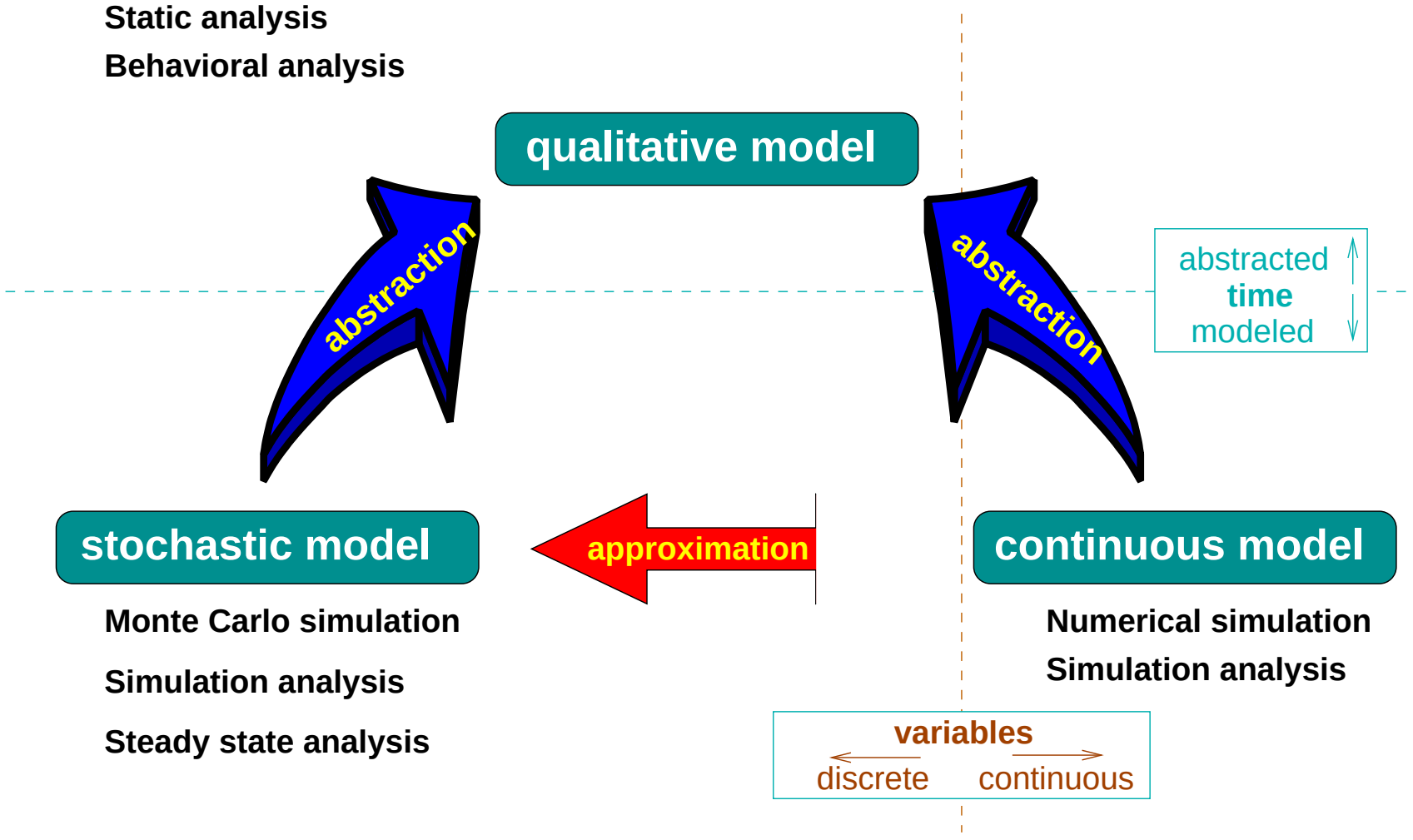
Example – positive autoregulation of gene expression



- 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

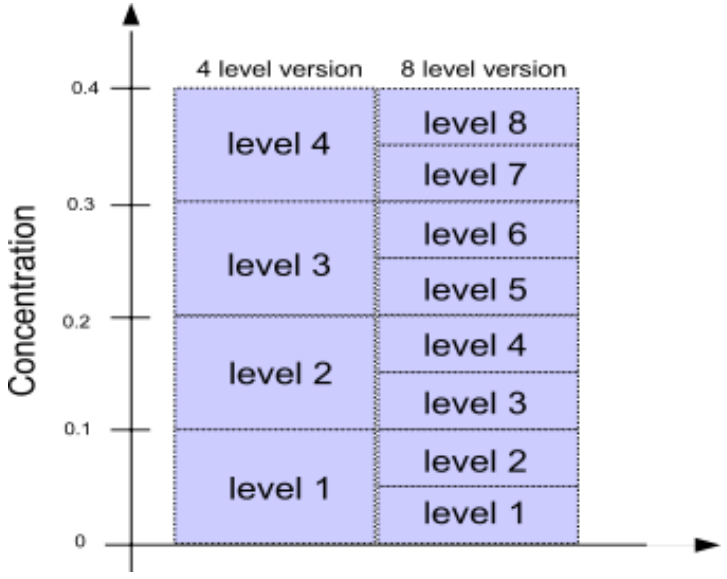
Stochastic Model



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 $\mathcal{N} = \langle S, R, f, v', m(0) \rangle$:

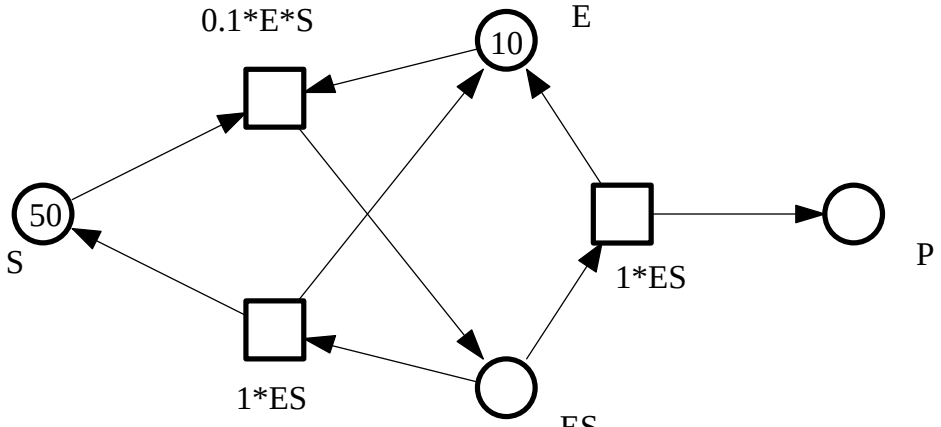
- $m(0) : S \to \mathbb{N}_0$ is *initial marking*
- v' assigns each transition a *hazard*:

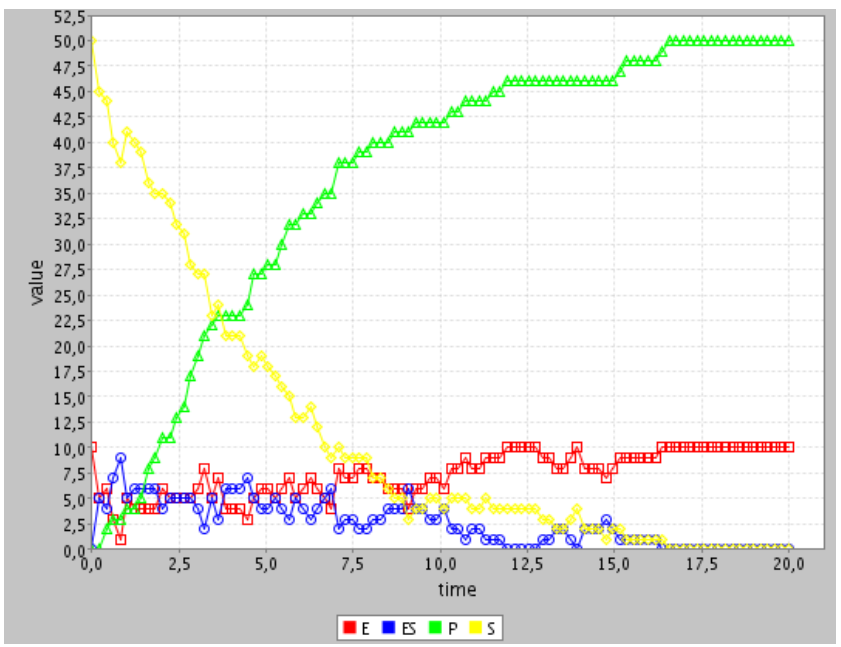
reaction type $r \in R$	$v(r) \to v'(r)$ transformation
$\to A$	$v'(r) = v(r)$
$A \to B$	$v'(r) = v(r)$
$A + B \to AB$	$v'(r) = \frac{v(r)}{\gamma}$
$A + A \to AA$	$v'(r) = \frac{2v(r)}{\gamma}$

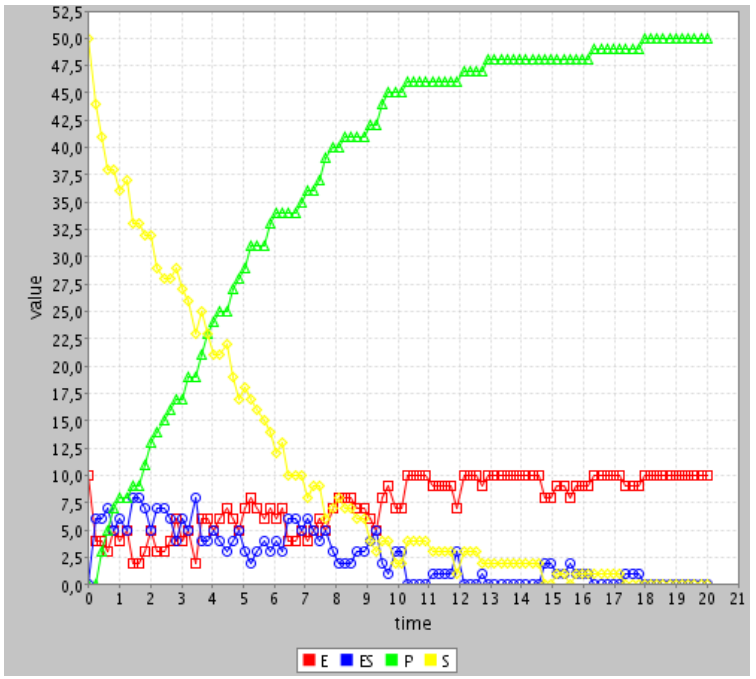
L. Cardelli (2008), "From Processes to ODEs by Chemistry". In 5th International Conference on Theoretical Computer Science, pages 261-281. DOI:10.1007/978-0-387-09680-3_18

Stochastic Petri Nets

Michaelis-Menten Stochastic Mass Action Kinetics Example





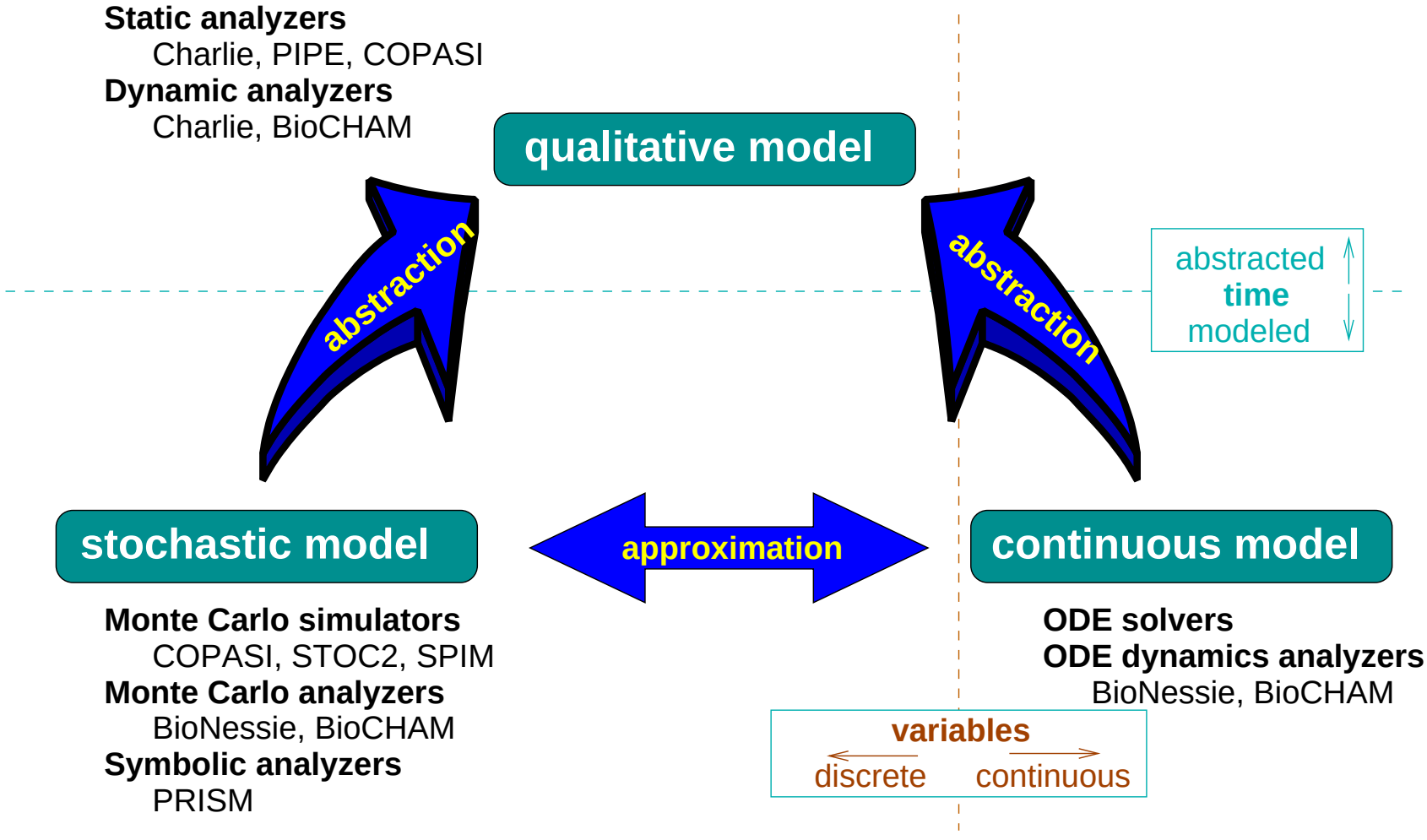


Tool Support

- 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



Literature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