Modelling Stochastic Processes in Biological Systems - slides modified after Ch. Diener

Szymon Stoma

Theoretical Biophysics
Humboldt University of Berlin
Invalidenstraße 42
10115 Berlin

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Central question

How to model dynamics of a chemical system? We assume that the system kinetics is described using the following equations:

$$R_0 : S_0 \rightarrow S_k$$

$$\ldots$$

$$R_m : S_m + S_l \rightarrow S_n$$

RRE

The traditional way is: using reaction rate equations (RRE):

- A set of coupled ODE equations
- Phenomenological approach
- Assumes that the system evolves continuously and deterministically
- Is empirically correct for large systems but fails for very small ones

How does RRE system looks?

E.g. Lotka-Voltera

$$
\begin{aligned}
Y_1 &\longrightarrow 2Y_1 \\
Y_1 + Y_2 &\longrightarrow 2Y_2 \\
Y_2 &\longrightarrow \emptyset
\end{aligned}
$$

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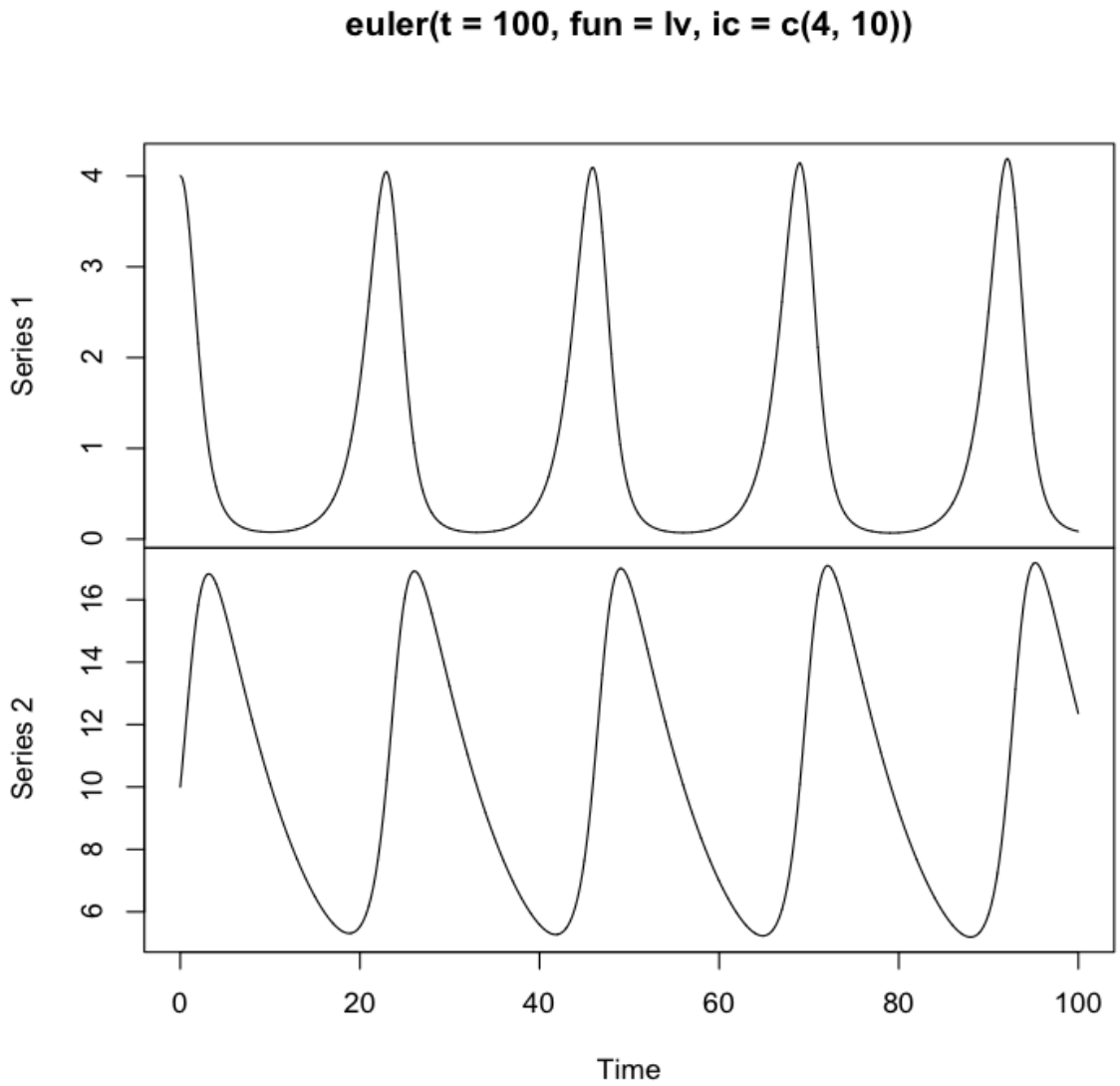
$$

$$
\begin{aligned}
\frac{d[Y_1]}{dt} &= k_1[Y_1] - k_2[Y_1][Y_2] \\
\frac{d[Y_2]}{dt} &= k_2[Y_1][Y_2] - k_3[Y_2]
\end{aligned}
$$

How does RRE system looks?

E.g. Lotka-Voltera



Why RRE system is phenomenological?

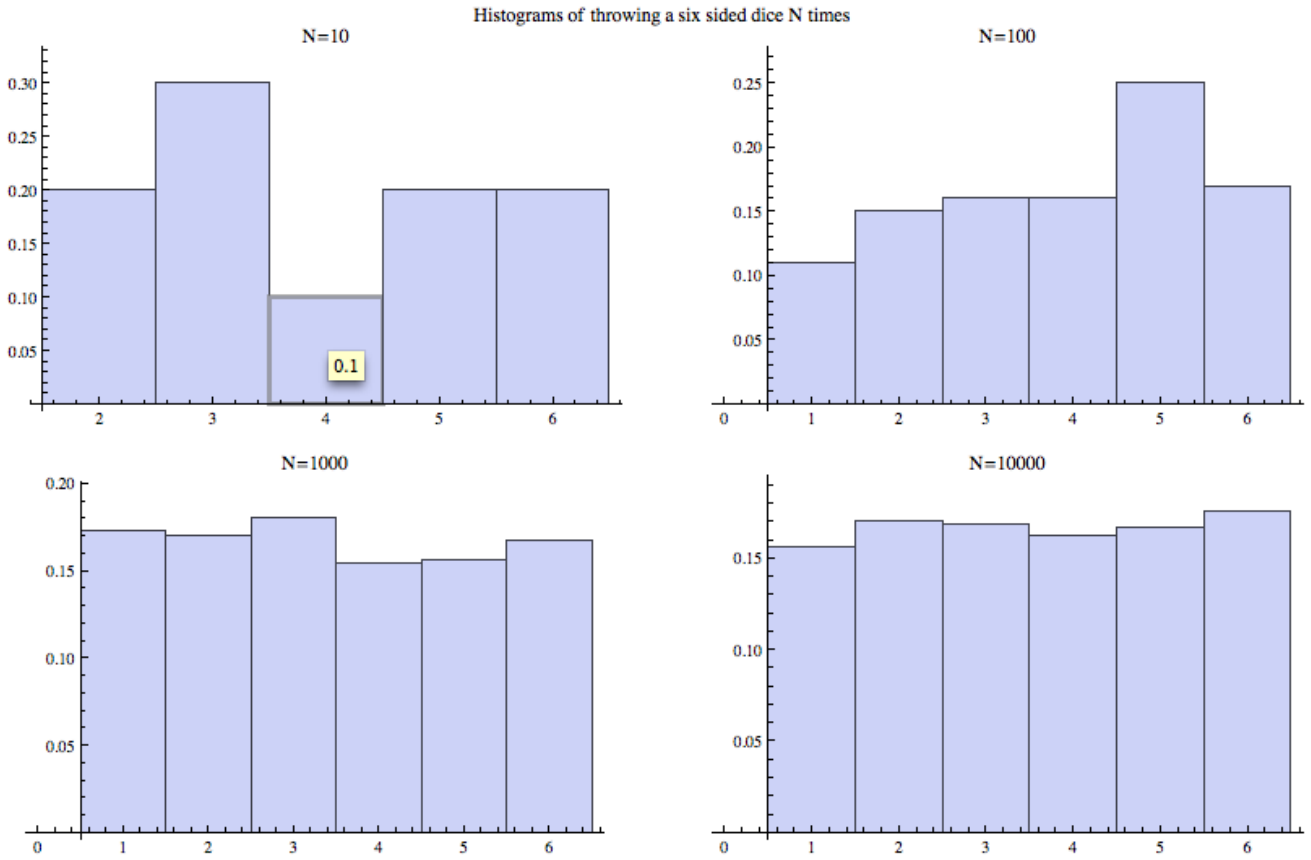
The RRE system is constructed:

- measure: stoichiometry, kinetics
- write the rules governing substance conversions

What are the consequences of being continuous and deterministic?

- The state (describing molecule number) is described by continuous variable, however these values can be only integers
- The true nature of the system is indeterministic:
  - Molecule numbers is not enough (i.e. velocities, accelerations are missing)
  - Quantum mechanics
  - Real systems have contact with ”outside”

Why RRE fails for small systems?



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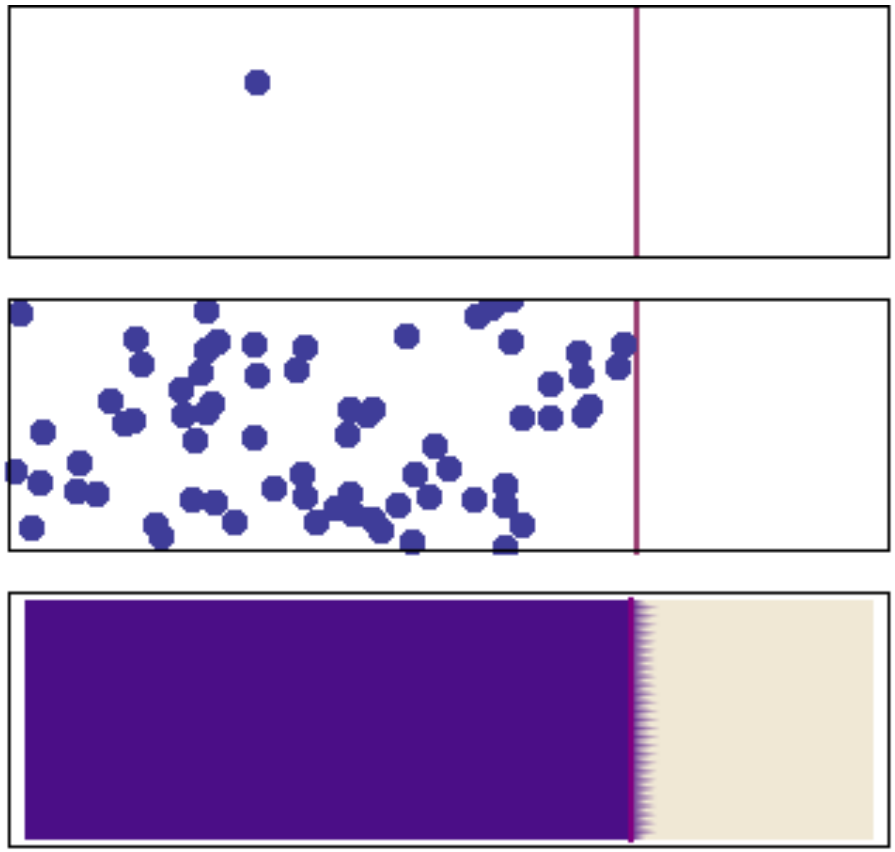

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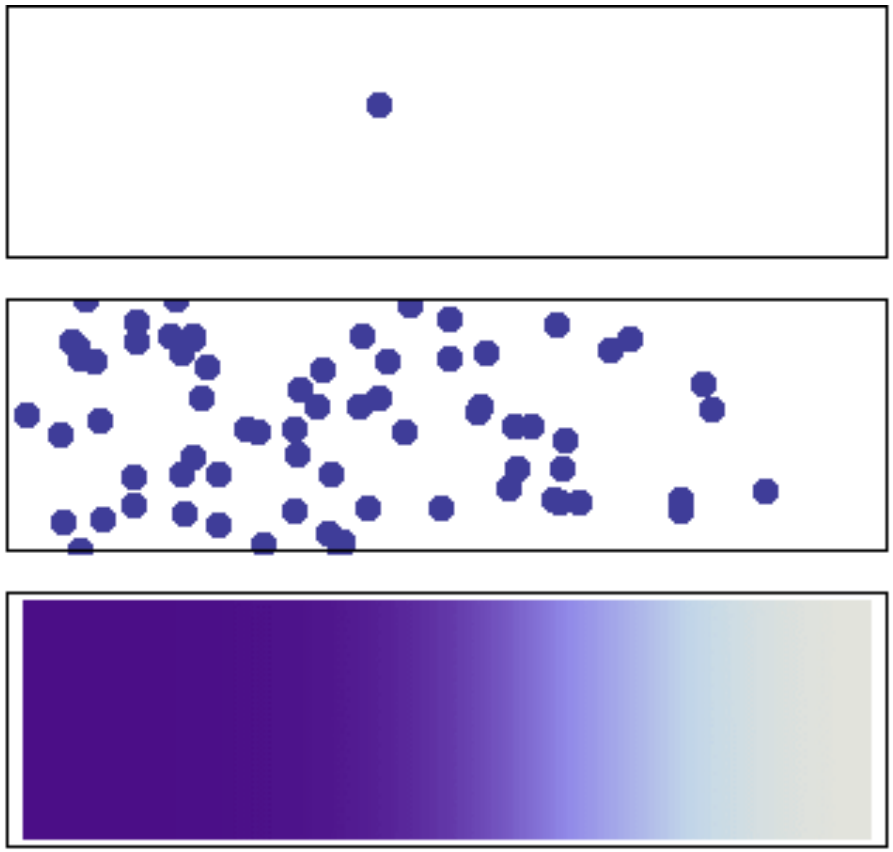

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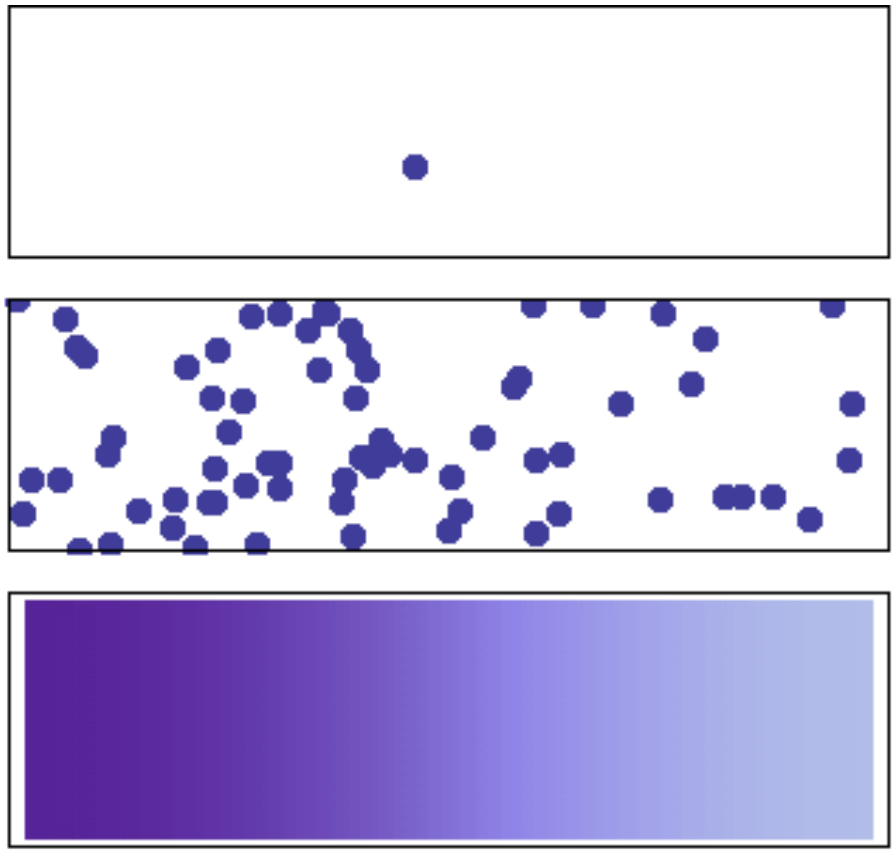
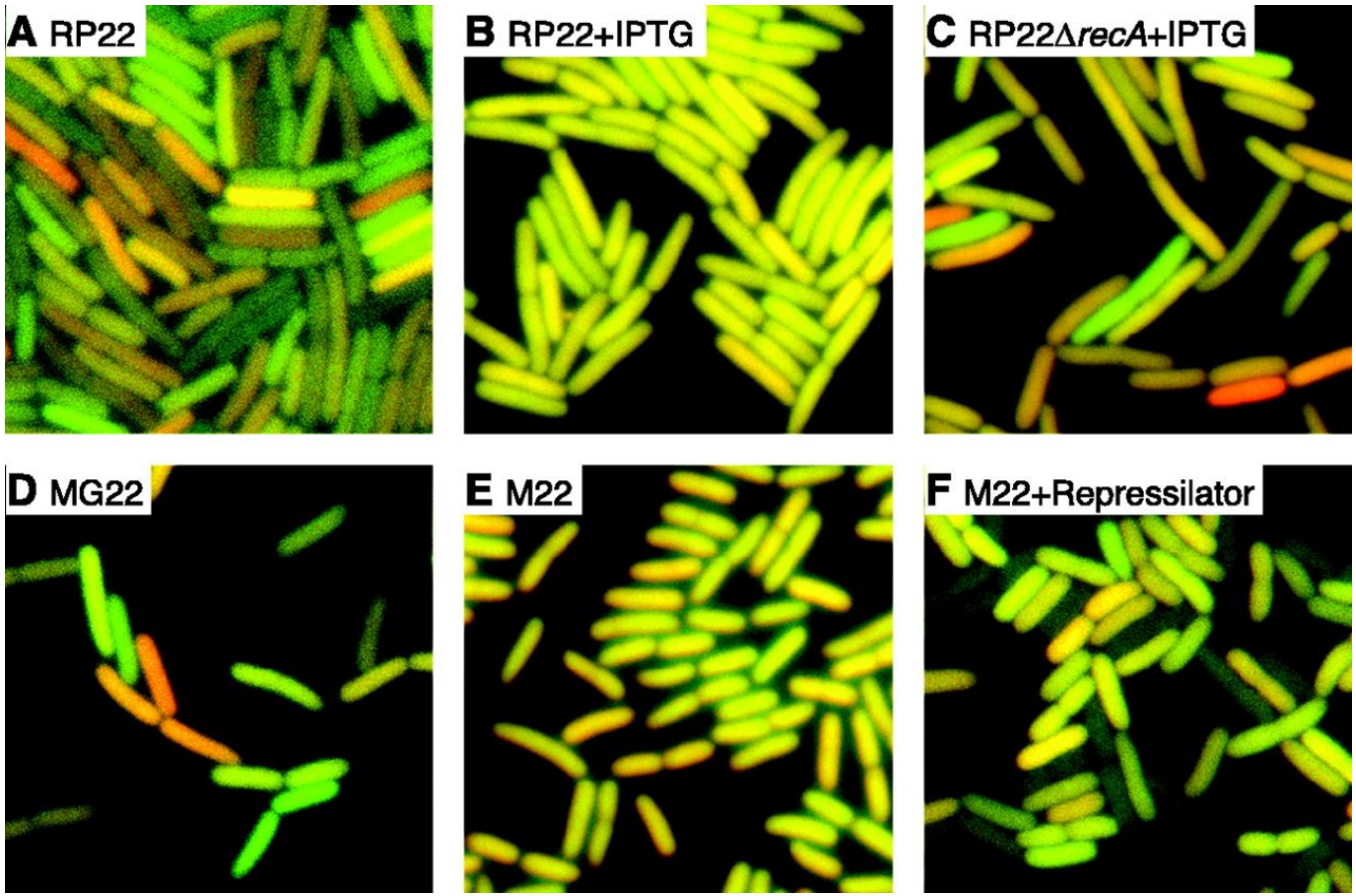


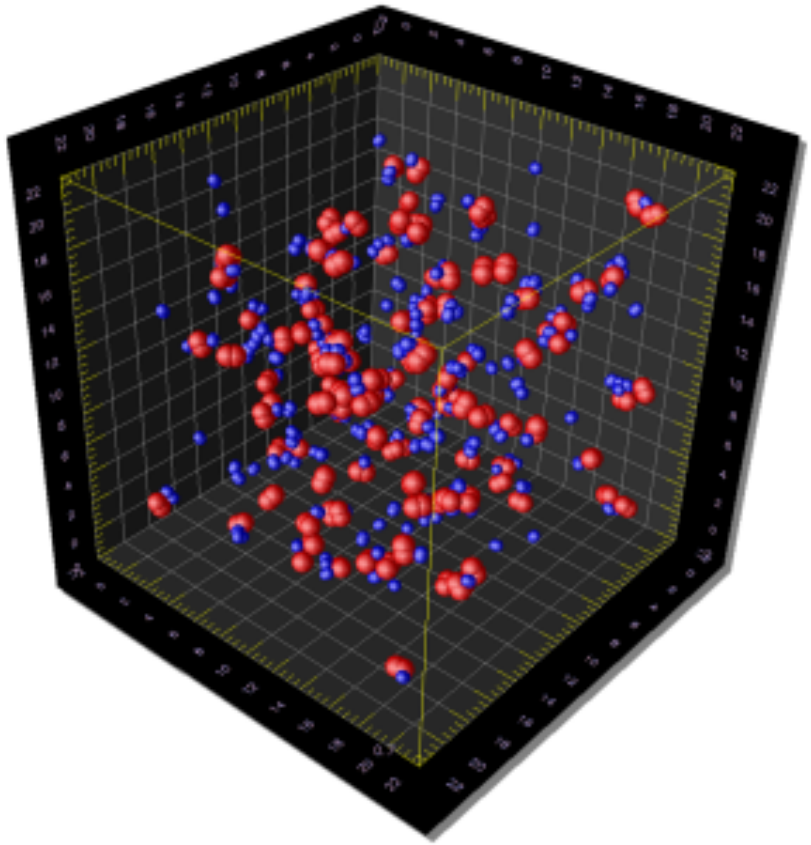
But.. is it really happening?

Noise in Gene Expression



Elowitz et. al., 2002

Molecular dynamics



Molecular dynamics

- We track positions, velocities, forces of every molecule creating a ”motion picture”
- It is exact way of describing of the system
- Show changes in the species populations as well as their spatial distributions
- but.. it is slooooow
- but.. quantum mechanics still is not included

Stochastical approach

A simplification is possible: we simulate only the reactive collisions and we assume that:

- the velocities of the molecules are randomized (Maxwell-Boltzmann distribution)
- the positions of the molecules are randomized (uniform distribution)

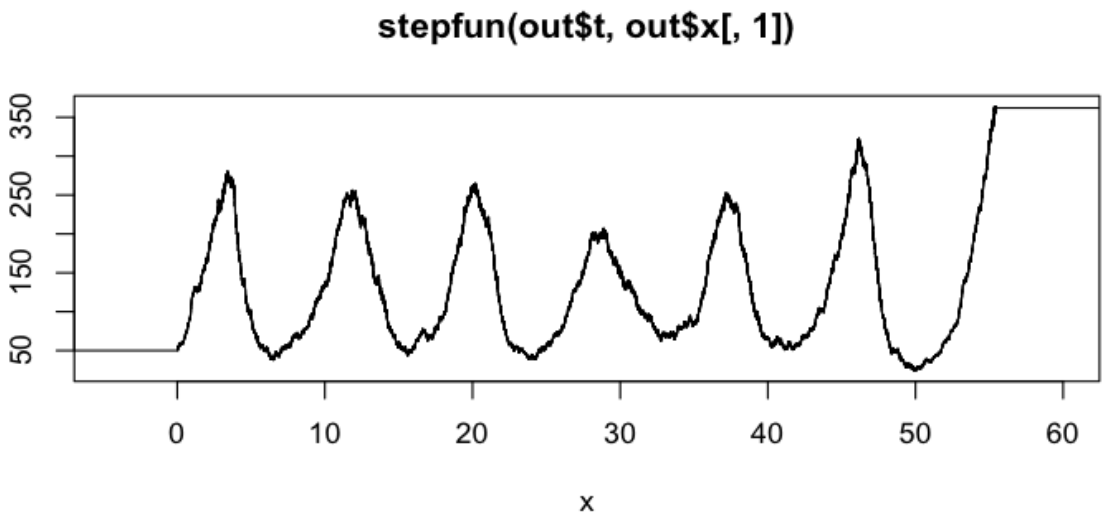
Then we can model the system as a stochastical process.

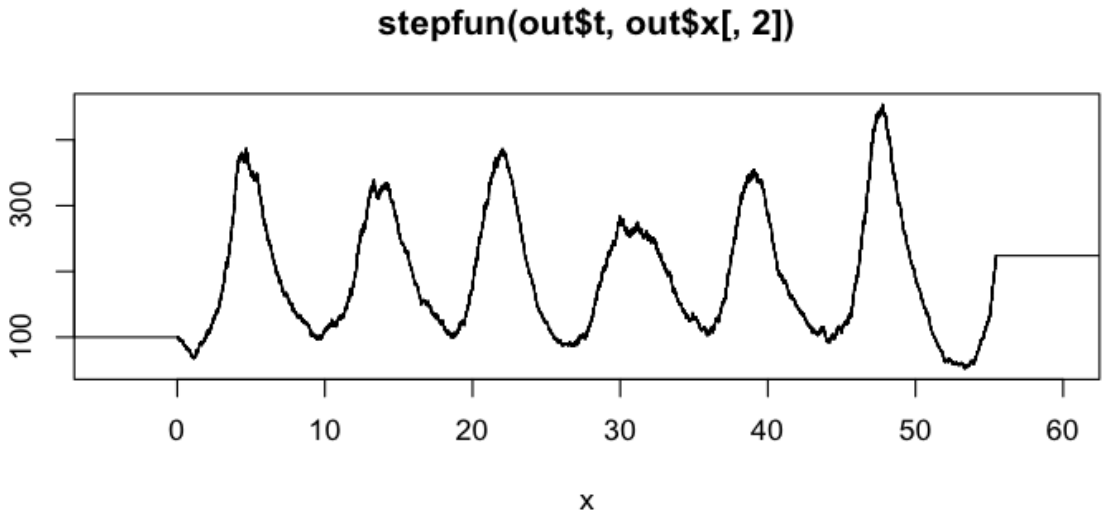
Basic Characterization

- The state **S** is a discrete property (e.g. number of molecules)
- No unique state $\mathbf{S}(t)$ associated with a time point t
- Only probabilities to be in a state in t $\rightarrow \mathbb{P}(\mathbf{S}, t)$
- Several “runs” do not produce same output $\rightarrow$ samples

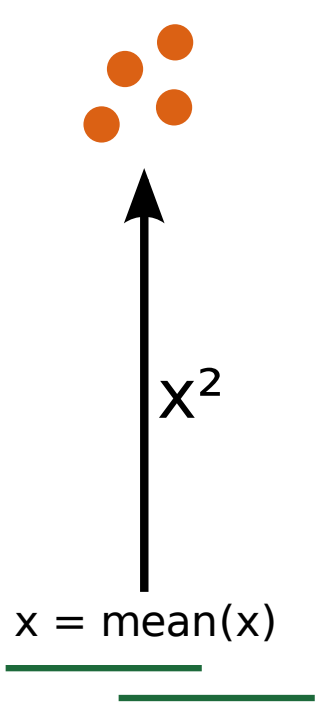
How does stochastic simulation look like?

E.g. Lotka-Voltera

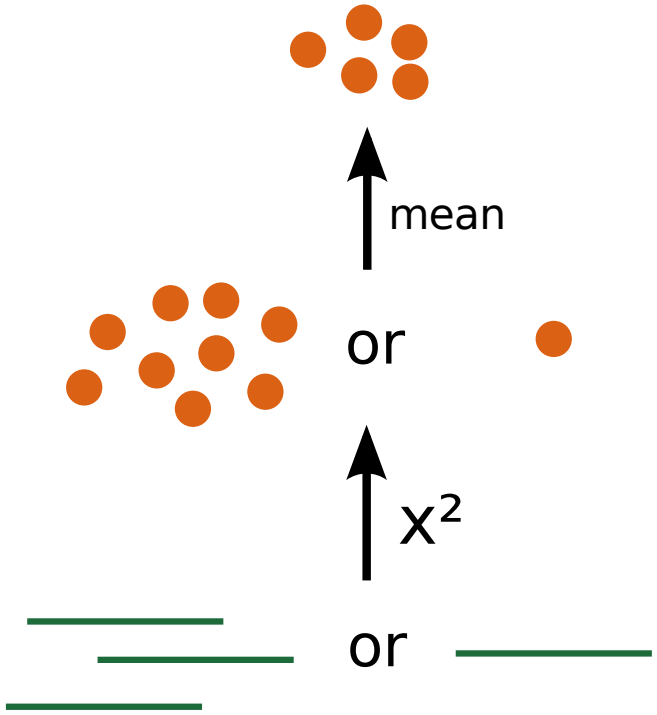




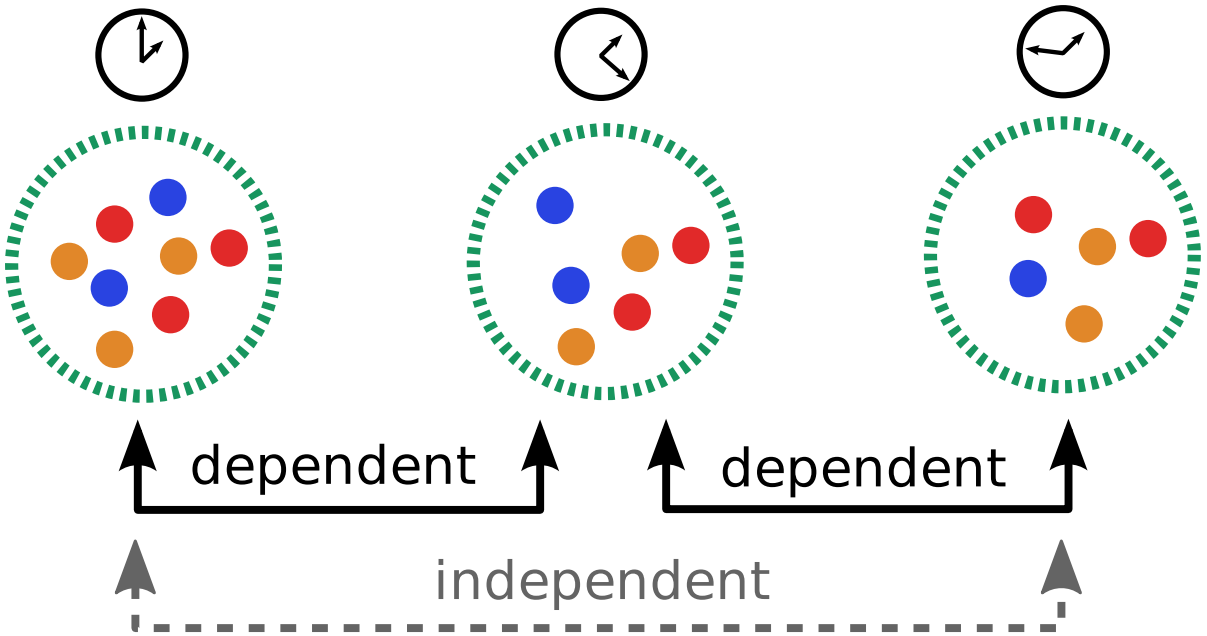
What's the difference?



deterministic



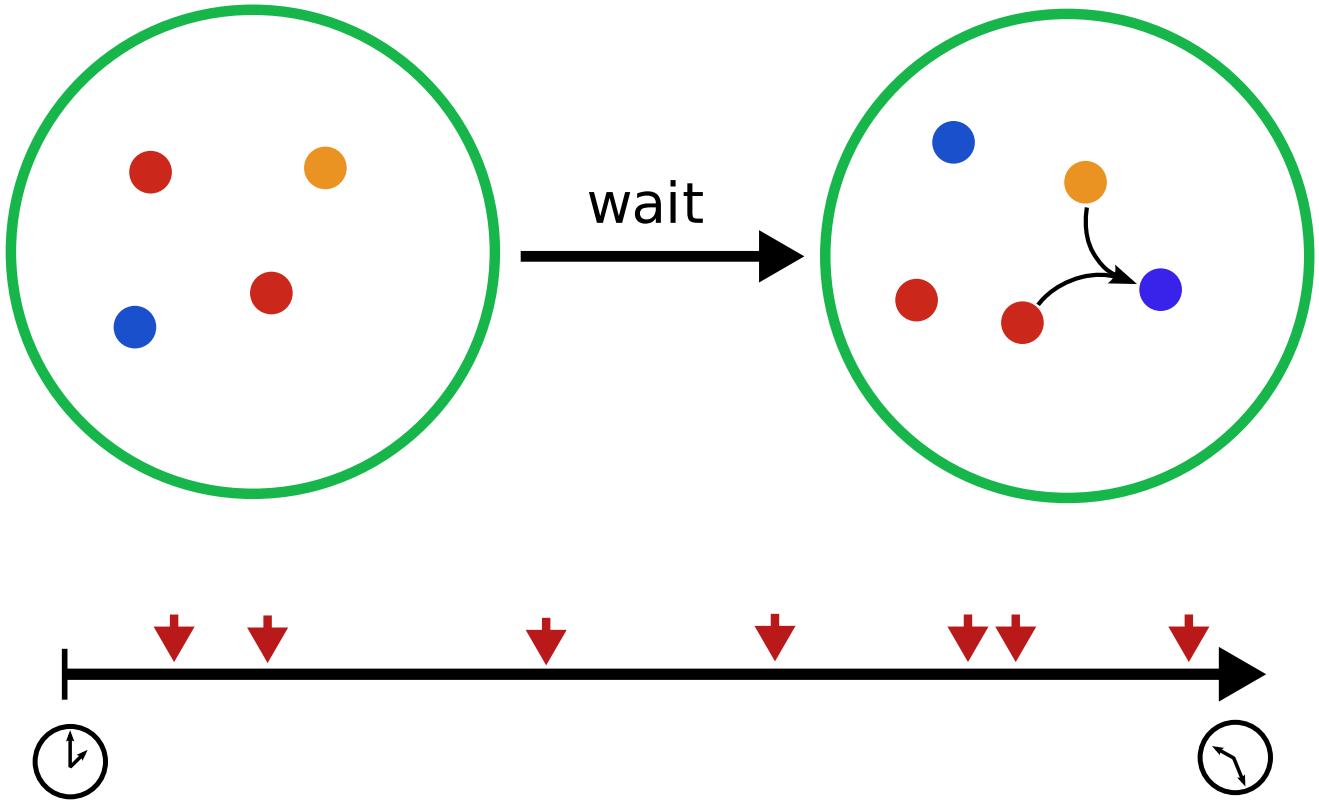
stochastic



Markov Property

For all countable subsets $\mathbf{t} = t_1, t_2, \ldots, t_n \in \mathbb{R}$ and corresponding realizations $\mathbf{S}(t_i) = \mathbf{S}_i \in \mathbb{N}_0^n$ holds:

$$\mathbb{P}(\mathbf{S}, t_n | \mathbf{S}_{n-1}, \mathbf{S}_{n-2}, \ldots, \mathbf{S}_1) = \mathbb{P}(\mathbf{S}, t_n | \mathbf{S}_{n-1}).$$



- finite probabilities for any reaction j, $\mathbb{P}(j, \Delta t)$

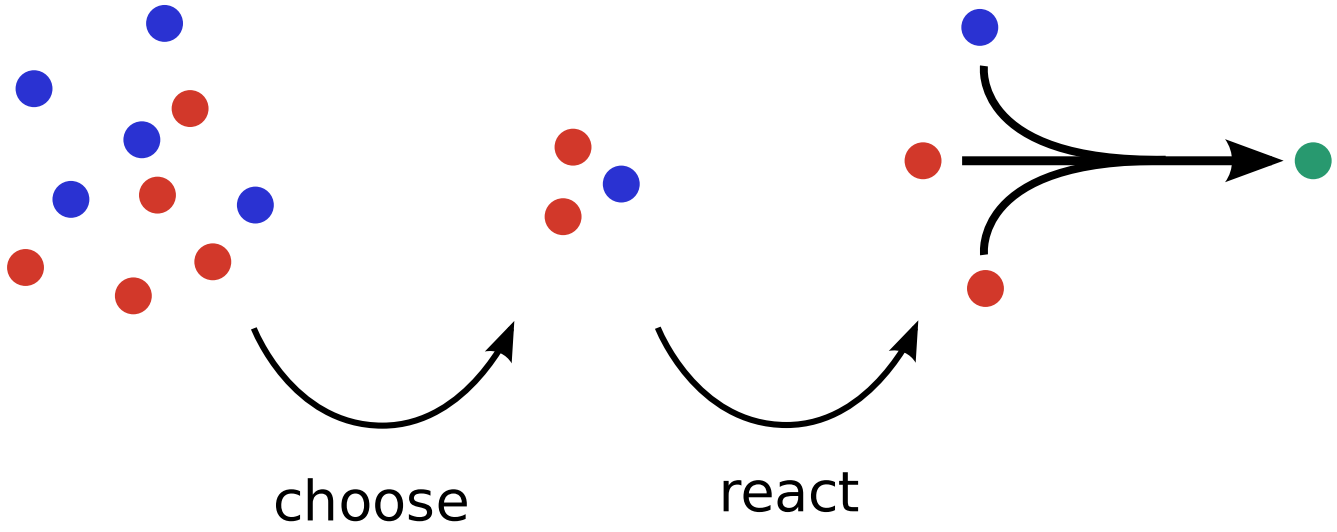
What is the probability for a reaction?

- Common sense implies linearity in small time steps Δt
- in perfect agreement with the underlying thermodynamics

Unique Reaction Probability

The probability for a single reaction j with a rate k_j and given substrates within $(t, t + \Delta t]$ is

$$\mathbb{P}(j, \Delta t) = k_j \cdot \Delta t.$$

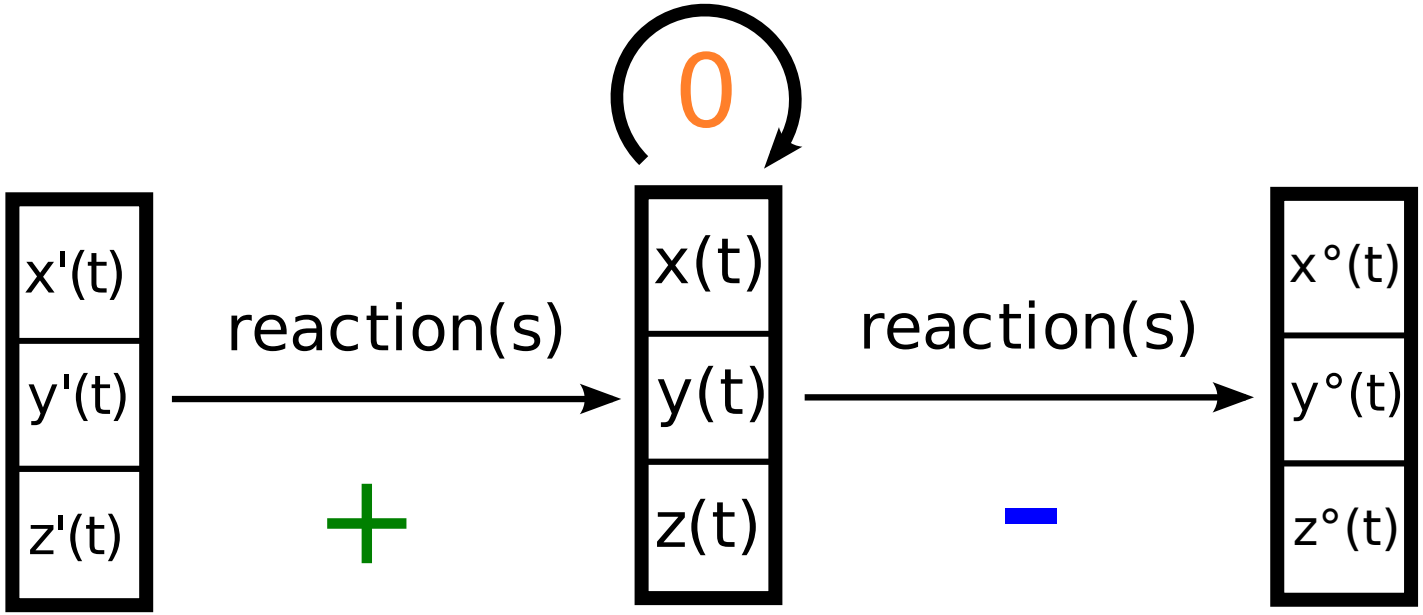


Single Reaction probability

Given the current system state $\mathbf{S}$ at time t and the required substrates a_k the probability for a *single* reaction taking place in $(t, t + \Delta t]$ is given by:

$$\mathbb{P}(j, \mathbf{S}, \Delta t) = k_j \cdot \prod_k \binom{S_k}{a_k} \cdot \Delta t =: r_j(\mathbf{S}, t) \cdot \Delta t \,.$$

The Chemical Master Equation (CME)

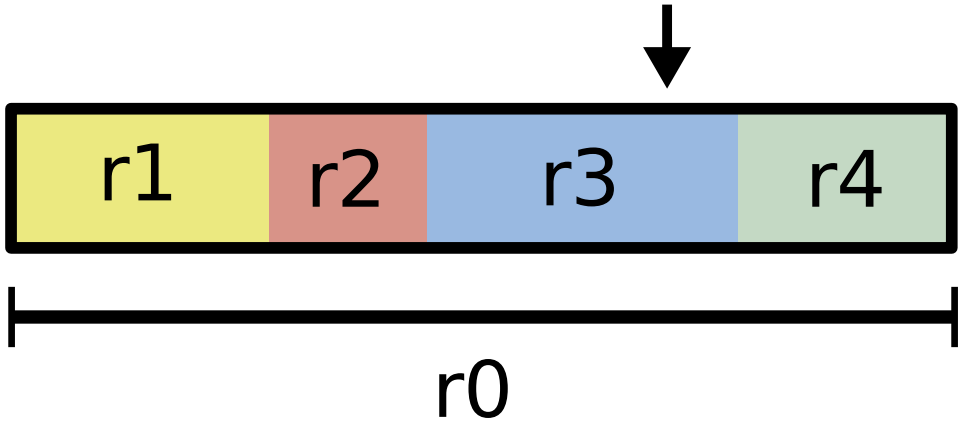


$$\frac{d\,\mathbb{P}(\mathbf{S},t|\mathbf{S}_0,t_0)}{dt} = \sum_j \left[\mathbb{P}(\mathbf{S}-\phi_j,t|\mathbf{S}_0,t_0)\cdot r_j(\mathbf{S}-\phi_j,t) - \mathbb{P}(\mathbf{S},t|\mathbf{S}_0,t_0)\cdot r_j(\mathbf{S},t)\right]$$

Waiting Time Distribution

The waiting time, $\mathbb{P}(\tau, 0)$, between two consecutive reactions follows an exponential distribution

$$\mathbb{P}(\tau, 0) = r_0(\mathbf{S}, t) \exp\left(-r_0(\mathbf{S}, t)\tau\right), \text{ with } r_0(\mathbf{S}, t) := \sum_{j=1}^{n} r_j(\mathbf{S}, t).$$

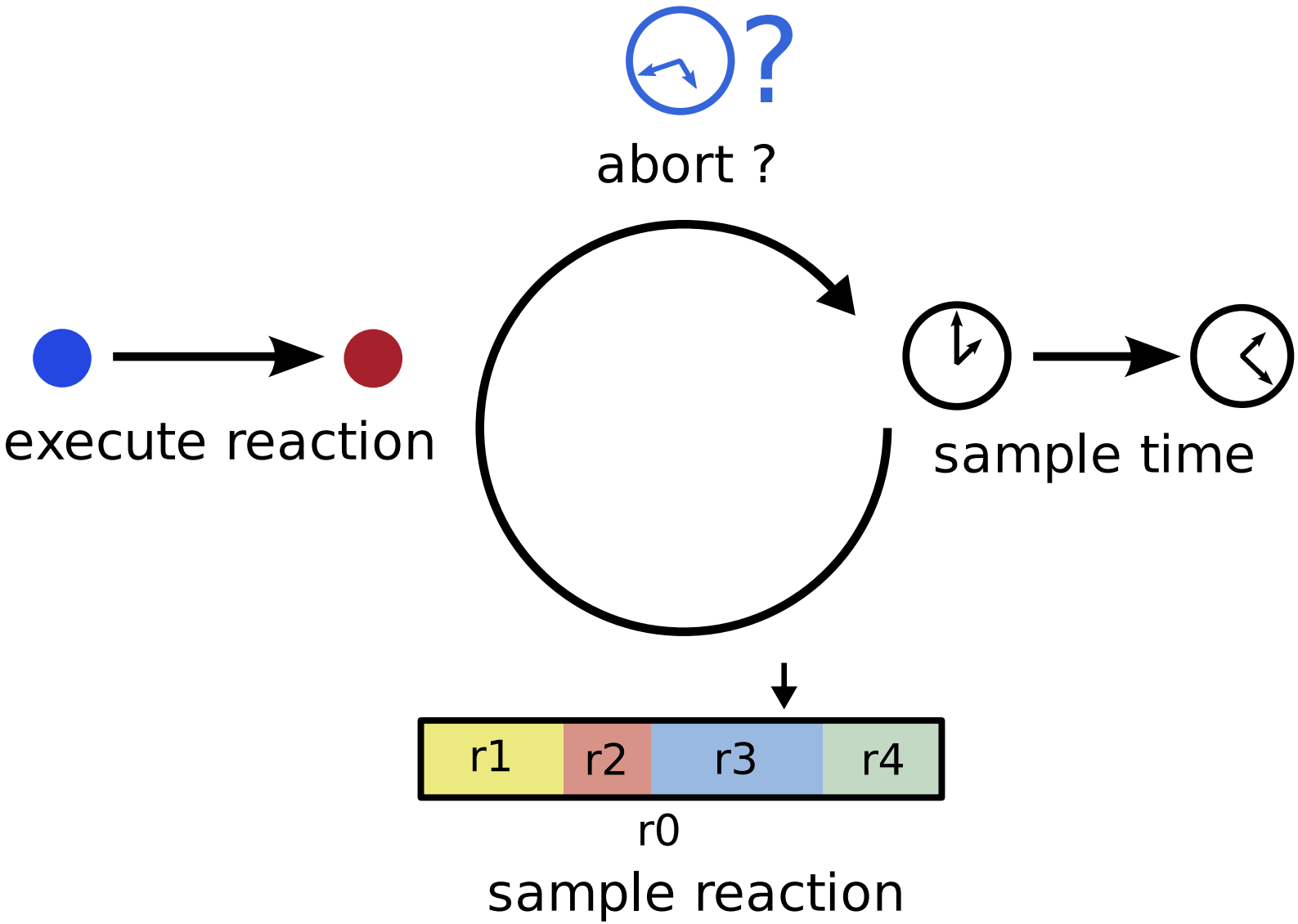


Reaction Type Probability

The probability that the next reaction will be of type j give that we waited τ is

$$\mathbb{P}(j|\tau) = \frac{r_j(\mathbf{S}, t)}{r_0(\mathbf{S}, t)}.$$

Stochastic Simulation Algorithm (SSA)



Example: Decay equation

A Simple Example: $S_1 \xrightarrow{c_1} 0$.

$$a_1(x_1) = c_1 x_1, \quad \nu_1 = -1. \text{ Take } X_1(0) = x_1^0.$$

RRE: $\dfrac{dX_1(t)}{dt} = -c_1 X_1(t)$. Solution is $X_1(t) = x_1^0 \, \mathrm{e}^{-c_1 t}$.

CME: $\dfrac{\partial P(x_1, t | x_1^0, 0)}{\partial t} = c_1 \left[(x_1 + 1) P(x_1 + 1, t | x_1^0, 0) - x_1 P(x_1, t | x_1^0, 0) \right]$.

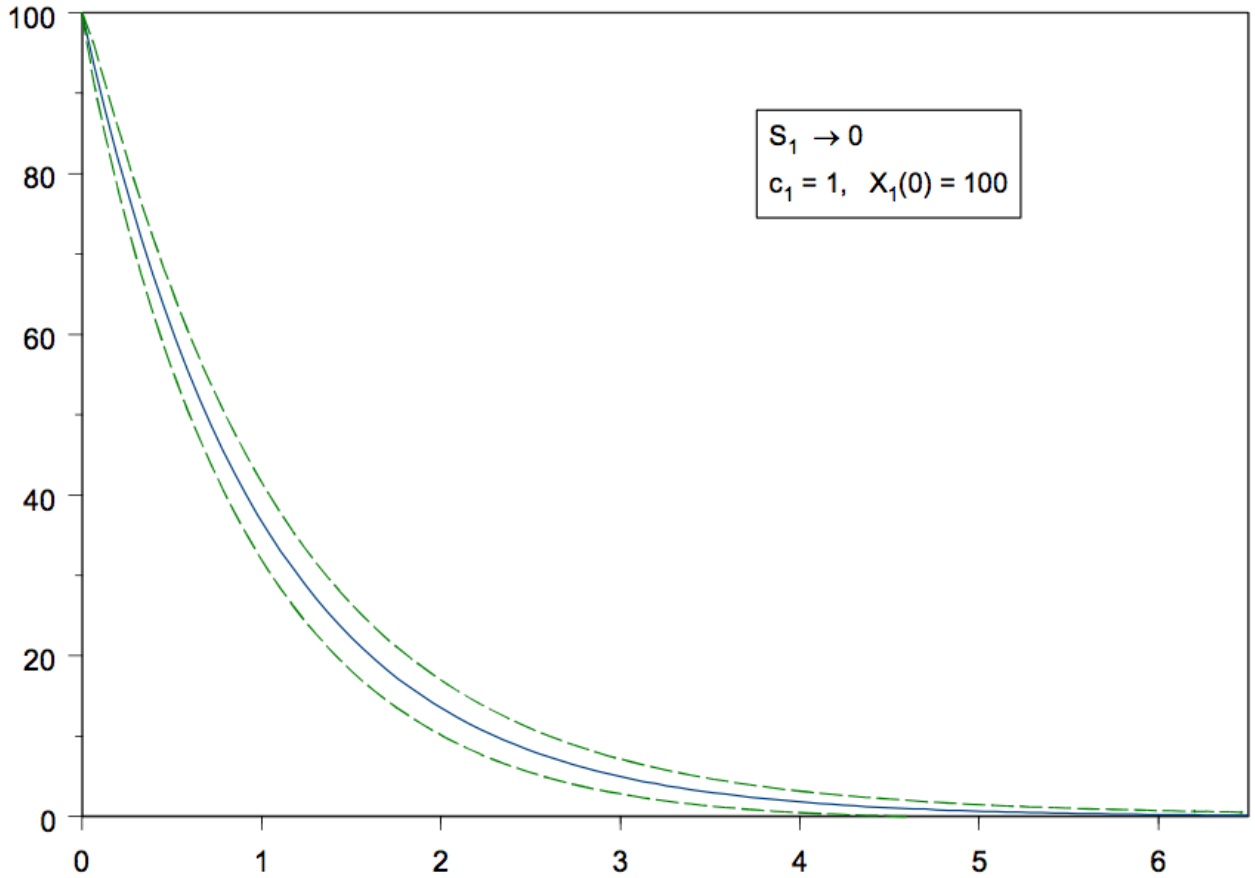
Solution: $P(x_1, t | x_1^0, 0) = \dfrac{x_1^0 !}{x_1 ! (x_1^0 - x_1)!} \mathrm{e}^{-c_1 x_1 t} \left(1 - \mathrm{e}^{-c_1 t}\right)^{x_1^0 - x_1} \quad (x_1 = 0, 1, \ldots, x_1^0)$

which implies $\langle X_1(t) \rangle = x_1^0 \, \mathrm{e}^{-c_1 t}$, $\mathrm{sdev}\{ X_1(t) \} = \sqrt{x_1^0 \, \mathrm{e}^{-c_1 t} \left(1 - \mathrm{e}^{-c_1 t}\right)}$.

SSA: Given $X_1(t) = x_1$, generate $\tau = \dfrac{1}{c_1 x_1} \ln\left(\dfrac{1}{r}\right)$, then update:

$$t \leftarrow t + \tau, \quad x_1 \leftarrow x_1 - 1.$$

Example: Decay equation



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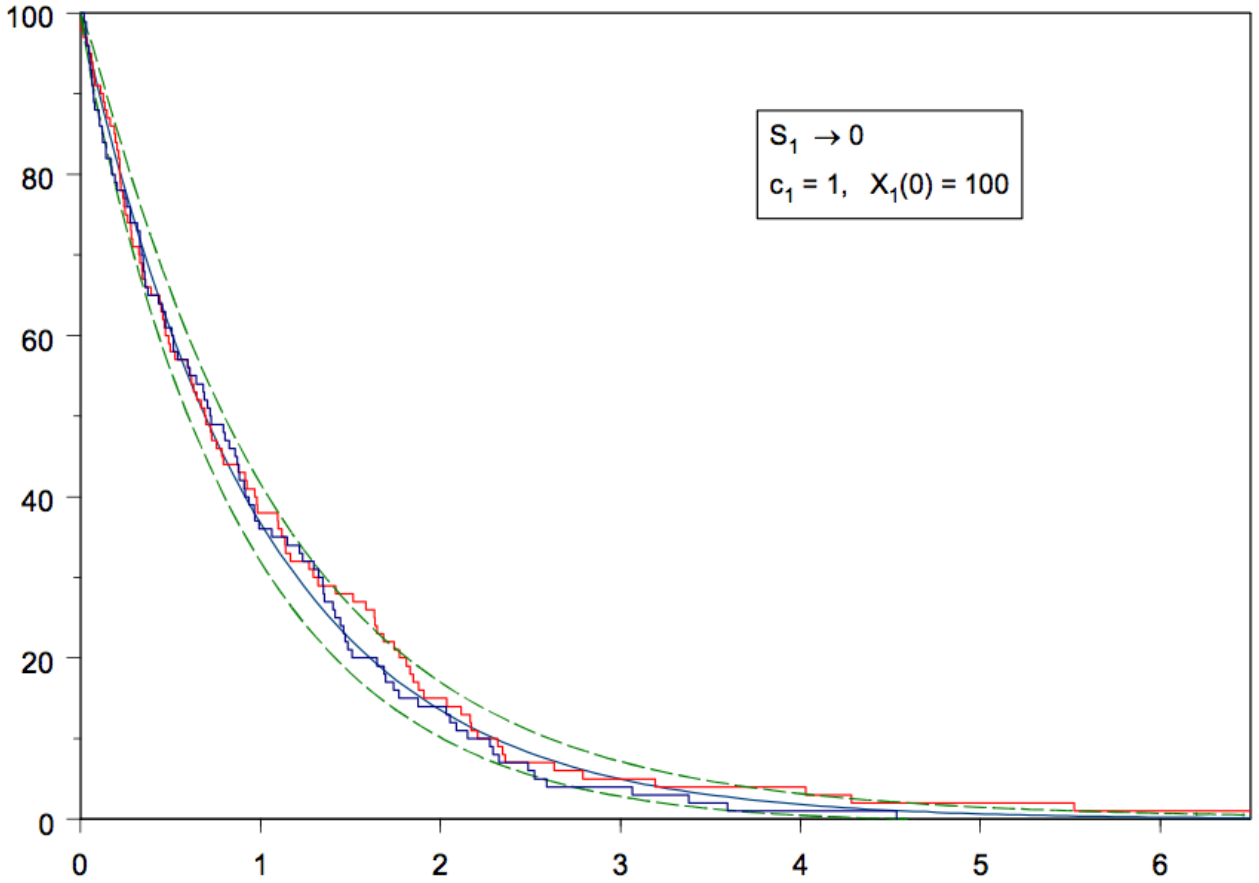

Thank you!