“Introduction to the Stochastic modelling of reaction networks”
Day 1: The Gillespie algorithm (intro)

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Deterministic vs. stochastic

- Deterministic: every set of variable states is uniquely determined by parameters in the model and by sets of previous states of these variables; therefore, a deterministic model always performs the same way for a given set of initial conditions.
- Stochastic trajectory: randomness is present, and every trajectory can be different from the others.
- Stochastic: calculate deterministically some variable of the stochastic distribution

Notation: Describing a chemical system over time

- The total volume of the system, *V*.
- A series of chemical species: S_i $(i = 1,2, \dots, N)$, N total number of chemical species.
- The quantities of those elements at time *t*: X_i $(i = 1,2, \dots, N)$
- The possible reactions: $R_\mu (\mu = 1,2, \dots, M)$ M, total number of reactions.
- Parameter for the evolution of the system:
  - k_μ (deterministic)
  - c_μ(stochastic)

The deterministic approach to chemical reactions

- Back to high-school: A simple equilibrium

$S_i = (A, B, C); X_i = (150, 100, 0);\ R = (R_1, R_2); k = (k_1 = 0.5, k_2 = 0.05);\ V{=}1$

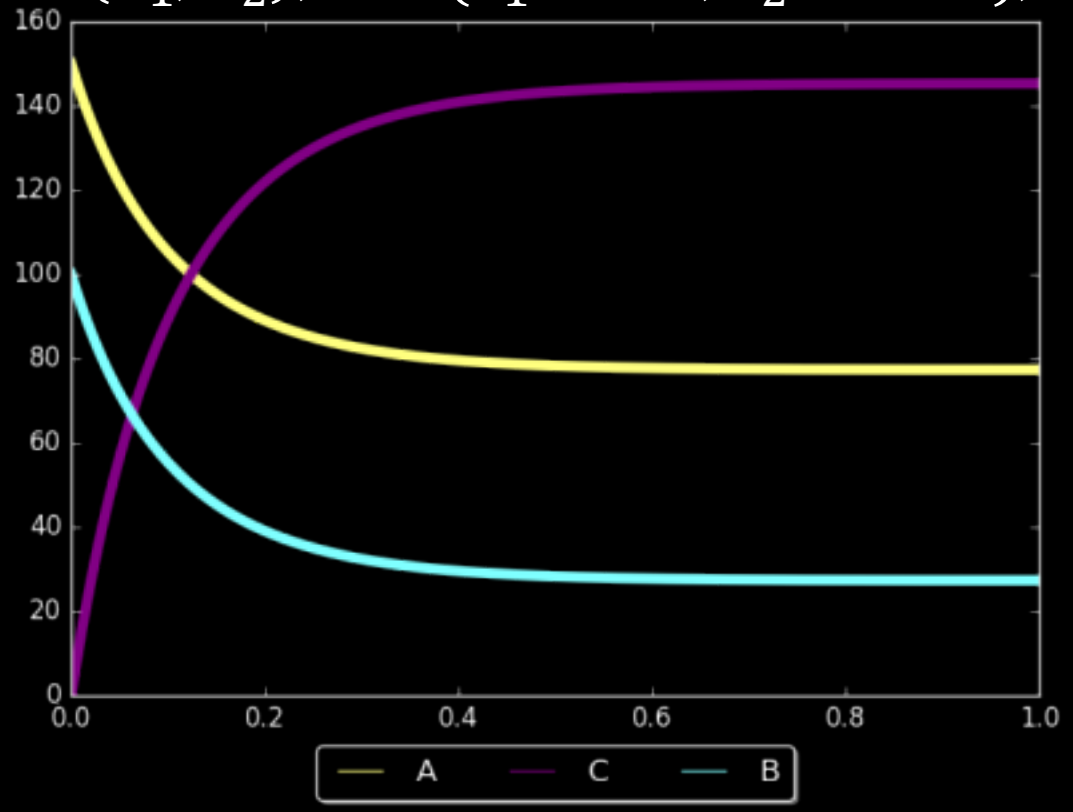
$R_1: A + B \xrightarrow{k_1} 2C$

$R_2: 2C \xrightarrow{k_2} A + B$

$$v_1 = \frac{dA}{dt} = \frac{dB}{dt} = -k_1[A][B]$$

$$v_2 = \frac{1}{2}\frac{dC}{dt} = -k_2[C]^2$$

$Only\ in\ the\ equilibrium: v_1 = v_2$

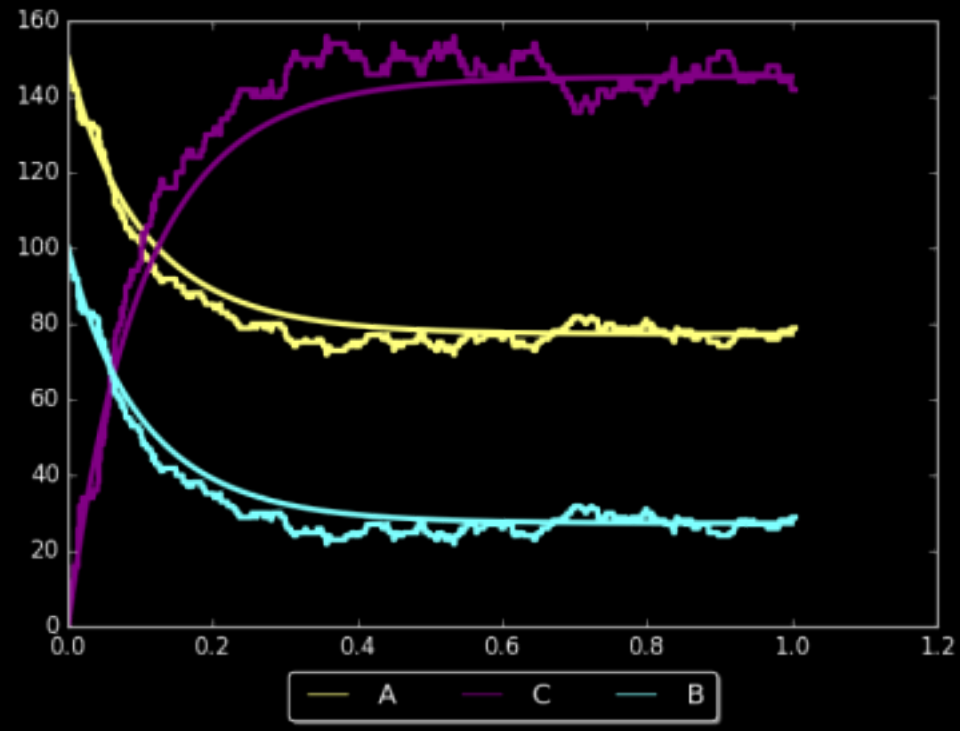


A stochastic approach to the chemical system

- Time evolution of a chemical system is **not continuous**, chemical species quantities can only change by discrete integer amounts.
- It is **not deterministic** if we take into account only the quantities of the chemical species. It is impossible to predict the exact molecular population levels at a future time.
- A better approach is to consider the process as a random walk

Stochastic model assumptions

- The volume *V* is fixed
- The molecules are in thermal equilibrium, collisions occur in a random manner. The mixture is spatially homogeneous.
- A reaction happens when two interacting molecules collide in an "appropriate way”.



Possible combinations

$$R_1: A + B \xrightarrow{k_1} 2C$$

$$R_2: 2C \xrightarrow{k_2} A + B$$

$$\frac{dP_{R_1}}{dt} = \frac{a_1}{dt} = c_1 n_A n_B$$

$$\frac{dP_{R_2}}{dt} = \frac{a_2}{dt} = \frac{c_2 n_C (n_c - 1)}{2}$$

$$v_1 = -k_1 \frac{n_A n_B}{V^2}$$

$$v_2 = -k_2 \frac{n_c^2}{V^2}$$

$$c1 = \frac{k_1}{V^2}$$

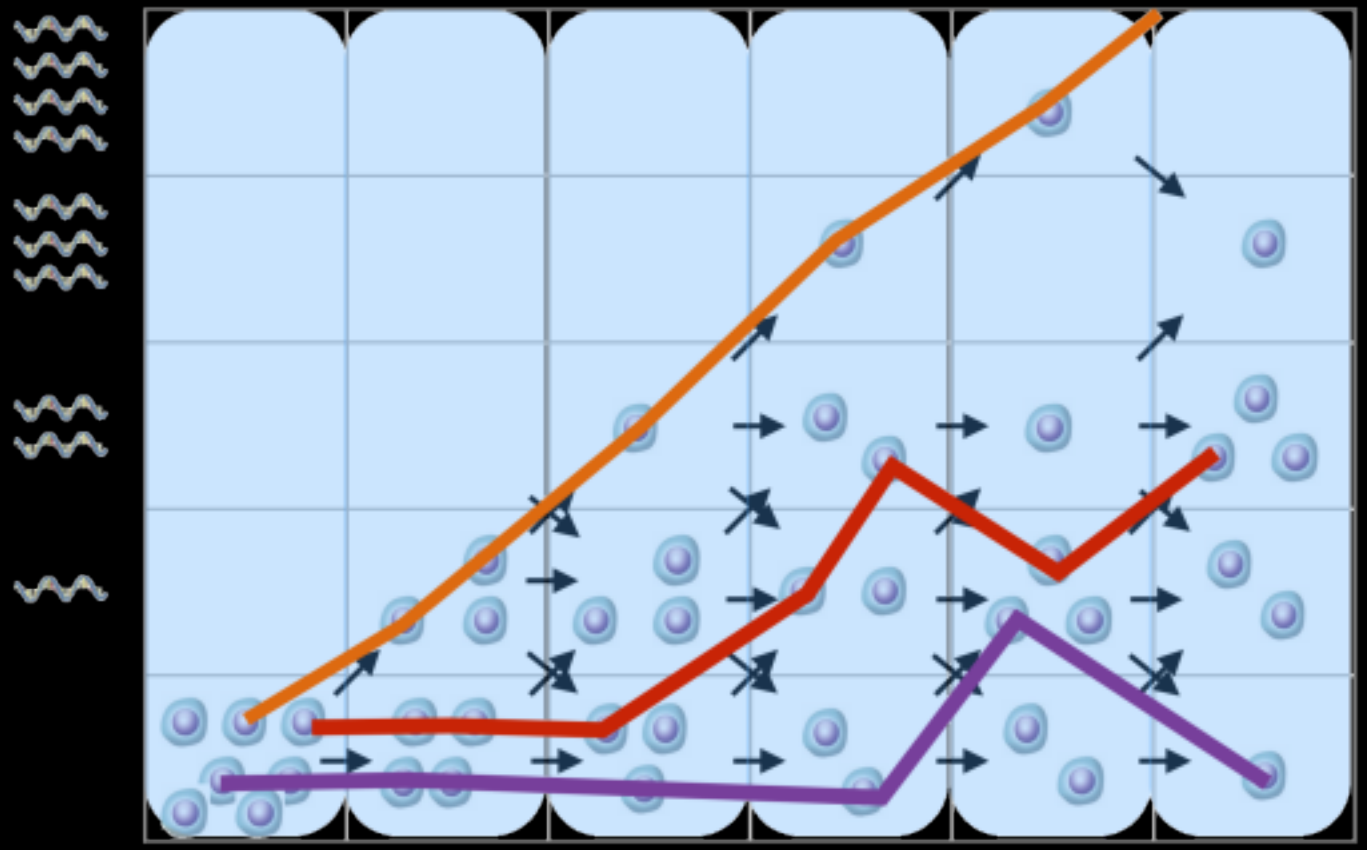
$$c2 = 2\frac{k_2}{V^2}$$

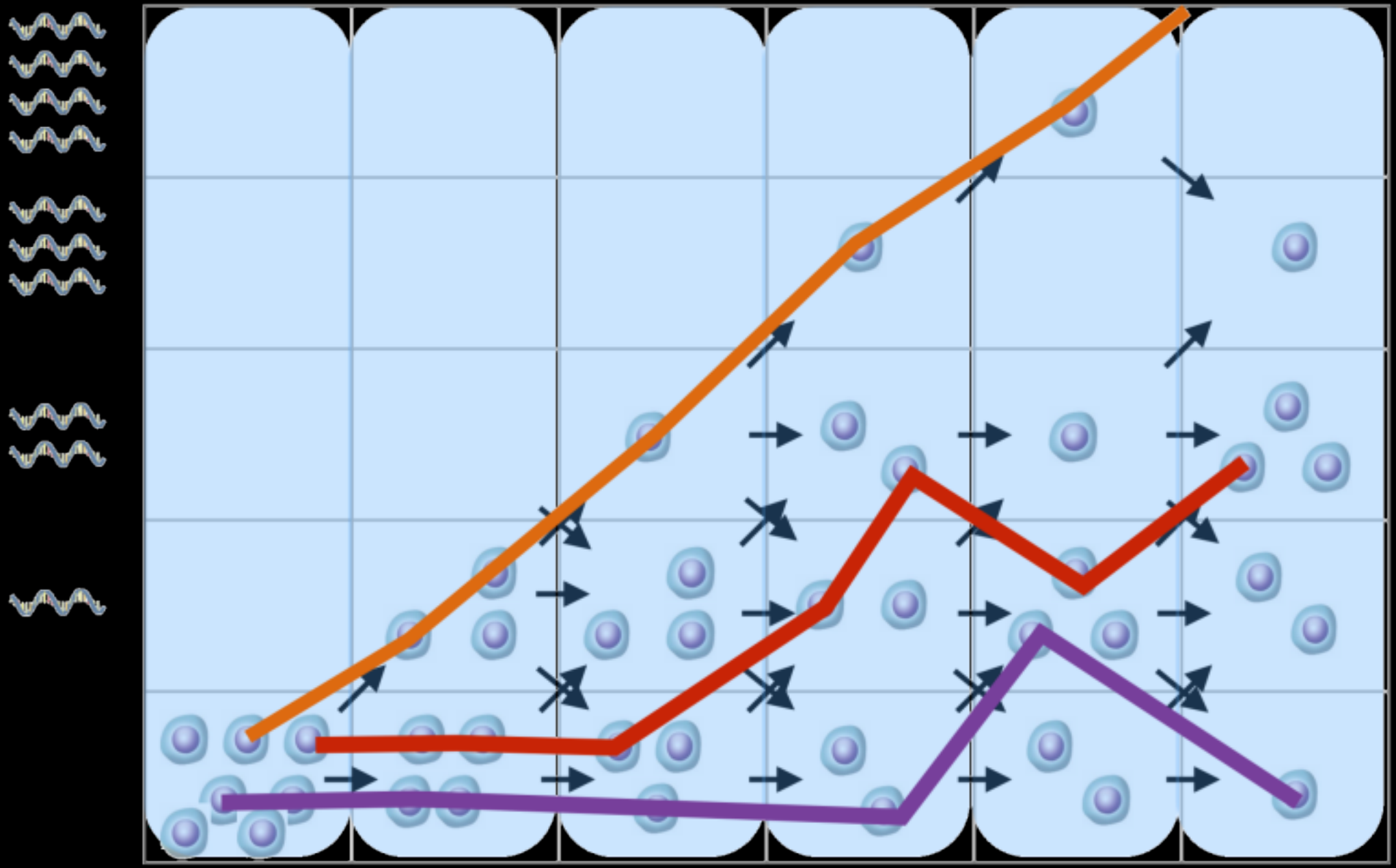
Units?

Volume effect?

Master equation vs. stochastic simulation algorithm

- Master equation: Probability distribution over time
- Stochastic simulation: Calculates a particular trajectory





The Gillespie algorithm

- Basically, we can simulate the evolution of a chemical system by repeatedly asking this two following questions:
  - *Which reaction will happen next?*
  - *When will it happen?*
- How to find the response to them?
  - This is the main goal of this session

The Gillespie algorithm: First, Refreshment

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- The quantities of those elements at time *t*: X_i $(i = 1,2, \dots, N)$
- The possible reactions: $R_\mu (\mu = 1,2, \dots, M)$ M, total number of reactions.
- Parameter for the evolution of the system: c_μ(stochastic)

$$\mathrm{R}_2\colon\ 2C \xrightarrow{k_2} A + B\ ; \frac{a_2}{dt} = \frac{c_2 n_C (n_c - 1)}{2} \rightarrow R_\mu\colon\ a_\mu = c_\mu h_\mu dt$$

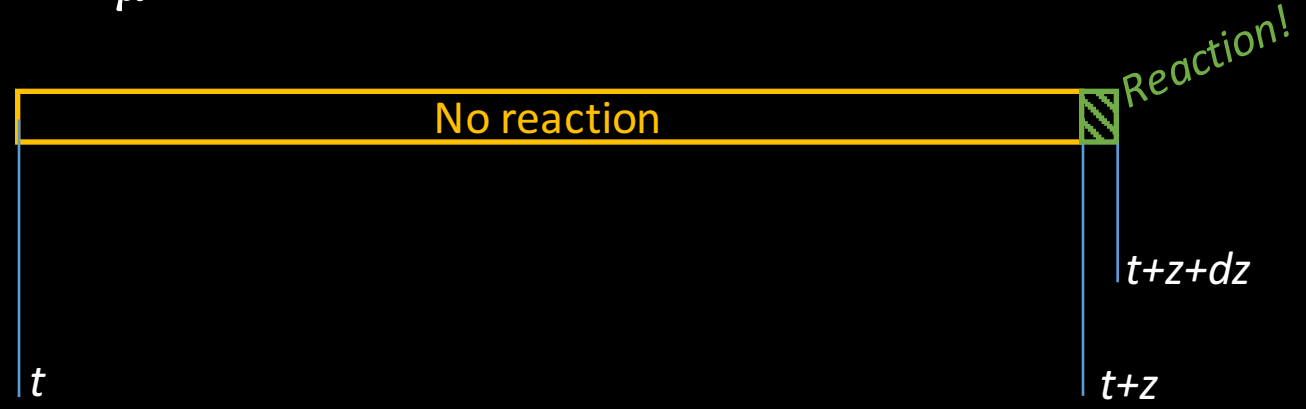
The Gillespie algorithm:

$$P(z,\mu)dz = P_0(z)a_\mu dz$$

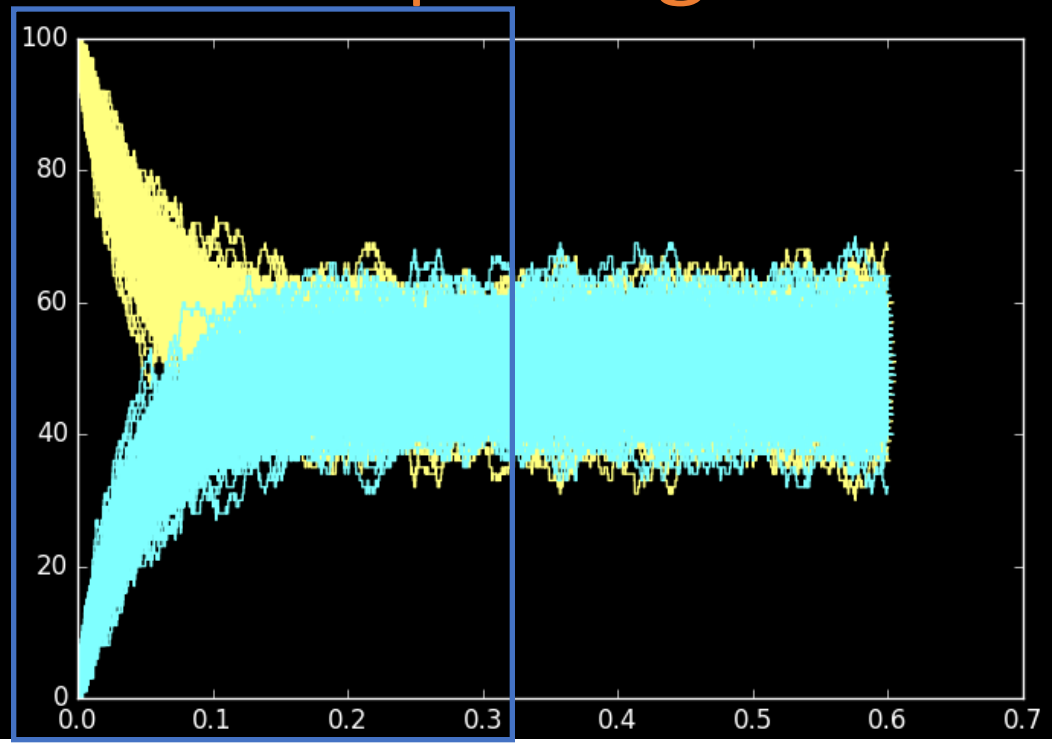
$P(z,\mu)dz$: probability that no reaction happens in the interval *(t, t+z)*, and THE NEXT reaction happens in the interval *(t+z,t+z+dz) and it's* R_μ.

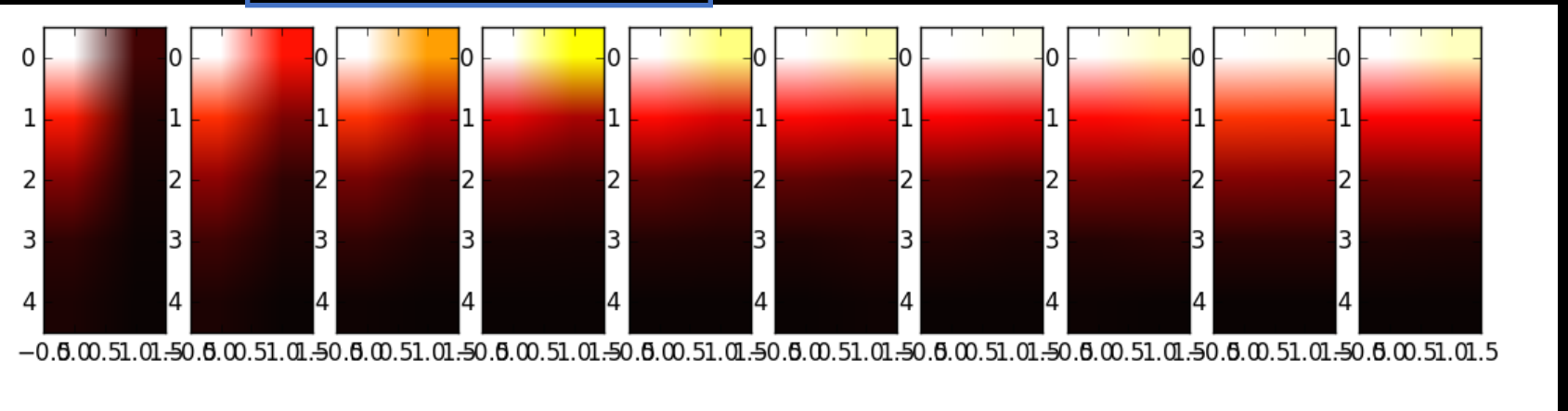
$P_0(z)$: probability that no reaction happens in interval *(t, t+z)*

$a_\mu dz$: probability that THE NEXT reaction happens in the interval *(t+z,t+z+dz) and it's* R_μ.



The Gillespie algorithm: what is $P(z, \mu)dz$?





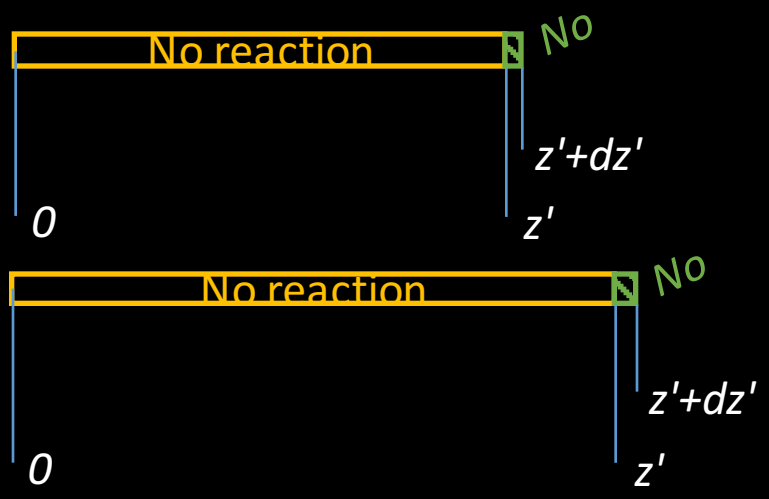
The Gillespie algorithm

$$P(z,\mu)dz = P_0(z)a_\mu dz$$

$$P_0(z' + dz') = P_0(z')\left[1 - \sum_{m=1}^{M} a_m dz'\right] = P_0(z') - P_0(z')a_0 d_z$$

Probability of no reaction

$$P_0(z' + dz') - P_0(z') = dP_0(z') = -P_0(z')a_0 d_z$$



$$\frac{dP_0(z')}{P_0(z')} = -a_0 dz' \rightarrow \ln(P_0(z')) = a_0 z' \rightarrow P_0(z) = e^{-a_0 z}$$

$$Substitute\ in\ the\ first\ equation\colon\ P(z,\mu)\cancel{dz} = e^{-a_0 z}a_\mu \cancel{dz}$$

$$P(z,\mu) = e^{-a_0 z}a_\mu$$

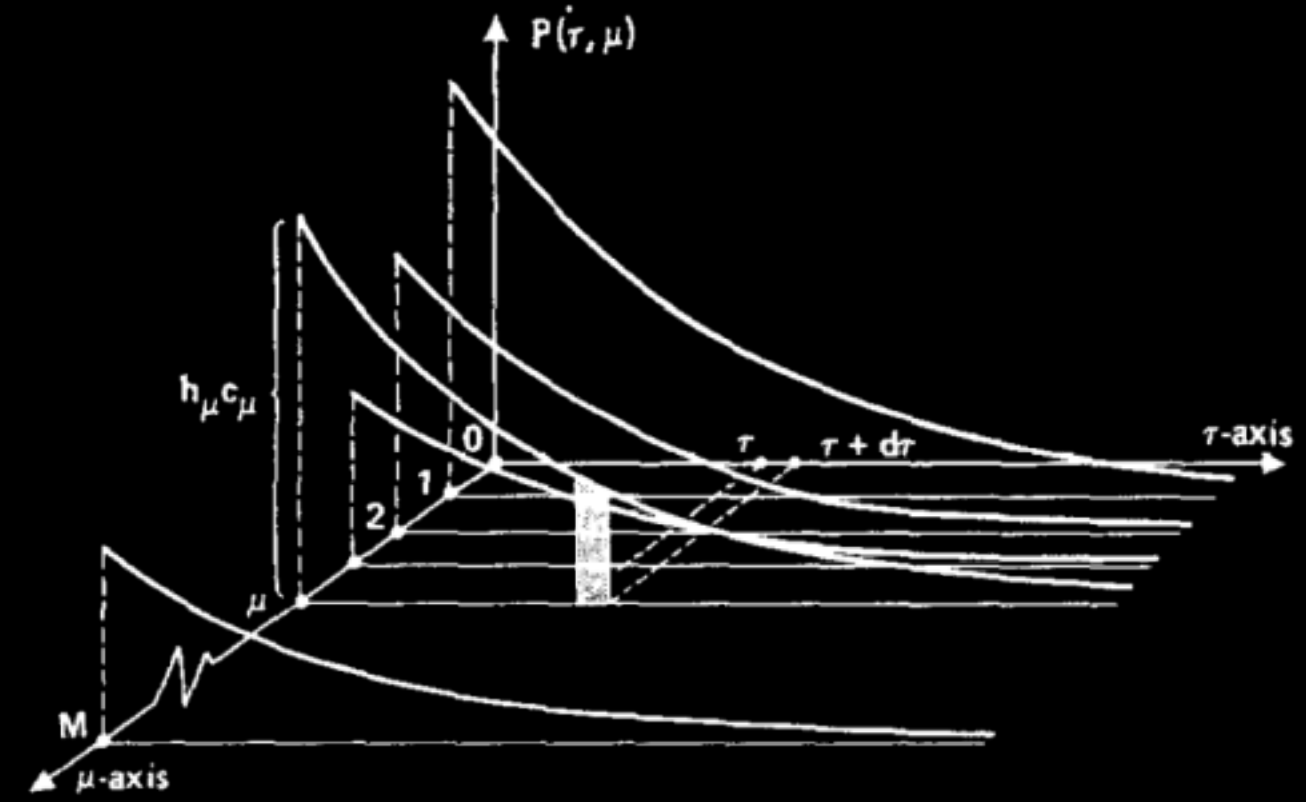
The Gillespie algorithm

$P(z,\mu) = e^{-a_0 z} a_\mu$ is a probability density function

What does it describe?

Why is it an exponential?

Is it useful for our purpose?



The Gillespie algorithm

Another way to think about it… $P(z,\mu) = a_\mu e^{-a_0 z}$

$$P(z,\mu) = P_{any}(z)P(\mu|z)$$

Probability of any reaction to happen during z * that reaction being μ

$$P_{any}(z) = \sum_{\mu=1}^{M} a_\mu e^{-a_0 z} = a_0 e^{-a_0 z}$$

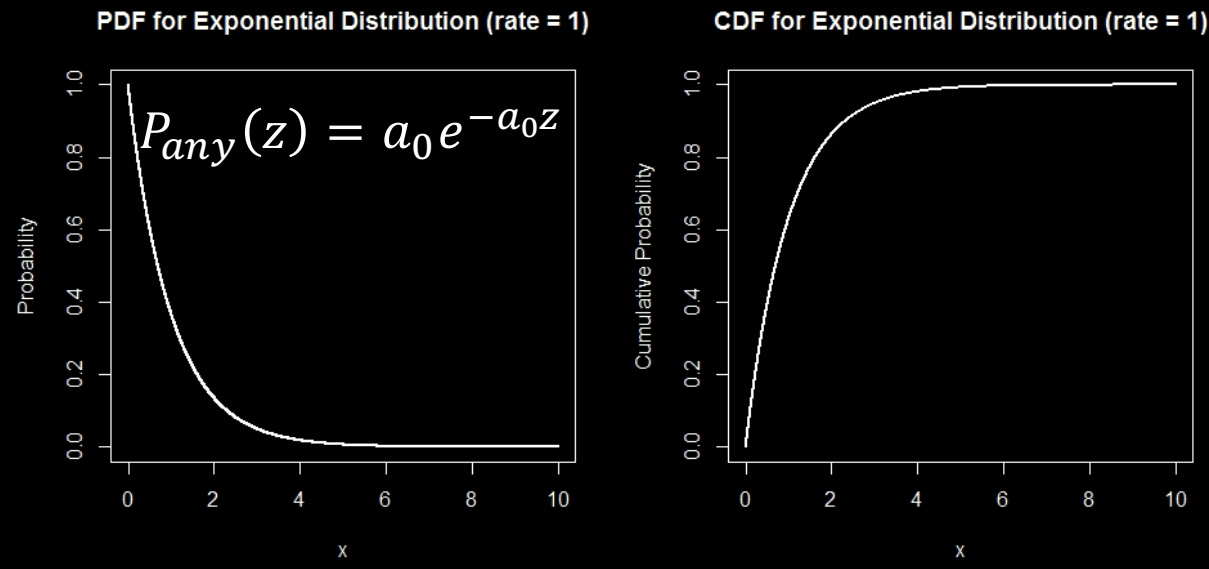
$$P(\mu|z) = \frac{a_\mu}{a_0}$$

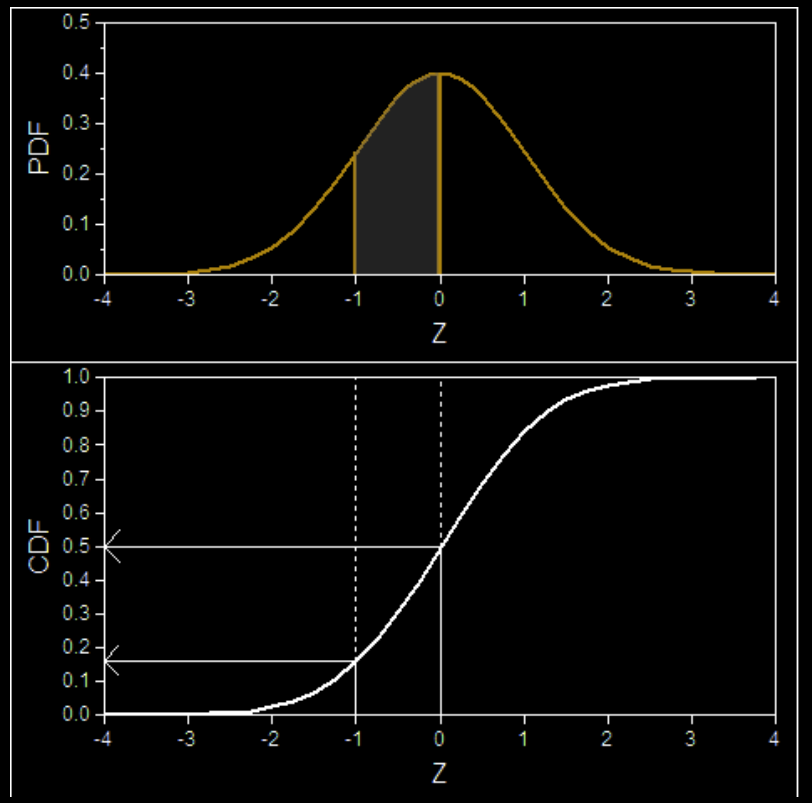
Two independent functions describe the probabilities of our questions

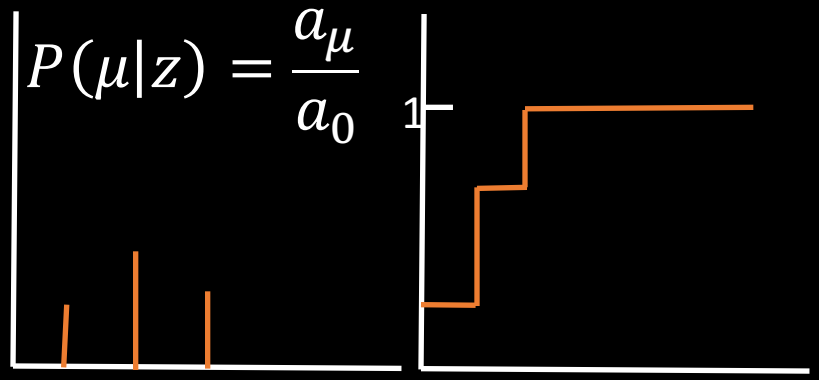
How do these pdfs look? What information can we extract from them?

How can we use pairs of (z,μ) that satisfy those pdfs?

How to sample random values from a PDF







Sampling doing F(x)=random number

How to sample values from a PDF

$$F(z) = \int_0^z P_{any}(z)\mathrm{dz} = \int_0^z a_0 e^{-a_0 z}\mathrm{dz} = 1 - e^{-a_0 z}$$

$$F(z) = 1 - e^{-a_0 z} \rightarrow \ln\big(1 - F(z)\big) = -a_0 z$$

$$z = \frac{1}{A}\ln\left(\frac{1}{1 - F(z)}\right)$$

$$z(r) = \frac{-1}{A}\ln(r)$$

Answer 1: When will the next reaction occur?

How to sample values from a PDF

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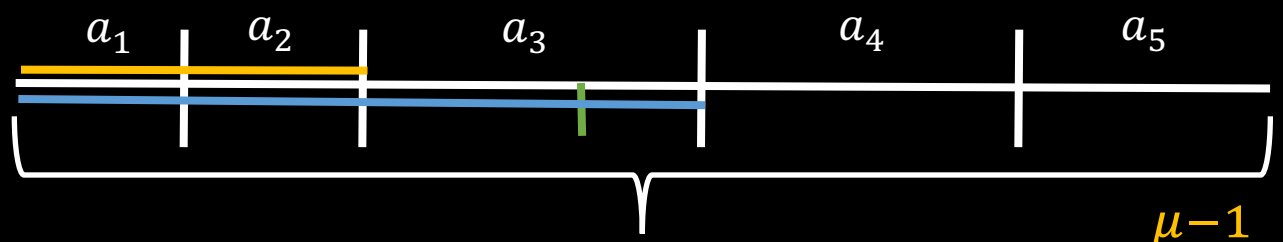
Answer 1: When will the next reaction occur?

How to sample values from a PDF

$$P(\mu|z) = \frac{a_\mu}{a_0}$$

- How to think about it in this discrete case?



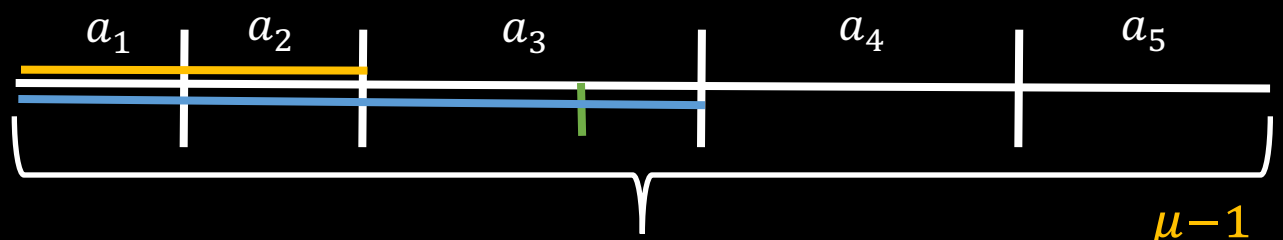
$$\mu \text{ is the integer for which: } \sum_{m=1}^{\mu-1} a_m < a_0 r \leq \sum_{m=1}^{\mu} a_m$$

Answer 2: What reaction will it be?

How to sample values from a PDF

$$P(\mu|z) = \frac{a_\mu}{a_0}$$

- How to think about it in this discrete case?



$$\mu \text{ is the integer for which: } \sum_{m=1}^{\mu-1} a_m < a_0 r \leq \sum_{m=1}^{\mu} a_m$$

Answer 2: What reaction will it be?

Possible projects

- Try it on your own data
- Build master equation
- Think of an example and compare stochastic and deterministic results
- How does tau change with time in different situations?
- Suggestions?