

Simulation and Modelling

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Chemical Reactions and Simulation

With thanks to Daniel Gillespie!

Daniel T. Gillespie, *Simulation Methods in Systems Biology*. SFM 2008, LNCS 5016, pp. 125–167, 2008. Springer-Verlag.

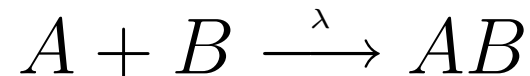
Daniel T. Gillespie, *Exact stochastic simulation of coupled chemical reactions*. *J. Phys. Chem.*, 81(25), pp. 2340–2361, 1977.
DOI: 10.1021/j100540a008

Simulating Large Stochastic Models

- ➔ **Examples:** Chemical reactions, biological systems, epidemic models and parallel and distributed systems
- ➔ Underlying genuinely stochastic models, often reasonable to assume Markovian behaviour, reactions between elements constitute synchronisation in a model

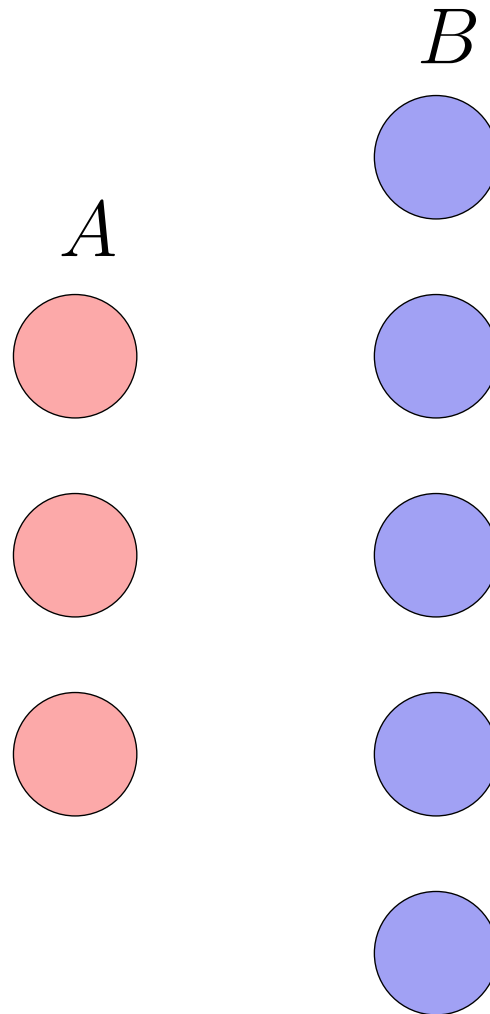
Reaction: Mass action

- ➔ Reaction between e.g. well-mixed fluids and gases
- ➔ Molecules diffuse (Brownian motion)
- ➔ Molecules can potentially react with any other co-reagent molecule
- ➔ Example reaction:

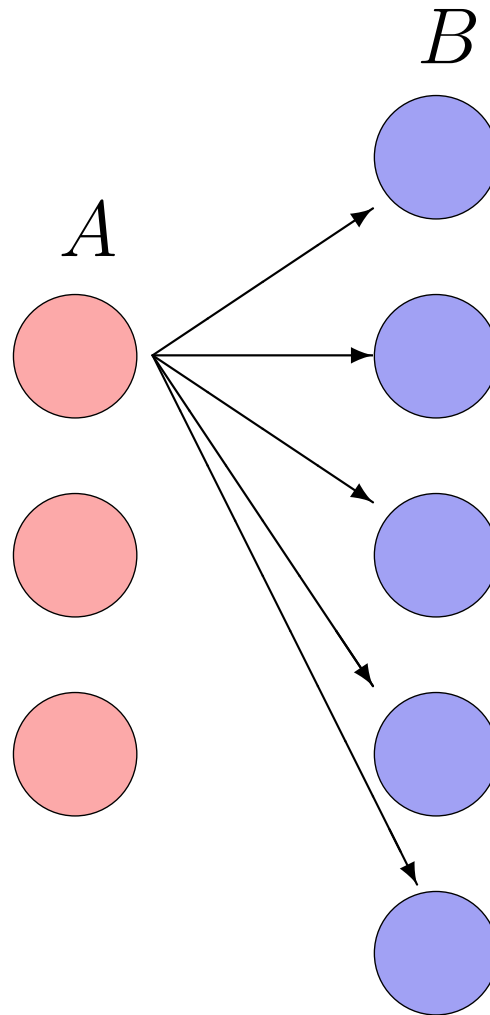


- ➔ Initially m A molecules, n B molecules

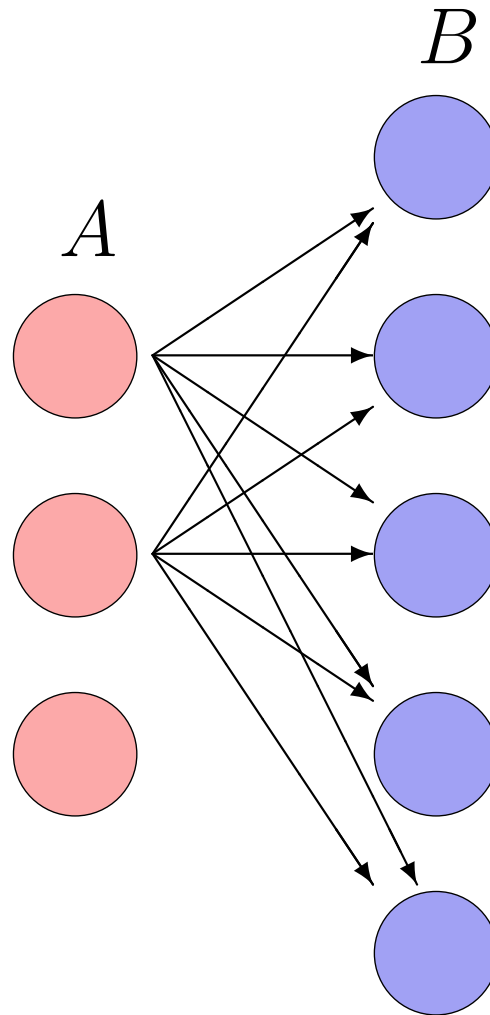
Reaction: Mass action



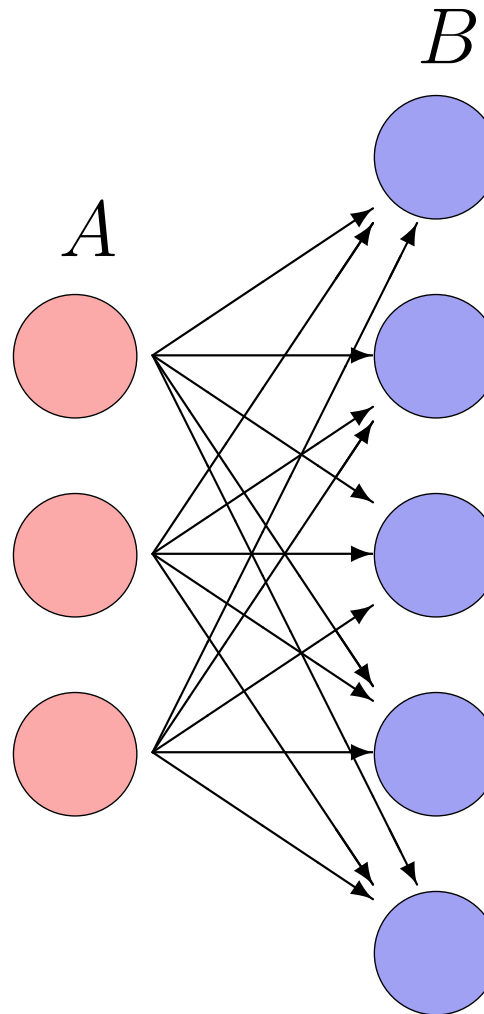
Reaction: Mass action



Reaction: Mass action

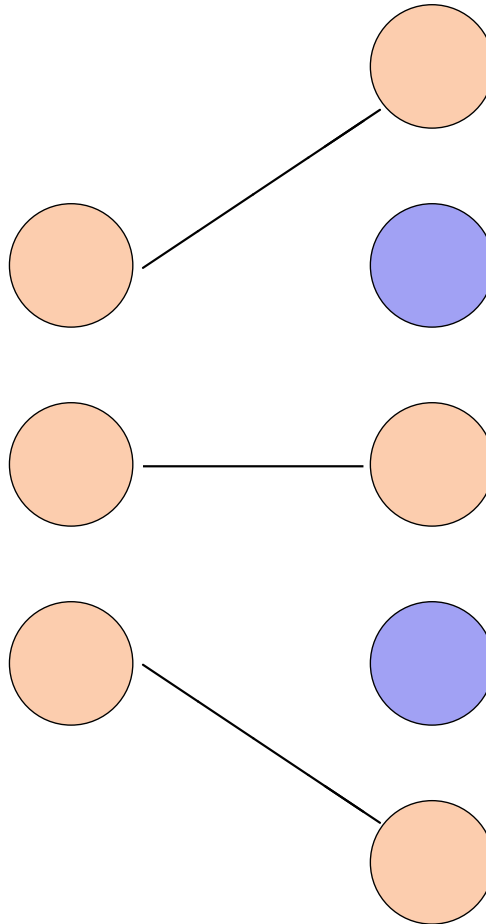


Reaction: Mass action



Total number of possible interactions: mn

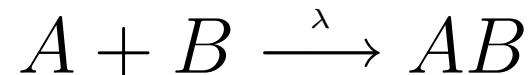
Reaction: Mass action



Total number of actual AB products: $\min(m, n)$

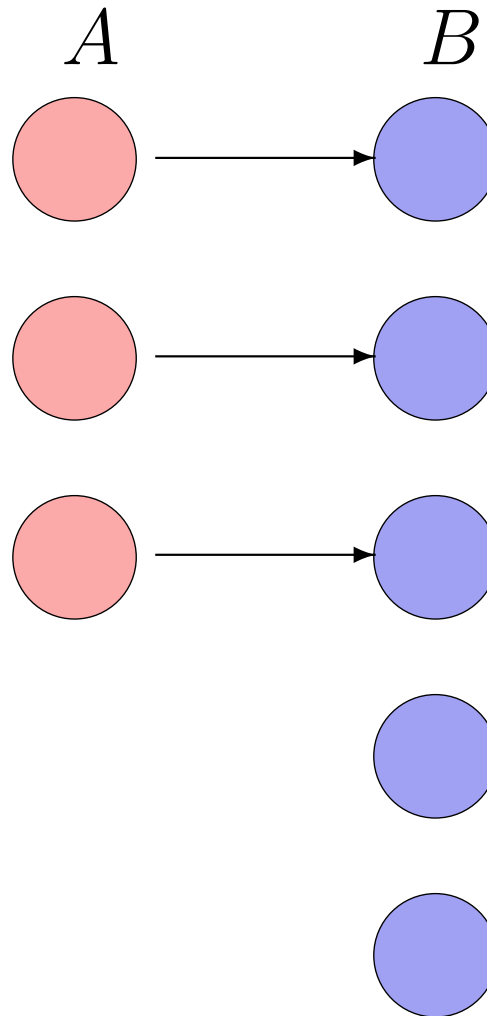
Reaction: Local action

- ➔ Reaction between e.g. surface of two solids, two jellies, two very viscous fluids
- ➔ No molecule diffusion
- ➔ Molecules react with closest local neighbour
- ➔ No reaction competition
- ➔ Example reaction:



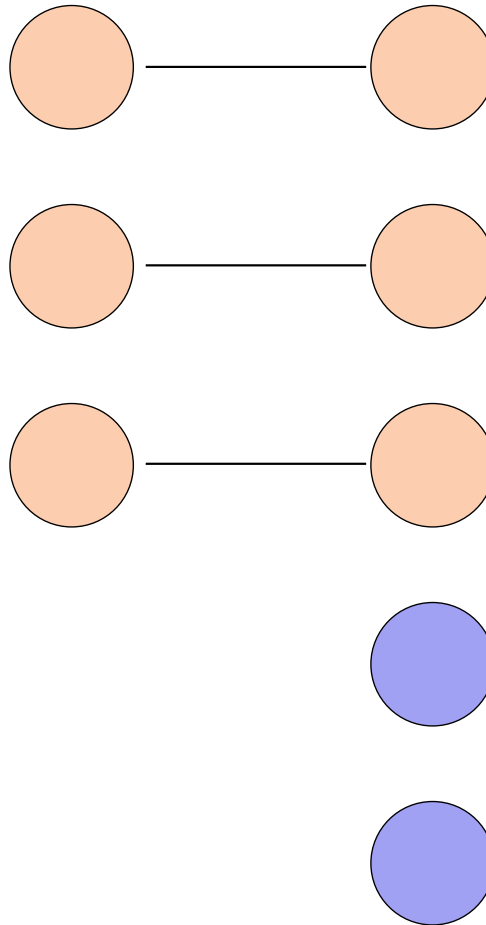
- ➔ Initially m A molecules, n B molecules

Reaction: Local action



Total number of possible reactions: $\min(m, n)$

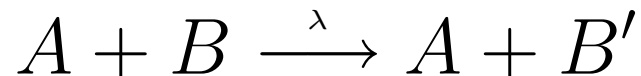
Reaction: Local action



Total number of AB products: $\min(m, n)$

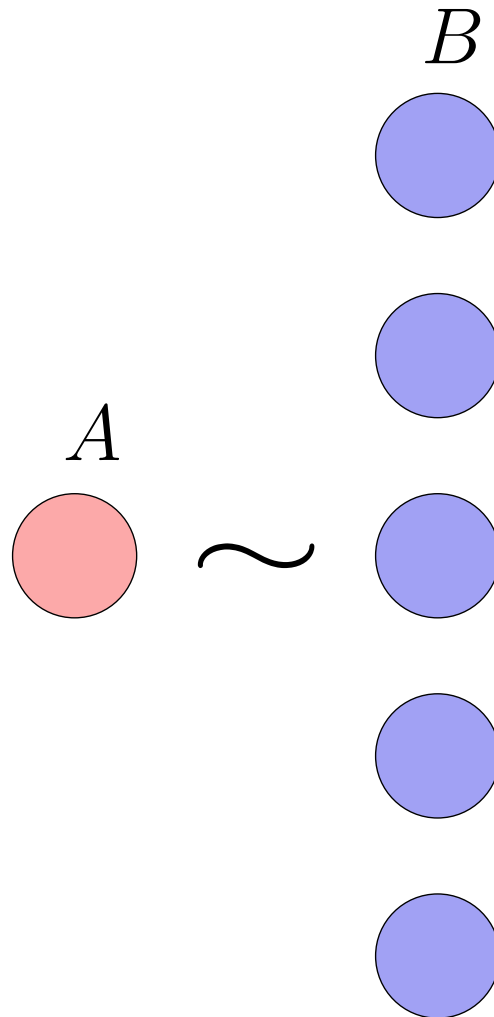
Reaction: Passive action

- ➔ Reaction catalysed by one or more passive molecules
- ➔ Heavily spatially dependent on catalyst shape/configuration
- ➔ Example reaction:



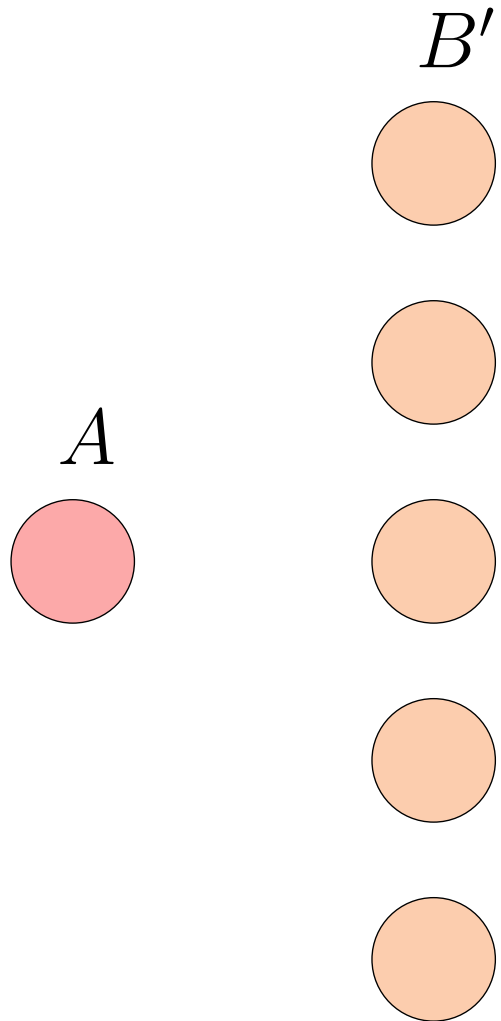
- ➔ Initially 1 A molecule, n B molecules

Reaction: Passive action



Total number of possible reactions: $I(m > 0) n$

Reaction: Catalyst



Total number of B' products: $I(m > 0) n$

Chemical Systems

- Consider a system of molecules of N chemical species $\{S_1, \dots, S_N\}$, which interact through M reaction channels $\{R_1, \dots, R_M\}$ in reaction vessel of volume Ω
- The state of a general chemical system requires giving the instantaneous position, velocity, and species of each molecule in the system

Chemical Systems

- ➔ Specifying the state of a *well-stirred system* is much easier – we need only specify the vector

$$\vec{X}(t) = (X_1(t), \dots, X_N(t))$$

where $X_i(t)$ is the number of S_i molecules contained in a container at time t

- ➔ The *state-change* vector $\vec{\nu}_j = (\nu_{1j}, \dots, \nu_{Nj})$ where ν_{ij} is defined to be the change in the S_i molecular population caused by one R_j reaction event

Propensity

- ➔ So now we can say that reaction R_j produces the following change in the system state

$$\vec{x} \rightarrow \vec{x} + \vec{\nu}_j$$

where x_i is the number S_i molecules in a particular state

- ➔ **Propensity function** $a_j(\vec{x})$ represents, for a given system state \vec{x} , the propensity of reaction R_j to occur

Propensity

- ➔ Fundamental premise of stochastic chemical kinetics, for a given system state \vec{x} :

$$a_j(\vec{x})\delta t = \mathbb{P}(\text{for state } \vec{x}, \text{ reaction } R_j \text{ will occur inside } \Omega \text{ in the next infinitesimal time interval } [t, t + \delta t) \mid \vec{X}(t) = \vec{x})$$

- ➔ Used to express Chemical Master Equation (CME) for finding $P(\vec{x}, t)$, probability system is in state \vec{x} at time t :

$$P(\vec{x}, t) = \mathbb{P}(\vec{X}(t) = \vec{x} \mid \vec{X}(t_0) = \vec{x}_0 \text{ for } t_0 \leq t)$$

Example Propensity Functions

Under reaction R_j happening with reaction rate constant c_j , there are 3 possibilities (assuming no n -way reactions for $n > 2$):

$$\text{If } S_1 \xrightarrow{c_j} \text{ products} \quad a_j(\vec{x}) = c_j x_1$$

$$\text{If } S_1 + S_2 \xrightarrow{c_j} \text{ products} \quad a_j(\vec{x}) = c_j x_1 x_2$$

$$\text{If } 2S_1 \xrightarrow{c_j} \text{ products} \quad a_j(\vec{x}) = c_j \frac{1}{2} x_1 (x_1 - 1)$$

Chemical Master Equation

Consider the possible ways that a system can reach state \vec{x} by time $t + \delta t$:

$$P(\vec{x}, t + \delta t) = \underbrace{P(\vec{x}, t) \times \left(1 - \sum_{j=1}^M (a_j(\vec{x}) \delta t) \right)}_{\mathbb{P}(\text{System does not undergo a reaction in } \delta t)} + \underbrace{\sum_{j=1}^M P(\vec{x} - \vec{\nu}_j, t) \times (a_j(\vec{x} - \vec{\nu}_j) \delta t)}_{\mathbb{P}(\text{System does undergo a reaction } R_j \text{ in } \delta t)}$$

(*)

Chemical Master Equation

Subtracting $P(\vec{x}, t)$ from both sides of (*), dividing by δx and letting $\delta x \rightarrow 0$, we get a partial derivative expression:

$$\frac{\partial P(\vec{x}, t)}{\partial t} = \sum_{j=1}^M [a_j(\vec{x} - \vec{\nu}_j)P(\vec{x} - \vec{\nu}_j, t) - a_j(\vec{x})P(\vec{x}, t)]$$

This is the **Chemical Master Equation (CME)** for the system

In theory the CME completely defines the behaviour of the system – in practice difficult to solve analytically for all but the simplest of $a_j(\cdot)$

Average Behaviour

If we define the mean behaviour of \vec{X} to be:

$$\mathbb{E}(f(\vec{X})) = \sum_{\vec{x}} f(\vec{x})P(\vec{x}, t)$$

We can sum CME over all possible states \vec{x} to get a simpler expression defining the average evolution of the system:

$$\frac{d\mathbb{E}(\vec{X})}{dt} = \sum_{j=1}^M \vec{\nu}_j \mathbb{E}(a_j(\vec{X}))$$

Reaction Rate Equation

If we assume that there is no variance in the individual trajectories of X_i , we can rewrite the previous equation as:

$$\frac{d\mathbb{E}(\vec{X})}{dt} = \sum_{j=1}^M \vec{\nu}_j(a_j(\mathbb{E}(\vec{X})))$$

This is the **Reaction Rate Equation**. It assumes that the mean trajectory dominates the system and any fluctuations in \vec{X} decay

This is the standard set of ODEs used to model many biochemical systems.

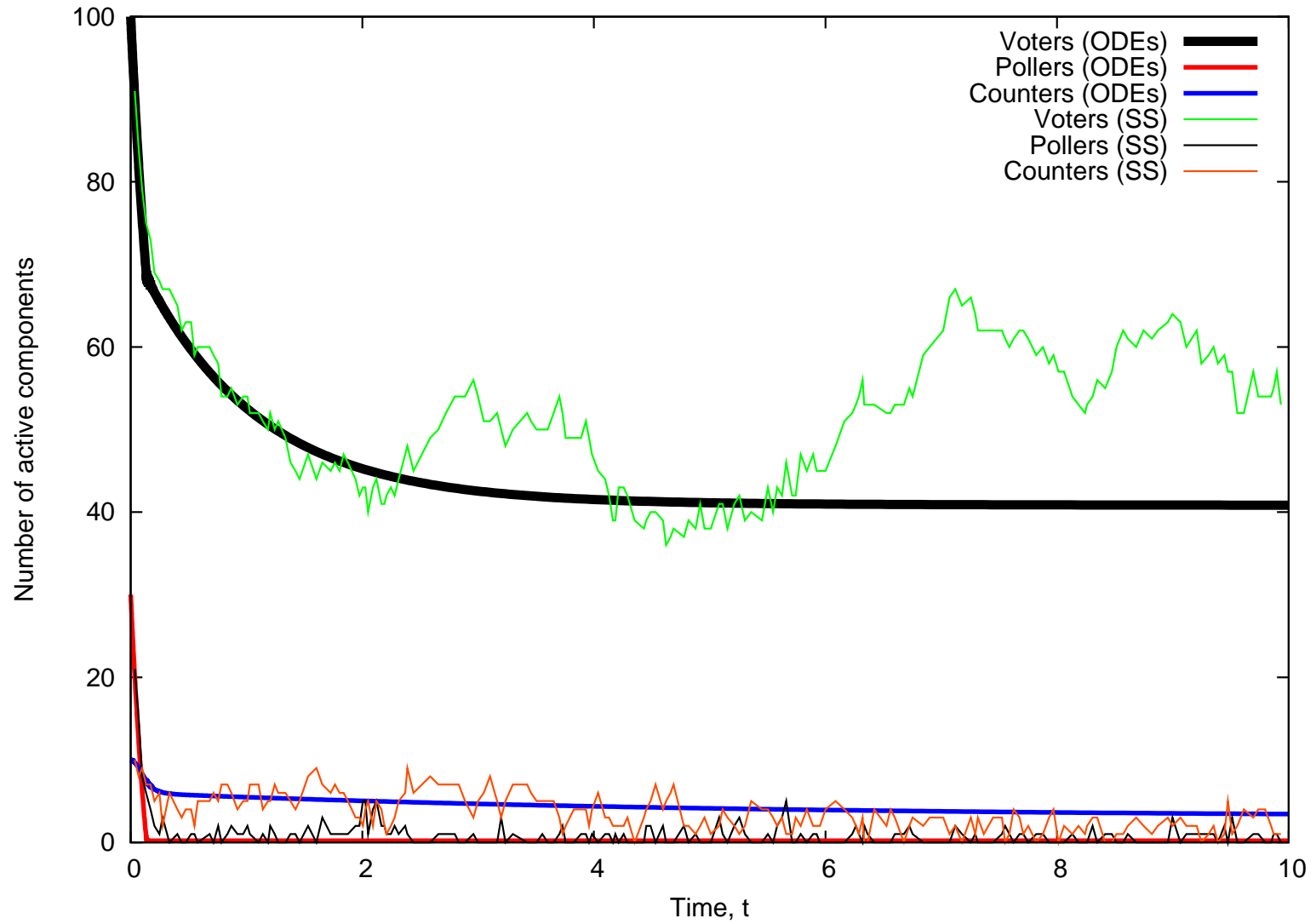
Gillespie's Algorithm

- Instead of trying to solve the CME, *Gillespie's Algorithm* produces a simulated trace of execution of $\vec{X}(t)$
- Looking at the mean of many such traces will usually give a good approximation to $\mathbb{E}(\vec{X})$

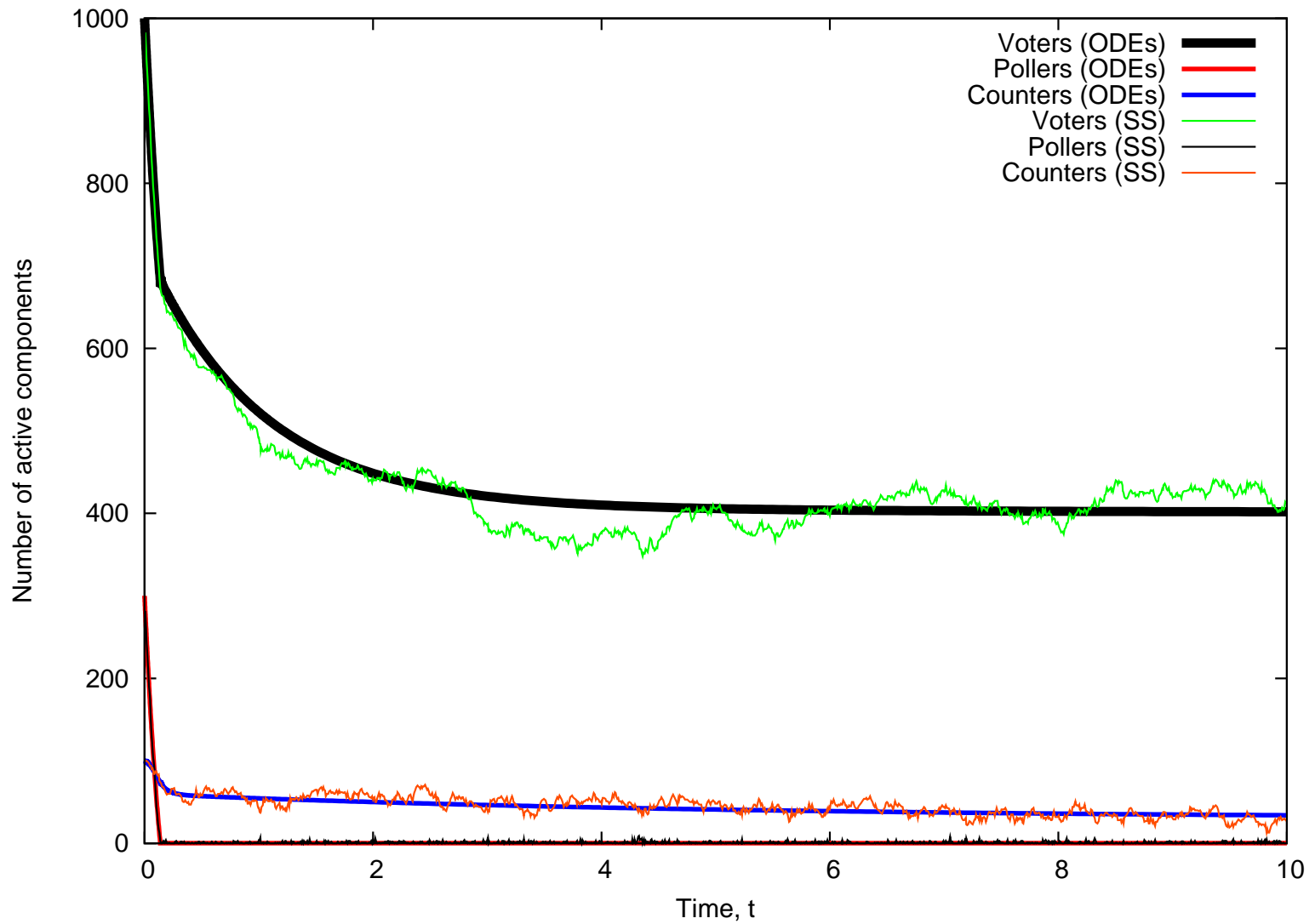
Gillespie's SSA

1. **Initialization:** Initialize no. of molecules in the system, reactions constants, and random number generators
2. **Monte Carlo Step:** Generate random nos. to determine next reaction to occur as well as time interval
3. **Update:** Increase the time step by the randomly generated time in Step 2. Update the molecule count based on reaction that occurred
4. **Iterate:** Go back to Step 2 unless no. of reactants is zero or the simulation time is exceeded

SSA in Action



SSA in Action



SSA in Action

