Stochastic Simulation.
(and Gillespie’s algorithm)

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There are two formalisms for mathematically describing the time behavior of a spatially homogeneous chemical system: the deterministic approach regards the time evolution as a continuous, wholly predictable process which is governed by a set of coupled, ordinary differential equations (the “reaction-rate equations”); the stochastic approach regards the time evolution as a kind of random-walk process which is governed by a single differential-difference equation (the “master equation”). Fairly simple kinetic theory arguments show that the stochastic formulation of chemical kinetics has a firmer physical basis than the deterministic formulation, but unfortunately the stochastic master equation is often mathematically intractable. There is, however, a way to make exact numerical calculations within the framework of the stochastic formulation without having to deal with the master equation directly. [...]

Outline

1 Stochastic Processes

2 The Gillespie algorithm
An exponential distribution models the time of occurrence of a (simple) random event.

It is given by a random variable $T$, with values in $[0, \infty)$, with density

$$f(t) = \lambda e^{-\lambda t},$$

where $\lambda$ is the rate of the exponential distribution. The probability of the event happening within time $t$ is

$$P(T \leq t) = 1 - e^{-\lambda t}.$$

Mean: $E[T] = \frac{1}{\lambda}$

Variance: $VAR[T] = \frac{1}{\lambda^2}$

$\lambda$ is the average density of frequency of events per unit of time.
What happens if we have more than one event competing?

In this case, there is a race condition between events: the fastest event is executed and modifies globally the state of the system.

Continuous Time Markov Chains

The is a discrete set of states, connected by transitions each with an associated rate of an exponential distribution.

In each state, transitions compete in a race condition: the fastest one determines the new state and the time elapsed.

In the new state, the race condition is started anew (memoryless property).
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In each state, we select the next state according to a probability distribution obtained normalizing rates (from $S$ to $S_1$ with prob. $\frac{r_1}{r_1+r_2}$).

The time spent in a state is given by an exponentially distributed random variable, with rate given by the sum of outgoing transitions from the actual node ($r_1 + r_2$).
Stochastic model of a chemical system

We have a set of chemical substances $S_1, \ldots, S_N$ contained in a volume $V$, with

$$X_i = \text{number of molecules of species } i,$$

subject to a set of chemical reactions

$$R_1, \ldots, R_M,$$

where each $R_j$ is of the form

$$R_j : X_{j_1} + X_{j_2} \rightarrow X_{j_1'} + \ldots + X_{j_{p_j}'},$$

$$R_j : X_{j_1} \rightarrow X_{j_1'} + \ldots + X_{j_{p_j}'},$$

$$R_j : \emptyset \rightarrow X_{j_1'} + \ldots + X_{j_{p_j}'}.$$

The system is supposed to be in thermal equilibrium.
**Stochastic Processes**

**The Gillespie algorithm**

**Stochastic model of a chemical system**

**Key Assumption**

Each reaction $R_j$ has associated a specific probability rate constant $c_j$:

$$c_j dt = \text{probability that a randomly chosen combination of } R_j \text{ reactant molecules inside } V \text{ at time } t \text{ will react according to } R_j \text{ in the next infinitesimal time interval } [t, t + dt].$$

**Key Observation**

The next reaction that will happen depends only on the current configuration of the system (number of molecules), not on past history (memoryless property).
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Let’s focus on a bimolecular reaction...

**Problem**

“... it is *physically meaningless* to talk about “the number of molecules whose centers lie inside $\delta V_{coll}$” in the required limit of vanishingly small $\delta t$. ...”
Under the hypothesis of thermal equilibrium, molecules are uniformly distributed in space, and velocities follow a Boltzmann distribution.

The collision volume swept on average is

$$\delta V = \pi r_{12}^2 \langle v_{12} \rangle \delta t.$$ 

The collision probability is therefore

$$\frac{\delta V}{V} = \frac{\pi r_{12}^2 \langle v_{12} \rangle \delta t}{V}.$$
The stochastic model

**Reaction probability**

\[ p_j \stackrel{\text{def}}{=} \text{probability that a } \text{colliding pair of } R_j \text{ reactant molecules will chemically react according to } R_j. \]

The basic rate of reaction \( c_j \) is therefore

\[ c_j = V^{-1} \pi r_{12}^2 \left\langle v_{12} \right \rangle p_j. \]
Rate functions

c_j gives the rate of reaction for a single pair of molecules involved in \( R_j \).

To determine the global rate of reaction \( R_j \), we need to count how many pairs of reacting molecules we have. We do this with the rate function \( h_j(c_j, X) \).

Reactants of different species

\[
X_{j_1} + X_{j_2} \rightarrow \quad h_j(c_j, X) = c_j X_{j_1} X_{j_2}
\]

Reactants of the same species

\[
2X_{j_1} \rightarrow \quad h_j(c_j, X) = c_j \frac{X_{j_1} (X_{j_1} - 1)}{2}
\]
From rate functions, we can derive a differential equations saying how the probability of being in different states (of having different number of molecules) varies over time. It is called the chemical master equation:

$$\frac{dP(X, t)}{dt} = \sum_{j=1}^{M} \left( h_j(c_j, X - \nu_j)P(X - \nu_j, t) \right) $$

A reaction $R_j$ happened in time $[t, t + dt]$ 

No reaction happened in $[t, t + dt]$

**PRO**

This equation is *everything we need to know* about the stochastic process.

**CONS**

This equation is *very difficult to solve*, even numerically.
The central notion becomes the following definition of reaction probability density function:

\[ P(\tau, j) = \text{def} \quad \text{probability that, given the state } X = (X_1, \ldots, X_N) \text{ at time } t, \text{ the next reaction in } V \text{ will occur in the infinitesimal time interval } (t + \tau, t + \tau + dt), \text{ and will be an } R_j \text{ reaction} \]
**Explicit form of** $P(\tau, j)$

$$P(\tau, j) = \underbrace{h_0(X)e^{-h_0(X)\tau}}_{\text{time elapsed}} \cdot \underbrace{\frac{h_j(c_j, X)}{h_0(X)}}_{\text{next reaction}}$$

**Intuitively...**

The equation says that the next reaction is chosen with probability $\frac{h_j}{h_0}$, while the time elapsed to see this reaction happen is exponentially distributed with rate $h_0$.

This stochastic process is a Continuous Time Markov Chain.
A random number generator can be used to draw random pairs $(\tau, \mu)$ whose probability density function is $P(\tau, \mu)$. Given $r_1$ and $r_2$ randomly generated, determine $\tau$ and $\mu$ such that:

$$\tau = \frac{1}{h_0} \log \left(\frac{1}{r_1}\right) \quad \sum_{\nu=1}^{j-1} h_\nu < r_2 h_0 \leq \sum_{\nu=1}^{j} h_\nu$$

A general Monte Carlo technique called inversion method: $x$ will be randomly drawn with probability density function $P(x)$ if $x = F^{-1}(r)$ with $r$ randomly drawn with uniform probability density function in $[0, 1]$ and $F$ is the probability distribution function ($\int_{-\infty}^{x} P(y)dy$).
The Gillespie algorithm

1. Set $t=0$ and $n=0$.
2. Generate $r_1$ and $r_2$ from $\text{URN}$.
   - Take $\tau = (1/a_0) \ln (1/r_1)$.
   - Take $\mu$ so that $\sum_{v=1}^{M} a_v = \mu$.
3. Set $t=t+\tau$.
   - Adjust $X_v$ values according to $R_v$.
   - Set $n=n+1$.

Figure 2. Schematic of the stochastic simulation algorithm.
Gillespie Algorithm and Petri Nets

2P ↔ P_2

h_1(1, X) = 1 \times (27 \times 28)/2 = 378
h_2(2, X) = 2 \times 12 = 24
h_0(X) = 378 + 24 = 402
p_1 = 0.94
p_2 = 0.06
time = 1/402
**Gillespie Algorithm and Petri Nets**

\[ h_1(c_1, x) = \frac{1 \times (27 \times 28)}{2} = 378 \]

\[ h_2(c_2, x) = 2 \times 12 = 24 \]

\[ h_0(x) = 378 + 24 = 402 \]

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Each channel has a basic rate $\lambda$ associated to it.

The global rate of a channel depends on how many agents are ready to communicate on it.

In this example:

$$\lambda MN$$

The functions $h_i$ are determined implicitly by the semantics of the language. Gillespie can be used to simulate stochastic $\pi$-calculus as well!!!
An example: genetic regulatory networks

Genes as logical gates

Repressilator

Repressilator in sCCP

A. Policriti
Stochastic Simulation