Stochastic Simulation.
(and Gillespie's algorithm)

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Quote of the day

D.T. Gillespie *Exact Stochastic Simulation of Coupled Chemical Reactions* J. of Physical Chemistry, 81(25), 1977

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

Exponential distribution

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 λ is the rate of the exponential distribution.
The probability of the event happening within time t is

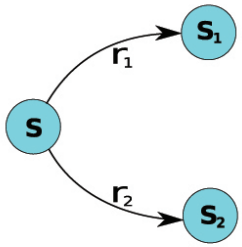
$$P(T \leq t) = 1 - e^{-\lambda t}.$$

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

λ is the average density of frequency of events per unit of time.

Continuous Time Markov Chains

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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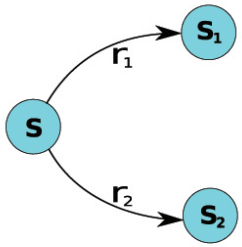

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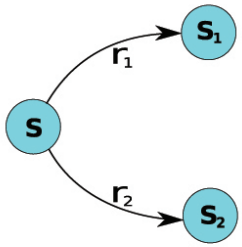

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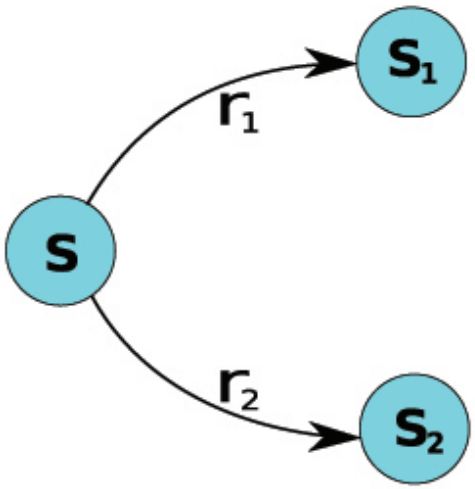

Equivalent Characterization

- 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

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

subject to a set of chemical reactions

$$R_1, \ldots, R_M,$$

where each R_j is of the form

$$R_j : X_{j_1} + X_{j_2} \to X_{j'_1} + \ldots + X_{j'_{p_j}},$$

$$R_j : X_{j_1} \to X_{j'_1} + \ldots + X_{j'_{p_j}},$$

$$R_j : \emptyset \to X_{j'_1} + \ldots + X_{j'_{p_j}},$$

The system is supposed to be in thermal equilibrium

Stochastic model of a chemical system

Key assumption

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

$c_j dt$ = probability that a randomly chosen combination of R_j reactant molecules inside V at time t will react according to R_j 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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Deriving kinetic parameters

Let's focus on a bimolecular reaction...

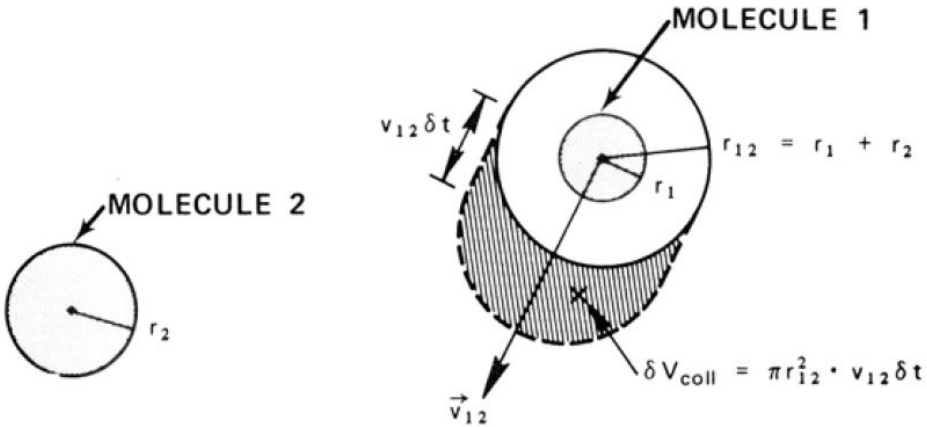

Figure 1. The "collision volume" δV_{coll} which molecule 1 will sweep out relative to molecule 2 in the next small time interval δt.

Problem

"... it is *physically meaningless* to talk about "the number of molecules whose centers lie inside δV_{coll}" in the required limit of vanishingly small δt. ..."

The stochastic model

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

$$p_j \quad =_{def} \quad \text{probability that a } \textit{colliding} \text{ pair of } R_j \text{ reactant molecules will chemically react according to } R_j.$$

The basic rate of reaction c_j is therefore

$$c_j = V^{-1}\pi r_{12}^2 \langle v_{12} \rangle p_j.$$

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 $h_j(c_j, \mathbf{X})$.

Reactants of different species

$$X_{j_1} + X_{j_2} \to \blacksquare \quad h_j(c_j, \mathbf{X}) = c_j X_{j_1} X_{j_2}$$

Reactants of the same species

$$2X_{j_1} \to \blacksquare \quad h_j(c_j, \mathbf{X}) = c_j \frac{X_{j_1}(X_{j_1}-1)}{2}$$

Chemical Master Equation

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:

$$\frac{dP(\mathbf{X},t)}{dt} = \sum_{j=1}^{M} \Bigg(\underbrace{h_j(c_j, \mathbf{X}-\nu_j)P(\mathbf{X}-\nu_j,t)}_{\text{A reaction } R_j \text{ happened in time } [t,t+dt]} - \underbrace{h_j(c_j,\mathbf{X})P(\mathbf{X},t)}_{\text{No reaction happened in } [t,t+dt]} \Bigg)$$

Pro

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

Cons

This equation is *very difficult to solve*, even numerically.

The approach of Gillespie

The central notion becomes the following definition of reaction probability density function:

$$P(\tau, j) \quad =_{def} \quad \begin{array}{l}\text{probability that, given the state } \mathbf{X} = \\ (X_1, \ldots, X_N) \text{ at time } t, \text{ the } \textit{next} \text{ reac-} \\ \text{tion in } V \text{ will occur in the infinitesimal} \\ \text{time interval } (t+\tau, t+\tau+dt), \textit{and} \text{ will} \\ \text{be an } R_j \text{ reaction}\end{array}$$

The approach of Gillespie

Explicit form of $P(\tau, j)$

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

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.

Numerically simulating $P(\tau, \mu)$

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A random number generator can be used to draw random pairs (τ, μ) whose probability density function is $P(\tau, \mu)$.
Given r_1 and r_2 randomly generated, determine τ and μ such that:

$$\tau = (1/h_0)\log(1/r_1) \qquad \Sigma_{\nu=1}^{j-1} h_\nu < r_2 h_0 \leq \Sigma_{\nu=1}^{j} h_\nu$$

The method

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 algorithm

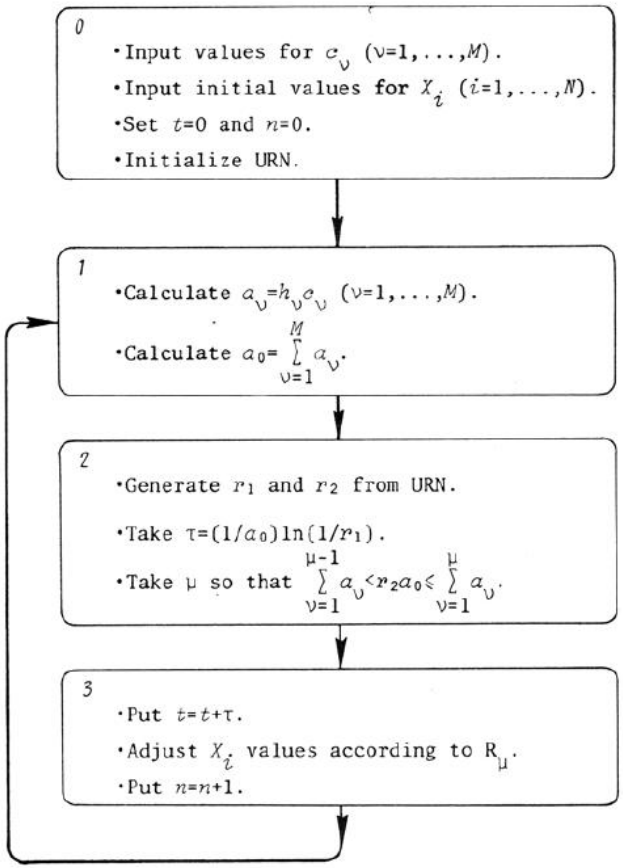
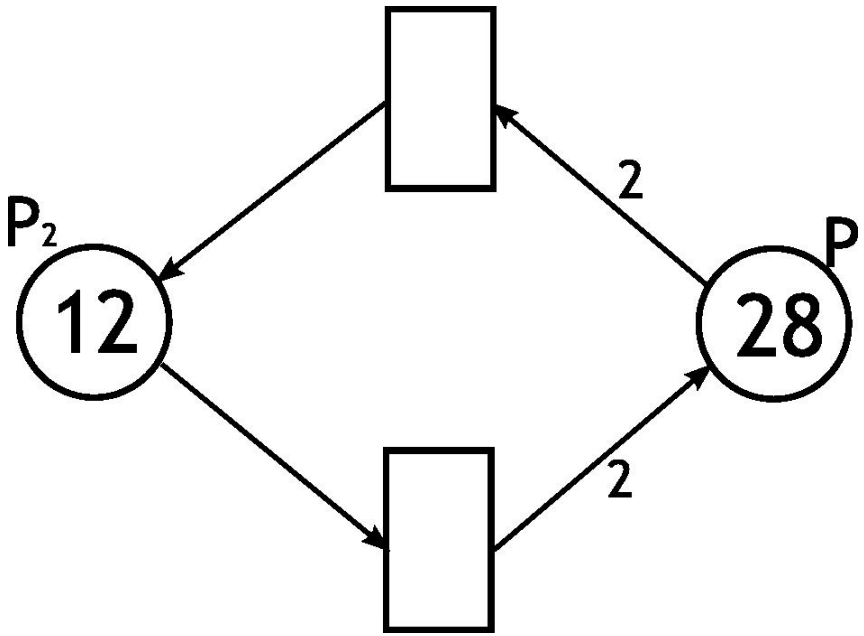


Figure 2. Schematic of the stochastic simulation algorithm.

Gillespie Algorithm and Petri Nets



$$2P \leftrightarrow P_2$$

$h_1(1, \mathbf{X}) = 1 * (27 * 28)/2 = 378$
$h_2(2, \mathbf{X}) = 2 * 12 = 24$
$h_0(X) = 378 + 24 = 402$
$p_1 = 0.94$
$p_2 = 0.06$
$\text{time} = 1/402$

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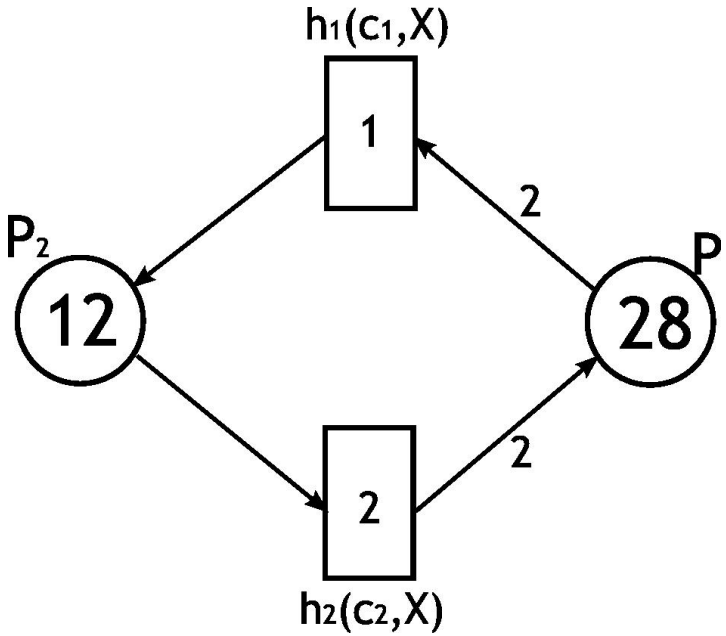

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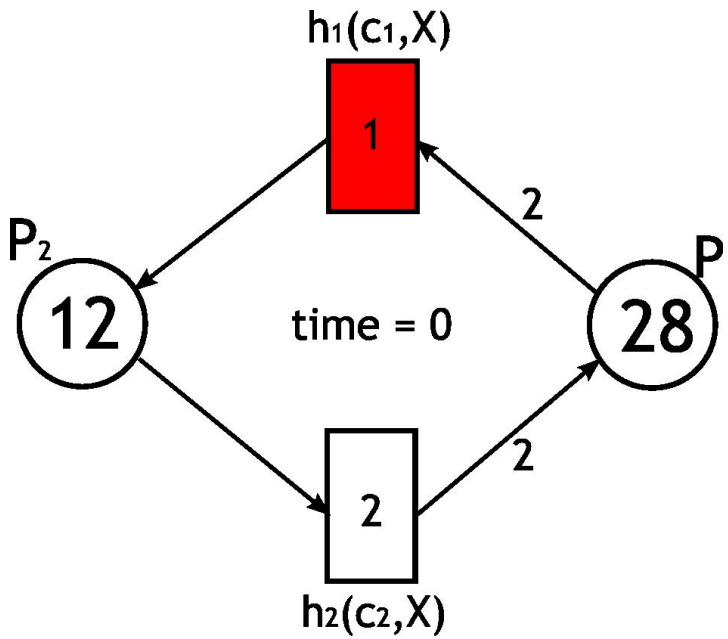

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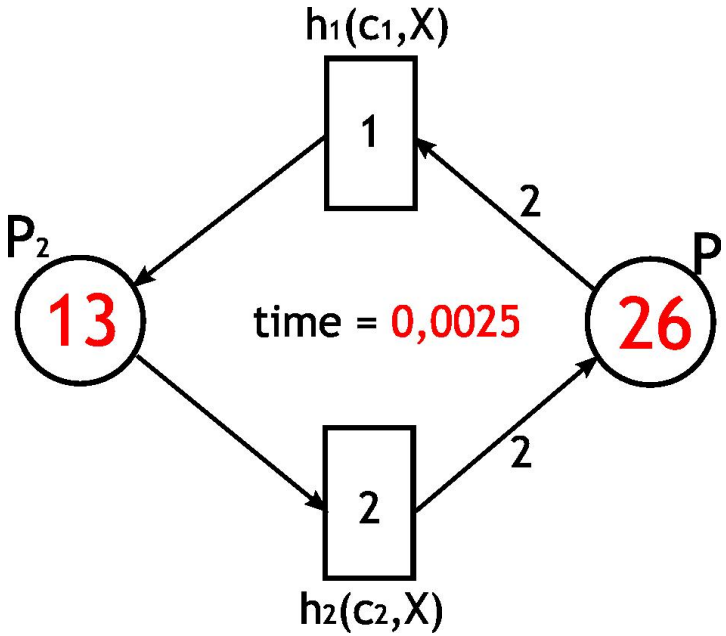

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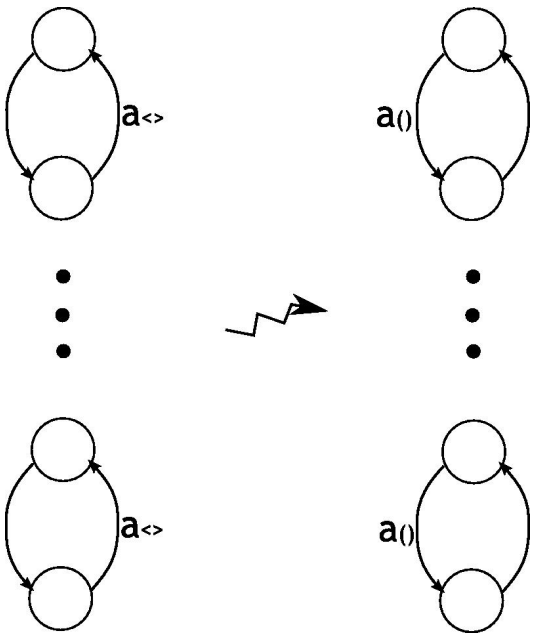
Gillespie Algorithm and π-calculus



Each channel has a basic rate λ associated to it.

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

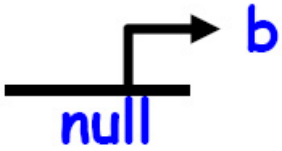
In this example:

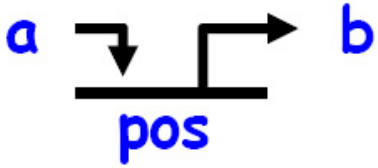
$$\lambda MN$$

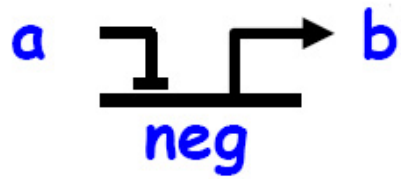
The functions h_i are determined implicitly by the semantics of the language. Gillespie can be used to simulate stochastic π-calculus as well!!!

An example: genetic regulatory networks

Genes as logical gates







Repressilator