

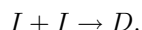
Stochastic Chemical Kinetics

Joseph K. Scott*

November 10, 2011

1 Introduction to Stochastic Chemical Kinetics

Consider the reaction



The conventional kinetic model for the concentration of I in a closed system is given by

$$\frac{dC_I}{dt}(t) = -kC_I(t)C_I(t),$$

where k is the rate constant. The stochastic approach to chemical kinetics is concerned with modeling chemical reactions in situations where the assumptions underlying equations of this type break down. In order to illustrate this, suppose that the reaction above is occurring in a drop of water of volume V , which contains only a very small number, say 3, of molecules of I . The kinetic equation above encounters the following complications:

1. *The state C_I changes in discrete increments.* We can rewrite the equation above in terms of the number of molecules of I as

$$\frac{dN_I}{dt}(t) = -\left(\frac{kN_{Av}}{V}\right)N_I(t)N_I(t),$$

where N_{Av} is Avogadro's number. Solving this ODE from some known initial condition, we are assuming that the number of molecules N_I changes continuously and can take any value in \mathbb{R} (this is called a *continuum assumption*). Surely, if we begin solving this equation with $N_I(t_0) = 3$, there will come a time t' at which $N_I(t') = 2.5$. However, in reality this quantity should only take integer values; it doesn't make physical sense to have 2.5 molecules. In cases where we have a very large number of molecules, say $N_I \approx 1 \times 10^{23}$, this issue can be easily overlooked because a difference of 0.5 out of 10^{23} causes very little error in the rate equation. However, the problem can become very serious for small numbers of molecules. In the worst case, if $N_I = 2$, then only one reaction can occur, after which $N_I = 0$ and the reaction rate must also be zero. However, the continuum approximation predicts a nonzero rate with, for example, $N_I = 0.5$.

2. *Reactions occur as discrete events.* The continuum approximation predicts a nonzero rate of reaction whenever, $N_I \neq 0$. However, in reality reactions are not always

occurring. Reactions occur when two molecules collide with each other in the proper orientation and with sufficient energy to cause a chemical change. Therefore, a correct model should have intervals of time in which no reactions occur, punctuated by instantaneous reaction events that change N_I in integer increments, according to the reaction stoichiometry. From this perspective, it is incorrect to talk about a reaction *rate* at all. Again, if there are very many molecules ($N_I \approx 10^{23}$), then reactive collisions will happen very frequently and, insofar as we are only interested in the macroscopic *average* number of these reaction events in a given interval of time, it is completely excusable to think in terms of reaction rates and apply the continuum approximation.

3. *Reaction events are stochastic.* Because the continuum approximation regards reactions as happening continuously with some rate, there is no need to worry about *when* the underlying reaction events occur. However, if we regard reactions as discrete events, how will we predict when these events will occur? Short of modeling the motion of every molecule in our system using Newton's equations of motion, we cannot answer this question precisely. We will have to settle for the *probability* that some reaction will occur in a given interval of time. From this perspective, our perceived behavior of systems with very few molecules is not deterministic. That is, in contrast to what the continuum approximation suggest, the initial condition of the system will not fully specify the system at later times. Rather, the state at later times depends on what sequence of reaction events occurs, which we can only characterize in terms of probabilities. Systems of this type are called *stochastic*.

To reiterate, we are concerned with studying (and ultimately simulating) the behavior of chemically reacting systems in situations where the continuum equations do not apply. In general, this will only happen when one or more reactions depend on a chemical species which is present in very small numbers. However, there are other situations involving unstable or metastable systems which also require a stochastic treatment because fluctuations in the number of molecules are important. Since the continuum model only captures some kind of *average* behavior, it cannot predict phenomena which depend on fluctuations.

1.1 Motivating Example

A very interesting system related to cell signaling pathways in human immune response was studied by researchers in Prof. Charkraborty's lab here at MIT. Their work shows that, not only is stochastic simulation warranted for these systems, but also that the stochastic model predicts fundamentally different behavior than does the continuum approximation, and this behavior is crucial to the functioning of the signalling pathway. If you are interested, see Artyomov et. al, *Purely stochastic binary decisions in cell signaling models without underlying deterministic bistabilities*, PNAS, 104, 48, 18958-18963, 2007. However, note that this is not an isolated application. Since the popularization of the stochastic approach in the 1970's, there has been a steady increase in its application and today the literature positively abounds with examples.

2 Formalization of the Stochastic Problem

Consider a volume V containing N chemically reacting species, S_1, \dots, S_N , and denote the number of molecules of each at time t by

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

These species can undergo M chemical reactions, R_1, \dots, R_M . Each reaction R_μ has an associated stoichiometry vector $\boldsymbol{\nu}_\mu$, which describes the discontinuous change in \mathbf{X} when the reaction R_μ occurs. For example, if $N = 3$, then the reaction



has stoichiometry vector $\boldsymbol{\nu} = (-1, -1, 1)$. If this reaction occurs at \hat{t} and the number of molecules immediately before \hat{t} is $\mathbf{X}(\hat{t} - dt) = (10, 10, 10)$, then after the reaction occurs we have $\mathbf{X}(\hat{t} + dt) = (9, 9, 11)$. In general, the occurrence of reaction R_μ at time \hat{t} changes the state vector according to

$$\mathbf{X}(\hat{t} + dt) = \mathbf{X}(\hat{t} - dt) + \boldsymbol{\nu}_\mu.$$

As mentioned previously, we will not simulate reacting systems in enough detail to say deterministically when a given reaction will occur. Instead, we assume that these reactions occur stochastically, according to some probability distributions. Our goal is to understand what these distributions are, and how they can be used to describe the state of the system at future times probabilistically. In the following subsections, we present some preliminary derivations concerning the probabilities of reaction events. In Sections 3 and 4, we use these derivations to construct numerical simulation methods.

2.1 The Number of Possible R_μ Reactions

In order for a reaction R_μ to occur in V , it is necessary that one molecule of each of the reactant species collide with each other at some time. At any given time, it is possible that there are many different combinations of reactant molecules that could collide and cause a reaction. Exactly, how many distinct combinations there are depends on how many of each molecule is present, i.e. on $\mathbf{X}(t)$. In general, we denote the number of unique groups of reactants that could collide to cause reaction R_μ by $h_\mu(\mathbf{X}(t))$.

Examples:

1. Consider the simple bimolecular reaction (1). If there are 2 molecules of S_1 and one molecule of S_2 , then there are 2 pairs of molecules that can collide to cause a reaction. In general,

$$h_\mu(\mathbf{X}(t)) = X_1(t)X_2(t).$$

2. A more interesting case is the reaction



In this case

$$h_\mu(\mathbf{X}(t)) = \frac{1}{2}X_1(t)(X_1(t) - 1),$$

not the expected $X_1(t)X_1(t)$. This is because the reaction requires two distinct S_1 molecules; we cannot use the same molecule twice. You can convince yourself that the factor $(X_1(t) - 1)$ is correct by considering the case where there is only one S_1 molecule in V . In this case, there are zero complete groups of reactants. The factor of $1/2$ comes from the fact that we do not care about the order of the molecules. For two distinct molecules of S_1 , call them S'_1 and S''_1 , the pair (S'_1, S''_1) constitutes a single group of reactants, regardless of whether we order them as (S'_1, S''_1) or as (S''_1, S'_1) .

3. Consider the isomerization



Isomerizations do not occur due to collisions at all, but rather due to some spontaneous change in the quantum state of the molecule. Nonetheless, if there are 2 molecules of S_1 , it is clear that there are 2 “groups” of reactant molecules. In general,

$$h_\mu(\mathbf{X}(t)) = X_1(t).$$

2.2 The Probability that Reaction R_μ Occurs in $[t, t + dt]$

2.2.1 The Fundamental Hypothesis

Supposing that at least one complete group of R_μ reactants exists in V , let $\pi_\mu(t, dt)$ denote the probability that a particular one of these groups will react in the time interval $[t, t + dt]$. The fundamental hypothesis of the stochastic approach to chemical kinetics is the following: *For each reaction R_μ , there is a constant c_μ such that*

$$\pi_\mu(t, dt) = c_\mu dt.$$

In words, the fundamental hypothesis states that, for small enough durations dt , the probability that a particular group of R_μ reactants will react in V during the interval $[t, t + dt]$ increases linearly with dt . This assumption is well justified for elementary unimolecular and bimolecular reactions. In the bimolecular case, one can derive the constant c_μ from the kinetic theory of gases (which you will study extensively in 10.65 next semester). The basic assumptions behind this derivation are:

1. the positions of the molecules in V are random and uniformly distributed throughout V ,
2. the velocities of the molecules in V are distributed according to the Maxwell-Boltzmann distribution.

Under these assumptions, it is possible to derive the probability of a collision between two molecules within a given time interval. The purpose of mentioning this is to point out that the stochastic approach to chemical kinetics will be valid for gas phase systems in thermal equilibrium, but not necessarily in other settings.

A consequence of the fundamental hypothesis, which greatly simplifies the analysis to follow, is that the probability that multiple reaction events, of any kind, occur in $[t, t + dt]$ can be shown to scale as $O(dt^2)$. Then, in the limit as $dt \rightarrow 0$, the probability of all such situations tends toward zero more rapidly than dt , and becomes dominated by the probability of the simpler outcomes where only a single reaction occurs in $[t, t + dt]$. For this reason, we can always assume in the following derivations that all single reaction events in $[t, t + dt]$ are mutually exclusive, because only one reaction can occur. Though this is not strictly true, the error in making this assumption will vanish as $dt \rightarrow 0$.

2.2.2 The Probability of an R_μ Reaction in $[t, t + dt]$

In order to understand how the state of a reacting system $\mathbf{X}(t)$ evolves probabilistically, we will require the probability that exactly one reaction occurs in V during $[t, t + dt]$, and it is an R_μ reaction. By the simplification that at most one reaction can occur during $[t, t + dt]$ this is equivalent (to within $O(dt^2)$) to several other probabilities:

$$\begin{aligned} &Pr(\text{exactly 1 rxn occurs in } [t, t + dt] \text{ and it is an } R_\mu \text{ reaction} \mid \mathbf{X}(t) = \mathbf{n}) \\ &= Pr(\text{exactly 1 } R_\mu \text{ rxn occurs in } [t, t + dt] \mid \mathbf{X}(t) = \mathbf{n}), \\ &= Pr(\text{at least 1 } R_\mu \text{ rxn occurs in } [t, t + dt] \mid \mathbf{X}(t) = \mathbf{n}). \end{aligned} \quad (4)$$

To compute this probability, recall that there are $h_\mu(\mathbf{X}(t))$ distinct groups of reactants that could possibly react in $[t, t + dt]$, each with probability $c_\mu dt$. Since we may assume that these h_μ possible reactions are mutually exclusive, then we may sum the individual probabilities to get

$$Pr(\text{exactly 1 } R_\mu \text{ rxn occurs in } [t, t + dt] \mid \mathbf{X}(t) = \mathbf{n}) = h_\mu(\mathbf{n})c_\mu dt.$$

2.2.3 The Connection with Rate Constants

In stochastic chemical kinetics, c_μ plays the role of the rate constant k_μ in deterministic, continuum kinetics equations. For example, for the reaction shown in (1) we have $h_\mu(\mathbf{X}(t)) = X_1(t)X_2(t)$, so the probability of observing exactly one R_μ reaction somewhere in V during $[t, t + dt]$ is

$$c_\mu X_1(t)X_2(t)dt,$$

which is very reminiscent of the *rate* expression in the continuum approximation,

$$r_\mu(t) = k_\mu C_1(t)C_2(t).$$

Of course, for the dimerization reaction (2), these expressions do not agree so well.

For the purposes of simulating stochastic reacting systems, we will always assume that the reaction parameters c_μ are known.

2.3 The Probability Exactly One Reaction Occurs in $[t, t + dt]$

From §2.2, we know that the probability that exactly one R_μ reaction will occur during $[t, t + dt]$ is

$$c_\mu h_\mu(\mathbf{X}(t))dt.$$

Since we need only consider the case where at most one reaction occurs in $[t, t + dt]$, the occurrences of each different type of reaction R_1, \dots, R_M are mutually exclusive. It follows that we can simply sum probabilities to get

$$\begin{aligned} &Pr(\text{exactly 1 rxn occurs in } [t, t + dt] \mid \mathbf{X}(t) = \mathbf{n}) \\ &= \sum_{\mu=1}^M Pr(\text{exactly 1 } R_\mu \text{ rxn occurs in } [t, t + dt] \mid \mathbf{X}(t) = \mathbf{n}), \\ &= \sum_{\mu=1}^M h_\mu(\mathbf{n})c_\mu dt \end{aligned}$$

2.4 The Probability that No Reactions Occur in $[t, t + \tau]$

In the stochastic view of chemical kinetics, there are periods of time in which nothing happens. That is, molecules diffuse around in V but, for some period of time, none of them collide in a such a way that a reaction occurs. In order to accurately simulate this situation, we need some way to characterize *when* the next reaction will happen. A formal way to ask this question is: *Given that $\mathbf{X}(t) = \mathbf{n}$, what is the probability that no reactions occur in V within the time interval $[t, t + \tau]$?* We denote this probability by $P_0(\tau, \mathbf{n})$.

We consider first the probability $P_0(\epsilon, \mathbf{n})$, where ϵ is small. For small enough ϵ , we may assume that at most one reaction occurs in V during $[t, t + \epsilon]$. It follows that

$$\begin{aligned} P_0(\epsilon, \mathbf{n}) &= 1 - Pr(\text{exactly 1 rxn occurs in } [t, t + \epsilon] \mid \mathbf{X}(t) = \mathbf{n}), \\ &= 1 - \sum_{\mu=1}^M h_{\mu}(\mathbf{n}) c_{\mu} \epsilon. \end{aligned}$$

In order to calculate $P_0(\tau, \mathbf{n})$, we divide $[t, t + \tau]$ into a large number K intervals of length $\epsilon = \tau/K$:

$$[t, t + \epsilon], [t + \epsilon, t + 2\epsilon], \dots, [t + (K - 1)\epsilon, t + K\epsilon].$$

Noting that

$$\begin{aligned} P_0(\tau, \mathbf{n}) &= Pr(\text{no rxn occurs in } [t, t + \epsilon] \\ &\quad \text{and no rxn occurs in } [t + \epsilon, t + 2\epsilon] \\ &\quad \text{and} \\ &\quad \vdots \\ &\quad \text{and no rxn occurs in } [t + (K - 1)\epsilon, t + K\epsilon] \mid \mathbf{X}(t) = \mathbf{n}), \end{aligned}$$

we can expand this probability as

$$\begin{aligned} P_0(\tau, \mathbf{n}) &= Pr(\text{no rxn occurs in } [t, t + \epsilon] \mid \mathbf{X}(t) = \mathbf{n}) \\ &\quad \times Pr(\text{no rxn occurs in } [t + \epsilon, t + 2\epsilon] \mid \\ &\quad \quad \quad \mathbf{X}(t) = \mathbf{n} \text{ and no rxn occurs in } [t, t + \epsilon]) \\ &\quad \vdots \\ &\quad \times Pr(\text{no rxn occurs in } [t + (K - 1)\epsilon, t + K\epsilon] \mid \\ &\quad \quad \quad \mathbf{X}(t) = \mathbf{n} \text{ and no rxn occurs in } [t, t + (K - 1)\epsilon]). \end{aligned}$$

For any $j \leq K$, whether or not a reaction occurs in the interval $[t + (j - 1)\epsilon, t + j\epsilon]$ is independent of the fact that no reaction occurred in $[t, t + (j - 1)\epsilon]$, except for the fact that this implies $\mathbf{X}(t + (j - 1)\epsilon) = \mathbf{X}(t)$. Then

$$\begin{aligned} P_0(\tau, \mathbf{n}) &= Pr(\text{no rxn occurs in } [t, t + \epsilon]) \\ &\quad \times Pr(\text{no rxn occurs in } [t + \epsilon, t + 2\epsilon] \mid \mathbf{X}(t + \epsilon) = \mathbf{n}) \\ &\quad \vdots \\ &\quad \times Pr(\text{no rxn occurs in } [t + (K - 1)\epsilon, t + K\epsilon] \mid \\ &\quad \quad \quad \mathbf{X}(t + (K - 1)\epsilon) = \mathbf{n}), \end{aligned}$$

from which it follows that

$$P_0(\tau, \mathbf{n}) = P_0(\epsilon, \mathbf{n}) \times P_0(\epsilon, \mathbf{n}) \times \dots \times P_0(\epsilon, \mathbf{n}).$$

Using the result for small ϵ ,

$$P_0(\tau, \mathbf{n}) = \left[1 - \sum_{\mu=1}^M \frac{c_\mu h_\mu(\mathbf{n})\tau}{K} \right]^K.$$

Since this is true for any sufficiently large K , it follows that

$$\begin{aligned} P_0(\tau, \mathbf{n}) &= \lim_{K \rightarrow \infty} \left[1 - \sum_{\mu=1}^M \frac{c_\mu h_\mu(\mathbf{n})\tau}{K} \right]^K, \\ &= \exp \left(- \sum_{\mu=1}^M c_\mu h_\mu(\mathbf{n})\tau \right). \end{aligned}$$

Therefore, the probability that no reaction occurs in the interval $[t, t + \tau]$ depends on all of the reaction parameters c_μ and decreases exponentially with the length of the interval τ .

3 The Master Equation

The classical approach to modelling the evolution of stochastic reacting systems is to use the so-called *chemical master equation*. The master equation does not describe the change in $X(t)$, as the continuum equations would, because this vector varies stochastically. Instead, the master equation describes the *grand probability function*

$$P(\mathbf{n}, t \mid \mathbf{n}_0, t_0) = Pr(\mathbf{X}(t) = \mathbf{n} \mid \mathbf{X}(t_0) = \mathbf{n}_0).$$

The master equation takes the form of a differential equation that describes how this probability function changes in time. To derive it, let's suppose that $P(\mathbf{n}, t \mid \mathbf{n}_0, t_0)$ is known for all \mathbf{n} and attempt to derive an expression for $P(\mathbf{n}, t + dt \mid \mathbf{n}_0, t_0)$. This is done by simply summing up the probabilities of the distinct (i.e. mutually exclusive) ways in which the system could come to be in state \mathbf{n} at time $t + dt$:

1. The system was in state \mathbf{n} at time t and no reactions occurred during $[t, t + dt]$,
2. The system was in the state $\mathbf{n} - \nu_\mu$ at time t and one R_μ reaction (and only this reaction) occurred during $[t, t + dt]$,
3. Some sequence of multiple reactions occurring in $[t, t + dt]$ led to \mathbf{n} at $t + dt$.

As a consequence of the fundamental hypothesis, it was argued in §2.2 that we can ignore the third possibility in the limit as $dt \rightarrow 0$. Accounting for the other two possibilities,

we have

$$\begin{aligned}
P(\mathbf{n}, t + dt \mid \mathbf{n}_0, t_0) &= P(\mathbf{n}, t \mid \mathbf{n}_0, t_0)P_0(dt, \mathbf{n}) + \sum_{\mu=1}^M P(\mathbf{n} - \boldsymbol{\nu}_\mu, t \mid \mathbf{n}_0, t_0)h_\mu(\mathbf{n} - \boldsymbol{\nu}_\mu)c_\mu dt, \\
&= P(\mathbf{n}, t \mid \mathbf{n}_0, t_0) \left[1 - \sum_{\mu=1}^M h_\mu(\mathbf{n})c_\mu dt \right] \\
&\quad + \sum_{\mu=1}^M P(\mathbf{n} - \boldsymbol{\nu}_\mu, t \mid \mathbf{n}_0, t_0)h_\mu(\mathbf{n} - \boldsymbol{\nu}_\mu)c_\mu dt.
\end{aligned}$$

Rearranging gives,

$$\begin{aligned}
\frac{P(\mathbf{n}, t + dt \mid \mathbf{n}_0, t_0) - P(\mathbf{n}, t \mid \mathbf{n}_0, t_0)}{dt} &= \sum_{\mu=1}^M [P(\mathbf{n} - \boldsymbol{\nu}_\mu, t \mid \mathbf{n}_0, t_0)h_\mu(\mathbf{n} - \boldsymbol{\nu}_\mu)c_\mu \\
&\quad - P(\mathbf{n}, t \mid \mathbf{n}_0, t_0)h_\mu(\mathbf{n})c_\mu],
\end{aligned}$$

which, in the limit as $dt \rightarrow 0$ gives the differential equation

$$\frac{dP(\mathbf{n}, t \mid \mathbf{n}_0, t_0)}{dt} = \sum_{\mu=1}^M [P(\mathbf{n} - \boldsymbol{\nu}_\mu, t \mid \mathbf{n}_0, t_0)h_\mu(\mathbf{n} - \boldsymbol{\nu}_\mu)c_\mu - P(\mathbf{n}, t \mid \mathbf{n}_0, t_0)h_\mu(\mathbf{n})c_\mu].$$

Supposing that, due to a limited number of reactant molecules in a closed system, we know that there are only a finite number of possible states of the system $\mathbf{n}^1, \dots, \mathbf{n}^Q$. Then the master equation is actually a system of Q coupled ODEs, with one ODE describing each of the time-varying probabilities

$$P(\mathbf{n}^1, t \mid \mathbf{n}_0, t_0), \dots, P(\mathbf{n}^Q, t \mid \mathbf{n}_0, t_0).$$

The solution of the master equation contains complete information about the stochastic behavior of the system. It describes the entire PDF of $\mathbf{X}(t)$ for every time t . Unfortunately, the master equation is very difficult to solve in general. This is because the master equation may involve a huge number of state variables. Note that the state variables of the master equation are the probabilities of every possible state of the reacting system. As a trivial example, in a system with only one chemical species A, the master equation has one ODE for the probabilities of each of the following states:

there is 1 molecule of A
there are 2 molecules of A
there are 3 molecules of A
 \vdots
there are j molecules of A
 \vdots

When there are multiple reacting species, we must account for every possible combination of molecule numbers, and the number of ODEs in the master equation easily reaches into the billions. Because the master equation ODEs are actually linear in these states (and very sparse), it is possible to numerically solve the master equation as an IVP in situations where the number of ODEs is surprisingly large. Researchers in Professor

Barton's laboratory have developed methods capable of solving master equations with up to 200 million ODEs. Even so, master equations of this size still correspond to very simple physical systems. For this reason, most researchers take a Monte Carlo approach, which provides less information but is more computationally tractable. We discuss this approach in the next section.

4 Gillespie's Algorithm

The solution of the master equation provides, at each time t , a PDF for the random vector $\mathbf{X}(t)$. This is a great deal of information, which is why the master equation is so difficult to solve. Rather than compute the complete PDF of $\mathbf{X}(t)$ for every t , Gillespie's algorithm computes a *sample* from this PDF. That is, it computes a single trajectory in time. Like the Monte Carlo methods we studied previously, Gillespie's algorithm produces a different result every time it is run. However, if it is run a large number of times for the same system, then the frequency of observing a state, say $\mathbf{X}(\hat{t}) = \mathbf{n}^*$, will be proportional to the value of the PDF that results from solving the master equation, $P(\mathbf{n}^*, \hat{t} \mid \mathbf{n}_0, t_0)$. Because only a sample is computed, a single run of Gillespie's algorithm is dramatically less expensive than solving the master equation. The down side, however, is that it may be necessary to do a huge number of Gillespie simulations in order to obtain an accurate description of the complete PDF.

Beginning from $\mathbf{X}(t)$ at some time t , a single step of Gillespie's algorithm first generates a random number τ which represents the time at which the next reaction occurs. Then, a random integer μ is generated which determines which reaction occurs at $t + \tau$. Once these numbers are known, we simply update the time to $t + \tau$ and the state vector to $\mathbf{X}(t + \tau) = \mathbf{X}(t) + \boldsymbol{\nu}_\mu$.

4.1 Determining the Next Reaction Time

We require the probability that the next reaction occurs in the infinitesimal time interval $[t + \tau, t + \tau + d\tau]$. Denote this probability by $P_{\text{next}}(\tau, \mathbf{n})d\tau$. This probability can be computed by noting that

$$\begin{aligned} P_{\text{next}}(\tau, \mathbf{n})d\tau &= Pr(\text{no rxn occurs in } [t, t + \tau] \mid \mathbf{X}(t) = \mathbf{n}) \\ &\quad \times Pr(\text{exactly one rxn occurs in } [t + \tau, t + \tau + d\tau] \mid \\ &\quad \quad \quad \mathbf{X}(t) = \mathbf{n} \text{ and no rxn occurs in } [t, t + \tau]), \\ &= Pr(\text{no rxn occurs in } [t, t + \tau] \mid \mathbf{X}(t) = \mathbf{n}) \\ &\quad \times Pr(\text{exactly one rxn occurs in } [t + \tau, t + \tau + d\tau] \mid \mathbf{X}(t + \tau) = \mathbf{n}), \\ &= P_0(\tau, \mathbf{n}) \times \left[\sum_{\mu=1}^M h_\mu(\mathbf{n})c_\mu d\tau \right], \\ &= \exp\left(-\sum_{\mu=1}^M h_\mu(\mathbf{n})c_\mu \tau\right) \left[\sum_{\mu=1}^M h_\mu(\mathbf{n})c_\mu d\tau \right]. \end{aligned}$$

To simplify notation, define the *total reaction propensity*:

$$a(\mathbf{n}) \equiv \sum_{\mu=1}^M h_\mu(\mathbf{n})c_\mu.$$

Then,

$$P_{\text{next}}(\tau, \mathbf{n}) = a(\mathbf{n}) \exp(-a(\mathbf{n})\tau).$$

For fixed \mathbf{n} , this is the PDF of the random variable τ . In order to determine the next reaction time for Gillespie's algorithm, we would like to sample this PDF. It turns out that this can be done by generating a random number r_1 from the uniform distribution on the interval $(0, 1)$ and computing

$$\tau = \frac{1}{a(\mathbf{n})} \ln\left(\frac{1}{r_1}\right).$$

This is an example of the *inversion method*, which is one of the available methods for converting the output of a uniform random number generator to a sample of a desired PDF.

4.2 Determining the Next Reaction Type

We now need to derive the probability that an R_μ reaction occurs in $[t + \tau, t + \tau + d\tau]$ given that $\mathbf{X}(t) = \mathbf{n}$ and the next reaction is known to occur in this same interval. As usual, we can neglect the possibility of multiple reactions occurring in this time interval, so that we are guaranteed that exactly one reaction occurs in $[t + \tau, t + \tau + d\tau]$. There are then M mutually exclusive possibilities, R_1, \dots, R_M , each with probability

$$h_\mu(\mathbf{n})c_\mu d\tau, \quad \mu = 1, \dots, M.$$

Clearly, the probability that reaction $R_{\mu'}$ occurs is

$$\frac{h_{\mu'}(\mathbf{n})c_{\mu'} d\tau}{\sum_{\mu=1}^M h_\mu(\mathbf{n})c_\mu d\tau} = \frac{h_{\mu'}(\mathbf{X}(t))c_{\mu'}}{a(\mathbf{n})}.$$

For fixed \mathbf{n} , this is the PDF of the random variable μ' , which we need to sample in order to determine the next reaction type in Gillespie's algorithm. This is done by sampling a number r_2 from the uniform distribution on $(0, 1)$ and choosing μ' to be the smallest integer such that

$$r_2 \leq \frac{\sum_{\mu=1}^{\mu'} h_\mu(\mathbf{n})c_\mu}{a(\mathbf{n})}.$$

In fact, this is another application of the inversion method. In this case it is easy to see that the probability of selecting μ' in this way is proportional to the length of the interval

$$\left[\frac{\sum_{\mu=1}^{\mu'-1} h_\mu(\mathbf{n})c_\mu}{a(\mathbf{n})}, \frac{\sum_{\mu=1}^{\mu'} h_\mu(\mathbf{n})c_\mu}{a(\mathbf{n})} \right],$$

which is simply

$$\frac{h_{\mu'}(\mathbf{n})c_{\mu'}}{a(\mathbf{n})},$$

as desired.

4.3 Algorithm

1. Initialize: $t = t_0$, $\mathbf{X}(t) = \mathbf{n}_0$.
2. While $t < t_f$:
 - (a) Compute the total reaction propensity $a(\mathbf{X}(t))$.
 - (b) Sample two random numbers, r_1 and r_2 , from the uniform distribution on $(0, 1)$.
 - (c) Determine the next reaction time as $\tau = \frac{1}{a(\mathbf{X}(t))} \ln \left(\frac{1}{r_1} \right)$.
 - (d) Determine the reaction type as the smallest μ' such that $r_2 \leq \sum_{\mu=1}^{\mu'} h_{\mu}(\mathbf{X}(t))c_{\mu}/a(\mathbf{X}(t))$.
 - (e) Carry out the reaction event determined above:
 - Set $t := t + \tau$.
 - Set $\mathbf{X}(t) := \mathbf{X}(t) + \boldsymbol{\nu}_{\mu'}$.

MIT OpenCourseWare
<https://ocw.mit.edu>

10.34 Numerical Methods Applied to Chemical Engineering
Fall 2015

For information about citing these materials or our Terms of Use, visit: <https://ocw.mit.edu/terms>.