Modelling in Systems Biology

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Formal representation of chemical reactions

- precise
- qualitative *and* quantitative
- suitable to introduce *discrete* and *stochastic* ingredients

We begin with

Network of coupled chemical reactions

$$m_1 R_1 + m_2 R_2 + \ldots + m_r R_r \rightarrow n_1 P_1 + n_2 P_2 + \ldots + n_p P_p$$

Definitions

1. R_i's: reactants;
2. P_j's: products;
3. m_i's and n_j's: *stoichiometry coefficients*.

The law of mass action

The reaction rates are proportional to product of the concentration

Collision theory justifies mass action kinetics.

Assumptions

- We assume the medium is well mixed;
- For the derivation of the DEs we assume a large number of molecules in a small volume V.
- In the presence of a catalyst then the law does not apply- See later in the course.

General Case from Chemical Reaction Notation

Assume $S_j, j \in \{1, 2, 3 \ldots\}$ a *Chemical Reaction Network* (CRN) is a set of chemical reactions $\mathcal{R}_i$ with $i \in \{1, 2, 3 \ldots\}$ such that:

$$\mathcal{R}_i : \sum_{j=1}^{n_s} \alpha_{ij} S_j \rightarrow_{k_i} \sum_{j=1}^{n_s} \beta_{ij} S_j$$

where

- $\alpha_{i,j}$ and $\beta_{i,j}$ are non-negative integers called the *stoichiometry coefficients*.
- S_j on the right-hand side of the arrow are called *reactants*, if the stoichiometry coefficients are non-zero ;
- S_j on the right-hand side of the arrow are called *products*, if the stoichiometry coefficients are non-zero ;

Stoichiometry Matrix

Given a CRN and its stoichiometry coefficients of the reactants and the product n_s and the number of the reactions n_r the entries of *stoichiometry matrix* **Q** of size $n_s \times n_r$ are defined as follows:

$$q_{ji} = \beta_{ij} - \alpha_{ij} \qquad i = 1, \ldots, n_r \quad j = 1, \ldots, n_s$$

Notice the inversion of the indexes.

Law of mass action

Let's denote $\mathcal{R}_i(S)$ to be the algebraic form of the *ith* reaction. We can rephrase the law of mass actions as:

$$\mathcal{R}_i(S) = \kappa_i \prod_{j=1}^{n_s} S_j^{\alpha_{ij}} \qquad \text{for all } i = 1, \ldots, n_r$$

This simply says that the reactions rate is proportional to product of the concentration of the reactants with higher exponent when more than one molecule is needed.
k_i is called the rate constant.

Derivation of the DE (II)

Let's denote $\mathcal{S}$ the vector of the reactants and $\mathcal{R}(\mathcal{S})$ the vector of the 'products'.

Vector of the reactants

$$\mathcal{S} = \begin{pmatrix} S_1 \\ S_2 \\ \vdots \\ S_n \end{pmatrix}$$

Vector of the reactions

$$\mathcal{R}(\mathcal{S}) = \begin{pmatrix} \mathcal{R}_1(S_1) \\ \mathcal{R}_2(S_2) \\ \vdots \\ \mathcal{R}_n(S_n) \end{pmatrix}$$

$$\frac{d\mathcal{S}}{dt} = \mathbf{Q}\mathcal{R}(\mathcal{S})$$

Example

Chemical Species

Assume we have the following chemical species:$\mathcal{S} = \{H, O, H_2O\}$. We enumerate them as follows: $H = 1, O = 2, H_2O = 3$

Chemical relations among the species

$$\begin{aligned} \mathcal{R}_1 : \quad 2H + O \quad &\rightarrow_{k_1} \quad H_2O \\ \mathcal{R}_2 : \quad H_2O \quad &\rightarrow_{k_2} \quad 2H + O \end{aligned}$$

Stoichiometry coefficients

For reaction $\mathcal{R}_1$ the stoichiometry coefficients of the reactants are:

$$\alpha_{11} = 2 \quad \alpha_{12} = 1 \quad \alpha_{13} = 0$$

Example (II)

Stoichiometry coefficients

The stoichiometry coefficients of the products are:

$$\beta_{11} = 0 \quad \beta_{12} = 0 \quad \beta_{13} = 1$$

For reaction $\mathcal{R}_2$ the stoichiometry coefficients of the reactants are:

$$\alpha_{21} = 0 \quad \alpha_{22} = 0 \quad \alpha_{23} = 1$$

and the stoichiometry coefficients of the products are are:

$$\beta_{21} = 2 \quad \beta_{22} = 1 \quad \beta_{23} = 0$$

Example (III)

In the previous example we have 2 reactions and 3 species this will give a stoichiometry matrix **Q** size 3×2 The entries are calculated as follows:

Calculation of the entries

$$
\begin{aligned}
q_{11} &= \beta_{11} - \alpha_{11} &&= -2 \\
q_{12} &= \beta_{21} - \alpha_{21} &&= 2 \\
q_{21} &= \beta_{12} - \alpha_{12} &&= -1 \\
q_{22} &= \beta_{22} - \alpha_{22} &&= 1 \\
q_{31} &= \beta_{13} - \alpha_{13} &&= 1 \\
q_{32} &= \beta_{23} - \alpha_{23} &&= -1
\end{aligned}
$$

The matrix

$$
\mathbf{Q} = \begin{pmatrix} -2 & 2 \\ -1 & 1 \\ 1 & -1 \end{pmatrix}
$$

Example (IV)

The vectors are:

Vector of the reactants

$$\mathcal{S} = \begin{pmatrix} H \\ O \\ H_2O \end{pmatrix}$$

Vector of the reactions

$$\mathcal{R}(\mathcal{S}) = \begin{pmatrix} k_1[H]^2[O] \\ k_2[H_2O] \end{pmatrix}$$

$$\frac{d\begin{pmatrix} H \\ O \\ H_2O \end{pmatrix}}{dt} = \begin{pmatrix} -2 & 2 \\ -1 & 1 \\ 1 & -1 \end{pmatrix} \begin{pmatrix} k_1[H]^2[O] \\ k_2[H_2O] \end{pmatrix}$$

Example (V)

Finally the DEs can be rewritten as follows:

$$\begin{aligned}
\frac{d[H]}{dt} &= -2k_1[H]^2[O] + 2k_2[H_2O] \\
\frac{d[O]}{dt} &= -k_1[H]^2[O] + k_2[H_2O] \\
\frac{d[H_2O]}{dt} &= k_1[H]^2[O] - k_2[H_2O]
\end{aligned}$$

What kind of analysis?

Once we have derived the DEs, we have provided a quantitative meaning to the CRN. It is possible:

- Try to find an analytical solution to the set of equations (generally very difficult).
- Simulate them numerically using appropriate software (Matlab, Mathematica, Maple). This is mostly what we are going to be concerned here. We will be mostly mostly using Dizzy. http://magnet.systemsbiology.net/software/Dizzy/.
- Make a steady state analysis.
- Make a bifucartion analysis.
- Make a sensitivity analysis: how robust is the system to change of parameters.

Exponential distribution

An exponential distribution models the time of occurrence of a (simple) random event.

It is given by a random variable X, 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

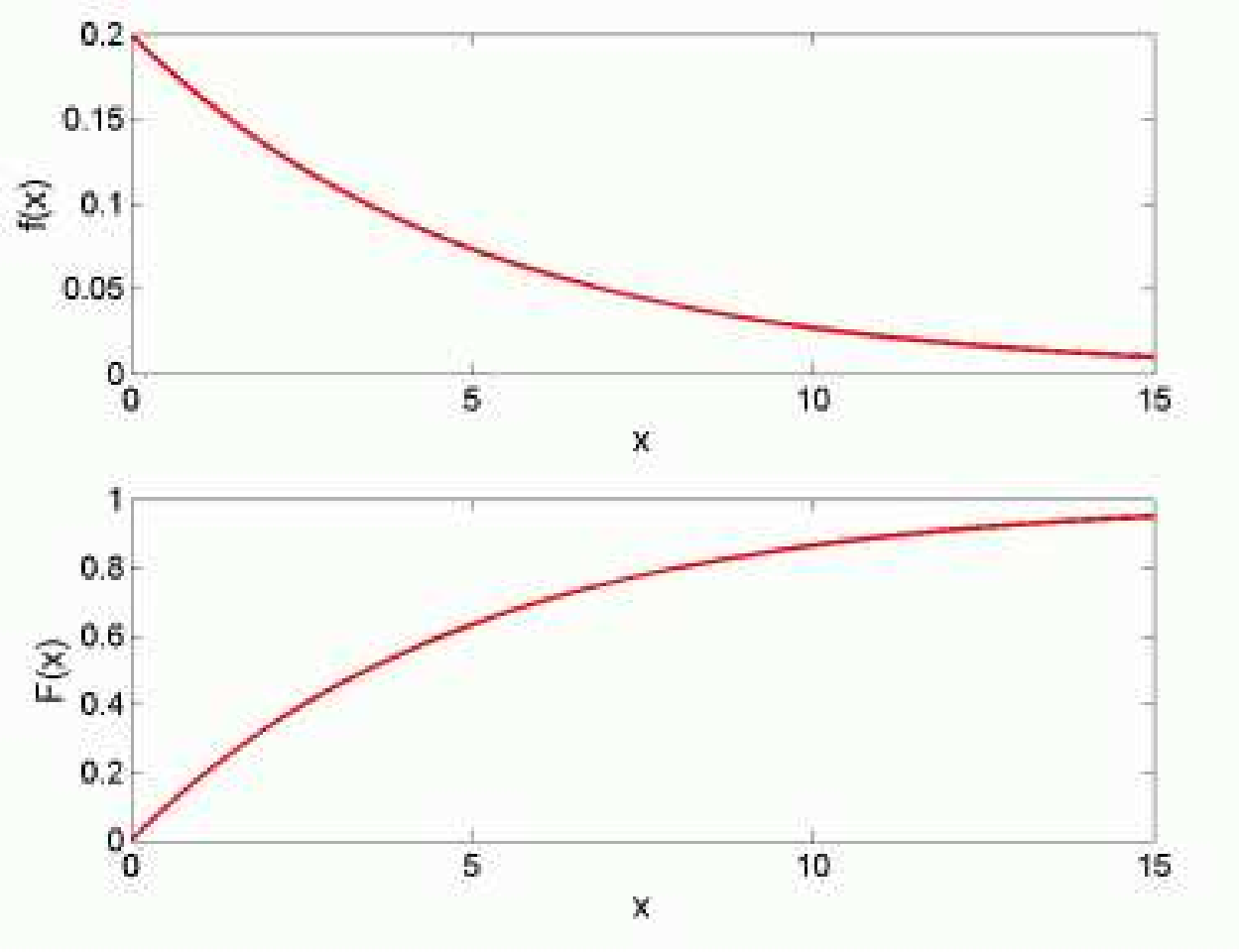
$$\mathbb{P}(X \leq t) = F(x) = 1 - e^{-\lambda t}.$$

λ is always positive.

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

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

Graph



P.D.F and C.D.F with rate 0.2.

Properties of the exponential distribution

Memoryless property

$$\mathbb{P}(X \leq (s+t)|X > t) = \mathbb{P}(X \leq s) \text{ for all } s, t$$

It does not matter what happened before time t.

Closure property

X_1 and X_2 are independent random variables exponentially distributed with parameters λ_1, λ_2 respectively.

$$\mathbb{P}(Y \leq t) = 1 - e^{-(\lambda_1+\lambda_2)t}$$

where $Y \equiv \min(X_1, X_2)$.
$\mathbb{P}(Z \leq t)$ is not exponentially distributed if $Z = \max(X_1, X_2)$.

Probability of being the fastest

X_1 and X_2 are independent random variables exponentially distributed with parameters λ_1, λ_2 respectively.

$$\mathbb{P}(X_1 \leq X_2) = \frac{\lambda_1}{\lambda_1 + \lambda_2}$$

For an infinitesimally small time interval dt

$$\mathbb{P}(X \leq dt) = 1 - e^{-\lambda dt} = \lambda dt + o(h)$$

$o(h)$ means a negligible term with respect to h. λ is also called the *hazard rate.*

Markov Chains

- Special class of stochastic processes that satisfy the Markov property (MP).
- Given the state of the process at time t, its state at time $t + s$ has probability distribution which is a function of s only. (i.e. the future behaviour after t is independent of the behaviour before t).
- Markov Chains are very intuitive. Moreover they are yet simple enough to facilitate effective mathematical analysis and simulation.
- Discrete Time Markov Chain have discrete time parameters: those are not considered in the course.
- We consider chains with continuous parameter (times $t \geq 0, t \in \mathbb{R}$: Markov Processes or Continuous Time Markov Chains.

Continuous Time Markov Chains

$\{X(t) : t > 0\}$ a family of random variables and
$S = \{s_i : i = 0, 1, 2 \ldots\}$ is the state space.

Markov property

$$\mathbb{P}(X(t_n) = s_n | X(t_1) = s_1, \ldots, X(t_{n-1}) = s_{n-1}) = \mathbb{P}(X(t_n) = s_n | X(t_{n-1}) = s_{n-1})$$

for each sequence $t_1 < t_2 < \ldots < t_{n-1} < t_n$

Time homogeneous CTMC

$$\mathbb{P}(X(t + \tau) = s_k | X(t) = s_i) = \mathbb{P}(X(\tau) = s_k | X(0) = s_i)$$

Conditional probability is independent of shifts of time.

CTMC and exponential distribution

By the Markov property and time homogeneity we have:

Sojourn time

S is the amount of time spent in the state $s_i \in S$.

$$P_u = \inf\{S(t+u) \neq s_i | S(u) = s_i\}$$

$$\mathbb{P}(P_u \leq t) = 1 - e^{-\lambda t}$$

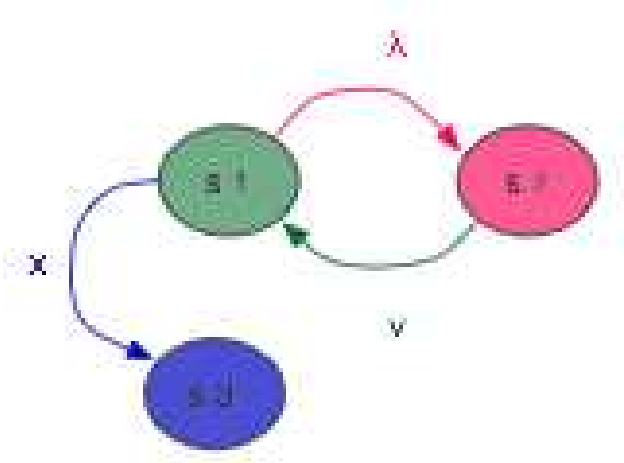
where lambda is the total rate out state s_i.

Summarising:

- The only continuous distribution that enjoys the memory-less property is the negative exponential.
- In a CTMC all random variables are exponentially distributed. We consider only time homogeneous CTMCs.

Continuous Time Markov Chains

$S = \{s_1, s_2, s_3\}$



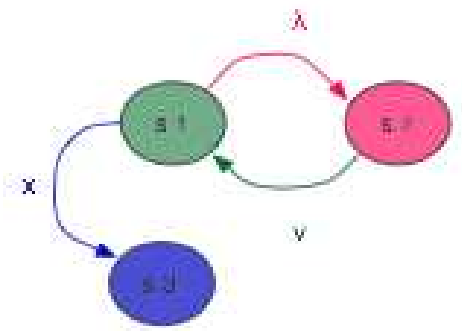
$$\begin{pmatrix} & s_1 & s_2 & s_3 \\ s_1 & -(\lambda + x) & \lambda & x \\ s_2 & \nu & -\nu & 0 \\ s_3 & 0 & 0 & 0 \end{pmatrix}$$

Equivalent Characterization

- CTMC is fully characterised by the state space (discrete) and the the generator matrix **Q**. The entries of **Q** are determined by the parameters of the exponential distribution.
- The is a discrete set of states, connected by transitions each with an associated rate of an exponential distribution.

Continuous Time Markov Chains

What happens if we have that 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.

Mathematically

$$\mathbb{P}(X(t) = s_1) = \mathbb{P}(Y \leq t) = 1 - e^{-(\lambda+x)t}$$

X_1 and X_2 are i. r. v. exponentially distributed with parameters λ, x and $Y \equiv \min(X_1, X_2)$

$$\lim_{dt \to 0} \mathbb{P}(X(t+dt) = s_2 | X(t) = s_1, X(t+dt) \neq s_1) = \frac{\lambda}{\lambda + x}.$$

Example

Consider the system:

$$\begin{aligned} \mathcal{R}_1 : P &\rightarrow_\lambda P2 \\ \mathcal{R}_2 : P2 &\rightarrow_\nu P \\ \mathcal{R}_3 : Q &\rightarrow_\mu Q2 \end{aligned}$$

1. P changes at rate λ to P_2
2. Q changes at rate x to Q_2

Our system $\mathbf{s_1} = (1, 1, 0, 0)$. contains: 1 molecule of P and 1 molecule of Q and no molecule of $P2, Q2$.

Example (II)

X_1

X_1 is the random variable associated to $\mathcal{R}_1$ i.e
$\mathbb{P}(X_1 \leq t) = 1 - e^{-\lambda t}$.

X_2

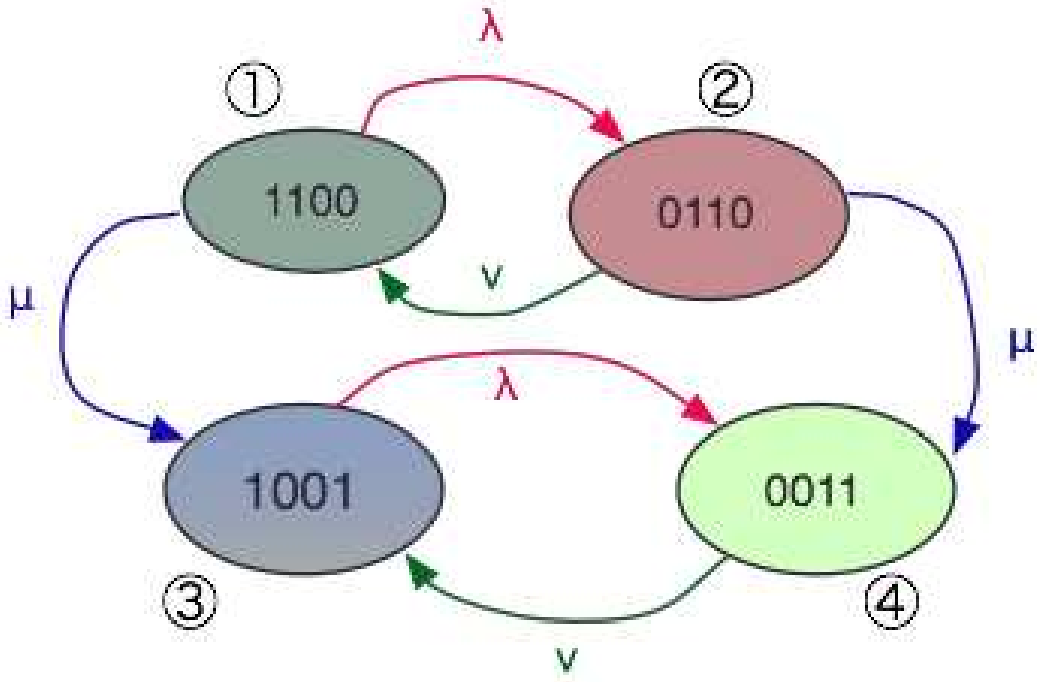
X_2 is the random variable associated to $\mathcal{R}_2$ i.e
$\mathbb{P}(X_2 \leq t) = 1 - e^{-\nu t}$.

X_3

X_3 is the random variable associated to $\mathcal{R}_3$ i.e
$\mathbb{P}(X_3 \leq t) = 1 - e^{-\mu t}$.

What is the random variable associate to $\mathbf{s_1} = (1, 1, 0, 0)$?
$\mathbb{P}(Y(t) = \mathbf{s_1}) = \mathbb{P}(\min(X_1, X_3) < t) = 1 - e^{-(\lambda+\mu)t}$.

Generator matrix



$$\mathbf{Q} = \begin{pmatrix} -(\lambda+\mu) & \lambda & \mu & 0 \\ \lambda & 0 & -(\lambda+\mu) & \mu \\ 0 & 0 & -\lambda & \lambda \\ 0 & 0 & \nu & -\nu \end{pmatrix}$$

Example 2

$$\begin{aligned} \mathcal{R}_1 : A + B &\rightarrow_\delta C \\ \mathcal{R}_2 : D &\rightarrow_\rho C \end{aligned}$$

Our system $\mathbf{s_0} = (4, 5, 10, 1)$ contains: 4 molecules of A and 5 molecules of B and 10 molecules of C and 1 molecule of D.

The exponential random variable (r.v.) X_1 with parameter δ is associated to $\mathcal{R}_1$ and the exponential random variable X_2 with parameter ρ is associated to $\mathcal{R}_2$.

Example 2 (II)

$\mathbf{s_0}$

$$\mathbb{P}(Y(t) = \mathbf{s_0}) = \text{the minimum r.v. 'enabled in the system'}$$

Informally R.V. 'enabled' $\mathbf{s_0}$

$10 \times \mathcal{R}_2$ and $(5 \times 4) \times \mathcal{R}_1$

$$\begin{aligned} \mathbb{P}(Y(t) = \mathbf{s_0}) &= \\ \mathbb{P}(min(Y_1, Y_2) \leq t) &= Y_1 = min(\underbrace{X_1, \ldots X_1}_{20}), Y_2 = min(\underbrace{X_2, \ldots X_2}_{10}) \\ &= 1 - e^{-[(20\delta)+(10\rho)]t} \end{aligned}$$

Example 3

$$\begin{array}{lrcl} \mathcal{R}_1: & A + A & \rightarrow_\delta & C \\ \mathcal{R}_2: & B & \rightarrow_\rho & C \end{array}$$

Our system $\mathbf{s_0} = (40, 5, 1)$. contains: 40 molecules of A and 5 molecules of B and 1 molecule of C.

The exponential random variable (r.v.) X_1 with parameter δ is associated to $\mathcal{R}_1$ and the exponential random variable X_2 with parameter ρ is associated to $\mathcal{R}_2$.

Example 3 (II)

$\mathbf{s_0}$

$$\mathbb{P}(Y(t) = \mathbf{s_0}) = ???$$

As before the total rate for $\mathcal{R}_2$
$5 \times \rho$ but and $(\frac{40 \times 39}{2})$ ways in which $\mathcal{R}_1$ occurs.

$$\begin{aligned} \mathbb{P}(Y(t) = \mathbf{s_0}) &= \\ &= 1 - e^{-[(780\delta)+(5\rho)]t} \end{aligned}$$

Chemical reaction network as stochastic process

- If we can assume that biochemical systems are deterministic, then for each reaction species we derive rate of change -according to appropriate law.
- If the system contains a small number of molecules, or for some reasons we need to take into account noise, then we can regard it as a CTMC.
- As CTMC to each reaction of biochemical systems a rate is associated, which can be interpreted as the number of reactions occurring for time units (on average).
- Assuming that the probability depends on the state of the system only, then the probability of a reaction to occur is fully determined by the number of molecules in the system and the rate of the reaction.

Gillespie's Abstract physical model

- Assume molecules are contained inside a volume V.
- Assume molecules are spheres (easy).
- We assume our molecules are distributed randomly and uniformly throughout the containing volume V.
- We assume a constant temperature: this means that the rate of collision between two molecules does not change as time goes by.
- Reaction happens when either two molecules collide (bimolecular) or by spontaneous reaction of one molecule.

Deriving kinetic parameters

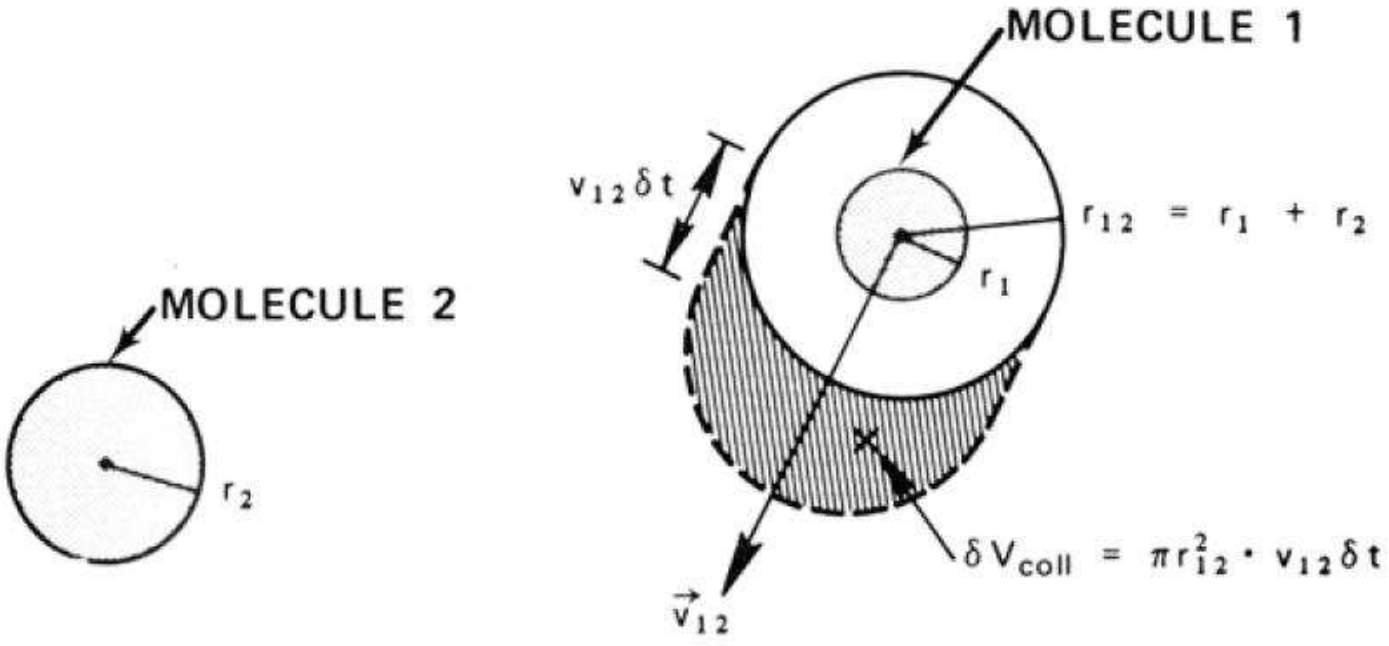


Figure 1. The "collision volume" δV_{coll} which molecule 1 will sweep out relative to molecule 2 in the next small time interval δt.

What we simulate?

Given a system with $S_1, ...S_N$ species with n_r reactions:

$$\begin{aligned} \mathcal{R}_1 : \quad & \alpha_{1,i} S_i + \alpha_{1,j} S_j \quad \rightarrow_{c_1} \quad \sum_{j=1}^{N} \beta_{ij} S_j \\ & \vdots \\ \mathcal{R}_{n_r} : \quad & \alpha_{1,k} S_k + \alpha_{1,h} S_h \quad \rightarrow_{c_{n_r}} \quad \sum_{j=1}^{N} \beta_{ij} S_j \end{aligned}$$

with $1 \leq i, j, k, h \leq N$ and $\alpha_{j,k} = 1$ or $\alpha_{j,k} = 0$.

We write **x** for the current state of the system and ν_i for the state-change vector.

How the chemical network will evolve in the time from 0 to T_{max}?

Rate functions

To determine the global rate of reaction $\mathcal{R}_j$, we need to count how many pairs of reacting molecules we have. We do this with the rate function or propensity function $h_j(\mathbf{x})$.

Reactants of different species

$$\mathcal{R}_j : S_k + S_i \rightarrow_{c_j} \blacksquare \quad h_j(\mathbf{x}) = c_j X_k X_i$$

$c_j X_k X_i$ is the parameter of the exponential distribution, (see example 2 $\mathcal{R}_1$ in the notes).

Rate functions

Reactants of the same species

$$\mathcal{R}_j : S_j + S_j \rightarrow_{c_j} \blacksquare \quad h_j(\mathbf{x}) = c_j \frac{X_j(X_j-1)}{2}$$

$c_j \frac{X_j(X_j-1)}{2}$ is the parameter of the exponential distribution, (see Example 3 $\mathcal{R}_1$ in the note).

Mono-molecular reaction

$$\mathcal{R}_j : S_i \rightarrow_{c_j} \blacksquare \; ??$$

Mono-molecular reactions are simply governed by random delay. The propensity function is:

$$\mathcal{R}_j : S_i \rightarrow_{c_j} \blacksquare \, h_j(\mathbf{x}) = c_j X_i$$

The simulation according to Gillespie

The key idea for the simulation algorithm is that in a CTMC, the time evolution of the chain is determined by two events:

1. The amount of time spent in a state;
2. The probability of choosing the next state.

That translates mathematically:

1. Calculating the density function of the amount of time spent in a state;
2. Calculating the instantaneous probability of the next reaction.

Numerically simulating $p_{j,\mathbf{x}}(\tau|t)$

Numerically simulating $p_{j,\mathbf{x}}(\tau|t)$

A random number generator can be used to draw random pairs (τ, μ) whose probability density function is $p_{j,\mathbf{x}}(\tau|t)$.
Given r_1 and r_2 randomly generated, determine τ and j such that:

$$\tau = (1/h_0)\log(1/r_1)$$

$$\text{the smallest } j \quad \Sigma_{\nu=1}^{j-1} h_\nu < r_2 h_0 \leq \Sigma_{\nu=1}^{j} h_\nu$$

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

- For each $i = 1, 2, ..., n_r$, calculate the propensity function $h_i(\mathbf{x})$.
- Calculate $h_0(\mathbf{x}) = \sum_{i=1}^{n_r} h_i(\mathbf{x})$.
- Simulate time to next event,t' , as an $p_{\mathbf{x}}(t')$.
- Simulate the next reaction index,j.
- Update $\mathbf{x} = \mathbf{x} + \nu_j$ and set $t = t + t'$
- Record $\mathbf{x}, t$ and if $t < T_{max}$, return to step 2, else stop.

The algorithm

- For each $i = 1, 2, ..., n_r$, calculate the propensity function $h_i(\mathbf{x})$.
- Calculate $h_0(\mathbf{x}) = \sum_{i=1}^{n_r} h_i(\mathbf{x})$.
- Generate two random numbers r_1, r_2 such that $0 \leq r_1, r_2 \leq 1$ and calculate t', j:

$$t' = \frac{1}{h_0(\mathbf{x})} \times \ln(\frac{1}{r_1})$$

$$\text{smallest } j \sum_{i=1}^{j} h_i(\mathbf{x}) > r_2 h_0(\mathbf{x})$$

- Update $\mathbf{x} = \mathbf{x} + \nu_j$ and set $t = t + t'$
- Record $\mathbf{x}, t$ and if $t < T_{max}$, return to step 2, else stop.

From concentration to numbers of molecules

- When we model chemical system in deterministic setting we generally think of species as concentrations $\mathbf{M} = \text{moles}/L$. The rate of the reaction is measured in $\mathbf{M}s^{-1}$.
- In stochastic model, species as measured in number of molecules.
- How do we relate numbers and concentration?

Rate conversion

Number of molecules

With a volume V measured in litre and $[X]$ is the concentration of the amount of a species X.

$$\text{number of molecules} = n_A[X]V$$

where $n_A = 6.023 \times 10^{23}$ Avogadro's constant.

Order of the reaction

In a deterministic setting the rate of reactions are categorised by order.

$$\mathcal{R}_i(S) = \kappa_i \prod_{j=1}^{n_s} S_j^{\alpha_{ij}}$$

The order of the reaction is $\mathcal{R}_i = \sum_{j=1}^{s} \alpha_{ij}$ where n_s is the number of species in the reaction.

Rate conversion

Assume volume V.

First order reaction

$$\underbrace{A \rightarrow_k \blacksquare}_{det} \qquad \underbrace{A \rightarrow_c \blacksquare}_{stoch}$$

the deterministic rate law is $k[A]\mathbf{M}s^{-1}$. Expressed in number of molecules is becomes $kn_A[X]V$. The hazard rate is cn where $n = n_A[A]V$. Assuming $cn_A[A]V = kn_A[A]V$ We obtain:

$$k = c$$

Second order reaction

$$\underbrace{A + B \rightarrow_k \blacksquare}_{det} \qquad \underbrace{A + B \rightarrow_c \blacksquare}_{stoch}$$

The deterministic rate law is $k[A][B]\mathbf{M}s^{-1}$. This means a rate as molecules per second is $k[A][B]n_A V$. In the stochastic model however we have that the hazard rate is cab where $a = n_A[A]V$ and $b = n_A[B]V$. Thus the stochastic rate is:

$$c = \frac{k}{n_A V}$$

Second order reaction (dimerisation-style-reaction)

$$\underbrace{A + A \rightarrow_k \blacksquare}_{det} \qquad \underbrace{A + A \rightarrow_k \blacksquare}_{stoch}$$

the deterministic rate law is $k[A]^2 \mathbf{M} s^{-1}$. This means a rate of molecules per second, where $kn_A[A]^2V$. In the stochastic model however we have that the function rate is $cn(n-1)$ where $n = n_A[A]V$. If we assume that as n tends to be large $n(n-1)$ tends to n^2 we can write $kn_A[A]^2V = cn^2$

$$c = \frac{2k}{n_A V}$$

Enzyme Catalysed reactions

How it started

People were interested in fermentation, and how a substrate can affect the rate of the reactions. Only in 1913 with Michaelis and Menten's experiments fully satisfactory model was obtained.

We shall see how the Michaelis-Menten rate is obtained we shall move 'outside' the law of mass action for reaction rates.

Michaelis-Menten enzyme kinetics

- The substrate S is converted to a product P only in the presence of a catalyst E and SE is the catalyst-enzyme compound.
- Catalysts facilitate the reaction converting substrate into product. The enzyme remain basically unchanged.
- Important enzymatic reactions are *phosphorylation*(due to the phophate group $P0_4$). Phosphorylation *activates* the proteins, and it is deems the beginning of many signalling pathways.
- Proteins do not stay phosphorylated for ever, they revert back to an inactive state ready to start the process again.

Michaelis-Menten enzyme kinetics

In CRN style the reactions are the following:

Reactions

$$\begin{aligned} \mathcal{R}_1 : &\quad S + E &\to_{k_1} &\quad SE \\ \mathcal{R}_2 : &\quad SE &\to_{k_2} &\quad S + E \\ \mathcal{R}_3 : &\quad SE &\to_{k_3} &\quad P + E \end{aligned}$$

Assume the Law of Mass Action, we can derive the DEs.

DEs

Stoichiometry Matrix

$$\mathbf{Q} = \begin{pmatrix} & \mathcal{R}_1 & \mathcal{R}_2 & \mathcal{R}_3 \\ S & -1 & 1 & 0 \\ E & -1 & 1 & 1 \\ SE & 1 & -1 & -1 \\ P & 0 & 0 & 1 \end{pmatrix}$$

Vector of the reactions

$$\mathcal{R}(\mathcal{S}) = \begin{pmatrix} k_1[S][E] \\ k_2[SE] \\ k_3[SE] \end{pmatrix}$$

DEs

$$\begin{aligned} \frac{d[S]}{dt} &= -k_1[S][E] + k_2[SE] && (1) \\ \frac{d[E]}{dt} &= (k_2 + k_3)[SE] - k_1[S][E] && (2) \\ \frac{d[SE]}{dt} &= k_1[S][E] - (k_2 + k_3)[SE] && (3) \\ \frac{d[P]}{dt} &= k_3[SE] && (4) \end{aligned}$$

Reduction of dimension

Step 1

We observe that the equation the product P in equation (4) does not appear in previous equations i.e. it does not influence the behaviour of the system.

This means that the first three equations can be solved separately.

Step 2

We observe that:

$$\frac{[dE]}{dt} + \frac{d[SE]}{dt} \equiv 0$$

We mean that the total amount of enzyme at all time t is $[E_0] = [E] + [SE]$. At time 0, $[SE] = 0$ so E_0 is the initial amount of enzyme.

New DEs

$$\begin{aligned} \frac{d[S]}{dt} &= -k_1[S]([E_0]-[SE]) + k_2[SE] && (1') \\ \frac{d[SE]}{dt} &= k_1[S]([E_0]-[SE]) - (k_2+k_3)[SE] && (3') \end{aligned}$$

Problem

We do not know how to measure $[SE]$.

Goal

Can we express $\frac{d[S]}{dt}$ and $\frac{d[P]}{dt}$ without mentioning $[SE]$?

Quasi steady state approximation

Steady state assumption

If we assume that in the presence of *large quantity of substrate* after a transient period the enzyme-substrate compound 'fills up', then $\frac{d[SE]}{dt}$ will not change any more. Then we can write:

$$\begin{aligned} 0 &= \frac{d[SE]}{dt} \\ &= k_1[S]([E_0] - [SE]) - (k_2 + k_3)[SE] \\ &= [S][E_0] - (K_m + [S])[SE] \qquad \text{where } K_m = \frac{k_2 + k_3}{k_1} \end{aligned}$$

Thus

$$[SE] = \frac{[S][E_0]}{K_m + [S]}$$

Continued

Now by substitution in $\frac{d[P]}{dt}$ in (4) we have:

$$\frac{d[P]}{dt} = k_3(\frac{[S][E_0]}{K_m + [S]}) = \frac{V_{max}[S]}{K_m + [S]}$$

where $V_{max} = k_3[E_0]$. Now by substitution in $\frac{d[S]}{dt}$ in $(1')$ we have:

$$\begin{aligned}
\frac{d[S]}{dt} &= -k_1[S]([E_0] - [SE]) + k_2[SE] \\
&= k_2\frac{[S][E_0]}{K_m+[S]} - k_1[S][E_0] + k_1[S]\frac{[S][E_0]}{K_m+[S]} \\
&\quad \frac{[S][E_0]}{K_m+[S]}(k_2 - k_1(K_m + [S]) + k_1[S]) \\
\frac{d[S]}{dt} &= -k_3(\frac{[S][E_0]}{K_m+[S]})
\end{aligned}$$

Michaelis-Menten Kinetics

We can reduce the reaction to

$$S \rightarrow P$$

where the rate of reaction is now given by the following equations:

$$\begin{aligned} \frac{d[P]}{dt} &= \frac{V_{max}[S]}{K_m + [S]} \\ \frac{d[S]}{dt} &= -\frac{V_{max}[S]}{K_m + [S]} \end{aligned}$$

V_{max} is the maximum velocity. and K_m is the so called *Michealis constant*.