

Master equation and mean-field abstractions of population dynamics

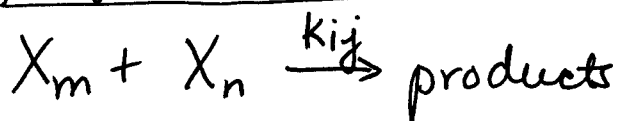
Spring Berman
MAE 598

- Reaction propensity a_{ij} :

$a_{ij} \delta t$ = probability that the reaction^{that} converts complex i into complex j will occur in the next δt .

- h_{ij} = current number of distinct combinations of elements that can undergo the reaction

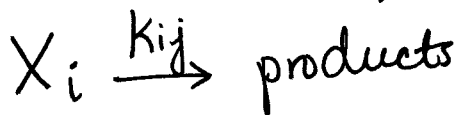
$$a_{ij} = c_{ij} \cdot h_{ij} \quad c_{ij} = \text{stochastic reaction constant}$$



N_i = number of elements of species i

$$c_{ij} = \frac{k_{ij}}{V}, \quad h_{ij} = N_m N_n \quad \text{if } m \neq n$$

$$c_{ij} = \frac{2k_{ij}}{V}, \quad h_{ij} = \frac{N_m(N_m-1)}{2} \quad \text{if } m=n$$



$$c_{ij} = k_{ij}, \quad h_{ij} = N_i$$

Mesoscopic Model - Abstraction of Microscopic Model

- Counts the number of entities in each species i
 N_1, N_2, \dots, N_S
- Ignores robot identities

②

The mesoscopic model models the time evolution of N_i , $i=1, \dots, S$, according to the Chemical Master Equation (CME), which is derived by applying the laws of probability to the fundamental hypothesis.

• $\underline{N}(t) \in \mathbb{R}^S = [N_1, N_2 \dots N_S]^T$ at time t .
integer populations in species $1, 2, \dots, S$

• The CME governs the time evolution of

$P(\underline{n}, t | \underline{n}_0, t_0) \equiv \text{Prob}(\underline{N}(t) = \underline{n} \text{ given } \underline{N}(t_0) = \underline{n}_0)$
and describes a continuous-time Markov process whose states are all possible species population vectors \underline{N} .

for $P(\underline{n}, t | \underline{n}_0, t_0)$

• Cannot be solved analytically¹ for more than a few simple cases; often difficult to solve numerically

⇒ Instead, we can characterize statistical properties of the mesoscopic model by generating numerical realizations of $\underline{N}(t)$ using a stochastic simulation algorithm (SSA) that is also derived from the fund. hypothesis.

One possible method is Gillespie's Direct Method.

Gillespie's Direct Method

③

- Equivalent to a microscopic model in which robots perform stochastic transitions at each time step Δt as described earlier.
task

Advantage: Faster to run than the microscopic model, which loops through all robots / other elements at each time step.

- Simulates a sequence of reactions in a CRN and their initiation times according to the reaction rate constants k_{ij} .

- ① Store initial N_i , $i=1, \dots, S$, in a counter and compute the propensities a_{ij} for each reaction.
- ② Select ^① the next reaction according to a uniform probability distribution over the a_{ij} , and ^② the time until the reaction's occurrence, ΔT , from an exponential distribution with $\sum_{\text{all reactions}} a_{ij}$ as its parameter.
- ③ Advance time by ΔT , simulate the reaction by decrementing the species populations in complex i and incrementing the populations in complex j .
↳ could be done at a future time that represents the completion of the reaction, such as the end of a robot's navigation between tasks at 2 sites.
- ④ Recalculate the a_{ij} and go back to Step ②.

Macroscopic Model

Abstraction of the
Mesoscopic Model

(4)

- Describes the time evolution of the expected values of the species concentrations, $\frac{N_i(t)}{V}$, with a set of ODE's. ($V =$ volume of environment)
- Only unimolecular reactions: can substitute the CME into the equation for $\frac{\partial E(N(t))}{\partial t}$ and use the linearity of expectation.

[Wilkinson, Stochastic Modelling for Systems Biology, 2006, Section 6.7]

- If there are bimolecular reactions: can demonstrate by using van Kampen's system size expansion of the CME [van Kampen, Stochastic Processes in Physics and Chemistry, 2007, Ch. 10]

concentration of species $i =$
 $x_i + \text{fluctuating component}$
 \uparrow
deterministic value

CME is Taylor-expanded near trajectories of x_i , in powers of $V^{-1/2}$

\Rightarrow ODE model governing time evolution of x_i
+ linear Fokker-Planck equation (the "linear noise approximation") that can be used to characterize moments of fluctuations around ODE solution

⑤

• Thermodynamic limit : $N_i \rightarrow \infty, V \rightarrow \infty,$
 $\frac{N_i}{V} \rightarrow \text{finite values}$

Concentration fluctuations become negligibly small ;
time evolution of system is accurately described
by ODE model.

$x_i(t)$ = continuous concentration of species i

$$\underline{x}(t) \in \mathbb{R}^S = [x_1(t) \ x_2(t) \ \dots \ x_S(t)]^T$$

2.6.1 Equations

We will use capital letters A, B, \dots for *names* of chemical substances (molecules, ions, etc), and lower-case a, b, \dots for their corresponding *concentrations*.

There is a systematic way to write down equations for chemical reactions, using a graph description of the reactions and formulas for the different kinetic terms. We discuss this systematic approach later, but for now we consider some very simple reactions, for which we can write equations directly. We simply use the mass-action principle for each separate reaction, and add up all the effects.

The simplest “reaction” is one where there is only one reactant, that can degrade²⁶ or decay (as in radioactive decay), or be transformed into another species, or split into several constituents.

In either case, the rate of the reaction is proportional to the concentration:

if we have twice the amount of substance X in a certain volume, then, per (small) unit of time, a certain % of the substance in this volume will disappear, which means that the concentration will diminish by that fraction.

A corresponding number of the new substances is then produced, per unit of time.

So, decay $X \xrightarrow{k} \cdot$ gives the ODE:

$$dx/dt = -kx,$$

a transformation $X \xrightarrow{k} Y$ gives:

$$dx/dt = -kx$$

$$dy/dt = kx,$$

and a dissociation reaction $Z \xrightarrow{k} X + Y$ gives:

$$dx/dt = kz$$

$$dy/dt = kz$$

$$dz/dt = -kz.$$

A bimolecular reaction $X + Y \xrightarrow{k_+} Z$ gives:

$$dx/dt = -k_+xy$$

$$dy/dt = -k_+xy$$

$$dz/dt = k_+xy$$

and if the reverse reaction $Z \xrightarrow{k_-} X + Y$ also takes place:

$$dx/dt = -k_+xy + k_-z$$

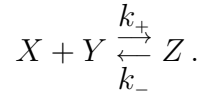
$$dy/dt = -k_+xy + k_-z$$

$$dz/dt = k_+xy - k_-z.$$

²⁶Of course, “degrade” is a relative concept, because the separate parts of the decaying substance should be taken account of. However, if these parts are not active in any further reactions, one ignores them and simply thinks of the reactant as disappearing!

Note the subscripts being used to distinguish between the “forward” and “backward” rate constants.

Incidentally, another way to symbolize the two reactions $X + Y \xrightarrow{k_+} Z$ and $Z \xrightarrow{k_-} X + Y$ is as follows:



Here is one last example: $X + Y \xrightarrow{k} Z$ and $Z \xrightarrow{k'} X$ give:

$$\begin{aligned} dx/dt &= -kxy + k'z \\ dy/dt &= -kxy \\ dz/dt &= kxy - k'z. \end{aligned}$$

Conservation laws are often very useful in simplifying the study of chemical reactions.

For example, take the reversible bimolecular reaction that we just saw:

$$\begin{aligned} dx/dt &= -k_+xy + k_-z \\ dy/dt &= -k_+xy + k_-z \\ dz/dt &= k_+xy - k_-z. \end{aligned}$$

Since, clearly, $d(x+z)/dt \equiv 0$ and $d(y+z)/dt \equiv 0$, then, for every solution, there are constants x_0 and y_0 such that $x+z \equiv x_0$ and $y+z \equiv y_0$. Therefore, once that these constants are known, we only need to study the following scalar first-order ODE:

$$dz/dt = k_+(x_0 - z)(y_0 - z) - k_-z.$$

in order to understand the time-dependence of solutions. Once that $z(t)$ is solved for, we can find $x(t)$ by the formula $x(t) = x_0 - z(t)$ and $y(t)$ by the formula $y(t) = y_0 - z(t)$.

Note that one is only interested in non-negative values of the concentrations, which translates into the constraint that $0 \leq z \leq \min\{x_0, y_0\}$.²⁷

The equation $dz/dt = k_+(x_0 - z)(y_0 - z) - k_-z$ is easily shown to have a unique, and globally asymptotically stable, positive steady state, subject to the constraint that $0 \leq z \leq \min\{x_0, y_0\}$.

(Simply intersect the line $u = k_-z$ with the parabola $u = k_+(x_0 - z)(y_0 - z)$, and use a phase-line argument: degradation is larger than production when to the right of this point, and viceversa.)

We'll see an example of the use of conservation laws when modeling enzymatic reactions.

2.6.2 Chemical Networks

We next discuss a formalism that allows one to easily write up differential equations associated with chemical reactions given by diagrams like



²⁷This is a good place for class discussion of necessary and sufficient conditions for forward-invariance of the non-negative orthant. To be added to notes.