

Math 289a Notes

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Strong Approximations

(Komlós-Major-Tusnády, 1975)

A Poisson process N (with rate 1) and a standard one-dimensional Brownian motion W can be constructed on a common probability space so that

$$\sup_{t \in [0, \infty)} \frac{|N(t) - t - W(t)|}{(\log t) \vee 2} = \xi < \infty \text{ a.s.}$$

where $E[\exp(\alpha \xi)] < \infty$ for some $\alpha > 0$. ($a \vee b$ means $\max(a, b)$.)

[Note that the renewal CLT for N states that, if $\hat{N}^n(t) = \frac{N(nt) - nt}{\sqrt{n}}$, $\forall t \geq 0$, then $\hat{N}^n$ converges in distribution to W .] See Ethier-Kurtz for more details.

Before moving on, here's a handy "bilingual dictionary" for probabilists talking with chemists:

<u>Chemistry</u>	<u>Probability</u>	
propensities	intensities	
master equation	Kolmogorov forward equation	(these first two relate to microscopic models)
Langevin equation	diffusion approximations	
van Kampen equation	(functional) central limit theorem	

Biochemical Reaction Networks

General references

1. T.G. Kurtz, "Strong approximations for density dependent Markov chains," *Stoch. Proc. & Applic.*, 6(1978), 223-240. (first and second order approximations of microscopic models)
2. D.F. Anderson, G. Craciun, T. Kurtz, "Product-form stationary distributions for deficiency zero chemical reaction nets," preprint. (first order and microscopic models)
3. J. Gunawardena, "Chemical reaction network theory for in-silico biologists," lecture notes, 2003. (first order models)

4. M. Feinberg, “Lecture notes for chemical reaction network theory,” 1979. (first order models)
5. D. Gillespie, “Exact stochastic simulation of coupled chemical reactions,” *J. Physical Chemistry*, 8 (1977), 2340-2361. (simulation of microscopic models)

Chemical Reaction Network

Denoted by the 3-tuple $(S, C, \mathcal{R})$.

S = finite set of species (e.g., $\{A_1, \dots, A_n\}$ or $\{A, B, C, D, E\}$)

C = finite set of complexes (a complex is the left- or right-hand side of a reaction). We represent elements of C by vectors in $\mathbb{N}^n$ – each element of C is an n -vector where the i th component of the vector designates the number of molecules of the i th species in the complex.

Examples: for the reaction $A + 2B \rightarrow C$, $A + 2B$ is represented by $\begin{pmatrix} 1 \\ 2 \\ 0 \end{pmatrix}$, and C is represented by $\begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$. For

$\emptyset \rightarrow A$ (an “inflow” reaction), $\emptyset = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$. ($A \rightarrow \emptyset$ would be an “outflow” reaction.)

Our model corresponds to a “continuous flow stirred tank reactor.” Imagine a mostly sealed tank with a stirrer in the middle, but with inflow and outflow tubes.

(Aside: If ν and ν' are complexes such that $\nu \rightarrow \nu'$ is a reaction, that reaction is “reversible” if $\nu' \rightarrow \nu$ is also a reaction.)

$\mathcal{R}$ is a finite set of reactions of the form $\nu \rightarrow \nu'$ where ν, ν' are in C .

Generically, a reaction has the form $\sum_{i=1}^n \nu_{ik} A_i \rightarrow \sum_{i=1}^n \nu'_{ik} A_i$. The k th reaction is $\nu_k \rightarrow \nu'_k$.

The *stoichiometric matrix* S has a row for each chemical species, and a column for each reaction. The k th column is equal to $\nu'_k - \nu_k$, i.e. the change in species counts that the k th reaction induces.

Microscopic Stochastic Model for Dynamics of Reaction Network

For each species i ,

$X_i(t)$ = number of molecules of species i at time t .

$X = (X_1, \dots, X_n)$ is assumed to be a Markov chain.

When the k th reaction is the only reaction that occurs at time t , $X(t) = X(t-) + \nu'_k - \nu_k$, where $t-$ represents a time infinitesimally before t .

Given $x = (x_1, \dots, x_n)$ as the current state of the system, assign to the k th reaction an exponential “alarm clock” with rate $\lambda_k(x)$ (intensity). (Note that exponential distributions are memoryless.)

Let $N_1, \dots, N_n$ be independent unit rate Poisson processes. Then for each k ,

$$R_k(t) = N_k \left(\int_0^t \lambda_k(X(s)) ds \right)$$

= number of times k th reaction has occurred by time t .

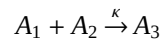
Then

$$X(t) = X(0) + \sum_{k=1}^K R_k(t)(v'_k - v_k) = X(0) + \mathbf{S}R(t),$$

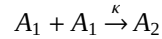
where $R(t) := \begin{pmatrix} R_1(t) \\ \vdots \\ R_K(t) \end{pmatrix}$.

Mass-action kinetics

Example: Examples of binary reactions



$$\lambda(x) = \kappa x_1 x_2, \quad \kappa = \text{reaction rate constant}$$



$$\lambda(x) = \kappa x_1(x_1 - 1)$$

More generally for $\sum_{i=1}^n \nu_{ik} A_i \xrightarrow{\kappa_k} \sum_{i=1}^n \nu'_{ik} A_i$,

$$\lambda_k(x) = \kappa_k \prod_{i=1}^n \nu_{ik}! \binom{x_i}{\nu_{ik}}.$$

We can define the concentration vector as $\frac{X(t)}{V}$ (where V is volume)

For the reaction $A + B \xrightarrow{\kappa} C$, the o.d.e. approximation for concentration is (where $c = (c_A, c_B, c_C)$ is the vector with all three species concentrations)

$$\dot{c}_A = -\kappa c_A c_B$$

$$\dot{c}_B = -\kappa c_A c_B$$

$$\dot{c}_C = \kappa c_A c_B$$

How does κ depend on volume: cf. Gillespie

Consider the binary reaction $A_1 + A_2 \rightarrow A_3$ with mass action kinetics. How does the rate constant κ depend on volume?

Probability of producing a new molecule of A_3 in a small time interval of length δt : $\lambda(x) \delta t$, which is proportional to the probability that some molecule of A_1 collides with some molecule of A_2 in δt .

Take one molecule of A_1 and one of A_2 . Geometrically, imagine A_1 as a sphere with radius r_1 , and A_2 as a sphere with radius r_2 , and let $r_{12} = r_1 + r_2$. A collision of the two occurs if the center of A_1 is within r_{12} of the center of A_2 . For the purposes of our calculation we can imagine the center of A_2 as having a fixed random position in the volume V and A_1 as moving (relative to A_2) at an average speed of v_{12} . Also, at any instant of time, the “reaction sphere of A_1 ” is the sphere with center A_1 and radius r_{12} (if the center of A_2 lies within this sphere, then A_1 will react with A_2 to produce A_3).

The new volume swept out by A_1 in δt is proportional to $\pi r_{12}^2 v_{12} \delta t$, so the probability that the randomly distributed center of A_2 falls in this volume is proportional to $\frac{\pi r_{12}^2 v_{12}}{V} \delta t$. So, to leading order, we have

$$\lambda(x) \delta(t) \propto \left(\frac{\pi r_{12}^2 v_{12} \delta t}{V} \right) \cdot (\text{number of ways of choosing a pair of molecules } (A_1, A_2))$$

so

$$\lambda(x) \delta(t) = \frac{\tilde{\kappa} x_1 x_2}{V} \delta t$$

for some constant $\tilde{\kappa}$.

More generally, $\lambda_k(x) = \frac{\tilde{\kappa}_k}{V^{m_k-1}} \prod_{i=1} v_{ik}! \binom{x_i}{v_{ik}}$, where m_k is the number of molecules consumed in reaction k , i.e., $m_k = \sum_{i=1}^n v_{ik}$.