

Office hours today 4-5 PM.

Homework 3 due Monday, November 23 at 2 PM.

To set up a model for continuous-time Markov chains, the natural framework is in terms of rates, just as deterministic differential equations (in continuous time) are set up in terms of rates of change.

So we will consider first the behavior of the probability transition function $P(t)$ over an infinitesimal time interval.

Write a Taylor expansion about $t = 0$ to describe the probability of transitions over a short time into the future.

$P(\Delta t) = P(0) + P'(0)\Delta t + o(\Delta t)$, where $o(\Delta t)$ denotes neglected "error" terms that satisfy the property: $\lim_{\Delta t \downarrow 0} \frac{o(\Delta t)}{\Delta t} = 0$.

$P(0) = I$ (identity matrix) because $P(X(s+0) = j | X(s) = i) = 1$ if $i = j$ and 0 otherwise.

The interesting part of the probability transition function enters into the first derivative term:

$$A = P'(0) = \lim_{\Delta t \downarrow 0} \frac{P(\Delta t) - P(0)}{\Delta t} = \lim_{\Delta t \downarrow 0} \frac{P(\Delta t) - I}{\Delta t}$$

This is known as the transition rate matrix or infinitesimal generator and modeling a CTMC amounts to specifying A and the initial condition.

Let's examine the entries of A

For the off-diagonal elements ($i \neq j$):

$$\begin{aligned} A_{ij} &= \lim_{\Delta t \downarrow 0} \frac{P_{ij}(\Delta t) - 0}{\Delta t} \\ &= \lim_{\Delta t \downarrow 0} \frac{P(X(t+\Delta t) = j | X(t) = i)}{\Delta t} \end{aligned}$$

which can be viewed as the rate at which the Markov chain makes a transition from state i to j . It is a rate, not a probability; units of inverse time.

For the diagonal entries, we will start by noting that

$$\sum_{j \in S} P_{ij}(t) = 1$$

Apply this to the Taylor expansion (take row sums):

$$\sum_{j \in S} P_{ij}(\Delta t) = 1 + \sum_{j \in S} A_{ij} \Delta t + o(\Delta t)$$

$$1 = 1 + \sum_{j \in S} A_{ij} \Delta t + o(\Delta t)$$

$$\sum_{j \in S} A_{ij} = -\frac{o(\Delta t)}{\Delta t}$$

$$\sum_{j \in S} A_{ij} = 0$$

This therefore allows us to express the diagonal elements in terms of the off-diagonal elements:

$A_{ii} = -\sum_{j \neq i} A_{ij} \equiv -\lambda_i$ where λ_i is a nonnegative quantity, which we will call the **total transition rate** out of state i .

We will see that specifying the transition rate matrix will allow us to compute (in principle) arbitrary statistics of the CTMC, so **when we formulate a CTMC model, we have to specify how to populate the transition rate matrix:**

- Focus first on the off-diagonal entries. $A_{ij} = 0$ unless it is possible to make a transition from state i to state j in one instant.
- If it is possible to make a transition from state i to state j in one instant, then the value of A_{ij} is the "rate" at which this transition happens, which often is usefully thought of as the **inverse of the time it would take for this transition to happen, if all other transitions out of state i are blocked from happening.**
- The diagonal entries of the transition rate matrix is then just the negative of the sum of all transition rates out of the corresponding state. These values $-\lambda_i$ which are the total transition rate out of state i correspond to the **inverse of the expected time until some transition out state i is made.**

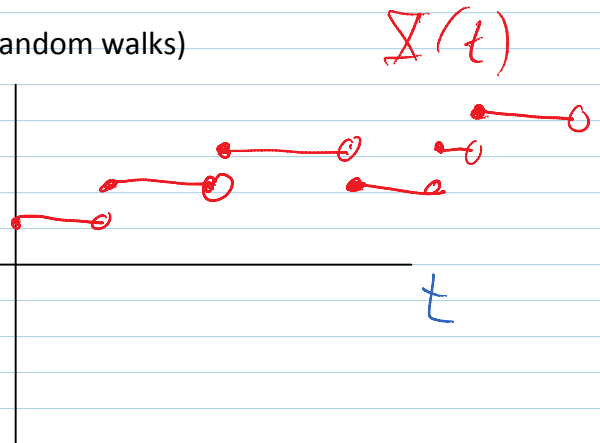
Also specify the initial probability distribution $\phi_j^{(0)} = P(X(0) = j)$.

Most choices of transition rate matrices will give rise to a well-defined CTMC, but if the state space is countably infinite, one does need to impose some **technical condition so the CTMC doesn't blow up in finite time** (Karlin and Taylor Ch. 4).

Some important classes of CTMCs are:

1) Birth-death processes (heterogenous continuous-time random walks)

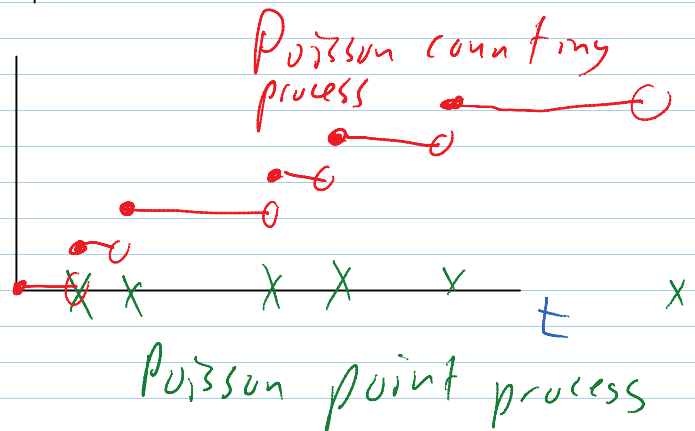
$$\begin{aligned} A_{i,i+1} &= \lambda_i \text{ aggregate birth rate} \\ A_{i,i-1} &= \mu_i \text{ aggregate death rate} \\ A_{i,j} &= 0 \text{ if } |i-j| > 1 \\ A_{i,i} &= -\lambda_i - \mu_i \end{aligned}$$



Some special cases of birth-death processes:

a) Poisson counting process

$$\begin{aligned} \lambda_i &\equiv \lambda \\ \mu_i &= 0. \end{aligned}$$



The Poisson counting process, **counts the number of Poisson points that have "occurred" up to a time t** , where Poisson points are randomly distributed on the time axis with **rate/intensity λ** .

b) continuous-time queuing models (k equally effective servers, no constraint on the queue length)

If the state of the CTMC describes the number of demands that are either waiting or in service, then we can describe the queueing process by a birth-death process with parameters:

$$\begin{aligned} \lambda_i &= \lambda \text{ (rate at which demands arise)} \\ \mu_i &= \begin{cases} k\mu & \text{for } i \geq k \\ i\mu & \text{for } i < k \end{cases} \end{aligned}$$

where μ is the service rate of one server (i.e., $1/(\text{average time to complete a service})$)

Note that for a CTMC model to be appropriate, the amount of time spent in a state must be memoryless, and therefore exponentially distributed. If this is inconsistent with the real situation, then a CTMC is not appropriate; think about renewal processes instead.

c) Population models

Here we can conduct a typical exercise of converting a deterministic differential equation to a stochastic version in the form of a CTMC. This is typically done if we think of the differential equation as a sort of "Law of Large Numbers limit" and the stochastic model as trying to actually track the fluctuations caused by randomness at the individual level.

DE model

$$\frac{dx}{dt} = \boxed{r x}$$

aggregate growth rate

$r =$ net growth rate per capita

$$r = \underset{\substack{\uparrow \\ \text{per capita birth rate}}}{b} - \underset{\substack{\uparrow \\ \text{per capita death rate}}}{d}$$

CTMC (birth-death processes)

$$\lambda_i = b_i$$

$$\mu_i = d_i$$

$$\frac{dx}{dt} = b x - \underbrace{c x^2}_{\text{aggregate death rate}}$$

$$\lambda_i = b_i$$

$$\mu_i = c i^2$$

$$\frac{dx}{dt} = \underbrace{b x^2}_{\substack{\text{sparse} \\ \text{or} \\ \text{promiscuous}}} - c x$$

$$\lambda_i = b i^2$$

$$\mu_i = c i$$

but this model can blow up in finite time.

2) Finite-state CTMCs

- atomic state transition
- conformational changes in biomolecules; compress data from molecular dynamics simulations (see [Christof Schuette](#))

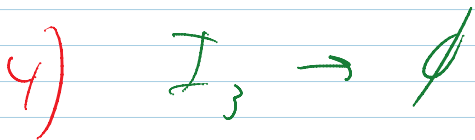
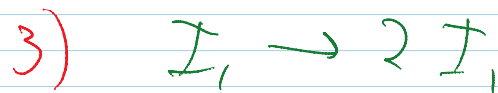
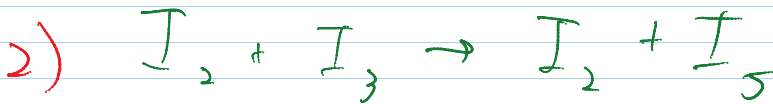
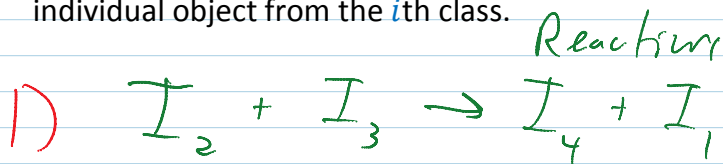
3) Reaction networks: chemical/biological reactions, genetic networks, ecology, disease spread

- see for example review article by [Goutsias and Jenkinson](#), "Markovian dynamics on complex reaction networks," *Physics Reports* 529 (2013), 199-264.

Suppose we have k classes of objects (chemical species, disease states, organism types), and we represent the state of the system by a vector $X(t) = (X_1(t), X_2(t), \dots, X_k(t))$ where $X_i(t)$ is the number of objects of type i present at time t . State space $S = \mathbb{Z}_{\geq 0}^k$.

Can't really write the transition rate matrix down directly, but one can use a sparse matrix representation of the transition rates to give a well-defined CTMC.

For this process, one lists the possible "reactions" that cause state changes along with their "reaction rates." For this purpose, we will use the symbol I_i to correspond symbolically to an individual object from the i th class.



Aggregate Rates:

$$\alpha_1(\vec{x}) = k_1 x_2 x_3$$

$$\alpha_2(\vec{x}) = k_2 x_2 x_3$$

$$\alpha_3(\vec{x}) = k_3 x_1$$

$$\alpha_4(\vec{x}) = k_4 x_3$$

Each reaction implies a transition of state:

1): $(x_1, x_2, x_3, x_4, x_5) \rightarrow (x_1 + 1, x_2 - 1, x_3 - 1, x_4 + 1, x_5)$

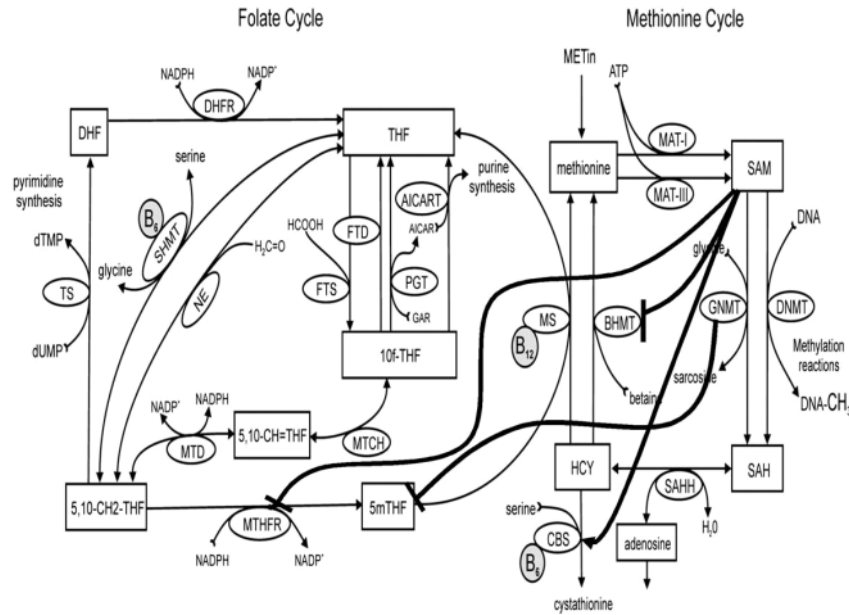
4) $(x_1, x_2, x_3, x_4, x_5) \rightarrow (x_1, x_2, x_3 - 1, x_4, x_5)$

This reaction rate formalism implicitly defines a transition rate matrix. Of course this transition rate matrix is hard to actually write down explicitly or

work with a computationally reasonable fashion. Very active research into how to deal with such CTMCs in practical way.

The reaction scheme for Folate-Mediated One-Carbon Metabolism:
Note nonlocal interactions!

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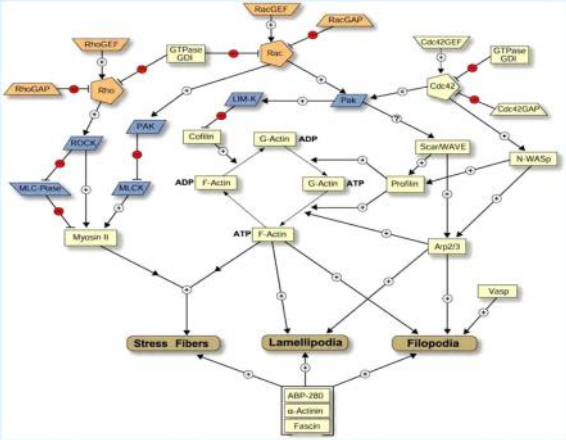


Reed, M. C. et al. J. Nutr. 2006;136:2653-2661, adapted as per
outstanding survey talk of Michael Reed (Duke):
<http://www.ima.umn.edu/videos/?id=392>

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Network Analysis

Details of the actin control network



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Hans Othmer, Minnesota

Simulating reaction networks with many random discrete events

Heat shock model

The following reaction network is given as a model for the heat shock response in E. Coli by Srivastava, Peterson and Bently [9]

| Reaction | Intensity | Reaction | Intensity |
|--|---------------------------------------|-----------------------------|---------------------------------------|
| $\emptyset \rightarrow S_8$ | 4.00×10^0 | $S_6 + S_8 \rightarrow S_3$ | $3.62 \times 10^{-4} X_{S_6} X_{S_8}$ |
| $S_2 \rightarrow S_5$ | $7.00 \times 10^{-1} X_{S_2}$ | $S_8 \rightarrow \emptyset$ | $9.99 \times 10^{-8} X_{S_8}$ |
| $S_2 \rightarrow S_2$ | $1.30 \times 10^{-1} X_{S_2}$ | $S_6 \rightarrow S_6 + S_8$ | $4.40 \times 10^{-8} X_{S_6}$ |
| $\emptyset \rightarrow S_2$ | $7.00 \times 10^{-3} X_{S_1}$ | $\emptyset \rightarrow S_1$ | 1.40×10^{-8} |
| $\text{stuff} + S_2 \rightarrow S_5 + S_2$ | $6.30 \times 10^{-3} X_{S_2}$ | $S_1 \rightarrow \emptyset$ | $1.40 \times 10^{-6} X_{S_1}$ |
| $\text{stuff} + S_2 \rightarrow S_4 + S_2$ | $4.88 \times 10^{-3} X_{S_2}$ | $S_7 \rightarrow S_6$ | $1.42 \times 10^{-6} X_{S_4} X_{S_7}$ |
| $\text{stuff} + S_2 \rightarrow S_6 + S_2$ | $4.88 \times 10^{-3} X_{S_2}$ | $S_5 \rightarrow \emptyset$ | $1.80 \times 10^{-8} X_{S_5}$ |
| $S_7 \rightarrow S_2 + S_6$ | $4.40 \times 10^{-4} X_{S_7}$ | $S_6 \rightarrow \emptyset$ | $6.40 \times 10^{-10} X_{S_6}$ |
| $S_2 + S_6 \rightarrow S_7$ | $3.62 \times 10^{-4} X_{S_2} X_{S_6}$ | $S_4 \rightarrow \emptyset$ | $7.40 \times 10^{-11} X_{S_4}$ |

Thomas Kurtz, Wisconsin



Finite-horizon statistics of CTMCs

Just as for discrete-time MCs, the Markov property allows us to decompose any finite-time statistic into statistics involving pairs of times and/or a single time:

$$P(X(t_1)=j_1, X(t_2)=j_2, \dots, X(t_n)=j_n | X(0)=i) \\ = P_{ij_1}(t_1) P_{j_1 j_2}(t_2 - t_1) \dots P_{j_{n-1} j_n}(t_n - t_{n-1})$$

To this end, we will use the Chapman-Kolmogorov equation, and decompose by an intermediate time that is infinitesimally close to the beginning or ending time. This will give two different equations for the same quantity, but both are useful, as we'll see.

First let's decompose with an intermediate time at Δt (near the beginning)

