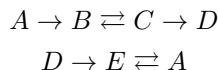


Modeling Complicated Reactions Using Transition Matrices

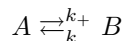
Our goal is to come up with a straightforward way to link together arbitrarily complicated reaction schemes. Imagine I have the following, which describes a signaling cascade:



While I might be able to analytically solve rate laws that describe the concentrations of all species, this would be very challenging. Instead, we'll look at a common numerical approach used to study reaction kinetics: a "Transition Matrix" or "Markov Matrix."

Reaction Probabilities Over Short Times

We will start by writing the probabilities of different outcomes over very short time steps (Δt) for the following reaction.



We'll start with A . Over Δt , a molecule of A can either become B (with probability $P_{A \rightarrow B; \Delta t}$) or remain A (with probability $P_{A \rightarrow A; \Delta t}$). Because these are the only possibilities:

$$P_{A \rightarrow A; \Delta t} + P_{A \rightarrow B; \Delta t} = 1,$$

so:

$$P_{A \rightarrow A; \Delta t} = 1 - P_{A \rightarrow B; \Delta t}$$

How do we figure out $P_{A \rightarrow B; \Delta t}$? We know that the *rate* of $A \rightarrow B$ is given by:

$$rate_{A \rightarrow B} = k_+[A]$$

If we assume that $[A]$ does not change over Δt —which is approximately true for a small enough Δt —the amount of new B is:

$$[B]_{new} = rate_{A \rightarrow B} \times time = k_+[A]\Delta t$$

The probability we got a new B is:

$$P_{A \rightarrow B; \Delta t} = \frac{[B]_{new}}{[leftover A] + [B]_{new}} = \frac{[B]_{new}}{([A] - [B]_{new}) + [B]_{new}} = \frac{k_+[A]\Delta t}{[A]} = k_+\Delta t$$

Finally, we can substitute this in:

$$P_{A \rightarrow B; \Delta t} = k_+\Delta t$$

$$P_{A \rightarrow A; \Delta t} = (1 - k_+\Delta t)$$

We can use similar logic to argue that:

$$P_{B \rightarrow A; \Delta t} = k_-\Delta t$$

$$P_{B \rightarrow B; \Delta t} = (1 - k_-\Delta t)$$

The Transition Matrix

Now let's stick this into a matrix \mathbf{T} . (The reason for doing this will become clear later).

$$\mathbf{T} = \begin{bmatrix} P_{A \rightarrow A; \Delta t} & P_{B \rightarrow A; \Delta t} \\ P_{A \rightarrow B; \Delta t} & P_{B \rightarrow B; \Delta t} \end{bmatrix}$$

This describes the probabilities of all transitions possible in the system. As a result, this is called a *transition matrix*. Note that column 1 of this matrix gives all possible ways A can transform over step Δt . Column 2 gives all possible ways B can transform over step Δt . As a result, each column sums to 1.0. A matrix with columns that sum to 1.0 is called a *left stochastic matrix* and has some very nifty properties. To see these, let's multiply this matrix and a vector of concentrations. Recall that matrix multiplication works in the following way:

$$\begin{bmatrix} a & b \\ c & d \end{bmatrix} \cdot \begin{bmatrix} E \\ F \end{bmatrix} = \begin{bmatrix} a \times E + b \times F \\ c \times E + d \times F \end{bmatrix}$$

This means, for our concentrations:

$$\begin{bmatrix} P_{A \rightarrow A; \Delta t} & P_{B \rightarrow A; \Delta t} \\ P_{A \rightarrow B; \Delta t} & P_{B \rightarrow B; \Delta t} \end{bmatrix} \begin{bmatrix} A(t) \\ B(t) \end{bmatrix} = \begin{bmatrix} P_{A \rightarrow A; \Delta t} A(t) + P_{B \rightarrow A; \Delta t} B(t) \\ P_{A \rightarrow B; \Delta t} A(t) + P_{B \rightarrow B; \Delta t} B(t) \end{bmatrix} = \begin{bmatrix} A(t + \Delta t) \\ B(t + \Delta t) \end{bmatrix}$$

Let's look at what happened to A . After Δt , A is:

$$A(t + \Delta t) = P_{A \rightarrow A; \Delta t} A(t) + P_{B \rightarrow A; \Delta t} B(t).$$

In words, this is the probability that each molecule of A stayed A , plus the probability that each molecule of B became an A .

- If $P_{A \rightarrow A; \Delta t} < 1.0$ and $A(t) > 0$, the first term will cause A to decrease over Δt because molecules of A are turning into B .
- If $P_{B \rightarrow A; \Delta t} > 0.0$ and $B(t) > 0$, the second term will make $A(t)$ increase over Δt because molecules of B are turning into molecules of A .

Similar statements can be written for $B(t + \Delta t)$.

Numerical Examples

Let's put in some real numbers to see how these work:

$$\mathbf{T} = \begin{bmatrix} P_{A \rightarrow A; \Delta t} & P_{B \rightarrow A; \Delta t} \\ P_{A \rightarrow B; \Delta t} & P_{B \rightarrow B; \Delta t} \end{bmatrix} = \begin{bmatrix} 0.99 & 0.01 \\ 0.01 & 0.99 \end{bmatrix}$$

This says that over Δt , there is a 99% chance A stays a A and a 1% chance that A becomes B . Likewise, there is a 99% chance of B staying B and a 1% chance of B becoming A . Now, let's start with $[A] = 100 \mu M$ and $[B] = 0 \mu M$. After Δt :

$$\mathbf{T} \cdot \begin{bmatrix} [A] \\ [B] \end{bmatrix} = \begin{bmatrix} 0.99 & 0.01 \\ 0.01 & 0.99 \end{bmatrix} \begin{bmatrix} 100 \\ 0 \end{bmatrix} = \begin{bmatrix} 0.99 \times 100 + 0.01 \times 0 \\ 0.01 \times 100 + 0.99 \times 0 \end{bmatrix} = \begin{bmatrix} 99 \\ 1 \end{bmatrix}$$

After this time step, we now have 99 μM A and 1 μM B . We had some A convert to B , but no B convert to A . Notice that the resulting vector still sums to 100, ($99 + 1 = 100$), so these matrices conserve mass. What about another time step?

$$\begin{bmatrix} 0.99 & 0.01 \\ 0.01 & 0.99 \end{bmatrix} \begin{bmatrix} 99 \\ 1 \end{bmatrix} = \begin{bmatrix} 0.99 \times 99 + 0.01 \times 1 \\ 0.01 \times 99 + 0.99 \times 1 \end{bmatrix} = \begin{bmatrix} 98.02 \\ 1.98 \end{bmatrix}$$

Over this time step, we still made a lot more B from A , but we had a tiny amount of B turn into A . Note that the concentration still sums to 100, but that we only added 0.98 μM B on this step as opposed to 1.0 μM B on the first step. Let's apply this one more time:

$$\begin{bmatrix} 0.99 & 0.01 \\ 0.01 & 0.99 \end{bmatrix} \begin{bmatrix} 98.02 \\ 1.98 \end{bmatrix} = \begin{bmatrix} 0.99 \times 98.02 + 0.01 \times 1.98 \\ 0.01 \times 98.02 + 0.99 \times 1.98 \end{bmatrix} = \begin{bmatrix} 97.0596 \\ 2.94040 \end{bmatrix}$$

We added only 0.96 μM B this time (rather than 0.98 μM from the step before). Hopefully you can see the pattern. We are accumulating B ever more slowly as we apply the matrix. This is because 1) there is less A to turn in to B and 2) some of our B turns into A .

What if we started with 0 μM A and 100 μM B ?

$$\begin{bmatrix} 0.99 & 0.01 \\ 0.01 & 0.99 \end{bmatrix} \begin{bmatrix} 0 \\ 100 \end{bmatrix} = \begin{bmatrix} 0.99 \times 0 + 0.01 \times 100 \\ 0.01 \times 0 + 0.99 \times 100 \end{bmatrix} = \begin{bmatrix} 1 \\ 99 \end{bmatrix}$$

With the same matrix, we are now running the reaction in reverse: because we started with excess B , we start converting B into A .

Matrices tend towards equilibrium

Whether we start with excess A or excess B , if we continue applying the matrix over and over again, we would see the values of $[A]$ and $[B]$ converge on their equilibrium values. Since $P_{A \rightarrow B; \Delta t} = P_{B \rightarrow A; \Delta t}$, it is hopefully intuitive that equilibrium will have equal concentrations of A and B . We can plug these values into check:

$$\begin{bmatrix} 0.99 & 0.01 \\ 0.01 & 0.99 \end{bmatrix} \begin{bmatrix} 50 \\ 50 \end{bmatrix} = \begin{bmatrix} 0.99 \times 50 + 0.01 \times 50 \\ 0.01 \times 50 + 0.99 \times 50 \end{bmatrix} = \begin{bmatrix} 50 \\ 50 \end{bmatrix}$$

Once we are at equilibrium, the matrix returns the same values we put in.

Multiplication

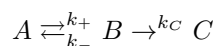
One of the key, powerful, things about these matrices is that you can apply them for very long time steps with relatively few operations. This is because you can simply raise \mathbf{T}^n to simulate n steps. This is illustrated below:

$$\mathbf{T} \cdot \vec{V}_0 = \vec{V}_1$$

$$\begin{aligned}
\mathbf{T} \cdot \vec{V}_1 &= \vec{V}_2 \\
\mathbf{T} \cdot \vec{V}_2 &= \vec{V}_3 \\
\mathbf{T} \cdot (\mathbf{T} \cdot (\mathbf{T} \cdot \vec{V}_0)) &= \vec{V}_3 \\
\mathbf{T}^n \cdot \vec{V}_0 &= \vec{V}_n
\end{aligned}$$

Complicated Reactions

What about a more complicated reaction? Let's think about the following:



For this, we simply construct a matrix that describes all possible transitions between the three states. (For sanity, I am going to use a more compact notation where I drop the arrows and Δt : $P_{AA} \equiv P_{A \rightarrow A; \Delta t}$):

$$\mathbf{T} = \begin{bmatrix} P_{AA} & P_{BA} & P_{CA} \\ P_{AB} & P_{BB} & P_{CB} \\ P_{AC} & P_{BC} & P_{CC} \end{bmatrix}$$

If we choose a short enough Δt , there is not enough time for a molecule to do more than one step. This means we never see something like $A \rightarrow B \rightarrow C$, so $P_{AC} = 0$. Also, just based on the arrows, there is also no way for $C \rightarrow B$ or $C \rightarrow A$, so P_{CB} and $P_{CA} = 0$. Substituting these in:

$$\mathbf{T} = \begin{bmatrix} P_{AA} & P_{BA} & 0 \\ P_{AB} & P_{BB} & 0 \\ 0 & P_{BC} & P_{CC} \end{bmatrix}$$

What are the values of these probabilities?

The value for P_{CC} is (hopefully) obviously 1.0, because a molecule of C has no option but to remain C .

We can use the same logic as we did above for P_{AA} and P_{AB} :

$$P_{AB} = k_+ \Delta t$$

$$P_{AA} = (1 - k_+ \Delta t).$$

What about B ? It's only slightly trickier than A .

$$P_{BA} = k_- \Delta t$$

$$P_{BB} = 1 - (k_- + k_C) \Delta t$$

$$P_{BC} = k_C \Delta t$$

This says that the probability of remaining B is 1 minus the probabilities of all moves away from B .

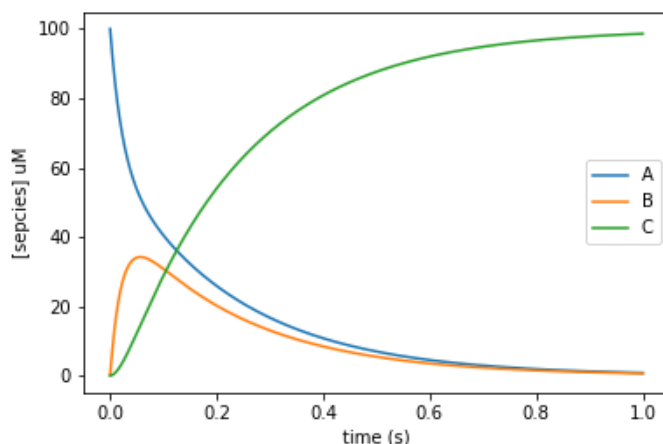
If we substitute this in, we find:

$$\mathbf{T} = \begin{bmatrix} (1 - k_+ \Delta t) & k_- \Delta t & 0 \\ k_+ \Delta t & 1 - (k_- + k_C) \Delta t & 0 \\ 0 & k_C \Delta t & 1.0 \end{bmatrix}$$

We can see how this works by running a calculation.

- $k_+ = 20 \text{ s}^{-1}$, $k_- = 20 \text{ s}^{-1}$, $k_C = 10 \text{ s}^{-1}$
- $\Delta t = 0.0001 \text{ s}$
- $[A]_0 = 100 \text{ }\mu\text{M}$, $[B]_0 = [C]_0 = 0 \text{ }\mu\text{M}$

The results follow:



Hopefully this makes some intuitive sense. We start with all A , which then converts to B . B begins to accumulate because the rate of $B \rightarrow C$ is slower than $B \rightarrow A$. Over a long time, however, C accumulates, eventually taking over the population. This is because the final $B \rightarrow C$ step, while slow, is irreversible.

Conclusion

There are many other cool properties of these matrices that can be unlocked using linear algebra. Hopefully, however, you can already see how they might be useful to describe complex chemical reactions. These can be used to model signaling networks, metabolism, protein folding, and even protein evolution. What we found above can be summarized as follows:

1. You can model arbitrarily complicated first-order reactions using transition matrices.
2. Reactions must be first-order. (You can model higher-order reactions, but then you have to have higher-dimensional matrices and things get very complicated...)

3. Protocol:

- (a) Make an $m \times m$ matrix, where m is the number of species.
- (b) The i^{th} column encodes the probability that species i stays itself or becomes some other species over time step Δt .
- (c) Matrix entries are zero unless there is an arrow connecting the two species in the reaction diagram.
- (d) The probability of species i becoming j over Δt is $k_{i \rightarrow j} \Delta t$.
- (e) The probability of species i remaining species i over Δt is $1 - \sum_j k_{i \rightarrow j} \Delta t$ where j sums over all non- i species.
- (f) Δt must be small. A good rule of thumb is that $\Delta t \times k_{fastest} < 0.1$. For a real simulation, you'd probably want to have this number be even smaller.
- (g) To determine the concentration of all species after $n\Delta t$ seconds, calculate $\mathbf{T}^n \cdot \vec{V}_0 = \vec{V}_n$ where \vec{V}_0 is a vector containing the initial concentrations of all species.