Entropy in Biology

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Lecture 3 — part 2

Proof of the Onsager relations for the steady state of a continuous-time Markov chain near equilibrium
Onsager Relations

The steady-state equations of a continuous-time Markov chain are

\[ \sum_{j=1}^{n} f_{ij} = 0, \quad i = 1 \ldots n \]

Where

\[ f_{ij} = P_i r_{ij} - P_j r_{ji}, \quad i, j = 1 \ldots n \]

and

\[ \sum_{i=1}^{n} P_i = 1 \]

Here, \( P_i \) is the steady-state probability that the system is in state \( i \), \( r_{ij} \) is the transition rate from \( i \to j \), and \( f_{ij} \) is the flux of probability from \( i \to j \).

We assume that all possible transitions are reversible. Thus, for any pair \((i, j)\), either \( r_{ij} \) and \( r_{ji} \) are both positive, or \( r_{ij} = 0 \) and \( r_{ji} = 0 \).
Because of the above assumption that all of the allowed transitions are reversible, we can associate with our Markov chain an undirected graph with the states as nodes and the allowed transitions as edges.

We assume that this graph is connected.

Note that it is then possible to go from any state to any other state through a sequence of allowed transitions.

Although we do not give the proof here, it can then be shown that the steady-state probabilities $p_1, \ldots, p_n$ are uniquely determined by equations (1-3), and moreover that all of them are positive:

\[ p_i > 0 \text{ for } i = 1 \ldots n \]

Note that our notation excludes self-loops, since (2) makes $f_{ii} = 0$ regardless of $y_{ii}$, and also that we only allow one transition in each direction between any pair of distinct states. These restrictions can be removed but we avoid the resulting complications here.
Now suppose that the transition rates are perturbed as follows:

\[ r_{ij} = r_{ij}^0 + \epsilon R_{ij} \]

with the result that

\[ p_i = p_i^0 + \epsilon P_i + \ldots \]

\[ f_{ij} = f_{ij}^0 + \epsilon F_{ij} + \ldots \]

Then

\[ f_{ij}^0 = p_{ij}^0 r_{ij}^0 - p_{ji}^0 r_{ji}^0 \]

\[ F_{ij} = P_i r_{ij}^0 - P_j r_{ji}^0 + p_{i}^0 R_{ij} - p_{j}^0 R_{ji} \]

We assume, moreover, that the unperturbed steady state satisfies the principle of detailed balance. That is,

*But with only positive rates perturbed, so that

\[ r_{ij}^0 = 0 \implies R_{ij} = 0 \]
\[ 0 = \mathcal{f}_{ij} = \rho_i r_{ij} - \rho_j r_{ji} \] 

for all pairs \( i,j \). A steady state that satisfies the principle of detailed balance, in which all net fluxes are equal to zero as in (9), is called a state of equilibrium.

We do not assume that the perturbed steady state is a state of equilibrium.

Let

\[ a_{ij} = a_{ji} = \rho_i r_{ij} = \rho_j r_{ji} \geq 0 \] 

Then \( F_{ij} \) can be rewritten as follows for all \( i,j \) such that \( a_{ij} > 0 \):

\[ F_{ij} = \frac{P_i}{\rho_i} \rho_0 r_{ij} - \frac{P_j}{\rho_j} \rho_0 r_{ji} \]

\[ + \rho_i r_{ij} \frac{R_{ij}}{r_{ij}} - \rho_j r_{ji} \frac{R_{ji}}{r_{ji}} \]

Therefore,
\( F_{ij} = a_{ij} \left( \Phi_i - \Phi_j + E_{ij} \right) \)

where
\[
E_{ij} = \frac{R_{ij}}{r_{ij}} - \frac{R_{ji}}{r_{ji}}
\]

\( \Phi_i = \frac{P_i}{p_{oi}} \)

Note that (12) holds also for \( a_{ij} = 0 \), provided we interpret it to mean that \( F_{ij} = 0 \), even though \( E_{ij} \) is undefined, when \( a_{ij} = 0 \).

As noted above, \( a_{ij} \) is symmetric, and we see from (13) that \( E_{ij} \) is anti-symmetric.

To first order in \( E \), equations (1) & (3) become

\[
\sum_{j=1}^{n} a_{ij} \left( \Phi_i - \Phi_j + E_{ij} \right) = 0, \quad i=1 \ldots n
\]

\[
\sum_{i=1}^{n} p_{oi} \Phi_i = \sum_{i} P_i = 0
\]
If we sum in (15) over \( i = 1 \cdots n \), we get \( 0 = 0 \) since \( a_{ij} \) is symmetric and \( \Phi_i - \Phi_j + E_{ij} \) is antisymmetric.

This shows that any one of the equations \( i = 1 \cdots n \) in (15) can be derived from the remaining \( n-1 \) equations.

The homogeneous system corresponding to (15) is

\[
(17) \quad \sum_{j=1}^{n} a_{ij} (\Phi_i - \Phi_j) = 0, \quad i = 1 \cdots n
\]

Multiplying both sides by \( \Phi_i \) and summing over \( i \), we get

\[
(18) \quad \sum_{ij=1}^{n} a_{ij} \Phi_i (\Phi_i - \Phi_j) = 0
\]

Interchanging \( i \) and \( j \) gives

\[
(19) \quad \sum_{ij=1}^{n} a_{ij} (-\Phi_j) (\Phi_i - \Phi_j) = 0
\]
Then, by adding (18) & (19), we get

$$\sum_{i,j=1}^{n} a_{ij} (\Phi_i - \Phi_j)^2 = 0$$

Since $a_{ij} \geq 0$, it follows that $\Phi_i = \Phi_j$ for all pairs $(i,j)$ such that $a_{ij} > 0$.

Now consider the graph in which there is an edge connecting node $i$ to node $j$ if and only if $a_{ij} > 0$. We assume that this graph is connected, and it then follows from (20) that the only solutions of the homogeneous system (17) are those in which $\Phi_i$ is constant, independent of the index $i$.

Since the singular system (15) is symmetric, it follows from the foregoing that solutions exist if and only if the vectors with components

$$\sum_{j=1}^{n} a_{ij} E_{ij}, \quad i = 1, \ldots, n$$

(21)
is orthogonal to any constant vector, and this
is indeed the case, since

$$\sum_{i=1}^{n} \sum_{j=1}^{n} a_{ij} E_{ij} = 0$$

since $a_{ij}$ is symmetric and $E_{ij}$ is antisymmetric.

Thus, solutions to (15) exist and they are
unique up to an additive constant in $\Phi$. This
constant can be determined by making use of (16). If $\Phi^*$ is any particular
solution of (15), then

$$\Phi_i = \Phi_i^* - \sum_{j=1}^{n} f_{ij} \Phi_j^*$$

is the unique solution of the system (15-16).

In the following, however, our interest will
be in evaluating the first-order flux $F_{ij}$,
see (12), and for this purpose the
non-uniqueness of $\Phi$ does not matter,
since an additive constant in $\Phi$ has no
effect on $F$. 
A particular solution of (15) can be found in the following way. First, we note that (15) is of the form

\[(25) \quad A\Phi = \Phi\]

where

\[(26) \quad A_{ij} = -a_{ij} \quad i \neq j\]

\[(27) \quad A_{ii} = \sum_{j=1}^{n} a_{ij} \quad j \neq i\]

and where

\[(28) \quad \Phi_i = -\sum_{j=1}^{n} a_{ij} E_j\]

so \(\Phi\) has the property that

\[(29) \quad \sum_{i=1}^{n} \Phi_i = 0\]

because of the symmetry of \(A\) and the antisymmetry of \(E\).
The matrix $A$ is symmetric, and the arguments made above show that it is positive semidefinite with a one-dimensional null space to which $I$ is orthogonal.

Let

$$\{ e^x, \alpha = 1 \ldots (n-1) \}$$

be an orthonormal set of eigenvectors of $A$, each of which is orthogonal to the null space of $A$, and let $\lambda_\alpha$ be the eigenvalue of $A$ corresponding to the eigenvector $e^x$. Then

$$\lambda_\alpha > 0 \quad \text{for} \quad \alpha = 1 \ldots n-1$$

and $I$ has the representation

$$I = \sum_{\alpha=1}^{n-1} e^x (e^x)^T I$$

and then

$$I = \sum_{\alpha=1}^{n-1} \frac{1}{\lambda_\alpha} e^x (e^x)^T I$$

is a particular solution of (25).
Let
\[
B = \sum_{\alpha=1}^{n-1} \frac{1}{\lambda_\alpha} \, e^\alpha (e^\alpha)^T
\]

The matrix $B$ is symmetric and positive semidefinite, with the same null space as $A$. It is a pseudo-inverse of $A$, since $B$ acts as the inverse of $A$ on the orthogonal complement of their common null space.

Writing out (33) in components we have

\[
\Phi_i = -\sum_{k,l=1}^{n} B_{ik} \, a_{kl} \, E_{kl}
\]

\[
\Phi_j = -\sum_{k,l=1}^{n} B_{jk} \, a_{kl} \, E_{kl}
\]

\[
= -\sum_{k,l=1}^{n} B_{jk} \, a_{kl} \, E_{lk}
\]

\[
= +\sum_{k,l=1}^{n} B_{jl} \, a_{kl} \, E_{kl}
\]
In the steps of (36), we first interchanged $k$ and $l$, and then we used $a_{kl} = a_{lk}$ and $E_{kl} = -E_{lk}$ to come back to the expression $a_{kl}E_{kl}$ but with a change of sign.

Substituting (35) and (36) into (12), we see that

\[ F_{ij} = a_{ij} E_{ij} - \sum_{k,l=1}^{n} a_{ij} (B_{ik} + B_{jl}) a_{kl} E_{kl} \]

which is of the form

\[ F_{ij} = \sum_{k,l=1}^{n} C_{ij,kl} E_{kl} \]

where

\[ C_{ij,kl} = a_{ij} d_{ik} d_{jl} - a_{ij} (B_{ik} + B_{jl}) a_{kl} \]

Note that

\[ C_{ij,kl} = C_{kl,ij} \]

since $B$ is symmetric. Equation (40) holds for all ordered pairs $(i,j)$ and $(k,l)$.

These are the Onsager relations.
We now turn to the interpretation of the driving terms $E_{ij}$.

In the unperturbed system, the state $i$ has a free energy $G_i^0$ and the transition rates satisfy

\[
\frac{V_{ij}^0}{v_{ij}^0} = \exp \left( - \frac{G_{ij}^0 - G_i^0}{kT} \right)
\]

This makes possible a state of detailed balance, in which

\[
P_i^0 = \frac{1}{Z} \exp \left( - \frac{G_i^0}{kT} \right)
\]

where $Z$ is such that $\sum_{i=1}^{n} P_i^0 = 1$.

Then we assume that the transition $i \rightarrow j$ can be acted upon by an external agent who does an amount of work $W_{ij}$.
Every time the transition \( i \rightarrow j \) occurs.

When the reverse transition, \( j \rightarrow i \), occurs we assume that the amount of work done by the agent is \(-\epsilon W_{ij}\). Finally, we assume that

\[
\frac{r_{ij}}{r_{ji}} = \exp \left( -\frac{G_i^0 - G_j^0}{kT} + \frac{\epsilon W_{ij}}{kT} \right)
\]

\[
\frac{r_{ij}}{r_{ji}} = \frac{r_{ij}^0}{r_{ji}^0} \exp \left( \frac{\epsilon W_{ij}}{kT} \right)
\]

\[
\log \frac{r_{ij}}{r_{ji}} = \log \frac{r_{ij}^0}{r_{ji}^0} + \frac{\epsilon W_{ij}}{kT}
\]
In this equation, we think of \( r_{ij} \) and \( r_{ji} \) as functions of \( \Theta \), see equation (4), and we differentiate with respect to \( \Theta \) and then set \( \Theta = 0 \). Recalling the definition (13) of \( E_{ij} \), we get

\[
E_{ij} = \frac{R_{ij}^0}{r_{ij}^0} - \frac{R_{ji}^0}{r_{ji}^0} = \frac{W_{ij}}{kT}
\]

Thus \( E_{ij} \) is equal to the work, in units of \( kT \), that is done on the system by an external agent every time that the transition \( i \rightarrow j \) occurs.

Note that \( W_{ij} \) cannot in general be put in the form of a difference

\[
W_{ij} = U_i - U_j
\]

In fact, if (47) holds, then the perturbed state is also a state of equilibrium with \( F_{ij} = 0 \). To see this note that a particular solution of (15) with \( F_{ij} = 0 \) can be constructed simply by setting

\[
\Phi_i = -\frac{U_i}{kT}
\]
The total work per unit time, with work expressed in units of $kT$, that is done by the external agents to keep the system out of equilibrium is given by

$$\frac{1}{2} \sum_{i,j=1}^{n} F_{ij} E_{ij} =$$

$$\frac{1}{2} \left( \sum_{i,j=1}^{n} a_{ij} \frac{E_{ij}^2}{(B_{ik} + B_{jl})a_{kl} E_{kl}} - \sum_{i,j=1}^{n} a_{ij} E_{ij} \right)$$

in which the factor $\frac{1}{2}$ is needed because each unordered pair $ij$ with $ji$ appears twice in the double sum on the left-hand side of (48), with equal contributions since $F_{ij}$ and $E_{ij}$ are both antisymmetric. Note that there is no contribution to the double sum from $i=j$, since $F_{ij}$ and $E_{ij}$ are both zero in this case.
On the right-hand side of (48), we have the difference of two non-negative expressions, so it is not immediately obvious that the result is non-negative.

We can prove this, however, by showing that

$$\sum_{i,j=1}^{n} F_{ij} E_{ij} = \sum_{(i,j): a_{ij} > 0} F_{ij}^2 / a_{ij}$$

Since the right-hand side of (49) is obviously non-negative.

To prove (49), it is helpful to start from equation (12) for $F_{ij}$, from which we derive both of the following:

$$\sum_{i,j=1}^{n} F_{ij} E_{ij} = \sum_{i,j=1}^{n} a_{ij} (\Phi_i - \Phi_j) E_{ij} + \sum_{i,j=1}^{n} a_{ij} E_{ij}^2.$$
\[
\sum_{ij} \frac{f_{ij}^2}{a_{ij}}
\]

\[
= \sum_{ij=1}^{n} a_{ij} (\Phi_i - \Phi_j)^2 + 2 \sum_{ij=1}^{n} a_{ij} (\Phi_i - \Phi_j) E_{ij}
\]

\[
+ \sum_{ij=1}^{n} a_{ij} E_{ij}^2
\]

Note that the restriction \( a_{ij} > 0 \) is not needed on the right-hand side of (51), since all terms with \( a_{ij} = 0 \) are zero anyway.

The right-hand sides of (50) & (57) look different, but they are actually the same. To see this, we start from equation (15), multiply both sides by \( \Phi_i \) and sum over \( i \). The result is
\begin{align}
(52) \quad \sum_{i,j=1}^{n} a_{ij} \Phi_i (\Phi_i - \Phi_j) + \sum_{i,j=1}^{n} a_{ij} \Phi_i E_{ij} &= 0 \\

\text{Interchanging } i \text{ and } j, \text{ and making use of} \\
\text{the symmetry of } a_{ij} \text{ and the antisymmetry} \\
of \Phi_i - \Phi_j \text{ and of } E_{ij}, \text{ we get} \\

(53) \quad \sum_{i,j=1}^{n} a_{ij} (-\Phi_i) (\Phi_i - \Phi_j) + \sum_{i,j=1}^{n} a_{ij} (-\Phi_i) E_{ij} &= 0 \\

\text{Adding } (52) + (53) \text{ gives the result} \\

(54) \quad \sum_{i,j=1}^{n} a_{ij} (\Phi_i - \Phi_j)^2 + \sum_{i,j=1}^{n} a_{ij} (\Phi_i - \Phi_j) E_{ij} &= 0 \\

\text{This shows that the right-hand sides of} \\
(50) \text{ and } (51) \text{ are indeed the same, and} \\
\text{thus it proves (49).}
\end{align}