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

(1) $$\sum_{j=1}^{n} f_{ij} = 0 \ , \qquad i = 1 \cdots n$$

where

(2) $$f_{ij} = p_i r_{ij} - p_j r_{ji} \qquad i,j = 1 \cdots n$$

and

(3) $$\sum_{i=1}^{n} p_i = 1$$

Here p_i is the steady-state probability that the system is in the state i, r_{ij} is the transition rate for $i \to j$, 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} and r_{ji} are both zero.

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 $p_1 \cdots p_n$ are uniquely determined by equations (1-3), and moreover that all of them are positive:

$$p_i > 0 \quad \text{for} \quad i = 1 \cdots n$$

Note that our notation excludes self-loops, since (2) makes $f_{ii} = 0$ regardless of r_{ii}, and note 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 *

(4) $$r_{ij} = r_{ij}^0 + \varepsilon R_{ij}$$

with the result that

(5) $$p_i = p_i^0 + \varepsilon P_i + \cdots$$

(6) $$f_{ij} = f_{ij}^0 + \varepsilon F_{ij} + \cdots$$

Then

(7) $$f_{ij}^0 = p_i^0 r_{ij}^0 - p_j^0 r_{ji}^0$$

(8) $$F_{ij} = P_i r_{ij}^0 - P_j r_{ji}^0 + p_i^0 R_{ij} - p_j^0 R_{ji}$$

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

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* but with only positive rates perturbed, so that

$$r_{ij}^0 = 0 \implies R_{ij} = 0$$

(9) $$0 = f_{ij}^0 = p_i^0 r_{ij}^0 - p_j^0 r_{ji}^0$$

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 <u>equilibrium</u>.

We do <u>not</u> assume that the perturbed steady state is a state of equilibrium.

Let

(10) $$a_{ij} = a_{ji} = p_i^0 r_{ij}^0 = p_j^0 r_{ji}^0 \geq 0$$

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

(11) $$F_{ij} = \frac{P_i}{p_i^0} p_i^0 r_{ij}^0 - \frac{P_j}{p_j^0} p_j^0 r_{ji}^0$$

$$+ p_i^0 r_{ij}^0 \frac{R_{ij}}{r_{ij}^0} - p_j^0 r_{ji}^0 \frac{R_{ji}}{r_{ji}^0}$$

Therefore,

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

where

(13) $$E_{ij} = \frac{R_{ij}'}{r_{ij}^0} - \frac{R_{ji}'}{r_{ji}^0}$$

(14) $$\Phi_i = \frac{P_i}{p_i^0}$$

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 ε, equations (1) & (3) become

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

(16) $$\sum_{i=1}^{n} p_i^0 \Phi_i = \sum_i P_i = 0$$

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

Multiplying both sides by Φ_i, and summing over i, we get

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

Interchanging i and j gives

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

Then, by adding (18) & (19), we get

$$\sum_{i,j=1}^{n} a_{ij}\left(\Phi_i - \Phi_j\right)^2 = 0 \tag{20}$$

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 Φ_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 vector with components

$$\sum_{j=1}^{n} a_{ij} E_{ij} \quad , \quad i = 1 \cdots n \tag{21}$$

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

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

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 Φ. This constant can be determined by making use of (16). If Φ^* is any particular solution of (15), then

(23) $$\Phi_i = \Phi_i^* - \sum_{j=1}^{n} \rho_j^0 \Phi_j^*$$

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 Φ does not matter, since an additive constant in Φ 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) $$A\,\Phi = \Psi$$

where

(26) $$A_{ij} = -a_{ij} \qquad i \neq j$$

(27) $$A_{ii} = \sum_{\substack{j=1 \\ j \neq i}}^{n} a_{ij}$$

and where

(28) $$\Psi_i = -\sum_{j=1}^{n} a_{ij} E_j$$

so Ψ has the property that

(29) $$\sum_{i=1}^{n} \Psi_i = 0$$

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 Ψ is orthogonal.

Let

(30) $$\left\{ e^{\alpha}, \quad \alpha = 1 \cdots (n-1) \right\}$$

be an orthonormal set of eigenvectors of A each of which is orthogonal to the null space of A, and let λ_α be the eigenvalue of A corresponding to the eigenvector e^α. Then

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

and Ψ has the representation

(32) $$\Psi = \sum_{\alpha=1}^{n-1} e^{\alpha} (e^{\alpha})^T \Psi$$

and then

(33) $$\Phi = \sum_{\alpha=1}^{n-1} \frac{1}{\lambda_\alpha} e^{\alpha} (e^{\alpha})^T \Psi$$

is a particular solution of (25).

Let

$$B = \sum_{\alpha=1}^{n-1} \frac{1}{\lambda_\alpha} e^\alpha (e^\alpha)^T \tag{34}$$

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

$$\Phi_i = -\sum_{k,l=1}^{n} B_{ik}\, a_{kl}\, E_{kl} \tag{35}$$

$$\Phi_j = -\sum_{k,l=1}^{n} B_{jk}\, a_{kl}\, E_{kl} \tag{36}$$

$$= -\sum_{k,l=1}^{n} B_{jl}\, a_{lk}\, E_{lk}$$

$$= +\sum_{k,l=1}^{n} B_{jl}\, a_{kl}\, E_{kl}$$

In the steps of (36), we first interchanged k and l, and then we used $a_{lk} = a_{kl}$ and $E_{lk} = -E_{kl}$ to come back to the expression $a_{kl} E_{kl}$ but with a change of sign.

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

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

which is of the form

(38) $$F_{ij} = \sum_{k,l=1}^{n} C_{ij,kl} E_{kl}$$

where

(39) $$C_{ij,kl} = a_{ij} \delta_{ik} \delta_{jl} - a_{ij} (B_{ik} + B_{jl}) a_{kl}$$

Note that

(40) $$C_{ij,kl} = C_{kl,ij}$$

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

$$\frac{r_{ij}^0}{r_{ji}^0} = \exp\left(-\frac{G_j^0 - G_i^0}{kT}\right) \tag{41}$$

This makes possible a state of detailed balance, in which

$$p_i^0 = \frac{1}{Z} \exp\left(-\frac{G_i^0}{kT}\right) \tag{42}$$

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

We then assume that the transition $i \to j$ can be acted upon by an external agent who does an amount of work εW_{ij}

every time the transition $i \to j$ occurs.
When the reverse transition, $j \to i$, occurs
we assume that the amount of work done
by the agent is $-\varepsilon W_{ij}$. Finally, we
assume that

(43) $$\frac{r_{ij}}{r_{ji}} = \exp\left(-\frac{G_j^0 - G_i^0}{kT} + \frac{\varepsilon W_{ij}}{kT}\right)$$

or

(44) $$\frac{r_{ij}}{r_{ji}} = \frac{r_{ij}^0}{r_{ji}^0} \exp\left(\frac{\varepsilon W_{ij}}{kT}\right)$$

(45) $$\log \frac{r_{ij}}{r_{ji}} = \log \frac{r_{ij}^0}{r_{ji}^0} + \frac{\varepsilon W_{ij}}{kT}$$

In this equation, we think of r_{ij} and r_{ji} as functions of ε, see equation (4), and we differentiate with respect to ε and then set $\varepsilon = 0$. Recalling the definition (13) of E_{ij}, we get

(46) $$E_{ij} = \frac{R_{ij}}{r_{ij}^0} - \frac{R_{ji}}{r_{ji}^0} = \frac{W_{ij}}{kT}$$

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 $i \to j$ occurs.

Note that W_{ij} <u>cannot</u> in general be put in the form of a difference

(47) $$W_{ij} = U_i - U_j$$

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

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

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

in which the factor $\frac{1}{2}$ is needed because

each unordered pair i,j with $i \neq j$ 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

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

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:

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

$$\sum_{(i,j):\, a_{ij}>0} F_{ij}^2 / a_{ij} \tag{51}$$

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

$$+ \sum_{i,j=1}^{n} a_{ij} E_{ij}^2$$

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) & (51) look different, but they are actually the same. To see this, we start from equation (15), multiply both sides by Φ_i and sum over i. The result is

$$\sum_{i,j=1}^{n} a_{ij}\,\Phi_i(\Phi_i-\Phi_j) + \sum_{i,j=1}^{n} a_{ij}\,\Phi_i\,E_{ij} = 0 \tag{52}$$

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

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

Adding (52) & (53) gives the result

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

This shows that the right-hand sides of (50) & (51) are indeed the same, and thus it proves (49).