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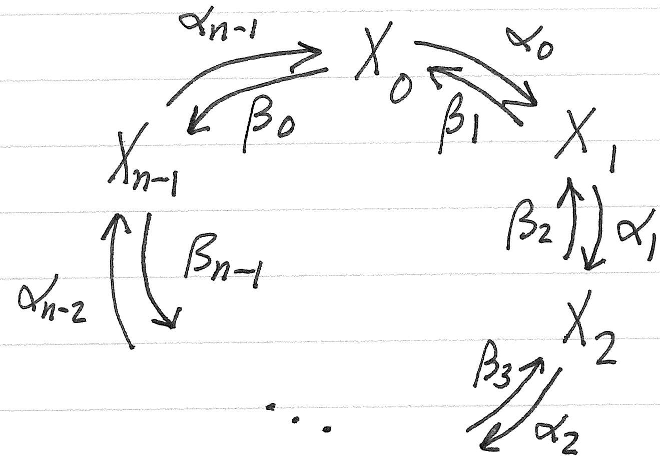
Principle of Detailed Balance

Many reaction networks contain loops, and when they do there is a constraint on the rate constants.

To study this, we consider the following reaction scheme



There are n species $X_0 \cdots X_{n-1}$ arranged in a circle. Each species can be converted into either of its neighboring species with rate constant α_j for the reaction $X_j \rightarrow X_{j+1}$ and rate constant β_j for the reaction $X_j \rightarrow X_{j-1}$. Subscript arithmetic is understood to be modulo n.

Now suppose the system is in a steady state. We could derive steady-state equations by setting

(1) $$\frac{d}{dt}[X_k] = 0 \quad , \quad k = 0 \ldots n-1$$

but an easier, and for our purposes more useful, way is to consider the net flux (if any) around the loop.

If there is such a flux in a steady state, it has to be the same for every reaction, otherwise some species would accumulate and others would be depleted, and that would imply that the system is not in a steady state.

Thus, if f is the net clockwise flux around the loop, we have the equations

(2) $$f = \alpha_0[X_0] - \beta_1[X_1] = \alpha_1[X_1] - \beta_2[X_2] = \cdots$$
$$= \alpha_{n-1}[X_{n-1}] - \beta_0[X_0]$$

These equations can be written as a linear system

$$AX = fU \tag{3}$$

where

$$X = \begin{pmatrix} [X_0] \\ [X_1] \\ \vdots \\ [X_{n-2}] \\ [X_{n-1}] \end{pmatrix} \qquad U = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \\ 1 \end{pmatrix} \tag{4}$$

$$A = \begin{pmatrix} \alpha_0 & -\beta_1 & & & \\ & \alpha_1 & -\beta_2 & & \\ & & \ddots & \ddots & \\ & & & \alpha_{n-2} & -\beta_{n-1} \\ -\beta_0 & & & & \alpha_{n-1} \end{pmatrix} \tag{5}$$

(entries not shown and not indicated by dots are equal to zero.)

We can solve (3) by determinants. To find the determinant of A, we expand by minors of the left-most column and recall that an upper-triangular or a lower-triangular matrix has a determinant equal to the product of its diagonal elements. This gives

(6) $$\det(A) = \alpha_0(\alpha_1 \cdots \alpha_{n-1}) + (-1)^{n-1}(-\beta_0)((-\beta_1)\cdots(-\beta_{n-1}))$$
$$= (\alpha_0 \cdots \alpha_{n-1}) - (\beta_0 \cdots \beta_{n-1})$$

Now we use Kramer's rule to solve for $[X_0]$. This gives

(7) $$[X_0] = \frac{f}{\det(A)} \det(D_0)$$

where

$$D_0 = \begin{pmatrix} 1 & -\beta_1 & & & & \\ 1 & \alpha_1 & -\beta_2 & & & \\ \vdots & & \ddots & \ddots & & \\ & & & & & \\ 1 & & & & \alpha_{n-2} & -\beta_{n-1} \\ 1 & & & & & \alpha_{n-1} \end{pmatrix} \tag{8}$$

We evaluate the determinant of D_0 by expanding in minors of the left-most column. This gives

$$\det(D_0) = \sum_{k=0}^{n-1} (-1)^k (-\beta_1)\cdots(-\beta_k)\,\alpha_{k+1}\cdots\alpha_{n-1} \tag{9}$$

$$= \sum_{k=0}^{n-1} \beta_1\cdots\beta_k\,\alpha_{k+1}\cdots\alpha_{n-1}$$

The term in the above sum with $k=0$ has no β factors and hence is equal to $\alpha_1\cdots\alpha_{n-1}$. Similarly the term with $k=n-1$ is equal to $\beta_1\cdots\beta_{n-1}$. Note that $\det(D_0)$ involves all of the rate constants <u>except</u> α_0 and β_0.

Substituting (6) & (9) into (7), we have

(10) $$[X_0] = \frac{f \sum_{k=0}^{n-1} (\beta_1 \cdots \beta_k)(\alpha_{k+1} \cdots \alpha_{n-1})}{(\alpha_0 \cdots \alpha_{n-1}) - (\beta_0 \cdots \beta_{n-1})}$$

and from this we get $[X_j]$ simply by rotating indices around the circle:

(11) $$[X_j] = \frac{f \sum_{k=0}^{n-1} (\beta_{j+1} \cdots \beta_{j+k})(\alpha_{j+k+1} \cdots \alpha_{j+n-1})}{(\alpha_0 \cdots \alpha_{n-1}) - (\beta_0 \cdots \beta_{n-1})}$$

Up to now, we have been treating f as known and determining the concentrations that are needed to achieve a given steady-state flux f, but we can easily solve for f in terms of the conserved quantity

(12) $$[X^*] = \sum_{j=0}^{n-1} [X_j]$$

Indeed, if we sum both sides of (11) over $j = 0 \cdots n-1$, make use of (12), and then solve for f, we get

(13) $$f = [X^*] \frac{(\alpha_0 \cdots \alpha_{n-1}) - (\beta_0 \cdots \beta_{n-1})}{\sum_{j=0}^{n-1} \sum_{k=0}^{n-1} (\beta_{j+1} \cdots \beta_{j+k})(\alpha_{j+k+1} \cdots \alpha_{j+n-1})}$$

Since $[X^*]$ and also the denominator of the above fraction are positive, we see that the direction of f is determined by the expression

(14) $$(\alpha_0 \cdots \alpha_{n-1}) - (\beta_0 \cdots \beta_{n-1})$$

and the steady-state flux is equal to zero if and only if

(15) $$\alpha_0 \cdots \alpha_{n-1} = \beta_0 \cdots \beta_{n-1}$$

As a mathematical phenomenon, there is nothing wrong with a system having a steady-state flux around a loop, but in a physical system this cannot happen unless there is a source of energy that is being drawn upon to drive the system.

To see why, imagine that we couple one of the reactions of the loop to something that does useful work, like charging a battery. If the loop runs in one direction, all by itself, without being driven by some source of energy, then we can charge up batteries for free. This is not possible.

Thus, for isolated systems, the rate constants must satisfy equation (15). Since this is a relationship among rate constants, it is also applicable when the system is not in a steady state, even though we derived (15) from steady-state considerations.

It is an interesting exercise to check equation (11) by evaluating

(16) $$\alpha_j [X_j] - \beta_{j+1} [X_{j+1}]$$

which should be equal to δ. This requires evaluating

(17) $$\alpha_j \sum_{k=0}^{n-1} (\beta_{j+1} \cdots \beta_{j+k})(\alpha_{j+k+1} \cdots \alpha_{j+n-1})$$

$$- \beta_{j+1} \sum_{k=0}^{n-1} (\beta_{j+2} \cdots \beta_{j+1+k})(\alpha_{j+1+k+1} \cdots \alpha_{j+1+n-1})$$

Try shifting the index k in one of the sums.

The principle of detailed balance states that in a system at thermodynamic equilibrium every process and its own reverse process run at the same average rate. This does not mean that the rate constants are equal. For example, in the reaction

(18)
$$A \underset{\beta}{\overset{\alpha}{\rightleftarrows}} B$$

the requirement is

(19)
$$\alpha [A] = \beta [B]$$

not $\alpha = \beta$. Note, however, the very strong requirement that every reaction must be separately in balance*. It is not allowed for one reaction to compensate for another. (This can certainly happen, but not at thermodynamic equilibrium.)

If you could make a movie showing what the molecules of a system are doing at thermodynamic equilibrium, the movie would look the same, statistically speaking, if you run it forwards or backwards.

*with its own reverse reaction

In our example, a steady state with net flux $f \neq 0$ is <u>not</u> a state of thermodynamic equilibrium, and an energy source is needed to drive the flux and maintain such a state. In the absense of such an energy source, the rate constants must obey equation (15), whether or not the system is in a steady state. Then, when the system reaches a steady state, that state will be one of thermodynamic equilibrium, with $f=0$.

Thus, there is an important distinction between a <u>steady state</u> and a state of <u>equilibrium</u>, although these terms are sometimes used interchangably. A steady state is simply a state that is not changing over time, so that the derivative with respect to time of the variables that define the state is zero. A state of equilibrium is a special kind of steady state in which the principle of detailed balance holds.

When equation (15) is satisfied, we can find all of the steady-state concentrations very simply. Since $f=0$, equation (2) implies

(20) $$[X_1] = \frac{\alpha_0}{\beta_1}[X_0]$$

(21) $$[X_2] = \frac{\alpha_1}{\beta_2}[X_1] = \frac{\alpha_1 \alpha_0}{\beta_2 \beta_1}[X_0]$$

$$\vdots$$

(22) $$[X_j] = \frac{\alpha_{j-1} \cdots \alpha_0}{\beta_j \cdots \beta_1}[X_0]$$

Note that we can go the other way around the circle to reach X_j, and then we get

(23) $$[X_j] = \frac{\beta_{j+1} \cdots \beta_{n-1} \beta_0}{\alpha_j \cdots\cdots \alpha_{n-1}}[X_0]$$

Equations (22) & (23) look different, but they are actually the same because of (15)! Similarly, if we go all of the way around the circle by setting $j=n=0$ (recall that subscript arithmetic here is modulo n), we get a consistent result in (22) or (23) only because of equation (15). This <u>path independence</u> is an extremely important consequence of the principle of detailed balance.

To solve for $[X_0]$, we can sum in (22) over $j=0\cdots(n-1)$ and use (12). This gives

$$[X_0] = \frac{[X^*]}{\sum_{j=0}^{n-1} \frac{\alpha_0 \cdots \alpha_{j-1}}{\beta_1 \cdots \beta_j}} \qquad (24)$$

The term $j=0$ in the above formula is understood to be equal to 1, since it has no factors of α/β. Another way to see this is to replace $j=0$ by $j=n$, and then that term becomes

$$\frac{\alpha_0 \cdots \alpha_{n-1}}{\beta_1 \cdots \beta_n} = \frac{\alpha_0 \cdots \alpha_{n-1}}{\beta_0 \cdots \beta_{n-1}} = 1 \tag{25}$$

Now rotating indices around the circle, we get a formula for $[X_k]$:

$$[X_k] = \frac{[X^*]}{\displaystyle\sum_{j=0}^{n-1} \frac{\alpha_k \cdots \alpha_{k+j-1}}{\beta_{k+1} \cdots \beta_{k+j}}} \tag{26}$$

Alternatively, we could replace j by k in (22) and substitute (24) into the result to obtain

$$[X_k] = \frac{[X^*] \dfrac{\alpha_0 \cdots \alpha_{k-1}}{\beta_1 \cdots \beta_k}}{\displaystyle\sum_{j=0}^{n-1} \frac{\alpha_0 \cdots \alpha_{j-1}}{\beta_1 \cdots \beta_j}} \tag{27}$$

Yet another formula for $[X_k]$ can be derived by substituting (13) into (11), and then interchanging j and k for easier comparison with (26) & (27). This gives

$$[X_k] = [X^*] \frac{\sum_{j=0}^{n-1} (\beta_{k+1} \cdots \beta_{k+j})(\alpha_{k+j+1} \cdots \alpha_{k+n-1})}{\sum_{k'=0}^{n-1} \sum_{j=0}^{n-1} (\beta_{k'+1} \cdots \beta_{k'+j})(\alpha_{k'+j+1} \cdots \alpha_{k'+n-1})} \tag{28}$$

We use k' in the denominator here to avoid confusion with the free index k in the numerator. Note that (28) was derived under the assumption that $f \neq 0$ and therefore that (15) does not hold. Otherwise, there is a 0/0 involved in equation (11), and equation (13) reduces to $0=0$, so the derivation fails. Nevertheless, we expect that the $[X_k]$ will be continuous functions of the rate constants, so (28) should be valid even in the special case that (15) holds. In that special case, it should be equivalent to (26) & (27).

We now give the proof that the three different formulae for $[X_k]$ are all equivalent when $\alpha_0 \cdots \alpha_{n-1} = \beta_0 \cdots \beta_{n-1}$.

Try to prove this for yourself before reading on!

To show that (26) & (27) are equivalent when (15) holds, we multiply the numerator and denominator on the right-hand side of (26) by

(29) $$\frac{\alpha_0 \cdots \alpha_{k-1}}{\beta_1 \cdots \beta_k}$$

This makes the numerator match the numerator on the right-hand side of (27). In the denominator, we get

(30) $$\sum_{j=0}^{n-1} \frac{\alpha_0 \cdots \alpha_{k+j-1}}{\beta_1 \cdots \beta_{k+j}} = \sum_{j'=+k}^{n+k-1} \frac{\alpha_0 \cdots \alpha_{j'-1}}{\beta_1 \cdots \beta_{j'}}$$

This almost matches the denominator on the right-hand side of (27), but note that the sum here is over $(+k \cdots n+k-1)$

whereas the sum in (27) is over $0 \ldots (n-1)$. Both sums are over one cycle of the index, so the different limits will not matter if the expression that is being summed is periodic with period n, as the individual rate constants are by definition.

Let

(31) $$W_j = \frac{\alpha_0 \cdots \alpha_{j-1}}{\beta_1 \cdots \beta_j}$$

Then

(32) $$W_{j+n} = \frac{\alpha_0 \cdots \alpha_{j+n-1}}{\beta_1 \cdots \beta_{j+n}}$$

Now, since $\alpha_0 \cdots \alpha_{n-1} = \beta_1 \cdots \beta_n$, we can cancel these factors and obtain

(33) $$W_{j+n} = \frac{\alpha_n \cdots \alpha_{j+n-1}}{\beta_{n+1} \cdots \beta_{j+n}} = W_j$$

by periodicity of each individual rate constant.

Thus, the expression (30) is actually the same as the denominator on the right-hand side of (27). This completes the proof that (26) and (27) are equivalent when (15) holds. (Although we only showed that (26) $\Rightarrow$ (27), all of the steps are reversible.)

Note the crucial role of (15) in proving the equivalence of (26) & (27). Indeed, when (15) is not satisfied, neither (26) nor (27) is correct, and we have to use the more complicated formula (28).

We still need to show that (28) reduces to (26) & (27) when $\alpha_0 \cdots \alpha_{n-1} = \beta_1 \cdots \beta_n$.

Instead of proving this directly, we will show that (28) satisfies the assumptions from which (26) & (27) were derived. These are

(34) $$\sum_{k=0}^{n-1} [X_k] = [X^*]$$

(35) $$\alpha_k [X_k] = \beta_{k+1} [X_{k+1}], \quad k = 0 \cdots n-1$$

From the form of (28), it is obvious that (34) is satisfied, since the sum of the numerators on the right-hand side of (28) is equal to the denominator.

Also, to verify (35), we just need to show that

(36) $$\alpha_k \sum_{j=0}^{n-1} (\beta_{k+1} \cdots \beta_{k+j})(\alpha_{k+j+1} \cdots \alpha_{k+n-1})$$

$$= \beta_{k+1} \sum_{j=0}^{n-1} (\beta_{k+2} \cdots \beta_{k+1+j})(\alpha_{k+1+j+1} \cdots \alpha_{k+1+n-1})$$

On the left-hand side, note that $\alpha_k = \alpha_{k+n}$.
On the right-hand side, replace j by $j-1$ and change the limits of the sum accordingly. What we need to show is then

(37) $$\sum_{j=0}^{n-1} (\beta_{k+1} \cdots \beta_{k+j})(\alpha_{k+j+1} \cdots \alpha_{k+n})$$

$$= \sum_{j=1}^{n} (\beta_{k+1} \cdots \beta_{k+j})(\alpha_{k+j+1} \cdots \alpha_{k+n})$$

These expressions differ <u>only</u> in the limits of summation. Thus, the two sides of (37) are equal if and only if the term with $j=0$ on the left is equal to the term with $j=n$ on the right. But the term with $j=0$ has no β factors and is equal to

$$\alpha_{k+1} \cdots \alpha_{k+n} = \alpha_0 \cdots \alpha_{n-1} \tag{38}$$

and the term with $j=n$ has no α factors and is equal to

$$\beta_{k+1} \cdots \beta_{k+n} = \beta_0 \cdots \beta_{n-1} \tag{39}$$

Thus we see that (35) is indeed satisfied if and only if $\alpha_0 \cdots \alpha_{n-1} = \beta_0 \cdots \beta_{n-1}$, as claimed.