

Determination of the total reaction entropy of cells

The ensemble method of statistical thermodynamics is applied for finding the total reaction entropy of the system if the reaction consists of the sum of fractional contributions by elementary modes. We consider the entire metabolic network of the cell as a canonical ensemble of n discrete states defined by elementary modes. Because each elementary mode starts with the uptake of glucose molecules, one can characterize each of the n discrete states by the reaction entropy ΔS_i per molecule glucose reacted and one can observe the number a_i molecules of glucose that are metabolized through each elementary mode. Thus, we can describe any one state of the ensemble by the following:

State No: 1, 2, 3, ..., n

Entropy generation: $\Delta S_1, \Delta S_2, \Delta S_3, \dots, \Delta S_n$

Molecule of glucose utilized: $a_1, a_2, a_3, \dots, a_n$

On the basis of mass conservation and entropy generation being extensive, the entire ensemble must satisfy the two constraints:

$$\sum a_i = A \quad (1)$$

$$\sum a_i \Delta S_i = Z \quad (2)$$

where a_i is the number of molecules of glucose metabolized by the i^{th} discrete state, ΔS_i is the reaction entropy generated by this discrete state, A is the total number of molecules of glucose being utilized by the entire ensemble, and Z represents the entropy formation of the ensemble.

The distribution of the A molecules of glucose such that a_1 is in the 1st discrete state, a_2 are in the 2nd discrete state, and so on can be achieved in many possible ways. The number of ways $W(a_1, a_2, a_3, \dots)$ that A identical, distinguishable molecules of glucose can be arranged into groups, each associated with a specific discrete state, is defined as:

$$W(a_1, a_2, a_3, \dots) = \frac{A!}{a_1! a_2! a_3! \dots} = \frac{A!}{\prod a_i!} \quad (3)$$

Consequently, the probability p_i that any given molecules of glucose is in the i^{th} discrete state is given by averaging over all the possible distributions

$$p_i = \frac{\langle a_i \rangle}{A} = \frac{\sum W(a_i) \cdot a_i}{A \sum W(a_i)} \quad (4)$$

If A is arbitrarily large, the distribution function $W(a_i)$ can be made arbitrarily narrow. The $W(a_1^*, a_2^*, a_3^*, \dots)$ where a_i^* is the set of a_i 's that maximizes the function $W(a_i)$ will be overwhelmingly huge as compared to $W(a_i)$ for other remaining set of a_i 's. Thus, the function $W(a_i)$ can be approximated as $W(a_1^*, a_2^*, a_3^*, \dots)$, that is the most probable distribution. We can then write the probability p_i

$$p_i = \frac{\langle a_i \rangle}{A} = \frac{\sum W(a_i) \cdot a_i}{A \sum W(a_i)}; \quad \frac{W(a_i^*) \cdot a_i^*}{A W(a_i^*)} = \frac{a_i^*}{A} \quad (5)$$

where a_i^* is the set of a_i 's associated with the i^{th} discrete state for the most probable distribution $W(a_i)$ of the ensemble.

Eq (5) reveals that we can compute the probability of the i^{th} quantum state by determining only the distribution of a set of a_i^* that maximizes a function $W(a_i)$ under the given

constraints. The solution of this problem can be obtained with the Lagrange multiplier method.

The function $W(a_i)$ can be simplified by taking the natural logarithm of $W(a_i)$ and with Stirling's approximation $\ln W(a_i)$ becomes

$$\ln W(a_1, a_2, a_3, \dots) = \ln \frac{A!}{\prod a_i!}; \quad A \ln A - \sum a_i \ln a_i \quad (6)$$

Applying the method of Lagrange multipliers, we next differentiate Eq (6) with respect to a_i , while enforcing the two constraints Eq. (1) and (2)

$$\frac{\partial}{\partial a_i} \left\{ \ln W(a_i) - \alpha \sum a_i - \beta \sum a_i S_i \right\} = 0, \quad (7)$$

$$i = 1, 2, \dots, n$$

where α and β are the Lagrange multipliers.

The set of a_i 's that maximizes $W(a_1, a_2, a_3, \dots)$ can be found from solving Eq (7). The solution of a_i 's for the most probable distribution for the systems making up the ensemble is

$$a_i^* = e^{-\alpha-1} \cdot e^{-\beta S_i} \quad i = 1, 2, \dots, n \quad (8)$$

Combining Eq (1) and (8), we obtain

$$A = e^{-\alpha-1} \sum e^{-\beta S_i} \quad (9)$$

We can then find an expression for the probability p_i in term of ΔS_i and β by substituting Eq (8) and (9) into Eq (5)

$$p_i = \frac{e^{-\alpha-1} \cdot e^{-\beta \Delta S_i}}{A} = \frac{e^{-\alpha-1} \cdot e^{-\beta \Delta S_i}}{\sum e^{-\alpha-1} \cdot e^{-\beta \Delta S_i}} = \frac{e^{-\beta \Delta S_i}}{\sum e^{-\beta \Delta S_i}} = \frac{e^{-\beta \Delta S_i}}{Q} \quad (10)$$

where Q is a partition function that has been defined as $Q = \sum e^{-\beta \Delta S_i}$

The expression of Eq (10), which is analogous to the Boltzmann distribution law, suggests that the usage probabilities of elementary modes can be determined based on the reaction entropy of individual elementary modes.

We can rewrite the probability function Eq (10) in terms of the reaction entropy of the i^{th} discrete state

$$\Delta S_i = -\frac{1}{\beta} \ln p_i - \frac{1}{\beta} \ln Q \quad (11)$$

At a temperature of absolute zero, the total entropy of a system has a value of zero, and the probability of generating zero entropy is 1, according to the Third law of thermodynamics. This leads to $Q = 1$.

With the constant $1/\beta$ being replaced by b , Eq (11) thus becomes

$$\Delta S_i = -b \cdot \ln p_i \quad (12)$$

Eq (12) expresses the reaction entropies of the individual elementary modes as a linear function of the natural log of the usage probabilities of the corresponding elementary modes.

Thus, the total reaction entropy of the cell system is

$$\Delta S_{TOT} = \langle S \rangle = \sum p_i \Delta S_i \quad (13)$$

Substituting Eq (12) into Eq (13), we obtain

$$\Delta S_{TOT} = -b \cdot \sum p_i \ln p_i \quad (14)$$

Eq (14) describes the total reaction entropy of the cell system as a weighted sum of the usage probabilities which is similar to the expression for Boltzmann's entropy. The total rate of entropy production of the cell system $r_{\Delta S_{TOT}}$ is then defined as the product of the uptake rate of glucose molecules and the total reaction entropy of the cell system.

$$r_{\Delta S_{TOT}} = r_g \cdot \Delta S_{TOT} \quad (15)$$

One can multiply Eq (12) with the asymptotic uptake rate of glucose (r_g^*) to obtain the rate of entropy production of individual modes for a fully evolved metabolism

$$r_{\Delta S_i}^* = -b^* \cdot \ln p_i^* \quad (16)$$

where the $r_{\Delta S_i}^*$ is equivalent to $r_g^* \cdot \Delta S_i$, and p_i^* is the pathway probability of elementary modes for a fully evolved metabolism.