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FLUX RESPONSE COEFFICIENTS OF LINEAR ENERGY CONVERTERS

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An isomorphism was found to exist between the flux response coefficients and the thermodynamic quantities, degree of coupling and force ratio, of a linear symmetric energy converter. From the description of this energy converter in terms of nonequilibrium thermodynamics several constraints were obtained for the possible values of the flux response coefficients. Conversely, the control theoretical description of the system gave insight into the flux response characteristics of the energy converter operating at different steady states. This information could not have been obtained from a thermodynamic description alone.

1. Introduction

Kacser and Burns [1] and, independently, Heinrich and Rappoport [2] introduced the concept of flux response in order to obtain information about the relative contribution of individual reaction steps to the control of the overall steady-state flow in metabolic networks. This parameter is defined as a fractional change of the net flow J due to a fractional change of an individual enzyme activity E in the network, i.e., $(\mathrm{d}J/J)/(\mathrm{d}E/E) = R_E^J$. According to a new and unified terminology the parameter R_E^J is called flux response coefficient (H. Kacser and S. Rappoport, personal communication). This coefficient is a global parameter of the system. It is important to note that R_E^J is a phenomenological quantity which can be determined experimentally without any detailed knowledge of the molecular mechanisms of the reaction network. Of course R_E^J can be calculated theoretically once the molecular mechanisms and precise enzyme parameters of a given network are known.

A similar phenomenological description of a reaction network has been adopted in nonequilibrium thermodynamics, where the net flows are related to thermodynamic forces via the phenomenological coefficients L. Again, these quantities can be experimentally measured without knowledge of reaction mechanisms, although they can be derived theoretically once these mechanisms are known. The main emphasis of these thermodynamic studies is placed on the energetic aspects of the system whereas in the case of the flux response coefficients it focuses mainly on control.

In this paper it will be demonstrated that these two phenomenological descriptions are closely related to each other and, in particular, that there exists an isomorphism between the flux response coefficients and the thermodynamic quantities, degree of coupling and force ratio of linear energy converters. The comparison of both descriptions enables us to derive constraints on the possible values of the flux response coefficients. Furthermore, we obtain insight into the control exerted by the driving and the driven process of an energy converter operating under different steady-state conditions.

2. Linear energy converters

A phenomenological description of a linear energy converter within the framework of nonequilibrium thermodynamics is given by the relations:

$$J_1 = L_{11}X_1 + L_{12}X_2 \quad (1)$$

$$J_2 = L_{12}X_1 + L_{22}X_2 \quad (2)$$

where J_1 and J_2 are the net flows at output and input, respectively [3,4]. X_1 is the output force and X_2 the force applied to the input of the energy converter. Conventionally, the input process is considered to be the driving spontaneous process running downhill, whereas the output represents the nonspontaneous process driven uphill. Therefore, $J_2 > 0$, $X_2 > 0$ and $J_1 > 0$, $X_1 < 0$. Note that the system defined by eqs. 1 and 2 obeys reciprocity in the sense of Onsager insofar as the cross coefficients L_{12} have the same value for both processes. Topological constraints require that any linear energy converter must obey this type of reciprocity (D. Mikulecky, personal communication). Hence, we can concentrate our discussion on linear and symmetric energy converters without loss of generality.

Several experimental studies of biological energy converters such as oxidative phosphorylation [4], redox-driven H^+ pumps [5] and Na^+-transport systems [6] have revealed linear relations between flows and forces within a physiological range. In addition, where measured, symmetry turned out to be fulfilled within reasonable experimental errors.

Neither of these theoretical nor the experimental investigations have, so far, yielded information about the flow control of linear and symmetric energy converters operating under different steady-state conditions. Inspired by the elegant phenomenological treatment of flux response by Kacser and Burns and by Heinrich and Rappoport we have attempted to apply this treatment to eqs. 1 and 2 in order to obtain information about regulatory properties of linear energy converters.

The flux response coefficients of our system are defined by

$$R^{J_i}_{L_{ij}} = \frac{\partial J_i}{J_i} / \frac{\partial L_{ij}}{L_{ij}} \quad (3)$$

since the values of the coefficients L_{ij} are linear functions of the enzyme activities. Applying the definition eq. 3 to eqs. 1 and 2 yields the four flux response coefficients:

$$R^{J_1}_{L_{11}} = \frac{X_1}{X_1 + \frac{L_{12}}{L_{11}}X_2} \quad (4)$$

$$R^{J_1}_{L_{12}} = \frac{X_2}{\frac{L_{11}}{L_{12}}X_1 + X_2} \quad (5)$$

$$R^{J_2}_{L_{12}} = \frac{X_1}{X_1 + \frac{L_{22}}{L_{12}}X_2} \quad (6)$$

$$R^{J_2}_{L_{22}} = \frac{X_2}{\frac{L_{12}}{L_{22}}X_1 + X_2} \quad (7)$$

These relations show that the coefficients $R^{J_i}_{L_{ij}}$ are functions of the forces X_i and the phenomenological coefficients L_{ij}. It is important to stress that the coefficients $R^{J_i}_{L_{ij}}$ used here should not be confused with the phenomenological resistance coefficients R_{ij} used in nonequilibrium thermodynamics when expressing eqs. 1 and 2 inversely as functions of flows on forces. Eqs. 4–7 allow us to derive relations between $R^{J_i}_{L_{ij}}$ and thermodynamic parameters used for the analysis of linear energy converters.

3. Relations between thermodynamic and control parameters

In the study of linear energy converters two dimensionless parameters have been used to replace some of the L_{ij}: the degree of coupling $q = L_{12}/\sqrt{L_{11}L_{22}}$ and the phenomenological stoichiometry $Z = \sqrt{L_{11}/L_{22}}$ [3,4]. From these definitions we note that $L_{12}/L_{11} = q/Z$ and $L_{12}/L_{22} = qZ$. Another convenient dimensionless and normalized quantity is the force ratio $x = ZX_1/X_2$ [4]. With these definitions eqs. 4–7 can be cast into the matrix form:

$$\boldsymbol{R} \triangleq \begin{bmatrix} R^{J_1}_{L_{11}} & R^{J_1}_{L_{12}} \\ R^{J_2}_{L_{12}} & R^{J_2}_{L_{22}} \end{bmatrix} = \begin{bmatrix} \frac{x}{x+q} & \frac{q}{x+q} \\ \frac{qx}{qx+1} & \frac{1}{qx+1} \end{bmatrix} \quad (8)$$

It is easy to see that the summation theorem [1]

$\Sigma_{j=1}^{n} R^{J_i}_{L_{ij}} = 1$ holds for both flows J_1 and J_2. This theorem imposes therefore a restriction on the possible values of the coefficients $R^{J_i}_{L_{ij}}$:

$$R^{J_1}_{L_{11}} = 1 - R^{J_1}_{L_{12}} \tag{9}$$

$$R^{J_2}_{L_{11}} = 1 - R^{J_2}_{L_{22}} \tag{10}$$

Thus, the system has only two degrees of freedom. Inspection of eq. 8 shows that the same applies to the thermodynamic formulation of the $R^{J_i}_{L_{ij}}$ in terms of the two parameters x and q. Consequently, a straightforward calculation yields the inverse formulation of q and x in terms of the $R^{J_i}_{L_{ij}}$:

$$q = \sqrt{\frac{R^{J_1}_{L_{12}} R^{J_2}_{L_{12}}}{R^{J_1}_{L_{11}} R^{J_2}_{L_{22}}}} \tag{11}$$

$$x = \sqrt{\frac{R^{J_1}_{L_{11}} R^{J_2}_{L_{12}}}{R^{J_1}_{L_{12}} R^{J_2}_{L_{22}}}} \tag{12}$$

An additional restriction on the values of the $R^{J_i}_{L_{ij}}$ is imposed by the second law of thermodynamics. The nonnegativity of entropy production requires that the $\boldsymbol{L}$ matrix be positive definite or $L_{11}L_{22} - L_{12}^2 > 0$. Stated alternatively this means that $0 < |q| < 1$ which leads to the inequality

$$|R^{J_1}_{L_{12}} R^{J_2}_{L_{12}}| > |R^{J_1}_{L_{11}} R^{J_2}_{L_{22}}| \tag{13}$$

Eqs. 8–12 constitute an isomorphism between the set of control parameters $R^{J_i}_{L_{ij}}$ and the set of thermodynamic parameters x and q: $\{R^{J_i}_{L_{ij}}\} \leftrightarrow \{x, q\}$. With the help of this mapping it is also possible to express other thermodynamic quantities of interest in terms of the $R^{J_i}_{L_{ij}}$. The flow ratio $j = J_1/J_2Z = (x+q)/(qx+1)$ becomes

$$j = \sqrt{\frac{R^{J_2}_{L_{12}} R^{J_2}_{L_{22}}}{R^{J_1}_{L_{11}} R^{J_1}_{L_{12}}}} \tag{14}$$

Finally, for the efficiency $\eta = -J_1X_1/J_2X_2$ we obtain

$$\eta = -\frac{R^{J_2}_{L_{12}}}{R^{J_1}_{L_{12}}} \tag{15}$$

The restriction of the efficiency to $0 < \eta < 1$ finally yields the constraint

$$|R^{J_2}_{L_{12}}| < |R^{J_1}_{L_{12}}| \tag{16}$$

4. Ratios and inequalities among flux response coefficients

The relations, eq. 8, permit definition of a set of six ratios between the $R^{J_i}_{L_{ij}}$ which have a particularly simple thermodynamic interpretation in terms of the parameters x, j and q:

$$R^{J_1}_{L_{11}}/R^{J_1}_{L_{12}} = x/q \tag{17}$$

$$R^{J_2}_{L_{11}}/R^{J_2}_{L_{22}} = qj \tag{18}$$

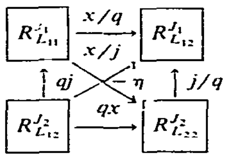
$$R^{J_1}_{L_{11}}/R^{J_2}_{L_{22}} = x/j \tag{19}$$

$$R^{J_2}_{L_{12}}/R^{J_1}_{L_{12}} = xj = -\eta \tag{20}$$

$$R^{J_2}_{L_{12}}/R^{J_1}_{L_{22}} = j/q \tag{21}$$

$$R^{J_2}_{L_{12}}/R^{J_2}_{L_{22}} = qx \tag{22}$$

These identities can be represented in the following scheme where the arrows point to the denominators:



These relations illustrate once more the unique connection between the control parameters and the thermodynamic quantities.

It is very instructive to study the inequalities between the different $R^{J_i}_{L_{ij}}$ imposed by the range of the force ration $-1 < x < 0$ and of the degree of coupling $0 < q < 1$. From eq. 8 we obtain the six inequalities

$$|R^{J_1}_{L_{12}}| \geqslant |R^{J_1}_{L_{11}}| \tag{23}$$

$$|R^{J_2}_{L_{22}}| \geqslant |R^{J_2}_{L_{12}}| \tag{24}$$

$$|R^{J_1}_{L_{11}}| \gtrless |R^{J_2}_{L_{22}}| \tag{25}$$

$$|R^{J_1}_{L_{12}}| \geqslant |R^{J_2}_{L_{12}}| \tag{26}$$

$$|R^{J_1}_{L_{12}}| \geqslant |R^{J_2}_{L_{22}}| \tag{27}$$

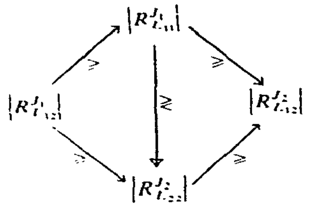
$$|R^{J_1}_{L_{11}}| \geqslant |R^{J_2}_{L_{12}}| \tag{28}$$

These inequalities permit the identification of the dominating flux response coefficient:

$$|R^{J_1}_{L_{12}}| \geqslant |R^{J_1}_{L_{11}}| \geqslant |R^{J_2}_{L_{12}}| \tag{29}$$

$$|R^{J_1}_{L_{12}}| \geqslant |R^{J_2}_{L_{22}}| \geqslant |R^{J_2}_{L_{12}}| \tag{30}$$

Clearly, for $q < 1$ the dominating coefficient is $R^{J_1}_{L,12}$ whereas the smallest coefficient is $R^{J_2}_{L,12}$. This result is also expressed in the constraint, eq. 16. The inequalities, eqs. 23–28, can be arranged in the following scheme



which again displays the dominance of $R^{J_1}_{L,12}$.

After these general observations we are now in a position to investigate the flux response coefficients at different steady states of the linear energy converter.

5. Flux response coefficients at different steady states of the energy converter

As pointed out in earlier studies, there are three steady states of the linear energy converter which are of particular interest: static head, level flow and the state of optimal efficiency [3,4]. Static head results form an open-circuited operation of the energy converter, i.e., no conductive load attached and is characterized by a vanishing flow ratio $j = 0$. Conversely, level flow corresponds to a short-circuited operation, i.e., an infinite conductive load attached to the energy converter. This steady state is characterized by a vanishing force ratio $x = 0$. Between these extremes is the state of optimal efficiency resulting from attaching a matched load [4]. Here, neither x nor j vanishes and they both have the same numerical values, i.e., $|x| = j$.

The definition of level flow $x = 0$ immediately yields the $\boldsymbol{R}$ matrix at the level-flow state by using eq. 8.

$$\boldsymbol{R}^{lf} = \begin{bmatrix} 0 & 1 \\ 0 & 1 \end{bmatrix} \tag{31}$$

From this we note that both the input and the output processes are only controlled by the reaction depending on the input force X_2 whereas the reactions depending on the output force X_1 have lost control at the level-flow state.

At static head the value of the force ratio is $x = -q$ [4]. From eq. 8 we thus obtain

$$\boldsymbol{R}^{sh} = \begin{bmatrix} -\infty & \infty \\ -\dfrac{q^2}{(1-q^2)} & \dfrac{1}{(1-q^2)} \end{bmatrix} \tag{32}$$

Thus, at static head the input and output processes are controlled by both reactions, by those depending on the input force X_2 as well as by those depending on the output force X_1. Note that the summation theorem allows also negative values of individual $R^{J_i}_{L,ij}$. A speciality of the static head is that both forces X_1 and X_2 affect the output process with infinite flux response coefficients pulling in opposite directions. This is due to the fact that $X_2 > 0$ and $X_1 < 0$ where one process runs downhill and the other uphill. Since $J_1 = 0$ at static head the two forces balance each other exactly without any resulting net output flow. This situation is expressed by infinite flux response according to eq. 32. The same would apply also to the input flow if the system were fully coupled, i.e., $q = 1$. In general, however, $q < 1$ and thus the flux response coefficients of the input process are functions of q.

The state of optimal efficiency is characterized by $x = -q/(1 + \sqrt{1-q^2})$. Substituting this value into eq. 8 yields the $\boldsymbol{R}$ matrix for the state of optimal efficiency

$$\boldsymbol{R}^{opt} = \begin{bmatrix} \dfrac{-1}{\sqrt{1-q^2}} & \dfrac{1+\sqrt{1-q^2}}{\sqrt{1-q^2}} \\ \dfrac{\sqrt{1-q^2}-1}{\sqrt{1-q^2}} & \dfrac{1}{\sqrt{1-q^2}} \end{bmatrix} \tag{33}$$

Here we note that the state of optimal efficiency is the only state where $|R^{J_1}_{L,11}| = |R^{J_2}_{L,22}|$. This means that the reaction of the output process depending on its own force X_1 and the reaction of the input process depending on its own force X_2 show exactly the same absolute value of the flux response. Thus, we have the remarkable result that the state of optimal efficiency permits a symmetric control of the straight reactions of the energy converter.

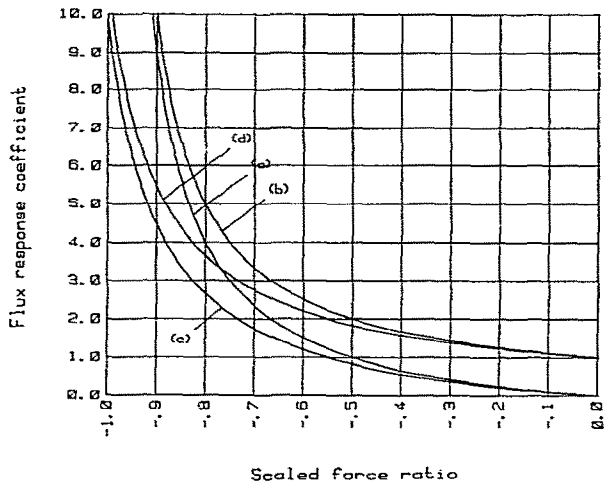


Fig. 1. Flux response coefficients of different steady states. The absolute values of the flux response coefficients defined in eq. 8 are plotted as a function of a scaled force ratio x/q in the interval $-1 \leqslant x/q \leqslant 0$. (a) $|R^{J_1}_{L_{11}}|$, (b) $|R^{J_1}_{L_{12}}|$, (c) $|R^{J_2}_{L_{12}}|$, (d) $|R^{J_2}_{L_{22}}|$. The degree of coupling was taken as $q_f^{ec} = 0.953$ (see ref. 4). This figure illustrates the dominance of $|R^{J_1}_{L_{12}}|$ within the whole interval of x/q. The point of intersection of $|R^{J_1}_{L_{11}}|$ and $|R^{J_2}_{L_{22}}|$ occurs at the state of optimal efficiency of the energy converter as defined in section 5. For further details see text.

The definitions of $R^{J_i}_{L_{ij}}$ in terms of q and x in eq. 8 permit representation of the control parameters as functions of x over the whole range of the force ratio $-q < x < 0$ as shown in fig. 1. At static head the absolute values of the flux response coefficients are maximal and tend to 1 or 0 as the steady-state operation of the energy converter tends to level flow. This again reflects the fact that the influence of the reactions associated with the output force in controlling the steady-state flows diminishes monotonously during a transition from static head to level flow. Thus, the application of control theory yields insights into the flux response behavior of linear energy converters which could not be obtained by thermodynamic studies alone.

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References

1 H. Kacser and J.A. Burns, Symp. Soc. Biol. 32 (1973) 65.
2 R. Heinrich and T.A. Rappoport, Eur. J. Biochem. 42 (1974) 89.
3 O. Kedem and S.R. Caplan, Trans. Faraday Soc. 21 (1965) 1897.
4 J.W. Stucki, Eur. J. Biochem. 109 (1980) 269.
5 D. Pietrobon, M. Zoratti, G.F. Azzone, J.W. Stucki and D. Walz, Eur. J. Biochem. 127 (1982) 483.
6 S.R. Caplan and A. Essig, Curr. Top. Membranes Transp. 9 (1977) 145.