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The Chemical Cycle Kinetics Close to the Equilibrium State and Electrical Circuit Analogy

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A free-energy transducing macromolecule, interacting with ligands, and cycling through discrete states, can be described by Hill's diagram. Close to equilibrium, where linear flux-force relationships hold, we develop a method of the construction of the electrical circuit corresponding to Hill's diagram. The method of mesh fluxes is used to form a general linear theory. Thevenin's theorem is used to find the efficiency of free-energy transduction. Maximal power transfer conditions are then found, too. A much more elegant proof of Jeans's 1923 theorem is then derived. We show that this theorem is equivalent to maximum entropy production principle for steady state linear electrical circuits. It follows that fluxes in the corresponding steady state enzymatic cycle kinetics (in the linear range for fixed ligand concentrations) distribute themselves so as to make the entropy production maximal. Prigogine's minimum entropy production theorem refers to the very special steady state and is much more restricted in its application than the maximum entropy production theorem.

Key words
Hill's diagram
Kirchhoff's rules
maximum entropy production
Thevenin's theorem

INTRODUCTION

T. L. Hill introduced the »diagram method« for analyzing the steady-state kinetics of macromolecular free energy-transducing systems. The method is described in great detail in the monograph by T. L. Hill.[1] A comprehensive outlook of this method is given by S. R. Caplan and A. Essig.[2] The method enables one to keep track of forces and fluxes, which are nonlinearly related in an arbitrary complex system. Close to the equilibrium, forces and fluxes are linearly related, which enables one to solve this problem, at least in principle, within the theory of linear thermodynamics.[3–5] In this paper we go a step forward constructing the electrical network analogue to the chemical cycle kinetics close to the equilibrium. In this way we achieve two goals. Firstly, the theory of electrical networks clarifies the interference between fluxes. Secondly, it enables us to analyze all thermodynamic processes in great detail.

The work is divided into six sections. In the second section (*Kirchhoff's Laws*) we briefly summarize the basic assumptions and results of the diagram method for enzymatic kinetics. In the third section (*Thermodynamic Ohm's Law, Dissipation Function*) we derive the rules, which make it possible to construct the electrical network analogue of the arbitrary steady-state kinetic scheme associated with the macromolecular energy transducing-system close to equilibrium. The formulation of laws corresponding to the Kirchhoff's and Ohm's laws is the subject of the second and third section, respectively. These laws provide rules, which are enlisted in the fourth section (*Electrical Network Analogue to Hill's Formalism*

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Close to the Equilibrium), for the construction of the electrical network analogous to the chemical cycle kinetics of the enzyme. In other words the one to one correspondence between the network of the biochemical reactions, in cycle kinetics, and the electric network is established. In this way our method could be very useful tool in the analysis of the stationary biochemical processes in the living systems. In order to grasp the problem mathematically we construct the system of linear equations in terms of the mesh fluxes.[6] Let us also note that the system of linear equations could be elegantly interpreted in terms of algebraic graph theory,[7] too. In the fifth (*Jean's Theorem and the Principle of Maximum Entropy Production*) and sixth (*Thevenin's Theorem, Maximum Power Transfer Theorem and Prigogine's Definition of the Steady State*) sections we show how powerful theorems of the linear electrical networks, like Jeans's and Thevenin's, make it possible to establish the important principle of maximum entropy production for the system with fixed forces. Applying these concepts to the field of macromolecular kinetics we show how one can find the characteristic parameters, like the efficiency of free energy transduction[1] and maximal rate of the free energy transduction. Finally, in the Discussion section, we briefly recapitulate the most important results.

RESULTS

The Diagram Method

The standard Hill's problem is the free energy transduction between two baths with non-equilibrium concentrations of ligands. The enzyme (macromolecule), embedded within membrane separating the baths, transports ligands (small molecules) between the baths, transducing in that way the free energy from one to another ligand subsystem.

Hill's has used standard expressions for the molar chemical potentials of the non-excited ligands in solution and for the subsystem of immobilized macromolecules in the *i*-th state,[8] *i.e.*

$$\mu = \mu^\circ + RT \ln c, \tag{1}$$

and

$$\mu_i = G_i + RT \ln p_i, \tag{2}$$

respectively. In the first equation (1) μ° and c are an arbitrary value and concentration of the ligand, respectively. In the second one (2) p_i and G_i / N_A are the probability of the occupancy if the *i*-th macromolecule level and the energy of the *i*-th macromolecule level, respectively. Here N_A is the Avogadro's number.

In order to get familiar with Hill's formalism let us reconsider the problem suggested by T. L. Hill[1] (Figure1). There is an ensemble of N macromolecules embedded within the membrane that transport the ligands through an, otherwise impermeable, membrane. This is the black box approach to the familiar cation-solute symport transport molecular mechanism.[9–12] The concentrations of the ligands L_1 and L_2 are higher in baths A and B, separated by membrane, respectively. The corresponding chemical potential differences are thermodynamic forces *i.e.*,

$$X_{11} \equiv \Delta \mu_1 = RT \ln (c_{1A}/c_{1B}), \tag{3}$$

and

$$X_{22} \equiv \Delta \mu_2 = RT \ln (c_{2A}/c_{2B}). \tag{4}$$

We use the double index notation for reasons that will be clarified later.

Close to the equilibrium, $c_{iA} \approx c_{iB}$, and above equations become

$$X_{ii} = RT(c_{iA} - c_{iB})/c_{iB}. \tag{5}$$

It is assumed that the chemical potential difference of the ligand L_1, between baths, overwhelms the one of the ligand L_2, *i.e.*

$$X_{11} > |X_{22}|. \tag{6}$$

In order to make the analysis as simple as possible we assume that the plain which halves the membrane is the element of the point group symmetry of the enzyme (see Figure 1). Further we suppose that ligand L_2 bounds to enzyme only if the ligand L_1 is already bound to it. In that way, due to the (6), there is a net transport of the ligand L_2 in the direction of the increase of its concentration. This process is schematically shown in the Figure 1. Although the details of the mechanism of facilitated symport transport are well explored[9] we prefer the black box approach to ligand transport »*via*« macromolecule. Then, conclusions derived from such an approach do not depend on the particular transport mechanism. Furthermore, the black box approach is free of details of the transport mechanism and enables one to make a simple, transparent and easily comprehensible theory.

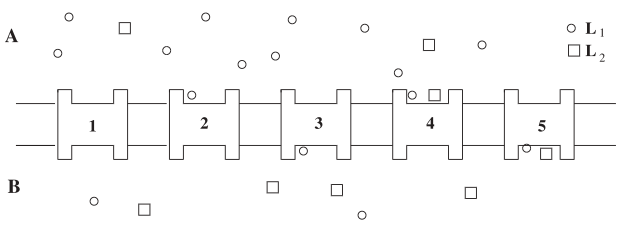

Figure 1. The symport transport scheme as described by T. L. Hill.[1] An ensemble of the macromolecules embedded in the membrane, which separates the environment (A) and the cell interior (B). The concentration of the ligands of the type L1 in the surrounding and L2 in the cell is higher than corresponding concentrations in the cell and in the surrounding, respectively. The five possible states of the macromolecule and the bound ligands are numerated.

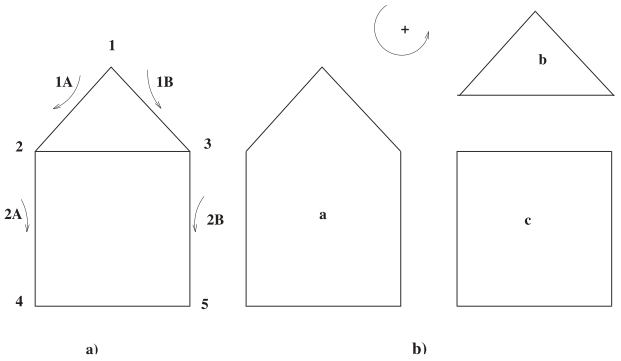

Figure 2. a) Vertices of Hill's diagram correspond to the states depicted in the Figure 1. The binding of the certain type of the ligand (1 or 2) in the certain bath (A or B) is indicated with the arrow. The transition line that has the same direction as the neighboring ligand arrow corresponds to the binding of the ligand (*e.g.* 1→2 and 1A). In the opposite case there is a dissociation of the ligand and macromolecule (*e.g.* 3→1 and 1B); b) All cycles for Hill's diagram.

It was T. L. Hill[1] who realized that processes shown on the Figure 1 could be represented by the diagram (see Figure 2a.). The vertices of the diagram represent possible states of the enzyme–ligand complex. The lines that connect two vertices represent transitions. Arrows entering the diagram indicate binding. For example transitions 2↔3 and 4↔5 are conformational changes, while 1→2 represents the binding of the ligand L_1. The overall set of connected transitions form cycles when the final state coincides with the starting one. Such transitions play particularly important role. The diagram (Figure 2a) has three cycles depicted in Figure 2b.

The rate constant α_{ij} for the transition $i \rightarrow j$ and the steady state probability p_i of the i-th state both determine the transition flux between states i and j, *i.e.* the frequency of the net transitions $i \rightarrow j$, in the ensemble of the N enzymes,

$$J_{ij} = N(\alpha_{ij}\, p_i - \alpha_{ji}\, p_j). \qquad (7)$$

The number of independent nonzero steady-state transition fluxes for a given diagram is obtained by subtracting the number of vertices in the diagram from the number of lines minus one. By means of the mathematical induction one shows that the number of independent fluxes is equal to the number of the *simple loops.* We call the loop a simple one if there is no loop within it. In the above example there are two simple loops 1231 and 24532 with corresponding independent transition fluxes J_{12} and J_{24}. Among the simple loops a special role is reserved for those, that do not share one or more transition lines with the other simple loops. We call these loops and transition lines *outer loops* and *outer transition lines*, respectively.

The power of Hill's method emerges from the algorithm for the calculation of state occupancies in terms of rate constants. This technique is clearly illustrated in several books[1,2,13] and will not be repeated here, but only the most important results will be recapitulated.

The key computational quantities of Hill's theory are directional and flux diagrams, respectively. The directional diagram is defined for the certain state and is obtained from Hill's diagram by drawing maximal number of the transition lines feeding into the state without closing any cycle. The numerical value associated with this diagram is equal to the product of the rates for corresponding transitions. The flux diagram is associated with the certain cycle and maximum number of the transition lines feeding into the cycle without forming any additional cycle. The numerical value associated with the flux diagram is the difference of the products of the rates of transitions that define cycle traversed in counterclockwise and clockwise directions, respectively, multiplied with the rates of the »feeding« transition lines.

The k-th cycle flux, where k is the cycle index, J_k is,

$$J_k = N(\Pi_k^{+} - \Pi_k^{-})\ \Sigma_k/\Sigma. \qquad (8)$$

Here $\Pi_k^{+} = \alpha_{1k2k}\alpha_{2k3k}\ldots\ \alpha_{nk1k}$ and $\Pi_k^{-} = \alpha_{1knk}\ldots\ldots\ \alpha_{3k2k}\alpha_{2k1k}$ are the products of the transition rates of the transitions that define counter and clockwise traversal of the cycle, respectively**.** We use here four index entries for transition rates, *i.e.* a pair of entries corresponds to the state of the enzyme-ligand complex. Entry common to all pairs (k) refers to the cycle, while other entries refer to the different states in the cycle**.** Σ_k is the sum of the products of the transition rates of the »feeding lines« of the k-th cycle. Finally Σ is the sum of numerical values associated with the directional diagrams for all states.[1,2]

It follows from Hill's theory that transition flux is the algebraic sum of all cycle fluxes containing a corresponding transition line. The transition fluxes of our simple model expressed in terms of cycle fluxes are,

$$J_{12} = J_a + J_b,\ J_{23} = J_b - J_c,\ J_{24} = J_a + J_c, \qquad (9)$$

and

$$J_{31} = J_{12},\ J_{24} = J_{45} = J_{53}. \qquad (10)$$

One should keep in mind that cycles do not mean that the whole system finds itself finally in the starting state. It is true for the enzyme only, while the system as whole steadily increases its entropy, *i.e.* it never returns to the previous state.

There are three different cycles with the corresponding fluxes. However, there are only two independent fluxes, *i.e.* the Hill's theory is the redundant one. Each cycle flux has its conjugate cycle force X_{kk}, which is given by the expression

$$\exp(X_{kk}/RT) = \Pi_k^{+}/\Pi_k^{-} = K_{1k2k}K_{2k3k}\ldots\ldots K_{mk1k}, \qquad (11)$$

where

$$K_{ij} = \alpha_{ij}/\alpha_{ji}, \quad (12)$$

is the equilibrium constant for the *i–j* transition. The four index entries in Eq. (11) have the same meaning as those in Eq. (8).

Kirchhoff's Laws

We are now in a position to write down Kirchhoff's law for transition fluxes. Once the macromolecular complex has passed from the state 1 to the state 2, its next state, excluding its return into state 1, must be either state 3 or 4, respectively. In terms of the fluxes this means the transition flux J_{12} is equal to the sum of J_{23} and J_{24}. The generalization of this statement: *The algebraic sum of all transition fluxes in each microscopic state of the system, in the steady state, equals zero,* is Kirchhoff's law for fluxes.

Let us separate the ensemble of the N enzymes into subsystems characterized by the state of the macromolecular complex, *i.e*. the states of the enzyme with or without bound ligands. The change of the molar chemical potentials of the ensemble and its surroundings baths for the intra-enzyme transitions is

$$\mu_j - \mu_i = G_j - G_i + RT \ln (p_j/p_i). \quad (13)$$

For transitions which include bound ligand

$$\mu_j - (\mu_i+\mu_L) = G_j - (G_i + \mu_L) + RT \ln (p_j/p_i). \quad (14)$$

Eqs. (13) and (14) can be written in a compact manner,

$$\Delta \mu'_{ij} = \Delta G'_{ij} + RT \ln (p_j/p_i), \quad (15)$$

where primes indicate that ligand chemical potentials have been taken into account where necessary.

In the equilibrium due to the principle of the detailed balance we have,

$$\alpha_{ij} p_{ei} = \alpha_{ji} p_{ej}, \quad (16)$$

where »e« indicates equilibrium values. By means of expression (13) we get,

$$K_{ij} = \alpha_{ij}/\alpha_{ji} = \exp[-(G_j - G_i)/RT], \quad (17)$$

for an intra-enzyme transition only, and

$$K_{ij} = \alpha_{ij}/\alpha_{ji} = \exp\{-[G_j - (G_i + \mu_L)]/RT\}, \quad (18)$$

if *j*-th state corresponds to the bound enzyme ligand complex. From Eqs. (11), (15) and (18) it follows:

$$X_{kk} = \Delta \mu'_{1k2k} + \Delta \mu'_{2k3k} + \ldots + \Delta \mu'_{mk1k}. \quad (19)$$

Here, like in Eq. (8), we use four index entries. A pairs of entries corresponds to the subsystems of macromolecular complexes. The entry common to all pairs (k) corresponds to the cycle while other entries correspond to different states, within the cycle, of the enzyme-ligand complex. As we have already stated these states define the subsystems**.** We read the above equation in the following way. The X_{kk} is the free energy of the complete system dissipated in the cyclic transition of the enzyme and bound ligands. In other words Eq. (19) is analogous to Kirchhoff's law for electromotive forces and voltages in the electrical loop. We call Eq. (19) Kirchhoff's loop law for thermodynamic forces and differences of the chemical potentials. In our case it states: *The thermodynamic force,* i.e*. the difference of the ligand chemical potentials, due to the concentration difference of the ligands in the baths, equals to the sum of differences of the chemical potentials associated with enzyme-ligand transitions within cycle.*

Thermodynamic Ohm's Law, Dissipation Function

In this section we derive the relationship between the fluxes and corresponding differences of the chemical potentials, for a system close to the equilibrium and introduce a dissipation function.

Transition fluxes and corresponding chemical potential differences are related nonlinearly. It follows from Eqs. (7), (18) and (15),

$$J_{ij} = N\alpha_{ji} p_j [\exp(\Delta \mu'_{ij}/RT - 1)]. \quad (20)$$

Close to the equilibrium above relationship becomes

$$J_{ij} = \Delta \mu'_{ij}/R_{ij}, \quad (21)$$

where

$$R_{ij} = RT/(N\alpha_{ji} p_j). \quad (22)$$

We call the relationship (21) thermodynamic Ohm's law, or Ohm's law analogue in biochemistry**.** The principle of the detailed balance is approximately valid close to the equilibrium, and by using the relationship (16) we get,

$$R_{ij} = R_{ji}, \quad (23)$$

i.e. Onsager's symmetry relationships are fulfilled.

One of the most important quantities in the non-equilibrium thermodynamics is the entropy production $d_i S/dt$. It is equal to the dissipation function Φ, divided with the absolute temperature, which can be written either in terms of thermodynamic forces (3,4) or transition changes of the chemical potentials (15), *i.e.*

$$\boldsymbol{T}\, d_i S/dt = \Phi = \Sigma_i X_{ii} J_i = \Sigma\Sigma_{ij} \Delta \mu'_{ij} J_{ij}. \quad (24)$$

Here J_i is flux of binding of the *i*-th small molecule, *i.e.* J_1 and J_2 are equal to J_{12} and J_{24} respectively. In Hill's theory these quantities are called operational fluxes. The above identity just states that the decrease of free energy of the system $\Sigma_i X_{ii} J_i$ is equal to the energy dissipated during the transitions of the enzyme-ligand complex.

Electrical Network Analogue to Hill's Formalism Close to the Equilibrium

It follows from the foregoing section that the thermodynamic forces, the differences of the chemical potentials due to different ligand concentrations, play, in the kinetics of the chemical cycle, the role of the electromotive force (EMF) in an electrical circuit. Close to the equilibrium differences of the chemical potentials between two states, which define transitions of the enzyme–ligand complex, and fluxes, play the role of voltages on the resistors and corresponding currents, respectively. We associate with each simple loop of the arbitrary Hill's diagram a mesh flux (see Figure 3), an analogue to the mesh current in electrical networks.[6] The mesh flux is associated with each mesh and they form a complete set of independent fluxes since the number of simple loops is equal to the number of independent fluxes. The transition flux associated with the transition line common to two loops is the algebraic sum of the corresponding mesh fluxes (see Figure 4). Evidently the transition fluxes in the outer lines of the outer loops are equal to their mesh currents. Note that mesh flux differs from the cycle flux since the former is defined for simple loops only, while the latter is defined for any loop (see previous definition of the cycle flux).

The question arises: which flux kind (transition, cyclic or mesh) gives the simplest mathematical description of the arbitrary planar Hill's diagram? Kirchhoff's law for fluxes is inherently embedded in the definition of the mesh fluxes (see Figure 4). This is not valid for transition fluxes and the theory based on the mesh currents has to be simpler than one based on the transition fluxes. Although the definition of the cyclic fluxes takes into account Kirchhoff's law for fluxes, cyclic fluxes are at a disadvantage regarding mesh fluxes, since they do not form a set of independent quantities. In short, mesh fluxes form the complete set of independent fluxes obeying Kirchhoff's law for fluxes and a theory founded on these quantities must be simpler than the theories founded on transition or cyclic fluxes.

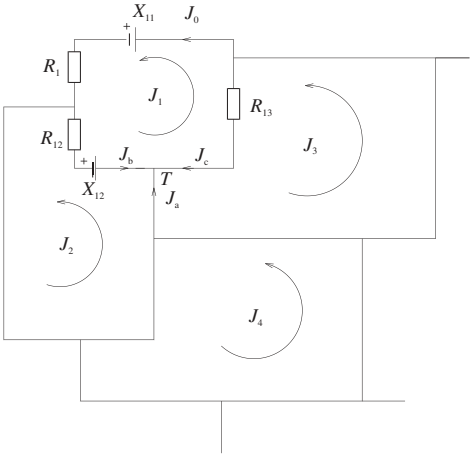

Figure 3. The planar network decomposed into simple loops with corresponding mesh fluxes. The details of the loop 1 are shown. The transition fluxes in outer branches are equal to the corresponding transition fluxes, *i.e.* $J_0 = J_1$. Transition fluxes in the branches common to the two simple loops is equal to the algebraic sum of the mesh fluxes of the corresponding simple loops, e.g. $J_a = J_2 - J_3$, $J_b = J_1 - J_2$, and $J_c = J_3 - J_1$.

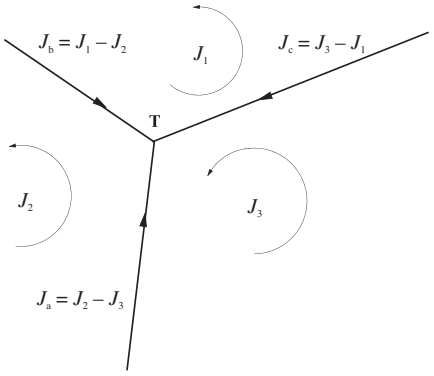

Figure 4. The blown up part of the network close to the point T from the Figure 3. Kirchhoff's law for fluxes is embedded into concept of mesh fluxes since $J_a + J_b + J_c = 0$.

We are now in a position to establish the rules, for a planar Hill's diagram, which enables one to construct the electrical network analogous to the biochemical cycle kinetics close to the equilibrium. These are:

i) Connect each pair of linked states (*i,j*) in Hill's diagram with the corresponding resistance R_{ij}.

ii) Draw within each simple loop the corresponding mesh flux oriented in a counter-clock wise direction.

iii) Insert the thermodynamic force, as the electromotive force EMF, in each transmission line (12 and 24 in Figure 2a) that describes the binding of the ligand to the enzyme in such way that the direction of the binding, in Hill's diagram ($1\rightarrow2$, $2\rightarrow4$ in Figure 2a), emerges from the positive pole of the corresponding EMF**.** The value of the thermodynamic force is the affinity of the ligand transport across the membrane. It coincides with Hill's definition of the thermodynamic force (11) in the case of single ligand transport assuming that Hill's cycle is a simple loop. We use double index notation for thermodynamic forces where indices correspond to the loops, which share common thermodynamic force, *e.g.* X_{12} in Figure 3. The thermodynamic forces in the outer branches, such as the X_{11} in Figure 3, have degenerate indices like those in expressions (3) and (4), respectively. The expressions for X_{ij} [like (3) or (4)] automatically take care of the correct sign of the thermodynamic

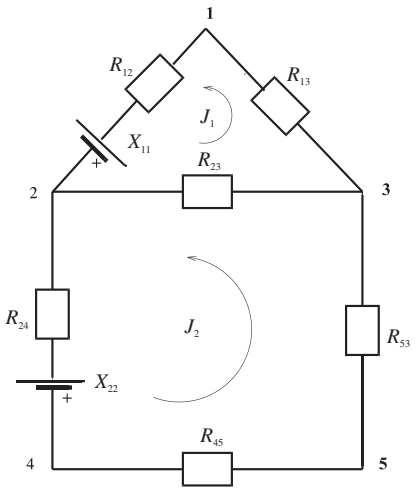

Figure 5. The electrical network equivalent to the chemical cycle kinetics of the enzyme-ligand complex close to the equilibrium constructed by means of Hill's diagram (see Figure 2). The values of the thermodynamic forces and resistances are given by expressions (5) and (22), respectively.

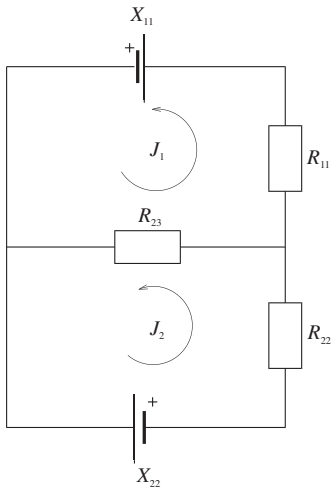

Figure 6. The electrical network from the Figure 5 after replacement of the resistance connected in the series with theirs equivalent resistances [see Eqs. (30) and (31)].

force, *i.e.* whether the ligand to be transported across the membrane is bound in the bath with its higher or lower concentration, $X_{ij} \geq 0$ or $X_{ij} \leq 0$, respectively. Evidently it holds

$$X_{ij} = -X_{ji}, \text{ for } i \neq j. \tag{25}$$

Using the above rules we construct in Figure 5 an electrical network equivalent to the biochemical cycle kinetics of the enzyme-ligand complex described by Hill's diagram in Figure 2a.

The problem can now be solved applying Kirchhoff's law for thermodynamic forces and differences of the chemical potentials for each simple loop. Due to the biochemical Ohm's law analogue (21) this system of linear equations reads,

$$\Sigma_i X_{ik} = R_{kk} J_k + \Sigma_i R_{ik}(J_k - J_i). \tag{26}$$

Here the left hand side of the equation is the algebraic sum of the thermodynamic forces within k-th simple loop. The thermodynamic force is positive if the k-th mesh flux comes out of the positive pole of the corresponding EMF. Otherwise it is negative. R_{kk} is the equivalent resistance in the outer branch, J_k is the mesh flux associated with the k-th simple loop and R_{ik} is the equivalent resistance common to the i-th and k-th simple loop. Eq. (26) applied to the simple loop in Figure 3 reads,

$$X_{11} - X_{12} = R_1 J_1 - R_{12}(J_1 - J_2) - R_{13}(J_1 - J_3). \tag{27}$$

Let us apply this method to the thermodynamic network in Figure 5. There are two simple loops that make a system of two linear equations. These are

$$X_{11} = R_{11} J_1 + R_{23}(J_1 - J_2), \tag{28}$$

$$X_{22} = R_{23}(J_2 - J_1) + R_{22} J_2, \tag{29}$$

where

$$R_{11} = R_{12} + R_{13}, \tag{30}$$

and

$$R_{22} = R_{24} + R_{53} + R_{45}. \tag{31}$$

Here X_{ii} and R_{ij} are given by the Eqs. (3), (4) and (22), respectively. The equivalent electrical scheme of the network shown in Figure 5 is shown in Figure 6.

Finally, one can easily verify that the above equations are in fact those obtained from Hill's formalism applied close to the equilibrium.

Jeans's Theorem and the Principle of Maximum Entropy Production

In this section we apply the theorem established by J. H. Jeans[14] in the case of planar network. J. H. Jeans introduced the F function, which can be expressed in terms of the mesh fluxes. This theorem states that steady state fluxes flowing through a network of the resistors $\{R_{ij}\}$ and thermodynamic forces $\{X_{ij}\}$ are distributed in such a way that function

$$F(\{J_i\}) = \Sigma_i R_{ii} J_i^2 + (1/2)\Sigma_{i,j} R_{ij}(J_i - J_j)^2 - 2\Sigma_i X_{ii} J_i - \Sigma_{i,j} X_{ij}(J_i - J_j) \tag{32}$$

has a minimum. Here X_{ii} is the algebraic sum of the thermodynamic forces in the outer line of the i-th outer loop and while $X_{ij} = -X_{ji}$ (25) is the algebraic sum of the thermodynamic forces in the transition lines common to i and j loops.

Proof: We first note that fluxes in expression (32) are mesh ones, *i.e.* Kirchhoff's law for currents is already embedded in the function *F*. The partial derivation of the *F* function regarding *i*-th mesh flux J_i generates equation,

$$R_{ii}\,J_i + \Sigma_j R_{ij}(J_i - J_j) - X_{ii} - \Sigma_{j\neq i} X_{ij} = 0, \qquad (33)$$

which is in fact Kirchhoff's law for thermodynamic forces and differences of the chemical potentials applied to the *i*-th simple loop [see Eq. (26)]. Since the quadratic term in the *F* function is the positive one, the extreme defined by the system of Eq. (33) is the minimum.

No restriction has been put on the fluxes in the above theorem, *i.e.* the equation (33) define the absolute extreme of the *F* function in the *n*-dimensional space, where *n* is the number of mesh fluxes $\{J_i\}$ or simple loops. In order to make this extreme problem closer to the real system we include the principle of energy conservation, (24),

$$\boldsymbol{T}\mathrm{d}_i S/\mathrm{d}t = \Phi = \Sigma_i X_{ii} J_i + (1/2)\Sigma_{i,j} X_{ij}(J_i - J_j) = \Sigma_i R_{ii}\,J_i^2 + 1/2\Sigma_{i,j} R_{ij}(J_i - J_j)^2 \qquad (34)$$

which simple states that free energy dissipated in the intra-molecular transitions must be equal to the free energy accumulated in the baths due to the non-equilibrium concentrations of the ligands. This requirement imposes the condition on the above extreme. Mathematically this means that we look for the extreme of the *F* function (32) on the hyper-surface, of the dimensionality *n*–1, defined by Eq. (34). It is the peculiarity of this problem that the solution of unconditional extreme incorporates the condition (34), *i.e.* the point in *n* dimensional space $\{J_i\}$ where function $F(\{J_i\})$ has its absolute minimum is the point of the hyper-surface. Indeed, multiplying the Eq. (33) by J_i and summing over all mesh currents one gets just the condition (34).

Let us consider a simple network that consists of two simple loops shown in Figure 7. In order to make the analysis as simple as possible we put $X_1 = X_2 = R_1 = R_2 = a$, *i.e.* the numerical values of all parameters in SI units are equal. The *F* function is

$$F/a = (J_1 - 1)^2 + (J_2 - 1)^2 - 2. \qquad (35)$$

It represents a circular paraboloid which has its minimum for the point M(1,1), *i.e.* when $J_1 = J_2 = 1$ (see Figure 8). Energy conservation law (34) now reads,

$$J_1 + J_2 = J_1^2 + J_2^2, \qquad (36)$$

or

$$\mathrm{C} \equiv (J_1 - 1/2)^2 + (J_2 - 1/2)^2 - 1/2 = 0, \qquad (37)$$

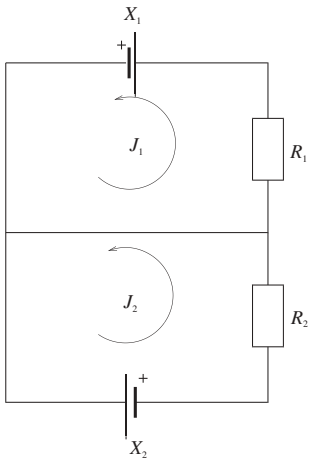

Figure 7. The electrical network with two loops and zero mutual resistance.

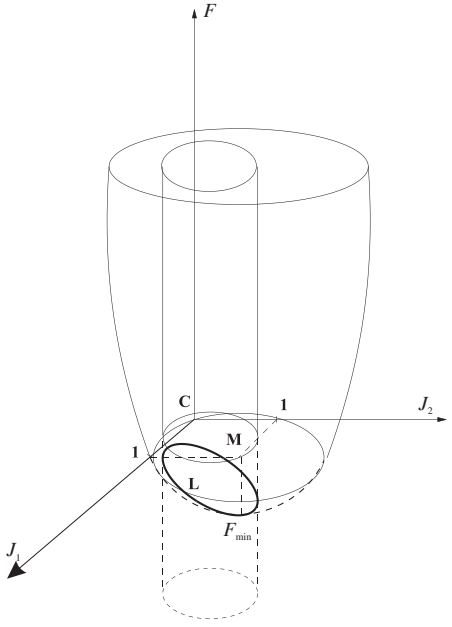

Figure 8. The entropy production is maximal for the point M, which is on the hyper surface C, in the case of the simple two loop network from the Figure 7.

which represents the circular cylinder of radius $(2)^{-1/2}$ in J_1, J_2 plane with a center at the point S(1/2,1/2) (see Figure 8), *i.e.* the circle C is hyper-surface in this case. The cross-section between paraboloid and cylinder, the curve **L**, represents all those values of the *F* function, which satisfy the energy conservation law (36). The minimum of the curve **L**, with respect to the axis perpendicular to J_1, J_2 plane, coincides with the minimum of the paraboloid, *i.e.* the point $F_{\min}$ where *F* exhibits the minimum.

From (32) and (34) a very interesting conclusion follows. The minimum of the *F* function implies the maximum of entropy production, *i.e.* the steady state is characterized by,

$$\mathrm{d}_i S/\mathrm{d}t = -F(\{J_i\}) = \text{maximum}. \qquad (38)$$

In other words the fluxes distribute themselves within the network in such a way as to produce the entropy at maximum rate. Note that this statement is not opposed to Prigogine's theorem on the minimum entropy production,[15] which is derived assuming that some of secondary forces X_i adjust themselves in such a way to vanish conjugate fluxes J_i.

In short, the steady state biochemical cycle kinetics close to the equilibrium is accompanied by maximum entropy production, assuming fixed non-zero thermodynamic forces. This conclusion has nothing to do with the fact that that entropy production vanishes in the equilibrium. Being close to equilibrium simply means that the thermodynamic forces are relatively small ones regarding the *RT*. The fluxes diminish as the thermodynamic forces do, when the system approaches to the equilibrium state. In the case of the adiabatic approach, which assumes that rates of the changes of the thermodynamic forces are much less than the rate of relaxation of the system, the system is described well in terms of the steady state theory. Then, regardless of how small the thermodynamic forces are, or expressed in another way, how close the system is to the equilibrium state, the fluxes always distribute themselves in order to achieve the steady state of maximum entropy production. It goes without saying that entropy production vanishes as the system approaches the equilibrium.

Thevenin's Theorem, Maximum Power Transfer Theorem and Prigogine's Definition of the Steady State

Relevant parameters of the biochemical cycle kinetics like efficiency of the free energy transduction,[13] close to the equilibrium, can be deduced in an elegant manner by means of the well developed theory of linear electrical networks.[16]

A very useful theorem in the linear network theory is Thevenin's theorem[16] which states: *Any linear network may, with respect to pair of terminals (port), be replaced by voltage source with EMF (thermodynamic force) equal to the open circuit voltage (the difference of the chemical potentials) between the terminals and with the internal resistance seen at this port (equivalent resistance between terminals).*

We apply Thevenin's theorem at the simple two-loop network from the Figure 6 in order to find the efficiency of the free energy transduction as defined by T. L. Hill:[13]

$$\eta = -(J_2 X_{22})/(J_1 X_{11}). \tag{39}$$

First we »cut« the network at terminals A,B (see Figure 9a) and find the voltage between them, which is equal to Thevenin's thermodynamic force, *i.e.*

$$X_{T11} = X_{11} R_{23}/(R_{11} + R_{23}). \tag{40}$$

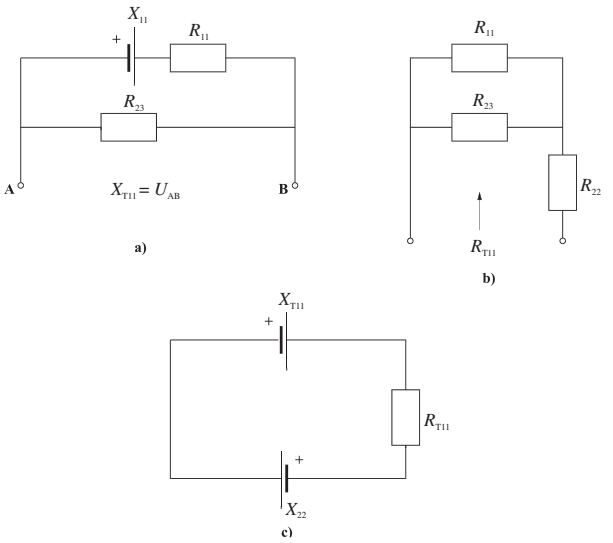

Figure 9. a) The part of the network which defines Thevenin's EMF, X_{T11}; b) and resistance R_{T11}; c) Replacement of the part of the network from the Figure 6 above the points A and B with Thevenin's source (X_{T11} and R_{T11}).

The resistance seen from the port (see Figure 9b) is

$$R_{T11} = R_{11} R_{23}/(R_{11} + R_{23}) + R_{22}. \tag{41}$$

Now we replace the part of the network above points A and B with Thevenin's source, as it is shown in the Figure 9c, which consist of Thevenin's thermodynamic force X_{T11}, and resistance R_{T11}.

Then Kirchhoff's law (26) gives the flux J_{22}

$$J_{22} = (X_{T11} + X_{22})/R_{T11.} \tag{42}$$

Analogously we obtain

$$J_{11} = (X_{T22} + X_{11})/R_{T22,} \tag{43}$$

where

$$X_{T22} = X_{22} R_{23}/(R_{22} + R_{23}), \tag{44}$$

and

$$R_{T22} = R_{22} R_{23}/(R_{22} + R_{23}) + R_{11}. \tag{45}$$

The efficiency (39) becomes

$$\eta = -X_{22} R_{T22} (X_{T11} + X_{22}) / [X_{11} (X_{T22} + X_{11}) R_{T11}]. \tag{46}$$

For a fixed thermodynamic force X_{11} and fixed resistances, efficiency of the free energy transduction becomes maximal for

$$X_{22} = -X_{11}(1 + R_{22}/R_{23}) \cdot \{1 - [1 - R_{23}^2/\{(R_{11} + R_{23})(R_{22} + R_{23})\}]^{1/2}\}. \tag{47}$$

In the case of small slippage $R_{23} > R_{11}\&R_{22}$ we have

$$\eta = 1 - [(R_{11} + R_{22})\ /R_{23}]^{1/2}, \tag{48}$$

and

$$X_{22} = - X_{11}\ \{1 - [(R_{11} + R_{22})\ /R_{23}]^{1/2}\}. \tag{49}$$

As could be expected slippage reduces efficiency. It is worthwhile to note that maximum efficiency of the free energy transduction does not coincide with the maximum rate of transduced free energy, *i.e.* the ability of the system to store the free energy. For small slippage efficiency is close to one, *i.e.* to its maximal value (see 48), but the rate of the free energy transduction (J_2X_{22}), which describes the capability of the system to store free energy,

$$J_2X_{22} = - X_{11}^2/[(R_{11} + R_{22})\ R_{23}]^{1/2}, \tag{50}$$

is close to zero, *i.e.* to its minimal value. The maximum rate of free energy transduction occurs for

$$X_{22\max} = -X_{T11}/2, \tag{51}$$

as one can easily verify. This is a well-known maximum power transfer theorem in the theory of linear electrical networks.[16] This theorem states that maximum power (free energy per time unit) transferred from source with the thermodynamic force $X_{11} > 0$ to the source with the thermodynamic force X_{22} occurs if $-X_{22}$ equals half of Thevenin voltage $X_{T11.}$ For $-X_{22} < X_{T11}/2$ there is an increment of the flux through the source with $-X_{22}$, with respect to the flux for the condition $X_{22\max} = - X_{T11}/2$, but the drop in the voltage overwhelms the rise in the flux. Analogously, for $-X_{22} > X_{T11}/2$ the decrease of the flux overwhelms the increase of the $-X_{22}$.

We now turn to the Prigogine[15] definition of the steady state. His formulation of linear thermodynamics does not rely on Kirchhoff's laws. Therefore he has not been in position to vary distribution of the fluxes, as we have done in this paper. His definition is more restricted, since he has required zero secondary flux, *i.e.* $J_{22} = 0$. Evidently in the Prigogine steady state secondary force X_{22} equals to the negative Thevenin's thermodynamic force $- X_{T11}$ (see Figure 9c) In terms of the slippage defined by Juretić[17] as $s_0 = R_{11}/R_{23}$ secondary force disappears or becomes equal to the negative primary thermodynamic force $-X_{11}$ in the case of infinite and zero slippage, respectively. In Prigogine's definition of the steady state, the secondary thermodynamic force is the only non-fixed variable. Then, by means of the definition of the entropy production (24) one easily finds that Prigogine's definition of the steady state is the state of the minimum entropy production. Of course this result does not oppose our result due to a different starting assumption.

DISCUSSION

It is quite natural to explore the conservation laws as the starting point of the theory. The well-known examples are the collision processes, based on the impulse and energy conservation laws, Bernoulli's equation on the motion of an ideal fluid, which exploits mass and energy conservation. The best-known theory of this kind is the theory of electrical circuits, developed in electrical engineering. It is based on Kirchhoff's laws, which reflect the principles of the charge and energy conservation. Strictly speaking the principle of energy conservation can be attributed to Kirchhoff's voltage law only in the case of stationary currents, but electrical engineers successfully applied it, with slight modifications, even in the case of time varying currents.

In the non-equilibrium thermodynamic processes, which include chemical reactions, mass conservation is the only certain conservation principle, which invokes no hypothesis, *i.e.* it should be present in any theory of non-equilibrium thermodynamic processes. The application of Kirchhoff's flux law in the non-equilibrium thermodynamics is usually justified by this principle.[3,18]

The standard assumption of the theory of non-equilibrium processes is the assumption about local thermodynamic equilibrium state and global non-equilibrium state. For example let us assume the gas flow through the porous wall, which separates two compartments (Joule--Thomson process). The gases in both compartments are in the equilibrium state (constant pressure over the whole compartment), but the gases themselves are not in equilibrium, *i.e.* there is a pressure difference on the wall sides, which forces flow of the gas from the compartment of the higher pressure to the one with lower pressure. In chemical reaction it is the non zero chemical affinity, the difference between the reactant chemical potentials, which keeps the chemical reaction continuing. In living cells these reactions could be extremely complicated. But regardless the complexity of the reaction system, in accordance to the previously mentioned principle of the local equilibrium, the system could be divided into subsystems with well-defined chemical potentials. For example let us consider reaction A↔B↔C. At each moment the global system is composed of three subsystems (A, B, C) which are internally in equilibrium, *i.e.* each subsystem is characterized by the chemical potential $\mu_{i.}$ Having in mind that chemical potential is the change of the internal energy of the subsystem, due to the addition of the one mole the identity

$$\Delta \mu_{AC} = \Delta \mu_{AB} + \Delta \mu_{BC}, \tag{52}$$

where

$$\Delta \mu_{ij} = \mu_i - \mu_j, \tag{53}$$

can be interpreted in the following way. The left side is the potential free energy per mole for the reaction A↔B↔C, since there is no direct chemical reaction A↔C, while the terms on the right side of the identity (52) are equal to the dissipated heat in reactions A↔B and B↔C, respectively. In this way the identity (52) is equivalent to Kirchhoff's loop law. This is in fact the content of the Kirchhoff's law for thermodynamic potentials and the differences of the chemical potentials, derived in the Second Section. We claim that Kirchhoff's loop law (52) is not restricted to the processes with macromolecule cycle kinetics, but is rather generally valid for each non-equilibrium process, which is analyzed on the basis of the local equilibrium state assumption. Similar Kirchhoff's loop law has been recently exploited by H. Qian *et al.* as the basic equation of the of the energy balance analysis[19] and non-equilibrium biochemical circuit theory.[18]

We stress once more that the most important result of this paper is the one to one correspondence between the network of the stationary biochemical reactions in the cycle kinetics and the electric network. Having in mind the above mentioned principle of the local equilibrium and global non-equilibrium this method could be, in principle, applied to any network of stationary chemical reactions close to the equilibrium, *i.e.* it could become powerful tool in the analysis of the networks of the stationary biochemical reactions in living cells.

The established analogy between the electric networks and the chemical cycle kinetics has enabled us to derive Jeans's theorem for the processes described by the planar Hill's diagrams, close to the equilibrium**.** We find that fluxes distribute themselves to achieve maximum entropy production. This result is in accordance with the analysis performed by L. Onsager,[20,21] and microscopic theories given by M. Kohler,[22] J. M. Ziman[23] and R. I. Dewar.[24] As we have already mentioned this statement is not opposed to the Prigoggine's theorem on the minimum entropy production due to different starting assumptions.

In short, in this paper the algorithm for the construction of the electrical circuit analogue to the enzymatic cycle kinetics, close to the equilibrium, is established. Using the results of the linear network theory we show how one can easily find the parameters relevant for the free energy transduction. Jeans's theorem[14] is used to show that the distribution of fluxes in the system with the fixed ligand concentrations is such that the entropy production is maximal.

Possible further work on this problem includes the extension of this method to non-planar diagrams, to arbitrary chemical processes, as well as inclusion of the non-linear relationship between fluxes and corresponding affinities. The principle of the maximal entropy production needs to be checked in the non-linear regime, too.

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SAŽETAK

Kinetika cikličkih kemijskih reakcija u blizini ravnotežnoga stanja i analogne električne mreže

Paško Županović i Davor Juretić

Hillovim dijagramom može se opisati pretvorba slobodne energije pomoću diskretnih stanja makromolekule koja međudjeluje s malim molekulama (ligandima). U blizini ravnotežnoga stanja, gdje vrijedi linearna ovisnost flukseva o termodinamičkim silama, razvijena je metoda konstrukcije linearne električne mreže koja odgovara Hillovom dijagramu. Rabi se metoda konturnih flukseva pri formiranju opće teorije linearnih mreža. Pomoću Theveninovoga teorema proračunana je efikasnost pretvorbe slobodne energije. Određeni su uvjeti najveće moguće efikasnosti pretvorbe slobodne energije. Na vrlo elegantan način izveden je Jeansov teorem iz 1923. Pokazano je da je ovaj teorem ekvivalentan principu maksimalne produkcije entropije u električnim mrežama. Za stalne koncentracije liganada slijedi, iz Jeansova teorema, da se fluksevi raspodijeljuju tako da produkcija entropije bude najveća moguća. Prigogineov teorem o minimalnoj produkciji entropije uspoređen je s teoremom o maksimalnoj produkciji entropije.