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Steady-state properties of coupled systems in mitochondrial oxidative phosphorylation

(forces/fluxes/linear relations/Onsager relations/efficiency)

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ABSTRACT At steady state there is effective coupling among various otherwise independent membrane and internal mitochondrial systems that share the same substrates or ligands (e.g., H^+, Ca^{2+}, P_i, ADP, ATP). The number of different systems, coupled through shared substrates or ligands, is no doubt very large. But, just as an infinite series can be approximated by a finite number of terms, here the number of systems included in the analysis can be limited, as an approximation. In two previous papers, the basic but oversimplified set of four tightly coupled systems was studied. These are: respiratory chain; reverse ATPase; proton–phosphate cotransport; and ADP–ATP exchange. Essentially as illustrations of the methodology required for a more realistic analysis, two much more complicated examples are formulated here: eight tightly coupled systems, and the original four systems but with the tight coupling relaxed in two of these four.

When several independent systems operate in the same closed vesicular membrane, there is an effective steady-state coupling among the different systems (1–3). This has been studied in some detail (2, 3) in the case of a four-system model (4) for oxidative phosphorylation. Essentially the same basic approach has been applied by van Dam and Westerhoff (5) to a different model of oxidative phosphorylation. Related thermodynamic analyses have been carried out by Caplan and Essig (6) and Stucki (7).

The four-system treatment (2, 3) given earlier is somewhat analogous to the ideal gas law: it contains the essence of the problem [if one accepts this stoichiometry (4)] but omits some real and significant complications, as already pointed out (3). The most important modification, to achieve greater reality in the model, is to increase the number of independent systems beyond four. In the first section below, the earlier treatment (3) is extended to *eight* systems. This is by no means exhaustive but it about reaches the limit of practicable algebra. Tight thermodynamic coupling between subforces and fluxes in each system is still (3) assumed here. Another possible refinement (3) is to relax the tight coupling just referred to. This could apply to any or all of those six (see below) of the eight systems that have two subforces. This possibility is illustrated in the second section below, using the original four systems (2, 3) and relaxing tight coupling in two of these four.

More complicated cases than those treated below, even with many more than eight systems, can easily be formulated. But in general, in such cases, one would have to forgo an explicit algebraic analysis in favor of numerical computer solution of linear algebraic equations in particular examples. The present paper will serve to illustrate the general method that can be applied.

Eight-system model

We use the same notation and general approach as before; hence, a number of details are omitted. The eight systems we consider are (on a per site per 2 e^- basis for system 1):

$$\left.\begin{array}{c} \tfrac{1}{3}[\mathrm{NADH(in)} \\ +\ \mathrm{H^+(in)} + \tfrac{1}{2}\mathrm{O_2(in)} \rightarrow \mathrm{NAD^+(in)} + \mathrm{H_2O}];\ \Delta G \\ \mathrm{4H^+(in)} \rightarrow \mathrm{4H^+(out)};\ -4\Delta\bar{\mu}_{\mathrm{H}} \end{array}\right\} J_1, X_1, \qquad [1]$$

$$\left.\begin{array}{c} \mathrm{H_2PO_4^-(out)} \rightarrow \mathrm{H_2PO_4^-(in)};\ \Delta\bar{\mu}_{\mathrm{P}} \\ \mathrm{H^+(out)} \rightarrow \mathrm{H^+(in)};\ \Delta\bar{\mu}_{\mathrm{H}} \end{array}\right\} J_2, X_2, \qquad [2]$$

$$\left.\begin{array}{c} \mathrm{H_2PO_4^-(in)} + \mathrm{ADP^{3-}(in)} \rightarrow \mathrm{ATP^{4-}(in)} + \mathrm{H_2O};\ \Delta G_{\mathrm{T}}^{(\mathrm{in})} \\ \mathrm{3H^+(out)} \rightarrow \mathrm{3H^+(in)};\ 3\Delta\bar{\mu}_{\mathrm{H}} \end{array}\right\} J_3, X_3, \qquad [3]$$

$$\left.\begin{array}{c} \mathrm{ADP^{3-}(out)} \rightarrow \mathrm{ADP^{3-}(in)};\ \Delta\bar{\mu}_{\mathrm{D}} \\ \mathrm{ATP^{4-}(in)} \rightarrow \mathrm{ATP^{4-}(out)}:\ -\Delta\bar{\mu}_{\mathrm{T}} \end{array}\right\} J_4, X_4, \qquad [4]$$

$$\mathrm{H^+(out)} \rightarrow \mathrm{H^+(in)};\ \Delta\bar{\mu}_{\mathrm{H}} \qquad J_5, X_5, \qquad [5]$$

$$\left.\begin{array}{c} \mathrm{ATP^{4-}(in)} + \mathrm{H_2O} \rightarrow \mathrm{H_2PO_4^-(in)} + \mathrm{ADP^{3-}(in)};\ -\Delta G_{\mathrm{T}}^{(\mathrm{in})} \\ \mathrm{A(in)} \rightarrow \mathrm{B(in)};\ \Delta \end{array}\right\} J_6, X_6, \qquad [6]$$

$$\mathrm{Ca^{2+}(out)} \rightarrow \mathrm{Ca^{2+}(in)};\ \Delta\bar{\mu}_{\mathrm{C}} \qquad J_7, X_7, \qquad [7]$$

and

$$\left.\begin{array}{c} \mathrm{Ca^{2+}(in)} \rightarrow \mathrm{Ca^{2+}(out)};\ -\Delta\bar{\mu}_{\mathrm{C}} \\ \mathrm{2H^+(out)} \rightarrow \mathrm{2H^+(in)};\ 2\Delta\bar{\mu}_{\mathrm{H}} \end{array}\right\} J_8, X_8. \qquad [8]$$

The fluxes J_i represent the number of reaction units per second for the entire mitochondrion, with units as written in Eqs. 1–8. The X_i are the corresponding thermodynamic forces driving the reactions in the directions written; these are the sum of the two (or one, in Eqs. 5 and 7) subforces indicated. The subforces as written are defined, as to sign, by *initial* − *final*. We assume tight coupling (see above) between the two processes in each of Eqs. 1–4, 6, and 8: the flux J_i is the same for the two processes. In the absence of adequate knowledge about the various kinetic mechanisms, we have to fall back on the phenomenological linear relations $J_i = L_i X_i$ for all eight systems, with the L_i assumed known (from kinetic studies on the separate systems). The electrochemical potential differences are (*out* − *in*)

$$\begin{aligned} \Delta\bar{\mu}_{\mathrm{H}} &= RT\ \ln(c_{\mathrm{HO}}/c_{\mathrm{H}}) - \epsilon\psi \\ \Delta\bar{\mu}_{\mathrm{D}} &= RT\ \ln(c_{\mathrm{DO}}/c_{\mathrm{D}}) + 3\epsilon\psi, \end{aligned} \qquad [9]$$

etc., depending on the charge on the ion, where O means "out," $\psi = \psi_{\mathrm{in}} - \psi_{\mathrm{out}}$ is the (negative) membrane potential, and ϵ is the charge on a proton.

The first four systems, above, have already been discussed

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(2, 3). System 5 is a proton leak (3). System 6 is the only non-membrane system. It represents in a formal and composite way the use of ATP *inside* the mitochondrion to drive various ATP-dependent activities (schematically, A → B in Eq. **6**). Thus, if there are various ATP-driven processes j, with total ATP flux

$$J_6 = \sum_j L_{6j}(-\Delta G_{\mathrm{T}}^{(\mathrm{in})} + \Delta_j),$$

and if we define

$$L_6 \equiv \sum_j L_{6j} \text{ and } \Delta \equiv \left(\sum_j L_{6j}\Delta_j\right) \Big/ \sum_j L_{6j},$$

then

$$J_6 = L_6(-\Delta G_{\mathrm{T}}^{(\mathrm{in})} + \Delta) = L_6 X_6,$$

corresponding to Eq. **6**. Δ (negative), in Eq. **6**, is smaller in magnitude than $-\Delta G_{\mathrm{T}}^{(\mathrm{in})}$ (positive), so that $X_6 > 0$. The formal nature of the two Ca^{2+} transport systems is obvious from Eqs. **7** and **8**.

The independent phenomenological forces we use are ΔG ("ox"), $\Delta G_{\mathrm{T}}^{(\mathrm{out})}$ ("phos"), and Δ, where (3)

$$\Delta G_{\mathrm{T}}^{(\mathrm{out})} = \Delta G_{\mathrm{T}}^{(\mathrm{in})} + \Delta\bar{\mu}_{\mathrm{P}} + \Delta\bar{\mu}_{\mathrm{D}} - \Delta\bar{\mu}_{\mathrm{T}} \qquad [10]$$

refers to external ATP synthesis. Usually ΔG is positive while $\Delta G_{\mathrm{T}}^{(\mathrm{out})}$ and Δ are negative. The various $\Delta\bar{\mu}$s are considered unknowns whose values depend on the unknown *inside* concentrations of the corresponding ions, as adjusted to achieve an overall steady state among the eight systems (1–3). The outside concentrations and ψ are assumed to be known.

At steady state, there will be zero net change in the interior concentrations:

$$\begin{aligned}
&\mathrm{H}^+: && -4J_1 + J_2 + 3J_3 + J_5 + 2J_8 = 0 && [11]\\
&\mathrm{H_2PO_4^-}: && J_2 - J_3 + J_6 = 0 && [12]\\
&\mathrm{ADP}^{3-}: && J_4 - J_3 + J_6 = 0 && [13]\\
&\mathrm{ATP}^{4-}: && J_3 - J_4 - J_6 = 0 && [14]\\
&\mathrm{Ca}^{2+}: && J_7 - J_8 = 0. && [15]
\end{aligned}$$

These relations follow from Eqs. **1–8** and "couple" the eight systems together at steady state. Eqs. **13** and **14** are equivalent; Eqs. **12** and **13** give $J_2 = J_4$. There are then four independent equations: Eqs. **11**, **12**, **15**, and $J_2 = J_4$. These four equations are now rewritten by (*i*) substituting L_iX_i for each J_i; (*ii*) replacing each X_i by the sum of subforces given in Eqs. **1–8**; and (*iii*) replacing $\Delta G_{\mathrm{T}}^{(\mathrm{in})}$ by $\Delta G_{\mathrm{T}}^{(\mathrm{out})}$, using Eq. **10**. We then have four linear algebraic equations in the four unknowns $\Delta\bar{\mu}_{\mathrm{H}}$, $\Delta\bar{\mu}_{\mathrm{P}}$, $\Delta\bar{\mu}_{\mathrm{D}} - \Delta\bar{\mu}_{\mathrm{T}}$, and $\Delta\bar{\mu}_{\mathrm{C}}$. On solving these equations, each unknown can be expressed as a linear form in the three phenomenological forces ΔG, $\Delta G_{\mathrm{T}}^{(\mathrm{out})}$, and Δ. On substituting these expressions for the X_i (subforce sum) in $J_i = L_iX_i$, the various fluxes can be written in the same way. In particular, those fluxes conjugate to the phenomenological forces—namely, J_1("ox"), J_4("phos") (recall $J_2 = J_4$), and J_6—are found to exhibit Onsager reciprocal relations, as expected.

The explicit expressions for the $\Delta\bar{\mu}$s, found in the above way, are:

$$\begin{aligned}
D\Delta\bar{\mu}_{\mathrm{H}}/&(L_7 + L_8)\\
&= 4L_1[L_2L_3L_4L_{\mathrm{P}}^{-1} + L_6(L_2 + L_4)]\Delta G\\
&\quad - L_2L_4(4L_3 + L_6)\Delta G_{\mathrm{T}}^{(\mathrm{out})}\\
&\quad + L_6[L_2L_4 - 3L_3(L_2 + L_4)]\Delta, \qquad [16]
\end{aligned}$$

$$\begin{aligned}
D\Delta\bar{\mu}_{\mathrm{P}} = {}& 4L_1(L_7 + L_8)(4L_3L_4 - L_2L_3L_4L_{\mathrm{P}}^{-1} - L_2L_6)\Delta G\\
&+ L_4\{(L_7 + L_8)[L_6(16L_1 + L_2 + 9L_3 + L_5)\\
&+ L_3(16L_1 + 4L_2 + L_5)]\\
&+ 4L_7L_8(L_3 + L_6)\}\Delta G_{\mathrm{T}}^{(\mathrm{out})}\\
&- L_6\{(L_7 + L_8)[L_4(16L_1\\
&+ L_2 + 9L_3 + L_5) - 3L_2L_3]\\
&+ 4L_4L_7L_8\}\Delta, \qquad [17]
\end{aligned}$$

and

$$\begin{aligned}
D(\Delta\bar{\mu}_{\mathrm{D}} - \Delta\bar{\mu}_{\mathrm{T}}) = {}& 4L_1L_2(L_7 + L_8)(4L_3 + L_6)\Delta G\\
&+ L_2\{(L_7 + L_8)[L_3(16L_1 + L_5 + 9L_6)\\
&+ L_6(16L_1 + L_5)] + 4L_7L_8(L_3 + L_6)\}\\
&\times \Delta G_{\mathrm{T}}^{(\mathrm{out})} - L_2L_6[(L_7 + L_8)(16L_1\\
&+ 12L_3 + L_5) + 4L_7L_8]\Delta \qquad [18]
\end{aligned}$$

$$\Delta\bar{\mu}_{\mathrm{C}} = 2L_8\Delta\bar{\mu}_{\mathrm{H}}/(L_7 + L_8), \qquad [19]$$

where

$$\begin{aligned}
D \equiv {}& (L_7 + L_8)[16L_1L_2L_3L_4L^{-1} + L_2L_3L_4L_5L_{\mathrm{P}}^{-1}\\
&+ L_6(L_2 + L_4)(16L_1 + 9L_3 + L_5) + L_2L_4L_6]\\
&+ 4L_7L_8[L_2L_3L_4L_{\mathrm{P}}^{-1} + L_6(L_2 + L_4)] \qquad [20]
\end{aligned}$$

and

$$L_{\mathrm{P}}^{-1} \equiv L_2^{-1} + L_3^{-1} + L_4^{-1}, L^{-1} \equiv L_1^{-1} + L_{\mathrm{P}}^{-1}. \qquad [21]$$

The flux expressions, referred to above, are

$$DJ_1 = L_{11}\Delta G + L_{14}\Delta G_{\mathrm{T}}^{(\mathrm{out})} + L_{16}\Delta, \qquad [22]$$

$$DJ_4 = L_{14}\Delta G + L_{44}\Delta G_{\mathrm{T}}^{(\mathrm{out})} + L_{46}\Delta, \qquad [23]$$

and

$$DJ_6 = L_{16}\Delta G + L_{46}\Delta G_{\mathrm{T}}^{(\mathrm{out})} + L_{66}\Delta, \qquad [24]$$

with

$$\begin{aligned}
L_{11} = {}& L_1(L_7 + L_8)\{16L_2L_3L_4 + L_2L_3L_4L_5L_{\mathrm{P}}^{-1}\\
&+ L_6[(L_2 + L_4)(9L_3 + L_5) + L_2L_4]\}\\
&+ 4L_1L_7L_8[L_2L_3L_4L_{\mathrm{P}}^{-1} + L_6(L_2 + L_4)], \qquad [25]
\end{aligned}$$

$$L_{14} = 4L_1L_2L_4(L_7 + L_8)(4L_3 + L_6), \qquad [26]$$

$$L_{16} = 4L_1L_6(L_7 + L_8)(-L_2L_4 + 3L_3L_4 + 3L_2L_3), \qquad [27]$$

$$\begin{aligned}
L_{44} = {}& L_2L_4\{(L_7 + L_8)[L_3(16L_1 + L_5) + L_6(16L_1\\
&+ 9L_3 + L_5)] + 4L_7L_8(L_3 + L_6)\}, \qquad [28]
\end{aligned}$$

$$L_{46} = -L_2L_4L_6[(L_7 + L_8)(16L_1 + 12L_3 + L_5) + 4L_7L_8], \qquad [29]$$

and

$$\begin{aligned}
L_{66} = {}& L_2L_3L_4L_6[(L_7 + L_8)(16L_1L^{-1} + L_5L_{\mathrm{P}}^{-1})\\
&+ 4L_7L_8L_{\mathrm{P}}^{-1}]. \qquad [30]
\end{aligned}$$

The rate of free energy dissipation is

$$\sum_{i=1}^{8} J_iX_i = J_1\Delta G + J_4\Delta G_{\mathrm{T}}^{(\mathrm{out})} + J_6\Delta > 0. \qquad [31]$$

The efficiency of synthesis of external ATP from the free energy expended by the respiratory chain is

$$\eta = J_4(-\Delta G_{\mathrm{T}}^{(\mathrm{out})})/J_1\Delta G. \qquad [32]$$

The conventional P/O ratio is $3J_4/J_1$. If we consider that (5, 7) state 4 corresponds to adjusting the value of $\Delta G_{\mathrm{T}}^{(\mathrm{out})}$ so that $J_4 = 0$, then Eq. **23** with $J_4 = 0$ allows us to express the state 4 $\Delta G_{\mathrm{T}}^{(\mathrm{out})}$ in terms of ΔG and Δ. If this expression is then substituted for $\Delta G_{\mathrm{T}}^{(\mathrm{out})}$ in Eqs. **22** and **24**, we obtain the state 4 J_1 and

J_6 in terms of ΔG and Δ. The above definition of state 4 ($J_4 = 0$) could not be used in ref. 3 because there $J_4 = 0$ only at equilibrium. All of the operations described in this paragraph can be carried out explicitly, but the algebra is tedious. A special case (systems 6, 7, and 8 absent) is discussed in *Appendix 1* of ref. 3.

It should be noted in Eq. **1** that ΔG depends on $c_H(\text{in})$. In numerical calculations (3), it is appropriate to start with ΔG_{out} rather than ΔG, where ΔG_{out} is defined as ΔG with c_H replaced by c_{HO}. Thus,

$$\Delta G = \Delta G_{\text{out}} - (1/3)\Delta\bar{\mu}_H - (1/3)\epsilon\psi. \qquad [33]$$

It we use Eq. **16** to eliminate $\Delta\bar{\mu}_H$ here, we have an explicit equation that gives ΔG in terms of ΔG_{out}, $\Delta G_T^{(\text{out})}$, Δ, and $\epsilon\psi$.

Relaxation of tight coupling: An example

Six of the eight systems above have two subforces and fluxes, but tight coupling of each pair has been assumed. This assumption can be avoided without any difficulty, in principle, but the linear equations encountered would have to be handled numerically.

To illustrate what is involved here, we confine the following discussion to systems 1 through 4, above, with tight coupling relaxed in systems 1 (respiratory chain) and 3 (ATP synthesis). Thus the linear flux-force relations we start with are (with obvious new notation)

$$1: \quad J_e = L_{ee}\Delta G + L_{eH}(-4\Delta\bar{\mu}_H) \qquad [34]$$

$$J_H^{(e)} = L_{eH}\Delta G + L_{HH}^{(e)}(-4\Delta\bar{\mu}_H), \qquad [35]$$

$$2: \quad J_2 = L_2(\Delta\bar{\mu}_P + \Delta\bar{\mu}_H), \qquad [36]$$

$$3: \quad J_S = L_{SS}\Delta G_T^{(\text{in})} + L_{SH}(3\Delta\bar{\mu}_H) \qquad [37]$$

$$J_H^{(S)} = L_{SH}\Delta G_T^{(\text{in})} + L_{HH}^{(S)}(3\Delta\bar{\mu}_H), \qquad [38]$$

and

$$4: \quad J_4 = L_4(\Delta\bar{\mu}_D - \Delta\bar{\mu}_T), \qquad [39]$$

where e refers to "electrons" and S to "synthesis." Corresponding to Eqs. **11–15**, we have here

$$H^+: \quad -4J_H^{(e)} + J_2 + 3J_H^{(S)} = 0, \qquad [40]$$

$$H_2PO_4^-: \quad J_2 - J_S = 0, \qquad [41]$$

$$ADP^{3-}: \quad -J_S + J_4 = 0, \qquad [42]$$

and

$$ATP^{4-}: \quad J_S - J_4 = 0. \qquad [43]$$

These steady-state relations couple the four systems together. Note, however, that J_e does not appear in Eqs. **40–43**. If we replace $\Delta G_T^{(\text{in})}$ with $\Delta G_T^{(\text{out})}$ in Eqs. **37** and **38**, using Eq. **10**, we then have four linear equations (Eq. **34**, Eq. **40**, $J_2 = J_S$, $J_2 = J_4$) in four unknowns (J_e, $\Delta\bar{\mu}_H$, $\Delta\bar{\mu}_P$, $\Delta\bar{\mu}_D - \Delta\bar{\mu}_T$). The phenomenological forces and fluxes are ΔG, $\Delta G_T^{(\text{out})}$, J_e, and J_S (= $J_2 = J_4$). On solving these linear equations we find

$$\begin{aligned} D\Delta\bar{\mu}_H = {} & 4L_{eH}(L_2L_4 + L_2L_{SS} + L_4L_{SS})\Delta G \\ & - L_2L_4(L_{SS} + 3L_{SH})\Delta G_T^{(\text{out})}, \end{aligned} \qquad [44]$$

$$\begin{aligned} D\Delta\bar{\mu}_P = {} & 4L_{eH}(3L_4L_{SH} - L_2L_4 - L_2L_{SS})\Delta G \\ & + L_4[-9L_{SH}^2 + 3L_2L_{SH} + L_{SS}(L_2 + 9L_{HH}^{(S)} \\ & + 16L_{HH}^{(e)})]\Delta G_T^{(\text{out})}, \end{aligned} \qquad [45]$$

$$\begin{aligned} D(\Delta\bar{\mu}_D - \Delta\bar{\mu}_T) = {} & 4L_2L_{eH}(L_{SS} + 3L_{SH})\Delta G \\ & + L_2[-9L_{SH}^2 + L_{SS}(9L_{HH}^{(S)} \\ & + 16L_{HH}^{(e)})]\Delta G_T^{(\text{out})} \end{aligned} \qquad [46]$$

$$\begin{aligned} DJ_e = {} & [DL_{ee} - 16L_{eH}^2(L_2L_4 + L_2L_{SS} + L_4L_{SS})]\Delta G \\ & + 4L_2L_4L_{eH}(L_{SS} + 3L_{SH})\Delta G_T^{(\text{out})}, \end{aligned} \qquad [47]$$

and

$$\begin{aligned} DJ_S = {} & 4L_2L_4L_{eH}(L_{SS} + 3L_{SH})\Delta G \\ & + L_2L_4[L_{SS}(9L_{HH}^{(S)} + 16L_{HH}^{(e)}) - 9L_{SH}^2]\Delta G_T^{(\text{out})}, \end{aligned} \qquad [48]$$

where

$$\begin{aligned} D = {} & 3L_{SH}(-3L_2L_{SH} + 2L_2L_4 - 3L_4L_{SH}) + L_2L_4L_{SS} \\ & + (9L_{HH}^{(S)} + 16L_{HH}^{(e)})(L_2L_4 + L_2L_{SS} + L_4L_{SS}). \end{aligned} \qquad [49]$$

Note the expected Onsager reciprocal relation in Eqs. **47** and **48**.

The rate of free energy dissipation is

$$J_e\Delta G + J_S\Delta G_T^{(\text{out})}. \qquad [50]$$

The efficiency of ATP synthesis is

$$\eta = J_S(-\Delta G_T^{(\text{out})})/J_e\Delta G, \qquad [51]$$

and the P/O ratio is $3J_S/J_e$. If $\Delta G_T^{(\text{out})}$ is considered adjusted to give $J_S = 0$ in Eq. **48** (state 4), the resulting expression for $\Delta G_T^{(\text{out})}$, in terms of ΔG, may be substituted into Eq. **47** to give the state 4 J_e, which is proportional to ΔG.

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