

# Finite time thermodynamic coupling in a biochemical network

Anjan Kr Dasgupta

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**Abstract** The paper describes some thermodynamic constraints and relations in biochemical or metabolic network and provides a basis for entropy enthalpy compensation. Conventional definition of macroscopic forces and fluxes leads to a paradox namely, non-existence of positive efficiency of a chemically driven process. This paradox is resolved by deriving an appropriate definition of macroscopic force using the local balance equations. Entropy enthalpy compensation, whose thermodynamic basis is so far unclear, also follows. The method provides an account of how reactive pathways are coupled, the strength of coupling between a pathway pair depending on the product of their respective enthalpies. The obligatory role of the presence of a common chemical intermediate in defining coupling becomes unnecessary; such intermediate-free coupling being a key feature of metabolic energy transduction. The redefined flux and force can also be exploited to explain surface to volume ratio dependence of coupled networks. Lastly, the thermodynamic rationale for the Bergman's eco-geographic rule, namely the reduced ability of larger animals to avoid stress follows from the generalized expression for coupling coefficients. Higher surface to volume ratio is shown to make the organism resistant to external perturbations.

**Keywords** Thermodynamic coupling · Entropy enthalpy compensation · Bergman eco-geographic rule

## Introduction

The formulation of large scale biological networks (Jeong et al. 2000) demands proper thermodynamic foundations. A

key feature that describes such network is the concept of thermodynamic coupling. One key concept that has remained obscure in this context is the appropriate definition of thermodynamic coupling (Hill 1977; Kedem and Caplan 1965; Oster et al. 1973; Boudart 1983).

A pair of coupled reactions bears the intuitive meaning that one of them drives its coupled partner. Opposite signs of free energy for such a couple is often considered to be the necessary condition for coupling (Leninger et al. 1993). The dependence of sign of free energy on reactant(s) and product(s) concentration however makes this definition over simplistic. The coupling may be kinetically defined by the law of mass action. A kinetically coupled reaction pair has common intermediate (chemical species). While this kinetic nomenclature for coupling has a broad range of validity, it fails to interpret coupling reactions in absence of common intermediates this being a fundamental attribute of all forms of chemiosmotic controls (Prebble 2002). There is however a general approach based on near equilibrium thermodynamics that permits an explicit definition of thermodynamic coupling.

A near equilibrium coupled chemical system can be described by the dissipation equation expressed in terms of flux (J) and force (X). The expression for the internal entropy ( $S_i$ ) production at temperature  $T$  is given by (Katchalsky and Curran 1975),

$$T \cdot dS_i/dt = \sum J_\rho \cdot X_\rho \geq 0 \text{ (by second law).} \quad (1)$$

The reaction network may be described by two indices  $\rho$  ( $\rho = 1, 2, \dots, r$ ) and ( $i = 1, 2, \dots, n$ ), the concentration of the  $i$ th component being  $c_i$ , and  $v_i\rho$  being the stoichiometry coefficient for  $i$ th component participating in the  $\rho$ th reaction. The macroscopic fluxes and forces can be expressed in more familiar thermodynamic format in terms of reaction velocity  $v_\rho$  (i.e.  $v_{\rho+} - v_{\rho-}$ ) and free energy  $\Delta G_\rho$  of the  $\rho$ th reaction,

A. K. Dasgupta (✉)  
Department of Biochemistry, University of Calcutta, Calcutta,  
India  
e-mail: adgcal@gmail.com; adbic@caluniv.ac.in

$$J_\rho = v_\rho = v_{\rho+} - v_{\rho-} \quad (2)$$

$$X_\rho = -\Delta G_\rho = RT \log(v_{+\rho}/v_{-\rho}) = -\sum_i \mu_i \nu_i \rho. \quad (3)$$

The expression for the chemical potential  $\mu_i$  for the  $i$ th chemical species ( $i = 1, 2, \dots, n$ ) is,

$$\mu_i = \mu_{oi} + RT \ln c_i \quad (4)$$

and the kinetic equation expressing the time evolution of the  $i$ th process being,

$$dc_i/dt = \sum_\rho \nu_{i\rho} \cdot v_\rho. \quad (5)$$

It follows from Eqs. (2) and (3) that for each  $\rho$ , the expression  $X_\rho J_\rho$  is positive as  $(v_{+\rho} - v_{-\rho}) RT \log(v_{+\rho}/v_{-\rho})$  is positive for each  $\rho$  independent of whether  $\Delta G_\rho < 0$  or  $\Delta G_\rho > 0$ . Thus for a coupling pair of reactions with ( $\rho = p, q$ ) it is impossible to have opposite signs for  $J_p \cdot X_p$  and  $J_q \cdot X_q$ . The paradox of coupling is thus expressible as,

$$J_\rho \cdot X_\rho \geq 0 \quad (6)$$

for each  $\rho$  ( $\rho = 1, 2, \dots, r$ ) in a biochemical or chemical reaction network described by  $r$  reactions and  $n$  components. Interestingly, many recent publications e.g. considers this instead of Eq. (1) as a consequence of second law. The coupling of thermodynamically coupled processes as defined recently in context of finite time thermodynamics becomes meaningless if the efficiency of such an engine is negative, the efficiency being expressible by ratio— $J_p \cdot X_p / J_q \cdot X_q$ , where the  $p$ -th process is driven by  $q$ -th process.

### Onsager approach to a biochemical network

There are some important evidences for validity of linear flux force relations (Rousseau and Schymkowitz 2005) in chemical systems and particularly so when they have coupled behavior that leads to energy transduction. The paradox in Eq. (6) becomes further evident if we go to the close to equilibrium domain and use the Onsager approach (Onsager 1931). Interestingly this approach has recently been revisited in context of finite time thermodynamics (Boudart 1983; Izumida and Okuda 2009). Onsager introduced a symbolic approach to linear thermodynamics through his famous phenomenological equations. According to this approach the fluxes and forces are related to each other by the matrix equation,

$$J_i = \sum L_{ij} X_j \quad (7)$$

The reciprocal equation also exists as  $L$ , by second law is a positive definite matrix, the symmetry of  $L$  being ensured by the famous Onsager equation  $L = L^T$ . Near equilibrium the forces and fluxes can be subjected to linearity approximation as their respective value approaches zero.

In a pure chemical system the force can thus be further approximated to the form (Hill 1977),

$$X_\rho = RT \ln(1 + v_\rho / (v_{\rho-})) \approx (RT) / (v_{\rho-}) \cdot J_\rho. \quad (8)$$

Equation (8) follows from  $\ln(1 + x) \sim x$  and in this case  $x$  being  $v_\rho / v_{\rho-}$  the term  $v_{\rho-}$ , actually representing equilibrium value of reverse (or forward) reaction  $v_{\rho-}$ . An important implication of Eq. (8) is that the Onsager matrix for any arbitrary biochemical network is diagonal.

$$L_{ij} = L_i \cdot \delta_{ij} \quad (9)$$

In Eq. (9)  $\delta_{ij}$  is a identity matrix implying non-existence of off-diagonal elements of  $L$ . This further highlights the limitations of the existing thermodynamic description of biochemical or even metabolic networks, where the absence of coupling between metabolic fluxes is an impossible condition. The falsification of Eq. (9) has been clearly demonstrated in a number of biochemical networks, e.g. oxidative phosphorylation, though in many of the theoretical approaches assumed therein, the diagonal nature of the Onsager matrix was ignored, even though free energy term was used as driving forces (Caplan and Essig 1969).

We may note that we have not included cyclic reactions in (9), the presence of cyclic reactions would lead to some pseudo cross coupling terms as a result of constraints imposed by mass action. It may also be intriguing to point out that Onsager in his famous paper on reciprocal relation had to cite the example of cyclic reaction  $A = B, B = C, C = A$ , without which he could not find example of coupling in chemical reactions. The coupling in Onsager approach is between the reduced flux descriptions and not by actual fluxes and forces, and similar definitions of stoichiometric networks depending on presence of reaction cycles, with dependent kinetic coefficients in which coupling had to be forcefully introduced have cited frequently in literature (Qian and Beard 2005; Qian et al. 2003).

### Introducing the enthalpy production

In most of the standard texts the local balance equations (Katchalsky and Curran 1975) can be expressed in terms of local heat flow rate  $qv$ , internal entropy production  $\sigma$ , entropy flux  $J_s$  and the flux of chemical species  $J_i$ .

$$\delta q_v / \delta t = -\nabla \cdot J_q \quad (10)$$

The definition of internal entropy production follows from the other balance equations

$$\delta s_v / \delta t = -\nabla \cdot J_s + \sigma \quad (11)$$

$$\delta c_i / \delta t = -\nabla \cdot J_i + \sum_\rho \nu_{i\rho} \cdot v_\rho. \quad (12)$$

The local Gibbs equation further demands that

$$\delta q_v / \delta t = T \delta s_v / \delta t + \sum_i \mu_i \delta c_i / \delta t \quad (13)$$

Equations (10–12) can substituted in Gibbs equation (13) and by comparing the divergent and non-divergent terms we obtain the expression for internal entropy production  $\sigma$  as given by,

$$\sigma = J_q \cdot \nabla(1/T) - \sum_i J_i \cdot \nabla(\mu_i/T) - \sum_{i\rho} v_{i\rho} \mu_i \cdot v_\rho / T \quad (14)$$

From Eqs. (3) and (14) it follows that the entropy production is,

$$\sigma = J_q \cdot \nabla(1/T) - \sum_i J_i \cdot \nabla(\mu_i/T) - \sum_\rho (\Delta G_\rho v_\rho) / (T) \quad (15)$$

The successive terms in the RHS of Eq. (15) contribute to the entropy production by heat flow, diffusion flow and the chemical reaction and serves as a more detailed form of Eq. (1).

The third term retains the standard definition of chemical force and flux as defined earlier in Eqs. (2) and (3). The paradox thus reappears.

However, a close look into the balance equation for heat flow (Eq. 10) reveals that source production of heat that is inevitable in a reaction network is omitted. Such source term will originate from the enthalpy  $\Delta H_\rho$ . If we include the same, in Eq. (10) we get,

$$\delta q_v / \delta t = -\nabla \cdot J_q + \sum \Delta H_\rho v_\rho \quad (16)$$

Using Eqs. (11)–(13) and (16) we obtain that,

$$\sigma = J_q \cdot \nabla(1/T) - \sum_i J_i \cdot \nabla(\mu_i/T) + \sum_\rho \Delta S_\rho v_\rho \quad (17)$$

where, we have assumed that,

$$\Delta G_\rho = \Delta H_\rho - T \cdot \Delta S_\rho \quad (18)$$

The Eq. (17) thus provides us a new definition of the driving force for a chemical reaction (Jeong et al. 2000) in a reaction network. Instead of the definition given by the Eq. (3) the chemical force is redefined by the entropy term ( $T\Delta S_\rho$ ) and the rate of change of internal entropy expressed in Eq. (1) is given by,

$$dS_i / dt(\text{chemical}) = \sum_\rho \Delta S_\rho \cdot \Delta v_\rho \quad (19)$$

If we further assume that the entropy supply is constant, then internal entropy production can be equated with the total entropy production. The Eq. (19) then has a simple meaning, namely total entropy change is inner product of the individual entropy changes and reaction velocities.

The inequality imposed in Eq. (6) that led to the stated paradox, is no more relevant as  $J_\rho \cdot X_\rho$  now can have both positive and negative signs. Using the earlier argument we can state that the coupling between reactions (in the sense that one drives the other) can be conceived as the internal entropy contributions from individual reactions can have

opposite signs. Similarly a positive efficiency of a chemical engine (Oster et al. 1973) consisting of a coupling pair of reaction ‘1’ and ‘2’ becomes definable:

$$\eta = -J_2 \cdot X_2 / J_1 \cdot X_1 \quad (20)$$

Equation (20) is particularly relevant as, the engine like work performance of biochemical network is well known and it is meaning to have a positive efficiency for such an engine (Stucki 1980; Stucki et al. 1983).

### A new insight towards enthalpy entropy compensation

Entropy enthalpy compensation has been widely observed in different systems (Prebble 2002; Agutter and Wheatley 2004; Nielsen and Jensen 1990; Rottenberg 1979; Izumida and Okuda 2008). A close inspection reveals that till this date there has not been any satisfactory thermodynamic theory that explains this compensation.

The new definition of the thermodynamic force (see Eq. 19) is expressed by  $T\Delta S_\rho$  rather than by  $\Delta G_\rho$ :

$$v_\rho = \sum l_{\rho\rho'} T \Delta S_{\rho'} \quad (21)$$

A careful inspection of Eq. (8) reveals that while the force definition has changed the simple proportionality between  $\Delta G_\rho$  and  $\Delta v_\rho$  is maintained in close to equilibrium systems. Rewriting the equation without invoking the macroscopic force term,

$$v_\rho = -\left(v_\rho^-\right) / RT \cdot \Delta G_\rho. \quad (22)$$

Equations (18) (21) and (22) provides a linear relation:

$$\Delta H_\rho = \sum \varepsilon_{\rho\rho'} \Delta S_{\rho'} \quad (23)$$

In Eq. (23) the interaction term  $\varepsilon$  is given by,

$$\varepsilon_{\rho\rho'} = T(\delta_{\rho\rho'} - RT \cdot l_{\rho\rho'} / v_\rho^-) \quad (24)$$

The enthalpy of a coupled reaction network is thus driven by linear relation expressed by the coefficient  $\varepsilon$  in Eq. (23). If we assume no coupling condition the slope of the enthalpy entropy graph is given by  $1 - RTl_{\rho\rho'} / v_\rho^-$ , a quantitative is which is always <1 (but can assume positive or negative value) as second law demands that the diagonal term of Onsager coefficients must be positive. It is further noted the sign of  $\varepsilon_{\rho\rho'}$  is critically dependent on temperature and a pair of driving and driven reaction may become parallel coupled reactions, or mutually inhibiting reactions as T is varied. The close relation between entropy enthalpy compensation and coupling of reaction steps is also an intrinsic feature of the Eq. (24). It predicts that in a coupled network the entropy of one reaction is actually determined by enthalpies of several other coupled reactions, the extent of compensation being critically dependent on the coupling strength between reactions.

Equation (24) also throws an important insight in the eco-geographic principle known as Bergman rule. Bergmann's rule implies that within a broadly distributed taxonomic clade, populations and species of larger size are found in colder environments, and species of smaller size are found in warmer regions. If we read this eco-geographic principle of reduced ability to avoid stress for larger animals, we immediately find that characteristic entropy enthalpy compensation operative in the respective taxonomic clades may unfold the thermodynamic basis of the approximately validated principle (Hill 1977).

### A metric for coupling coefficients

A thermal steady state in which the LHS of Eq. (16) is leads to,

$$\nabla \cdot J_q = \Sigma \Delta H_\rho v_\rho \quad (25)$$

If we consider the integral  $\int_V \nabla \cdot J_q dv = \int_S J_q \cdot ds$ , assuming further that the surface flux of heat over a hypothetical surface element  $S$  remains constant we can rewrite the Eq. (25) further. The simplified expression is given by,

$$J_q = (V/S) \cdot \Sigma_\rho \Delta H_\rho v_\rho \quad (26)$$

where the LHS is the surface average of the heat flux and the RHS is the volume averaged enthalpy production. Within the range of validity of this uniformity approximation in the surface  $S$  enclosing volume  $V$ , we can further consider a reciprocal of the flux force relation in which the forces are expressed as linear function of fluxes. This is acceptable due to the positive definite nature of the Onsager matrix. This reciprocal relation can be expressed in a mesoscopic system by the relation,

$$\Delta(1/T) = R_q \cdot J_q + \Sigma_i R_{qi} \cdot J_i + \Sigma_{\rho'} R_{q\rho'} v_{\rho'} \quad (27)$$

$$\Delta(\mu_i/T) = R_{qi} \cdot J_q + \Sigma_j R_{ij} \cdot J_j \quad (28)$$

$$\Delta S_\rho = R_{q\rho} J_q + \Sigma R_{\rho\rho'} v_{\rho'} \quad (29)$$

In equation we have ruled out the direct coupling between the chemical and diffusional fluxes as by Curie principle direct coupling between such fluxes can be ruled out. The Eqs. (27)–(29) expresses the general conditions for thermogenesis and it can be also shown that if we combine Eqs. (26) and (29) we obtain,

$$\Delta S_\rho = \Sigma r_{\rho\rho'} v_{\rho'} \quad (30)$$

where, the coupling coefficient  $r$  assumes the form,

$$r_{\rho\rho'} = R_{\rho\rho'} + (V)/(S) \cdot R_{q\rho} \Delta H_{\rho'} \quad (31)$$

The Onsager symmetry demands that,  $r_{\rho\rho'} = r_{\rho'\rho}$  and this leads to a symmetry relation,

$$R_{q\rho} \Delta H_\rho = R_{q\rho'} \Delta H_{\rho'} \quad (32)$$

The symmetry in Eq. (32) however demands that,

$$R_{q\rho} = \alpha \cdot \Delta H_\rho \quad (33)$$

where  $\alpha$  is a constant. Substituting Eq. (33) in (31) we obtain,

$$r_{\rho\rho'} = R_{\rho\rho'} + \alpha/(S/V) \cdot \Delta H_\rho \Delta H_{\rho'} \quad (34)$$

Equation (34) expresses a simple way of evaluating or computing coupling strength between reactions from their respective enthalpies. Like the analysis in the work of Izumida and Okuda (2009) the cross diagonal elements of the Onsager matrix is related to surface volume ratio. None of the available metabolic network approaches emphasize the importance of surface volume ratio in dictating the metabolic coupling. This however follows automatically from the analysis described above.

The significance of Eq. (34) is that even if there is no direct coupling between the reactions (i.e.  $R_{\rho\rho'} = 0$  for different reactions) still there will be a steady state coupling that is proportional to the enthalpies  $\Delta H_\rho \Delta H_{\rho'}$ . As it is possible to predict (Kedem and Caplan 1965) entropy and free energy from basic molecular dynamic principles the estimation of such coupling is computable. The argument can be extended to metabolic networks once coupling strength between elementary reaction pair is known.

The variation of surface to volume ratio among animal and plant kingdom is also known for another reason (Nielsen and Jensen 1990; Agutter and Wheatley 2004). In many cases one finds scaling relations between metabolic rates and surface to volume ratio. It is tempting to speculate the origin of such scaling relation originates from the stated thermodynamic coupling.

We once more refer to the Bergman rule whose validity was critically dependent on the size of the species concerned. There seems to be a tendency for larger-bodied animals to conform more closely than smaller-bodied animals, at least up to certain latitudes, perhaps reflecting a reduced ability to avoid stressful environments by burrowing or other means. As the surface to volume ratio is smaller the enthalpy product term is likely to dominate in determining the coupling term between enthalpy and entropy. If we describe larger and smaller species in terms of metabolic network bounded by larger or smaller volume to surface ratio, we can see that in the former case the entropy enthalpy compensation will be dictated (in Eqs. (24) and (34)  $r = L - 1$ ) primarily by the enthalpy products of the individual reactions steps and any perturbation by environment is likely to cause large shift in coupling profile in such reactions. Such variations would be however significant if the length scale of the organism in question varies significantly.

## Conclusion

The paper starting from a general thermodynamic framework provides a basis of coupling, for which satisfactory quantitative description was absent in literature. Two important inferences that follow are:

1. Enthalpy entropy compensation experimentally validated, but having any thermodynamic basis, follow from simple linear thermodynamic law.
2. The entropy enthalpy compensation is closely related to the thermodynamic coupling. This implies that extent of this experimentally validated compensation is not the property of an individual reaction, but that of a network.
3. The coupling coefficients are expressible in terms of enthalpy product of the coupling states. This property is likely to be manifested in systems showing typical surface volume relations and may have eco-geographic implications and may have implications in complex interaction network.
4. The basis of association between pathways may be derivable on the basis of thermodynamic parameters of the individual steps. A reaction pair with opposite changes in enthalpy is thus likely to tightly couple with each other as in such cases one of the pairing partners becomes 'driving' and another becomes 'driven'.

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