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Network Thermodynamic Modelling of Chemical Reactions

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The network thermodynamic formalism has been applied to chemical reactions to obtain the equations for steady state reaction velocities. The rate equations thus obtained have been shown to match those based on chemical kinetic considerations. The examples chosen are: (i) a unimolecular reaction of the type A = B + C; and (ii) enzyme-catalysed reactions. The three cases of enzyme inhibition, viz. non-competitive, competitive and uncompetitive have also been discussed.

Network thermodynamic formalism, developed by Oster *et al.*[1,2], in which classical and irreversible thermodynamics are combined with modern network theory, is a notable recent development. A recent monograph by Schnakenberg[3] gives a concise account of the application of network thermodynamics in the analysis of biological systems. Although network thermodynamics is a valuable tool for the study of chemical, biochemical and biophysical systems it has not received the attention it deserves. Even in chemical reaction systems where it can be fruitfully utilised, not many attempts have been made. Recently Yashonath[4] and Srivastava and coworkers[5] using this formalism, obtained expressions for relaxation times and other relevant parameters of single step and coupled reactions.

Network thermodynamics is, in a way, irreversible thermodynamics in bond graph terms. The use of bond graphs in network thermodynamic formalism gives it a distinct advantage over the usual kinetic or non-equilibrium thermodynamic methods. The bond graph of a dynamic system is essentially a topographical map. The main advantage is that the dynamical equations are generated algorithmically from the bond graph. Therefore one can design a computer program that will accept the bond graph as its input and then compute the dynamical behaviour directly from the graph without dealing with the differential equations explicitly. In many complex cases where an analytical solution is precluded it is easier to deal directly with the graphical representation.

In the present paper the network thermodynamic formalism has been applied to chemical reaction systems. Bond graphs have been made and expressions for steady state reaction velocities obtained. For this two examples have been chosen: (i) A unimolecular reaction of the type A = B + C; and (ii) an enzyme-catalysed reaction. In both the cases the expressions for steady state reaction velocities match those obtained using the methods of chemical kinetics. The three cases of enzyme inhibition, viz. non-competitive, competitive and uncompetitive have also been discussed.

Unimolecular Reactions

Let us consider the reaction A = B + C. In accordance with the Lindemann-Hinshelwood theory[6] the mechanism of the reaction can be set up as follows:

Step 1: *Activation by collisions*

$$A + A \xrightarrow{k_1} A' + A \qquad \ldots(1)$$

where A′ is the activated molecule.

Step 2: *Deactivation by collisions*

$$A' + A \xrightarrow{k_2} A + A \qquad \ldots(2)$$

Step 3: *Spontaneous reaction*

$$A' \xrightarrow{k_3} B + C \qquad \ldots(3)$$

The steps (1) and (2) can be written as

$$A + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A' + A \qquad \ldots(4)$$

In order to be able to construct the network analogue let us write the step (3) also as a reversible reaction, i.e.

$$A' \underset{k_4}{\overset{k_3}{\rightleftharpoons}} B + C \qquad \ldots(5)$$

However, in the final expression for steady state reaction velocity obtained using network thermodynamic method, the velocity constant, k_4 can be put equal to zero to obtain the expression for the situation where the step (3) is not reversible. In view of the mechanism shown in Eqs (4) and (5), the bond graph and the consequent network analogue of the unimolecular reaction, A = B + C, can be represented as shown in Fig. 1 (a and b).

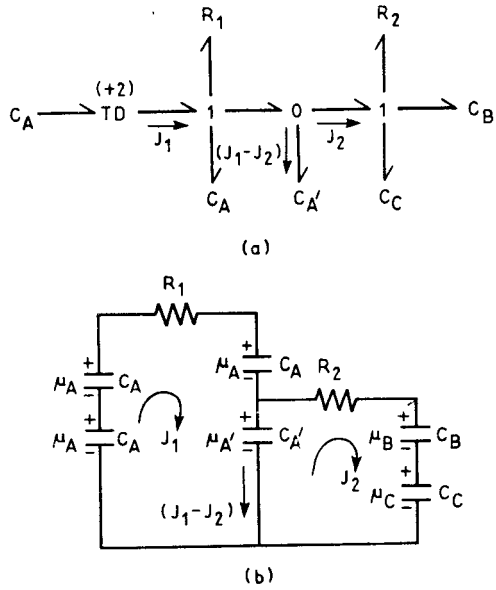


Fig. 1—(a) Bond graph representation of the unimolecular reaction, A = B + C, according to Lindemann-Hinshelwood mechanism as represented by Eqs (4) and (5) where R's represent resistances, C's the capacitances and μ's the potentials across the capacitors.

(b) Equivalent network of the bond graph shown in Fig. 1(a).

Now considering the network shown in Fig. 1, it is evident that

$$J_1 = \frac{\mu_A - \mu_{A'}}{R_1} \qquad \ldots(6)$$

and $$J_2 = \frac{\mu_{A'} - \mu_B - \mu_C}{R_2} \qquad \ldots(7)$$

At the steady state where $J_1 = J_2 = \bar{J}$, we can write from the circuit shown in Fig. 1.

$$\bar{J} = \frac{\mu_A - \mu_B - \mu_C}{R_1 + R_2} \qquad \ldots(8)$$

Making use of the definition of chemical potential, i.e.

$$\mu_i = \mu_i^0 + RT \ln [i] \qquad (i = A, B, C) \qquad \ldots(9)$$

where square brackets represent the concentration and R the usual gas constant, Eq. (8) can be written as

$$\bar{J} = \frac{\mu_A^0 - \mu_B^0 - \mu_C^0 + RT \ln \left(\frac{[A]}{[B][C]} \right)}{R_1 + R_2} \qquad \ldots(10)$$

where R_1 and R_2 stand for resistive elements. Since the chemical potentials μ_A^0, μ_B^0, μ_C^0 of A, B and C respectively in the standard state satisfy the relation

$$\mu_A^0 - \mu_B^0 - \mu_C^0 = -\Delta G^0 = RT \ln K_{eq} = RT \ln \left(\frac{k_1 k_3}{k_2 k_4} \right) \qquad \ldots(11)$$

Eq. (10) can be rewritten as

$$\bar{J} = \frac{RT \ln \left(\frac{k_1 k_3 [A]}{k_2 k_4 [B][C]} \right)}{R_1 + R_2} \qquad \ldots(12)$$

Expanding $\ln[(k_1 k_3[A])/(k_2 k_4[B][C])]$ in the neighbourhood of equilibrium and neglecting the second and higher order terms we get from Eq. (12)

$$\bar{J} = RT \left(\frac{k_1 k_3 [A] - k_2 k_4 [B][C]}{k_2 k_4 [B][C](R_1 + R_2)} \right) \qquad \ldots(13)$$

To find the explicit values of the resistive elements, R_1 and R_2 we utilise the kinetic rate equations for chemical equations (4) and (5). Thus we can write

$$J_1 = k_1 [A]^2 - k_2 [A'][A] \qquad \ldots(14)$$

and

$$J_2 = k_3 [A'] - k_4 [B][C] \qquad \ldots(15)$$

Using Eq. (9), Eqs (14) and (15), in the near equilibrium situation, can be transformed into Eqs (16) and (17) respectively

$$J_1 = \frac{k_1 [A]^2}{RT} (\mu_A - \mu_{A'}) = \frac{k_2 [A][A]}{RT} (\mu_A - \mu_{A'}) \qquad \ldots(16)$$

$$J_2 = \frac{k_3 [A']}{RT} (\mu_{A'} - \mu_B - \mu_C) = \frac{k_4 [B][C]}{RT} (\mu_{A'} - \mu_B - \mu_C \qquad \ldots(17)$$

Now comparing Eqs (6) and (7) with (16) and (17) respectively we can write for the resistive elements, R_1 and R_2

$$R_1 = \frac{RT}{k_1 [A]^2} = \frac{RT}{k_2 [A'][A]} \qquad \ldots(18)$$

$$R_2 = \frac{RT}{k_3 [A']} = \frac{RT}{k_4 [B][C]} \qquad \ldots(19)$$

Using Eqs (18) and (19) for R_1 and R_2 in Eq. (13) we can write for the steady state reaction velocity

$$\bar{J} = \frac{k_1 k_3 [A]^2 - k_2 k_4 [A][B][C]}{k_3 + k_2 [A]} \qquad \ldots(20)$$

If the step-3 (Eq. 5) is irreversible then $k_4 = 0$ and the Eq. (20) reduces to

$$J = \frac{k_1 k_3 [A]^2}{k_3 + k_2 [A]} \qquad \ldots(21)$$

which is in agreement with the rate equation obtained using the methods of chemical kinetics[6].

Enzyme-Catalysed Reactions

Let us consider a simple enzyme-catalysed reaction shown in the reaction scheme represented by Eq. (22)

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P \qquad \ldots(22)$$

In Eq. (22) E stands for enzyme, S for substrate, P for product and ES for enzyme-substrate complex. In order to be able to construct the network analogue let us write all the steps of Eq. (22) as reversible steps, i.e.

$$E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \qquad \ldots(23)$$

$$ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E+P \qquad \ldots(24)$$

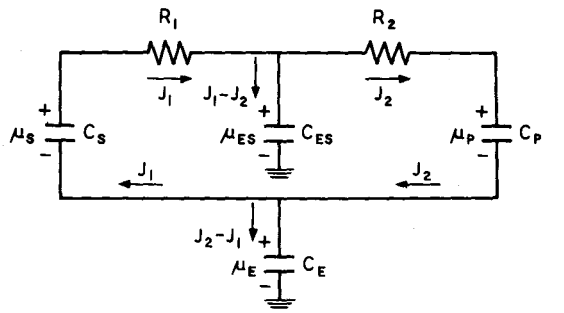
However, in the final equation for steady state reaction velocity we can put $k_{-2}=0$ to obtain the expression for the reaction scheme represented by Eq. (22). The network analogue and the bond graph are shown in Fig. 2 (a and b).

At the steady state we can write from the network shown, the expression for $\bar{J}$ as

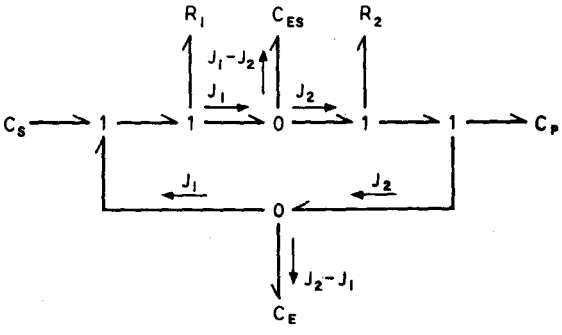
$$\bar{J}=\frac{\mu_S-\mu_P}{R_1+R_2} \qquad \ldots(25)$$

Following the procedure outlined in the case of unimolecular chemical reaction (cf. Eqs 8-13), Eq. (25) can be transformed into

$$\bar{J}=\frac{(k_1k_2[S]-k_1k_2[P])RT}{k_1k_2[P](R_1+R_2)} \qquad \ldots(26)$$



(a)



(b)

Fig. 2—(a) Network analogue for the enzymic reaction scheme (22) where R's, C's and μ's stand for the resistances, capacitances and potentials across the capacitors respectively.

(b) Bond graph representation of the network shown in Fig. 2(a).

The resistive elements, R_1 and R_2 can also be evaluated following the procedure adopted earlier (cf. Eqs 14-19). Thus we get

$$R_1=\frac{RT}{k_1[E][S]}=\frac{RT}{k_1[ES]} \qquad \ldots(27)$$

$$R_2=\frac{RT}{k_2[ES]}=\frac{RT}{k_{-2}[E][P]} \qquad \ldots(28)$$

For the flow through the capacitors representing enzyme-substrate complex and the enzyme (Fig. 2) one can write

$$J_1-J_2=C_{ES}\frac{d\mu_{ES}}{dt}$$

$$\ldots(29)$$

$$J_2-J_1=C_E\frac{d\mu_E}{dt}$$

From Eq. (29) it follows that

$$C_E\frac{d\mu_E}{dt}+C_{ES}\frac{d\mu_{ES}}{dt}=0 \qquad \ldots(30)$$

Making use of the definition[1-3] of generalised capacitance, i.e.

$$C_{ES}=\frac{[ES]}{RT}$$

and $\qquad \ldots(31)$

$$C_E=\frac{[E]}{RT}$$

and integrating Eq. (30) under the boundary condition i.e. at $t=0$, $[ES]=0$ and $[E]=[E_0]$, we get

$$[E_0]=[E]+[ES] \qquad \ldots(32)$$

Using Eq. (32) and the Eqs (27) and (28) for the resistive elements, we can write

$$[ES]=\frac{k_1[E_0][S]}{k_1[S]+k_1}=\frac{k_{-2}[E_0][P]}{k_{-2}[P]+k_2} \qquad \ldots(33)$$

Substituting Eqs (33), (27) and (28) in Eq (26) we can write for the steady state reaction velocity

$$\bar{J}=\frac{k_1k_2[S]-k_{-1}k_{-2}[P]}{k_1\frac{[S]}{[E_0]}+\frac{k_{-2}[P]}{[E_0]}+\frac{k_{-1}+k_2}{[E_0]}} \qquad \ldots(34)$$

Putting $k_{-2}=0$ (if the reaction-24 is irreversible) we get from Eq. (34)

$$\bar{J}=\frac{V_{max}[S]}{K_m+[S]} \qquad \ldots(35)$$

where $V_{max}=k_2[E_0]$; $K_m=k_2+k_{-1}/k_1$ ...(36)

Equation (35) is the well known Michaelis-Menten equation.

Enzyme Inhibition

Let us first consider the case of a simple non-competitive inhibition having the various steps (37a-37d)

$$E+S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \qquad ...(37a)$$

$$ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E+P \qquad ...(37b)$$

$$E+I \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} EI \qquad ...(37c)$$

$$ES+I \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} ESI \qquad ...(37d)$$

In the above reaction scheme I stands for the inhibitor. The step (37b) which infact is irreversible has also been written as a reversible reaction in order to be able to construct the network analogue—the network analogue and the corresponding bond graph are shown in Fig. 3 (a and b). In the final expression for the steady state reaction velocity obtained from network thermodynamic considerations, however, the velocity constant k_{-2} can be put equal to zero.

From the circuit shown in Fig. 3, it is clear that the flow through the capacitors representing E, EI, ES, and ESI becomes zero at steady state and the steady state reaction velocity $\bar{J}$ can be written as

$$\bar{J}=\frac{\mu_S-\mu_P}{R_1+R_2} \qquad ...(38)$$

Using the procedure already described (cf Eqs 8-13), Eq. (38) can be transformed into

$$\bar{J}=\left[\frac{k_1k_2[S]-[k_{-1}k_{-2}[P]}{k_{-1}k_{-2}[P](R_1+R_2)}\right]RT \qquad ...(39)$$

The values of resistive elements, R_1 and R_2 can also be calculated, in the same way as has been done in the analysis of enzyme-catalysed reaction, in terms of velocity constants and concentrations (cf Eqs 14-19). Thus

$$R_1=\frac{RT}{k_1[E][S]}=\frac{RT}{k_{-1}[ES]} \qquad ...(40)$$

$$R_2=\frac{RT}{k_2[ES]}=\frac{RT}{k_{-2}[E][P]} \qquad ...(41)$$

For the flow through the capacitors representing, ES, E, EI and ESI we can write from the network shown in

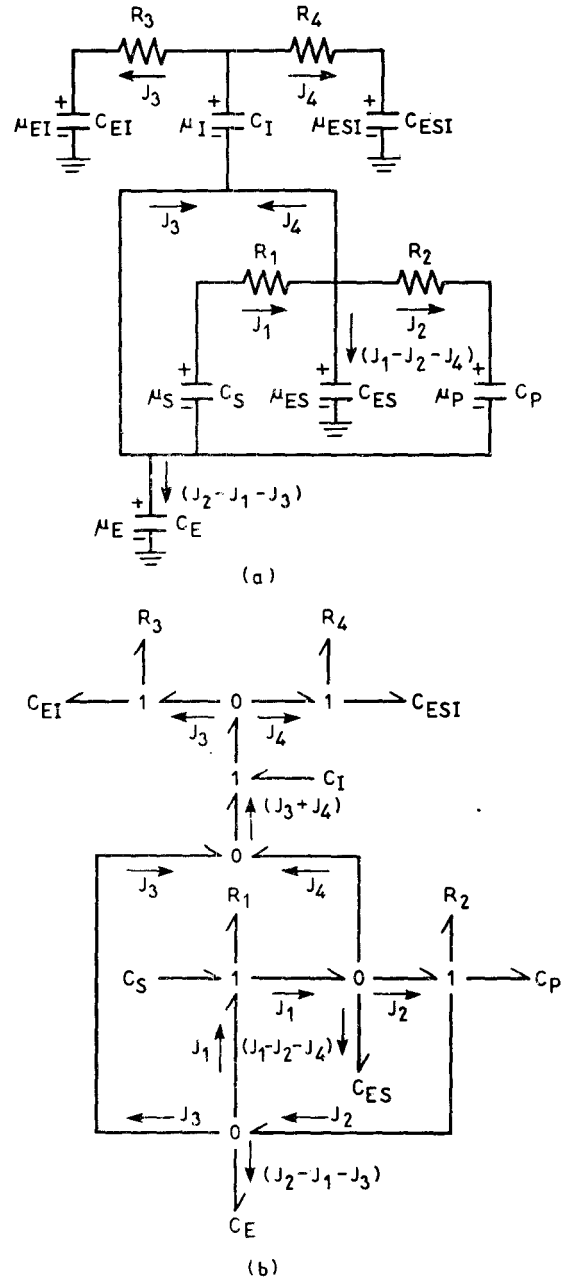


Fig. 3 (a) Network analogue for the non-competitive enzymic inhibition reaction scheme as represented by Eqs (37a) to (37d).

(b) Bond graph representation of the network shown in Fig. 3(a).

Fig. 3(a)

$$C_{ES}\frac{d\mu_{ES}}{dt}=J_1-J_2-J_4$$

$$C_E\frac{d\mu_E}{dt}=J_2-J_1-J_3$$

$$C_{EI}\frac{d\mu_{EI}}{dt}=J_3$$

$$C_{ESI}\frac{d\mu_{ESI}}{dt}=J_4 \qquad ...(42)$$

From Eq. (42) it follows that

$$C_{ES}\frac{d\mu_{ES}}{dt}+C_{E}\frac{d\mu_{E}}{dt}+C_{EI}\frac{d\mu_{EI}}{dt}+C_{ESI}\frac{d\mu_{ESI}}{dt}=0 \quad ...(43)$$

Integrating Eq. (43) after substituting the values of generalised capacitance (cf Eq. 31) and using the boundary conditions that at $t=0$, $[E]=[E_0]$, $[ES]=0$, $[EI]=0$, $[ESI]=0$, we get

$$[E]+[ES]+[ESI]+[EI]=[E_0] \quad ...(44)$$

Using Eq. (44) the following expressions for [ES] can be obtained from Eqs (37a) to (37d)

$$[ES]=\frac{k_1[S][E_0]}{k_{-1}+k_1[S]\left[1+\frac{k_4}{k_{-4}}[I]+\frac{k_3}{k_{-3}}\frac{k_{-1}}{k_1}\frac{[I]}{[S]}\right]} \quad ...(45)$$

Substituting Eq. (45) in Eqs (40) and (41) and rearranging the terms, (R_1+R_2) is obtained as

$$R_1+R_2=\frac{1}{k_{-1}k_{-2}[P][E_0]}\left[k_2+k_{-2}[P]+k_{-2}\frac{k_4}{k_{-4}}[P][I]+k_2\frac{k_3}{k_{-3}}[I]+k_{-1}+k_1[S]+k_1\frac{k_4}{k_{-4}}[S][I]+\frac{k_3}{k_{-3}}k_{-1}[I]\right] \quad ...(46)$$

Now substituting the value of (R_1+R_2) from Eq. (46) into Eq. (39) and putting $k_{-2}=0$, in view of the fact that the reaction (37b) is irreversible, we get

$$\bar{J}=\frac{k_2[E_0][S]}{K_m\left[1+\frac{[I]}{K_I}\right]+\left[1+\frac{[I]}{K_{SI}}\right][S]} \quad ...(47)$$

where $K_m=\frac{k_2+k_{-1}}{k_1}$; $K_I=\frac{k_{-3}}{k_3}$; $K_{SI}=\frac{k_{-4}}{k_4}$

If $K_I=K_{SI}$ which means that the complex ES binds with inhibitor I to the same extent as it binds with enzyme E, the Eq. (47) reduces to Eq. (48)

$$\bar{J}=\frac{V[S]}{(K_m+[S])\left[1+\frac{[I]}{K_I}\right]} \quad ...(48)$$

with $V=k_2[E_0]$.

Equations (47) and (48) obtained from network thermodynamic considerations can be seen to be in agreement with the rate equations obtained from kinetic considerations[7].

The rate equations for the competitive and uncompetitive inhibitions can be deduced from Eq. (47). For simple competitive inhibition where $k_4=0$, we get from Eq. (47)

$$\bar{J}=\frac{k_2[E_0][S]}{K_m\left[1+\frac{[I]}{K_I}\right]+[S]} \quad ...(49)$$

Similarly for simple uncompetitive inhibition where $k_3=0$, Eq. (47) yields

$$\bar{J}=\frac{k_2[E_0][S]}{K_m+\left(1+\frac{[I]}{K_{SI}}\right)[S]} \quad ...(50)$$

The rate Eqs (49) and (50) are also in agreement with those obtained from kinetic considerations[7].

Acknowledgement

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References

1 Oster G, Perelson A & Katchalsky A, *Nature, London*, **234** (1971) 393.
2 Oster G, Perelson A & Katchalsky A, *Q Rev Biophys*, **6** (1973) 1.
3 Schnakenberg J, *Thermodynamic network analysis of biological systems* (Springer-Verlag, Berlin), 1977.
4 Yashonath S, *J phys Chem*, **85** (1981) 1808.
5 Srivastava R C, *J scient ind Res*, **42** (1983) 197.
6 Frost A A & Pearson R G, *Kinetics and mechanism*, (John Wiley, New York) 1961, 70.
7 Laidler K J & Bunting P S, *The chemical kinetics of enzyme action* (Clarendon Press, Oxford) 1973.