CHAPTER FIVE

Entropy Demystified: The "Thermo"-dynamics of Stochastically Fluctuating Systems

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Contents

Abstract

In fluctuating enzyme reaction systems represented in terms of Markov processes, we show that entropy and the Second Law of Thermodynamics are mathematical consequence of the stochastic dynamics. In this kinetic approach to entropy, the Second Law is quantified with a positive entropy production rate. We argue that the concept of entropy is really a mathematical one which arises from any stochastic dynamics. Two examples from molecular biophysics, the efficiency of a motor protein ATPase and the substrate specificity of a phosphorylation-dephosphorylation cycle are discussed.

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1. Introduction

One of the most difficult concepts in molecular biophysics and enzymology is *entropy*. One becomes comfortable with it only after spending a great deal of time studying equilibrium thermodynamics and statistical physics. Entropy is associated with the changing of Gibbs free energy with respect to temperature when the pressure is held constant: $S = -(\partial G/\partial T)_{\rm p}$. But what is Gibbs free energy?

On the other hand, most people are comfortable with the concept of energy, another key term in molecular biophysics and enzymology. One talks about it and one feels about it, even in everyday life. But if we trace a little history of the term, we discover that energy was as elusive a term as entropy at its inception when Gottfried Leibniz, the seventeenth century German mathematician and philosopher (Antognazza, 2008; Bardi, 2007), first introduced it. More importantly, the concept of energy was really made concrete through mathematic constructions! It was via Newton's second law of motion that the energy conservation was first clearly being demonstrated (Goldstein, 1950).

In many different areas of science, there are differential equations other than Newton's second law of motion that characterize dynamics of systems that have nothing to do with energy *per se*. For example, the epidemiological dynamics of viral infection. The mathematical concept of "energy," it turns out, is equally valid in the dynamical systems. It is now widely understood that a large class of differential equations has the "Hamiltonian structure." One example is a mathematical model for the interacting dynamics between populations of a predator and a prey. There is a conservation even though both the predator and prey populations oscillate (Murray, 2003). The mathematical concept of energy also played an important role in John Hopfield's theory of neural networks (Hopfield, 1982).

The purpose of this chapter is to show, via some simple mathematical manipulations, that the concept of entropy arises from any stochastic dynamical systems. The term "stochastic" is the key here. In thermal physics, the stochasticity comes from molecular collisions at finite temperature. But in economics, it comes from the million of individuals in the market trading; and in evolution, it comes from random mutations in the genome. These are completely different physical and biological phenomena. However, when their dynamics can be cast in terms of stochastic equations, there will be an "entropy" and even a "Second Law" which might have nothing to do with thermal physics. They are purely mathematical constructions.

At the present time, in other areas of biology, such as evolutionary dynamics and neural coding, information theory has been applied as a useful tool. Central to the mathematical theory of communication, originally developed be Claude Shannon, is a quantity called Shannon entropy (Shannon and Weaver, 1949). Shannon's information entropy has an identical mathematical

expression as that given by Gibbs except a trival unit in terms of $k_B T$, where k_B is Boltzmann's constant and T is temperature in Kelvin.

The situation has been very confusing. Whether the Gibbs entropy and Shannon entropy are related or not has become a highly controversial subject in ''entropy research.'' Adding to the confusion are many other theories and thoughts based on entropy, for example, the entropy theory of social values (Chen, 2005).

But there is indeed a common thread running through all the above-mentioned systems: They are all stochastic with fluctuations; all should and could be understood in terms of appropriate stochastic dynamical models called Markov processes (Taylor and Karlin, 1998).

After having decided on the title *Entropy Demystified* for the present chapter, a search of the literature led me to Arieh Ben-Naim's wonderful book with a similar title. The subtitle of his book is *The Second Law Reduced to Plain Common Sense*. In a way, my objective is very different—the analysis presented in the present chapter will take the concept of entropy out of the realm of thermal physics. I claim that it is a much more general concept associated with a wide class of dynamical systems with stochastic motion, be it stock market or evolutionary dynamics, communications or atomic physics. It just happened that the term first arrived in the atomic physics in connection to thermodynamics.

Another book deserves a special mentioning. Michael Mackey has written a book on *Time's Arrow: The Origins of Thermodynamic Behaviour* (Mackey, 2003). His thesis shares very much the spirit of the present chapter. However, it turns out that the detailed mathematical structures of his and ours are quite different. Interestingly, when applied to isothermal closed molecular systems, the two structures emerge. How to reconcile these two mathematical structures in an abstract mathematical theory remains an open question.

Perhaps, the most nontrivial aspect of thermodynamic entropy is that it can do work (Dill and Bromberg, 2003). So the classical mechanical energy is *not conserved* after all! It is this realization that led to the new physics of matters in the nineteenth century (Shachtman, 2000).

2. Energy

2.1. Equilibrium and nonequilibrium steady state

Let us first consider the simple conformational transition between two states of an enzyme:

$$A \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} B. \tag{5.1}$$

The molecule is left alone in a test tube at a constant temperature and pressure. Then one has in equilibrium

$$\frac{c_{\mathrm{A}}^{\mathrm{eq}}}{c_{\mathrm{B}}^{\mathrm{eq}}} = \frac{\beta}{\alpha} = \frac{\mathrm{e}^{-G_{\mathrm{A}}^{\circ}}}{\mathrm{e}^{-G_{\mathrm{B}}^{\circ}}}, \tag{5.2}$$

where $c_{\mathrm{A}}^{\mathrm{eq}}$ and $c_{\mathrm{B}}^{\mathrm{eq}}$ are equilibrium concentrations of A and B. The standard state Gibbs free energy G_{A}° and G_{B}°, as well as all the energy below, are measured in unit $k_{\mathrm{B}}T$. Gibbs entropy will be in unit k_{B}. Therefore,

$$\Delta G^{\circ} = G_{\mathrm{B}}^{\circ} - G_{\mathrm{A}}^{\circ} = \ln\left(\frac{\beta}{\alpha}\right). \tag{5.3}$$

The ΔG° between states A and B is a property of the molecule (in an appropriate solvent). It is more or less determined by the molecular structures. The most important aspect of an equilibrium state of a biochemical reaction system is that it does not, on average, absorb nor dissipate energy (the First Law), and it does not, on average, convert energy from one form to another (the Second Law).

But many biochemical reactions in a living cell are not at their equilibria. Rather, the concentrations of A and B are sustained at a relatively constant levels in homeostasis. This is because the reaction in Eq. (5.1) is not in isolation in a cell, the production of a protein from its biosynthesis and its degradation are regulated and balanced. So in this case, one has a constant, *steady-state flux* in the reaction

$$J^{\mathrm{ss}} = \alpha c_{\mathrm{A}} - \beta c_{\mathrm{B}}, \tag{5.4}$$

in which $\alpha c_{\mathrm{A}} = J_{+}^{\mathrm{ss}}$ is the amount of A → B per unit time, and $\beta c_{\mathrm{B}} = J_{-}^{\mathrm{ss}}$ is the amount of B → A per unit time.

In energetic terms, from the elementary physical chemistry, we have the Gibbs free energy of A at concentration c_{A}, and of B at concentration c_{B}:

$$G_{\mathrm{A}} = G_{\mathrm{A}}^{\circ} + \ln c_{\mathrm{A}}, \quad G_{\mathrm{B}} = G_{\mathrm{B}}^{\circ} + \ln c_{\mathrm{B}}. \tag{5.5}$$

We see that when A and B are at their equilibrium, that is, $\ln(c_{\mathrm{A}}^{\mathrm{eq}}/c_{\mathrm{B}}^{\mathrm{eq}}) = \Delta G^{\circ}$,

$$\Delta G = G_{\mathrm{B}} - G_{\mathrm{A}} = \Delta G^{\circ} + \ln\left(\frac{c_{\mathrm{B}}^{\mathrm{eq}}}{c_{\mathrm{A}}^{\mathrm{eq}}}\right) = 0. \tag{5.6}$$

This is precisely the meaning of chemical equilibrium, according to Gibbs: that left-hand side and right-hand side (rhs) of a reaction have equal Gibbs free energy.

However, when A and B are not at their chemical equilibrium, $\ln(c_{\mathrm{A}}/c_{\mathrm{B}}) \neq \Delta G^{\circ}$, then $\Delta G \neq 0$. Furthermore, if $\Delta G > 0$, then

$$G_B^o + \ln c_B - G_A^o + \ln c_A > 0, \qquad \Rightarrow \frac{e^{-G_A^o} c_A}{e^{-G_B^o} c_B} > 1.$$

Using the relation in Eq. (5.3), we have

$$\frac{\alpha c_A}{\beta c_B} > 1, \qquad \Rightarrow J^{ss} > 0.$$

Similarly, if $\Delta G < 0$, then $J^{ss} < 0$. One should think of this result as "electrical current runs from high voltage to low voltage." In fact, the product of $J^{ss} \times \Delta G$ is precisely the heat dissipated from the chemical reaction sustained under a nonequilibrium steady state (NESS). We note that even though ΔG can be either positive or negative, the product is always positive. The inequality $J^{ss} \times \Delta G \geq 0$ is in fact the Second Law of Thermodynamics according to Lord Kelvin: One can not covert 100% heat to work in an isothermal reaction, and the heat dissipation is zero if and only if the reaction is in an equilibrium $J^{ss} = \Delta G = 0$. This is also known as De Donder inequality (De Donder and Rysselberghe, 1936).

2.2. Cycle kinetics, thermodynamic box and detailed balance

In many cell biology applications, when one takes a more careful look of the conformational transitions between states A and B of an enzyme, one will find that the transition is accompanied with turnover of some cofactors (regulators, ligands, substrates). Furthermore, from biological functional perspective, A state of the enzyme is itself inactive while the B state is active. Let us now continue the above analysis by considering this more complex, but clearly realistic scenario, in terms of the following kinetic scheme:

$$A + S \underset{k_{-1}}{\overset{k_1^o}{\rightleftharpoons}} AS, \qquad AS \underset{k_{-2}^o}{\overset{k_2}{\rightleftharpoons}} B + P_1, \qquad B \underset{k_{-3}^o}{\overset{k_3}{\rightleftharpoons}} A + P_2. \tag{5.7}$$

The rate constants $k_i^o (i = 1, -2, -3)$ are second order, while $k_j (j = -1, 2, 3)$ are first order.

We note that if we combine the three reactions in Eq. (5.7), we have the net reaction

$$S \rightleftharpoons P_1 + P_2. \tag{5.8}$$

Let us consider the case in which the concentrations of S, P_1, and P_2 are all kept at constant in the reaction system, let us say with c_S, c_{P1}, and c_{P2}. Then the NESS has

$$\Delta G = G_{P_1} + G_{P_2} - G_S = -\ln K_{eq} + \ln \frac{c_{P_1} c_{P_2}}{c_S}, \tag{5.9}$$

where the equilibrium constant for the reaction in Eq. (5.8) $K_{eq} = k_1^o k_2 k_3 / k_{-1} k_{-2}^o k_{-3}^o$. This last equality is widely known in chemical kinetics as the *thermodynamic box*. k_1^o/k_{-1}, k_2/k_{-2}^o, k_3/k_{-3}^o are equilibrium constants for the three reactions in Eq. (5.7), respectively. *The equilibrium constant for the overall reaction is the product of the individual reaction steps*.

Substituting this relation into Eq. (5.9), we have

$$\Delta G = \ln \frac{k_{-1} k_{-2}^o c_{P_1} k_{-3}^o c_{P_2}}{k_1^o c_S k_2 k_3}. \tag{5.10}$$

$\Delta G = 0$ if and only if when the concentrations of S, P_1, and P_2 are in their chemical equilibrium: $c_{P_1}^{eq} c_{P_2}^{eq} / c_S^{eq} = K_{eq}$.

We now introduce a very important concept: The pseudo-first-order rate constants. Since the concentrations of S, P_1, and P_2 are kept constant in the reaction system in Eq. (5.7), and since one is mainly interested in the conformational transition of the enzyme among the three states A, AS, B, we can simplify the kinetics in Eq. (5.7) into a pseudo-unimolecular cycle kinetics:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AS, \quad AS \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B, \quad B \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} A, \tag{5.11}$$

in which $k_1 = k_1^o c_S, k_{-2} = k_{-2}^o c_{P_1}, k_{-3} = k_{-3}^o c_{P_2}$ are pseudo-first-order rate constants.

The cyclic reaction system, in terms of the first-order and pseudo-first-order rate constants $k_{\pm i}$ $(i = 1, 2, 3)$, has the following important properties:

(1) When the rate constants satisfy

$$\frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} = 1, \tag{5.12}$$

all the cofactors are in chemical equilibrium, and *vice versa*. The enzyme reaction kinetics in Eq. (5.11) eventually reaches an equilibrium, in which

$$k_1 c_A^{eq} = k_{-1} c_{AS}^{eq}, \; k_2 c_{AS}^{eq} = k_{-2} c_B^{eq}, \; k_3 c_B^{eq} = k_{-3} c_A^{eq}. \tag{5.13}$$

The relation in Eq. (5.13) is known as detailed balance. The relation in Eq. (5.12) is called Wegscheider, or Kolmogorov, cycle condition (Beard and Qian, 2008). The equations in Eq. (5.13) also indicate that the fluxes in the reactions are zero.

(2) When the left-hand side of Eq. (5.12), denoted by γ, is greater than 1,

$$\gamma \equiv \frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} > 1, \tag{5.14}$$

the cofactor concentrations are sustained at an nonequilibrium level. The free energy difference in Eq. (5.10) in fact is

$$\Delta G = -\ln \gamma. \tag{5.15}$$

To the cycle kinetics of enzyme in Eq. (5.11) the $\ln \gamma$ is the driving force which keeps the reaction out of equilibrium. In the steady state, there will be a nonzero cycle flux going through A → AS → B → A:

$$J^{ss} = k_1 c_A^{ss} - k_{-1} c_{AS}^{ss} = k_2 c_{AS}^{ss} - k_{-2} c_B^{ss} = k_3 c_B^{ss} - k_{-3} c_A^{ss} = \frac{(k_1 k_2 k_3 - k_{-1} k_{-2} k_{-3}) c_T}{k_2 k_3 + k_3 k_{-1} + k_{-1} k_{-2} + k_3 k_1 + k_1 k_{-2} + k_{-2} k_{-3} + k_1 k_2 + k_2 k_{-3} + k_{-3} k_{-1}}, \tag{5.16}$$

in which $c_T = c_A + c_{AS} + c_B$ are the total concentration of the enzyme. We again note that when $\Delta G = -\ln \gamma = 0$, $J^{ss} = 0$, and *vice versa*. Equation (5.16) indicates that for a biochemical reaction system under a chemical driving force reaches a NESS. Detailed balance is not preserved in such "open chemical systems" (Qian, 2007).

If one substitutes all the second-order rate constants in Eq. (5.7) back to the Eq. (5.16), one will recover the well-known Michaelis–Menten–Briggs–Haldane equation for reversible, ordered-uni-bi enzyme kinetics (Segel, 1975):

$$J^{ss} = \frac{V_{max}^{f} \frac{[S]}{K_{mS}} - V_{max}^{r} \frac{[P_1][P_2]}{K_{mP}}}{1 + \frac{[S]}{K_{mS}} + \frac{[S][P_1]}{K'_{mS}} + \frac{[P_1]}{K_{mP1}} + \frac{[P_2]}{K_{mP2}} + \frac{[P_1][P_2]}{K_{mP}}}, \tag{5.17}$$

where

$$V_{max}^{f} = \frac{k_2 k_3 c_T}{k_2 + k_3}, \quad V_{max}^{r} = k_{-1} c_T, \quad K_{mS} = \frac{(k_{-1} + k_2) k_3}{k_1^o (k_2 + k_3)},$$
$$K'_{mS} = \frac{(k_{-1} + k_2) k_3}{k_1^o k_{-2}^o}, \quad K_{mP1} = \frac{(k_{-1} + k_2) k_3}{k_{-1} k_{-2}^o},$$
$$K_{mP2} = \frac{k_3}{k_{-3}^o}, \quad K_{mP} = \frac{(k_{-1} + k_2) k_3}{k_{-2}^o k_{-3}^o}.$$

3. Entropy and "Thermo"-dynamics of Markov Processes

We are now in the position to make a conceptual leap, an mathematical abstraction. In the theory of probability, Markov processes are widely used to model stochastic dynamics, just as differential equations are widely used to model deterministic dynamics. A discrete state Markov model is in generally depicted exactly like that in Eq. (5.11), which has three states. A four-state Markov process in general has 12 possible transitions:

$$\mathrm{A} \underset{q_{21}}{\overset{q_{12}}{\rightleftharpoons}} \mathrm{B}, \quad \mathrm{B} \underset{q_{32}}{\overset{q_{23}}{\rightleftharpoons}} \mathrm{C}, \quad \mathrm{C} \underset{q_{43}}{\overset{q_{34}}{\rightleftharpoons}} \mathrm{D}, \quad \mathrm{A} \underset{q_{31}}{\overset{q_{13}}{\rightleftharpoons}} \mathrm{C}, \quad \mathrm{B} \underset{q_{42}}{\overset{q_{24}}{\rightleftharpoons}} \mathrm{D}. \tag{5.18}$$

Of course, some of the transitions could have rate constants being zero, effectively nonexistent. For a stochastic dynamical system, one no longer asks in which state the system is at time t, rather one asks what the probability is the system in state i at time t, $p_i(t)$. Then the $p_i(t)$ satisfies a set of equations known as the master equation:

$$\frac{\mathrm{d}p_j(t)}{\mathrm{d}t} = \sum_i (-p_j q_{ji} + p_i q_{ij}). \tag{5.19}$$

where i can be A, B, C, D, or 1, 2, 3, 4.

The conceptual leap is this: While the states in Eq. (5.18) can be the conformational states of a single enzyme, they could also be the different states of a cell in which gene expressions are now known to be stochastic, or different state of a genome in evolution in which randomness comes from genetic random mating and mutation. In the latter two cases, there is no connection to Gibbs free energy, nor molecular thermodynamics, *per se*. Nevertheless, as we shall show, the concepts of energy, and *entropy*, are abstract mathematical concepts intimately associated with any Markov process.

3.1. Entropy and entropy balance equation

The mathematics in this section is not difficult, but the steps are rather abstract. We shall "define" the entropy S associated with a Markov process, and then find out how entropy changes with time if the system's probability distribution follows Eq. (5.19).

We consider the master equation in Eq. (5.19), with $1 \le i, j \le N$. The system has N states. Let

$$S[\{p_j(t)\}] = -\sum_j p_j(t) \ln p_j(t). \tag{5.20}$$

Then we have the time derivative of S according to the chain rule:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \sum_j \frac{\mathrm{d}p_j}{\mathrm{d}t} \ln p_j \\
&= \sum_{i,j\neq i} \ln p_j (p_j q_{ji} - p_i q_{ij}) \\
&= \frac{1}{2} \sum_{i,j\neq i} [\ln p_j (p_j q_{ji} - p_i q_{ij}) + \ln p_i (p_i q_{ij} - p_j q_{ji})] \\
&= \frac{1}{2} \sum_{i,j\neq i} (p_i q_{ij} - p_j q_{ji}) \ln \left(\frac{p_i q_{ij}}{p_j q_{ji}} \right) - \sum_{i>j} (p_i q_{ij} - p_j q_{ji}) \ln \left(\frac{q_{ij}}{q_{ji}} \right).
\end{aligned} \tag{5.21}$$

We shall now name a few things:

$$\text{epr} = \frac{1}{2}\sum_{i,j\neq i}(p_i q_{ij} - p_j q_{ji})\ln\left(\frac{p_i q_{ij}}{p_j q_{ji}}\right) \tag{5.22}$$

is called *entropy production rate*; and

$$\text{edr} = \sum_{i>j}(p_i q_{ij} - p_j q_{ji})\ln\left(\frac{q_{ij}}{q_{ji}}\right) \tag{5.23}$$

is called *free energy dissipation rate*. Then Eq. (5.21) becomes

$$\frac{\mathrm{dS}}{\mathrm{d}t} = \text{epr} - \text{edr}. \tag{5.24}$$

We call this the entropy balance equation.

We would like to provide a more precise meaning for the term edr: For an isothermal chemical reaction system with constant chemical energy input, the edr is the free energy dissipation which include enthalpy and entropy parts; it contains the work done by the system against its environment, such as by a molecular motor.[1]

3.2. "Equilibrium" and time reversibility

The reason we use quotation marks for "equilibrium" and "thermo"-dynamics is because these concepts only existed in molecular physics in the past. But now we consider them as abstract mathematical concepts associated with any stochastic dynamics in terms of Markov processes. For any Markovian stochastic dynamics, there is an entropy of the system. The entropy production is always positive. This is easy to verify from Eq. (5.22). Note that each term in the summation is the product $J \times \Delta G$ for the transitions (forward and reverse reactions) between states i and j.

A part of the entropy of the system is dissipated as "heat." When a stochastic dynamics reaches its stationary state, the S no longer change with time and $\mathrm{dS}/\mathrm{d}t = 0$. Hence epr = edr. Let us denote the stationary probability by p_i^{ss}. If a system satisfies

$$p_i^{\mathrm{ss}} q_{ij} = p_j^{\mathrm{ss}} q_{ji} \tag{5.25}$$

in its steady state, then it has zero entropy production, as well as zero free energy dissipation. The steady state is in fact an equilibrium. In this case, the stochastic, stationary dynamics is said to be detail balanced. In fact, one can

[1] In fact, one also has the change of enthalpy and free energy of an isothermal, driven chemical system (Qian and Beard, 2005) $\mathrm{d}H/\mathrm{d}t = \text{ceir} - \text{edr}$ and $\mathrm{d}G/\mathrm{d}t = \text{ceir} - \text{epr}$, where ceir is the chemical energy input rate. Therefore, in an NESS, the edr = ceir means energy conservation and ecir = epr is the Clausius equality for isothermal processes. For abstract stochastic dynamics, however, one usually can not define the enthalpy H.

show that the stochastic dynamics has identical statistics with respect to time reversal.

What kind of stochastic systems will reach an equilibrium? Motivated by the discussions on enzyme reactions above, we have the following result: If each and every state in the system has a "standard state free energy," say E_i° for state i, and the transition rate constants

$$\frac{q_{ij}}{q_{ji}} = \mathrm{e}^{-E_j^{\circ}+E_i^{\circ}}, \tag{5.26}$$

then the stationary probability distribution p_i^{ss} is proportional to $\mathrm{e}^{-E_i^{\circ}}$. Furthermore, we can introduce another quantity, called "free energy" of the whole stochastic system:

$$F[\{p_j(t)\}] = \sum_j p_j(t)E_j^{\circ} - \mathrm{S}(t). \tag{5.27}$$

Then, the Eq. (5.24) can be rewritten as

$$\begin{aligned} -\mathrm{epr} &= -\mathrm{edr} - \frac{\mathrm{dS}}{\mathrm{d}t} \\ &= -\sum_{i>j}(p_i q_{ij} - p_j q_{ji})\ln\left(\frac{q_{ij}}{q_{ji}}\right) - \frac{\mathrm{dS}}{\mathrm{d}t} \\ &= \sum_{i>j}(p_i q_{ij} - p_j q_{ji})(E_j^{\circ} - E_i^{\circ}) - \frac{\mathrm{dS}}{\mathrm{d}t} \\ &= \sum_{i,j\neq i}(p_i q_{ij} - p_j q_{ji})E_i^{\circ} - \frac{\mathrm{dS}}{\mathrm{d}t} \\ &= \sum_i \frac{\mathrm{d}p_i}{\mathrm{d}t}E_i^{\circ} - \frac{\mathrm{dS}}{\mathrm{d}t}, \end{aligned} \tag{5.28}$$

that is

$$\frac{\mathrm{d}F}{\mathrm{d}t} = -\mathrm{epr} \leq 0. \tag{5.29}$$

Equation (5.29) is well known in isothermal statistical physics. But more importantly to our discussion, it is a mathematical result for any Markov dynamics with standard state energy. This class of Markov processes is called reversible, or symmetric, Markov process.

3.3. "Free energy" and relative entropy

The inequality in Eq. (5.29) is a very important property of any reversible, symmetric Markov process. It corresponds to a nondriven molecular system. We now generalize this result to any Markov system (Mackey, 2003).

Combining Eqs. (5.25) and (5.26), we have $E_i^{\circ} = -\ln p_i^{ss} + C$ where C is a simple constant independent of i. Therefore, one can rewrite the F in Eq. (5.27)

$$F[\{p_j(t)\}] = \sum_j p_j(t) \ln\left(\frac{p_j(t)}{p_j^{ss}}\right). \tag{5.30}$$

The constant C is set to zero with no consequences.

The quantity in Eq. (5.30) is called *relative entropy*. For most Markov models (technically called irreducible Markov processes), irrespective of whether symmetric (reversible) or not, the stationary probability distribution $\{p_j^{ss}\}$ is unique. Then we have for a general Markov dynamics:

$$\begin{aligned}
\frac{dF}{dt} &= \sum_j \frac{dp_j}{dt} \ln\left(\frac{p_j}{p_j^{ss}}\right) \\
&= \sum_{i,j} (p_i q_{ij} - p_j q_{ji}) \ln\left(\frac{p_j}{p_j^{ss}}\right) \\
&= \sum_{i,j} \left[p_i q_{ij} \ln\left(\frac{p_j}{p_j^{ss}}\right) - p_i q_{ij} \ln\left(\frac{p_i}{p_i^{ss}}\right) \right] \\
&= \sum_{i,j} p_i q_{ij} \ln\left(\frac{p_j p_i^{ss}}{p_j^{ss} p_i}\right) \\
&\le \sum_{i,j} p_i q_{ij} \left(\frac{p_j p_i^{ss}}{p_j^{ss} p_i} - 1\right) \\
&= \sum_{i,j} \left(\frac{p_j p_i^{ss} q_{ij}}{p_j^{ss}} - p_i q_{ij}\right) \\
&= \sum_{i,j} \left(\frac{p_j p_j^{ss} q_{ji}}{p_j^{ss}} - p_i q_{ij}\right) \\
&= 0.
\end{aligned} \tag{5.31}$$

In the above derivation, we have used the inequality $\ln x \le x - 1$. Furthermore, we have

$$\begin{aligned} F[\{p_j(t)\}] &= \sum_j p_j(t)\ln\left(\frac{p_j(t)}{p_j^{ss}(t)}\right) \\ &= -\sum_j p_j(t)\ln\left(\frac{p_j^{ss}(t)}{p_j(t)}\right) \\ &\geq -\sum_j p_j(t)\left(\frac{p_j^{ss}(t)}{p_j(t)} - 1\right) \\ &\geq -\sum_j p_j^{ss}(t) + \sum_j p_j(t) \\ &= 0. \end{aligned} \tag{5.32}$$

Therefore, the generalization of free energy F, called relatively entropy, is a nonnegative quantity, and is never increasing in a Markovian stochastic dynamics. It continuous decreases until it reaches zero, when the stochastic system reaches its steady state.

The entropy balance equation (5.24) and the monotonic decreasing relative entropy, Eq. (5.31), are two important equations for the "thermo"-dynamics of any stochastically fluctuating systems modeled in terms of general Markov processes. This "thermo"-dynamic structure is not unique to molecular systems and biological macromolecules, but also to other biological systems such as stochastic cell dynamics, infectious disease dynamics, Darwinian evolutionary process, and maybe even economics. It is tempting to suggest that if one can find the entropy analogues in evolutionary process (Ao, 2008) and economic theory (Chen, 2005), it would be a significant progress in the respective field.[2]

We shall now return to enzyme systems and give two examples of how the above theory is applied to modeling enzyme kinetics and functions.

4. A Three-State Two-Cycle Motor Protein

A motor protein is an enzyme, usually an ATPase, that converts chemical energy from ATP hydrolysis to mechanical movement. In fact, it can move against an external load (Howard, 2001; Qian, 2005, 2008). Figure 5.1A shows a very simple kinetic scheme of a motor protein. For simplicity, we assume that the motor can move a step on its track, from n to $n + 1$, when it hydrolyzes the bound ATP. However, we do not assume

[2] Based on the present discussion of entropy, a hypothesis on *market value* of a commodity could be such: market value = intrinsic value + speculative value, where the speculative value = −"temperature" × entropy. The "temperature" in a market theory measures the randomness of the speculative market (Marx, 1992).

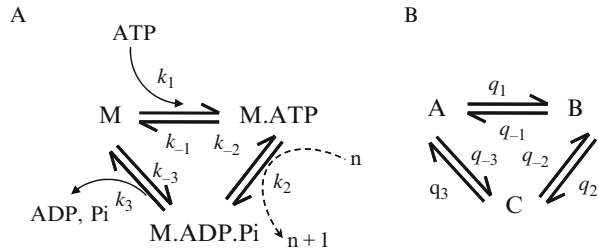

Figure 5.1 (A) The biochemical kinetic scheme of a simple motor protein model. The step M.ATP → M.ADP.Pi is loosely coupled to the motor translocation on its track moving a step forward. When it "slips," the ATP hydrolysis is "futile." We assume the probability of slippage to be $1/(1+\sigma)$. The biochemical kinetic scheme in (A) can be mapped into the Markov model in (B) using the pseudo-rate constants: $q_1 = k_1[\mathrm{ATP}]$, $q_2(f) = k_2^{\circ}(1+\sigma e^{-(1-r)f\delta})$, $q_{-2}(f) = k_{-2}^{\circ}(1+\sigma e^{rf\delta})$, $q_{-3} = k_{-3}[\mathrm{ADP}][\mathrm{Pi}]$. The parameter r, known as a slitting parameter, represents the position of the transition state (Hill, 1981; Qian, 2006).

that the stepping necessarily occurs. There is a finite rate, with rate constant k_2°, of hydrolysis without the motor translocation. Therefore, with the presence of a resistant force f, then the rate

$$k_2 = k_2^{\circ}\left(1+\sigma e^{-(1-r)f\delta}\right), \tag{5.33}$$

where δ is the step size of the motor, r characterizes the location of the transition state (Hill, 1981; Qian, 2006), and σ is the ratio of the mechanical to futile steps. Such a motor has its chemical and chemomechanical cycles not being tightly coupled.

When there is no external load, $f = 0$, and the ATP, ADP, and Pi are at chemical equilibrium, one has

$$\left(\frac{[\mathrm{ATP}]}{[\mathrm{ADP}][\mathrm{Pi}]}\right)^{\mathrm{eq}} = K_{\mathrm{ATP}} = \frac{k_{-1}k_{-2}^{\circ}k_{-3}}{k_1 k_2^{\circ} k_3}. \tag{5.34}$$

In a living cell, however, the [ATP]/[ADP][Pi] is very large, on the order of 10^{10} times the equilibrium ratio:

$$\gamma = e^{\Delta G_{\mathrm{ATP}}} = \frac{[\mathrm{ATP}]}{K_{\mathrm{ATP}}[\mathrm{ADP}][\mathrm{Pi}]} = \frac{q_1 q_2(0) q_3}{q_{-1} q_{-2}(0) q_{-3}}. \tag{5.35}$$

The steady-state biochemical flux of the motor enzyme is, thus

$$J^{\mathrm{ss}} = \frac{q_1 q_2 q_3 - q_{-1} q_{-2} q_{-3}}{q_2 q_3 + q_3 q_{-1} + q_{-1} q_{-2} + q_3 q_1 + q_1 q_{-2} + q_{-2} q_{-3} + q_1 q_2 + q_2 q_{-3} + q_{-3} q_{-1}}. \tag{5.36}$$

The J^{ss} consists of two parts: A chemomechanical cycle A $\rightleftharpoons$ B $\rightleftharpoons$ C $\rightleftharpoons$ A with rate constants $\sigma k_2^0 e^{-(1-r)f\delta}$ and $\sigma k_{-2}^o e^{rf\delta}$ for the second step, which is coupled to motor stepping of a distance δ against a force f. This gives the motor velocity:

$$V^{ss}=\frac{q_1 k_2^o \sigma e^{-(1-r)f\delta} q_3 - q_{-1} k_{-2}^o \sigma e^{rf\delta} q_{-3}}{q_2 q_3 + q_3 q_{-1} + q_{-1} q_{-2} + q_3 q_1 + q_1 q_{-2} + q_{-2} q_{-3} + q_1 q_2 + q_2 q_{-3} + q_{-3} q_{-1}}\delta. \tag{5.37}$$

Another is a futile cycle A $\rightleftharpoons$ B $\rightleftharpoons$ C $\rightleftharpoons$ A with rate constants k_2^o and k_{-2}^o for the second step. Hydrolysis of an ATP does not lead to motor movement.

The efficiency of the motor, therefore, is

$$\eta = \frac{V^{ss} f}{J^{ss} \Delta G_{ATP}} = \frac{f\delta}{\left(1 + \frac{(\gamma-1)e^{-rf\delta}}{\sigma(\gamma e^{-f\delta}-1)}\right)\ln\gamma}. \tag{5.38}$$

The term

$$\frac{(\gamma-1)e^{-rf\delta}}{\sigma(\gamma e^{-f\delta}-1)} \tag{5.39}$$

is the ratio between the flux of the futile cycle and that of the chemomechanical cycle. The futile cycle flux is zero if and only if $\gamma = 1$, that is, there is no energy in ATP hydrolysis; the chemomechanical cycle flux is zero if $f = f_{max} = (1/\delta)\ln\gamma$, when the motor stop moving. f_{max} is known as the stalling force. Figure 5.2 shows the η as a function of resistant force f with various values of the parameters r and σ.

When the motor moves, the enzyme kinetics is in a NESS. There is a balance equation for the free energy difference of each and every reactions in the system, similar to the Kirchoff's loop law of electrical circuit (Beard and Qian, 2008):

$$\Delta G_{AB} + \Delta G_{BC}(f) + \Delta G_{CA} = \Delta G_{ATP}. \tag{5.40}$$

The rhs should be thought as a battery. Each time the enzyme transits from state A to B, it dissipates the amount of free energy ΔG_{AB}. Same can be said for the transition C $\rightarrow$ A. For the step B $\rightarrow$ C, part of the $\Delta G_{BC}(f)$ is dissipated, but another part is used to do work against the force f in the amount of $f\delta$. In an isothermal biochemical reaction system, the amount of entropy production is simply the amount of chemical energy being used up outside of the system.

Now recall the Eqs. (5.22) and (5.23) from the previous section. The rhs of Eq. (5.22) contains the terms in the form of $(J_+ - J_-)\ln(J_+/J_-)$, where i stands for each and every reaction. For the motor model in Fig. 5.1B, all three

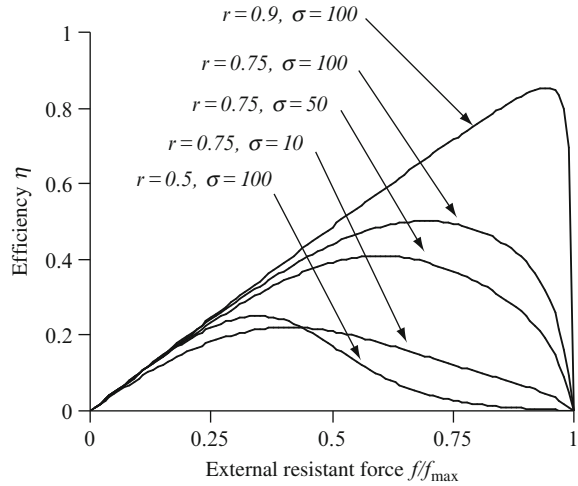

Figure 5.2 Motor efficiency η as a function of external load f according to Eq. (5.38). The maximal force $f_{max} = (1/\delta) \ln \gamma$. In the calculations, $\gamma = 10^{10}$ corresponding to the $f_{max}\delta = 21$. For both small and large f, the efficiency is low. The maximal efficiency increases with r and σ.

reactions have the same J^{ss}. Hence, the epr in Eq. (5.22) is simply epr $= J^{ss}$ $\Delta G_{ATP} - f V^{ss}$, the first term is the denominator in the Eq. (5.38).

5. Phosphorylation–Dephosphorylation Cycle Kinetics

From the previous discussion, we see that an absolutely irreversible chemical reaction is incompatible with thermodynamics: If the reaction A → B is irreversible, then the free energy difference between A and B must be infinite. This is unrealistic. In kinetic study of biochemical reactions, one often assumes irreversible reactions. This is acceptable if one is only interested in kinetics but not thermodynamics. Almost all the kinetic studies on the phosphorylation–dephosphorylation cycle (PdPC) kinetics in cellular signaling assumes irreversible kinase and phosphatase (as we shall do ourselves in Sections 5.2 and 5.3).

5.1. PdPC signaling switch and phosphorylation energy

In this section, we introduce a thermodynamic and kinetic combined analysis of reversible PdPC kinetics:

$$\mathrm{E}+\mathrm{K}\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}EK\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}}\mathrm{E}^*+\mathrm{K},\quad \mathrm{E}^*+\mathrm{P}\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}}\mathrm{E}^*\mathrm{P}\underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}}\mathrm{E}+\mathrm{P}, \tag{5.41}$$

in which E is a substrate enzyme, K and P are protein kinase and phosphatase, respectively. The rate constant $k_1 = k_1^{\mathrm{o}}[\mathrm{ATP}]$, $k_{-2} = k_{-2}^{\mathrm{o}}[\mathrm{ADP}]$, $k_{-4} = k_{-4}^{\mathrm{o}}[\mathrm{Pi}]$. We assume that the cellular concentrations of ATP, ADP, and Pi are constant.

It is clear that every cycle of phosphorylation and dephosphorylation of an E turns an amount of chemical free energy into heat. From the traditional physical perspective, there is no work done. Hence the PdPC are widely called futile cycle (Qian and Beard, 2006). However, as has been recently suggested, signal transduction are information processing and delivering processes, and information processing requires free energy dissipation, accompanied with entropy production (Qian, 2007).

Following the standard Michaelis–Menten kinetics, but let us assume that the amount of kinase and phosphatase are large in comparison with their respective Michaelis constants, then the kinetics in Eq. (5.41) can be represented by a Markov model

$$\mathrm{E}\underset{q_{-1}}{\overset{q_1}{\rightleftharpoons}}\mathrm{E}^*\underset{q_{-2}}{\overset{q_2}{\rightleftharpoons}}\mathrm{E}, \tag{5.42}$$

with

$$q_1 = \frac{k_1^{\mathrm{o}}k_2[\mathrm{ATP}][\mathrm{K}]}{k_{-1}+k_2},\quad q_{-1} = \frac{k_{-2}^{\mathrm{o}}k_{-1}[\mathrm{ADP}][\mathrm{K}]}{k_{-1}+k_2},$$
$$q_2 = \frac{k_3k_4[\mathrm{P}]}{k_{-3}+k_4},\quad q_{-2} = \frac{k_{-4}^{o}k_{-3}[\mathrm{Pi}][\mathrm{P}]}{k_{-3}+k_4}.$$

Same as in Eq. (5.35), we have

$$\gamma = \frac{q_1q_2}{q_{-1}q_{-2}} = \frac{k_1^{\mathrm{o}}k_2k_3k_4[\mathrm{ATP}]}{k_{-4}^{\mathrm{o}}k_{-3}k_{-2}^{\mathrm{o}}k_{-1}[\mathrm{ADP}][\mathrm{Pi}]} = \mathrm{e}^{\Delta G_{\mathrm{ATP}}}. \tag{5.43}$$

Then the fraction of substrate being phosphorylated:

$$f = \frac{[\mathrm{E}^*]}{[\mathrm{E}]+[\mathrm{E}^*]} = \frac{q_1+q_{-2}}{q_1+q_2+q_{-1}+q_{-2}} = \frac{\theta+\mu}{\theta+\mu+1+\theta/(\gamma\mu)}, \tag{5.44}$$

where

$$\theta = \left(\frac{k_1^{\mathrm{o}}k_2(k_{-3}+k_4)[\mathrm{ATP}]}{k_3k_4(k_{-1}+k_2)}\right)\frac{[\mathrm{K}]}{[\mathrm{P}]},\quad \mu = \frac{k_{-3}k_{-4}^{\mathrm{o}}[\mathrm{Pi}]}{k_3k_4}.$$

θ represents the activation strength, that is, the level of kinase [K] to that of phosphatase [P] as an upstream signal. μ represents the basal level of activation in the absence of the kinase.

In a living cellular environment, the μ is very small but $\gamma \sim 10^{10}$ is very large. In fact the product $\gamma\mu$ is very large. Hence we have $f \approx \theta/(1+\theta)$, a hyperbolic curve. This is widely expected when one increases the kinase activity to increase the level of phosphorylation. However, Eq. (5.44) also shows that if $\gamma = 1$, then $f = \mu/(1+\mu)$, which is independent of the level of kinase and phosphatase whatsoever. This is precisely what one expects from a test tube experiment of PdPC in a chemical equilibrium: An enzyme is a catalyst that speeds up a biochemical reaction without changing its equilibrium.

Figure 5.3 shows the fraction of phosphorylation f, according to Eq. (5.44), as a function of θ and other parameters. We note that for large γ, that is, high level of phosphorylation potential, the PdPC as a signaling switch behaves as expected. However, if the energy level is low, then the signal activation can be significantly compromised. More interestingly, we note that the level of irreversibility of the dephosphorylation reaction, μ, plays a critical role. The level of energy, γ, has to be sufficiently greater than the μ^{-1} in order for the biological switch to function properly.

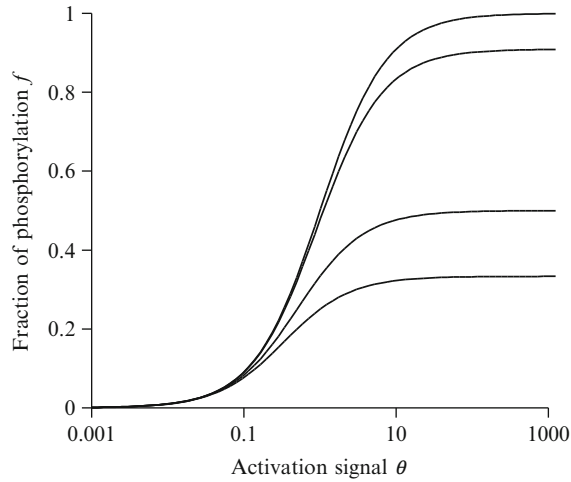

Figure 5.3 Fraction of phosphorylation according to the Eq. (5.44) based on simple reversible kinetics. From top to bottom: $\gamma = 10^{10}$, 10^7, 10^6, and 0.5×10^6, respectively. $\mu = 10^{-6}$ for all the four curves.

5.2. PdPC with Michaelis–Menten kinetics

We now consider the PdPC in Eq. (5.41) following the Michaelis–Menten kinetics (Murray, 2003; Segel, 1975). We assume both the kinase and the phosphatase catalyzed reactions are irreversible. This problem was first worked out by Goldbeter and Koshland (1981); see Qian (2003) for reversible PdPC with Michaelis–Menten kinetics and the consequence of nonequilibrium thermodynamics. The analyses presented below, thus, should be considered as the limiting situation of $\gamma = \infty$. Even though it is not realistic, it gives the upper bound on the various phenomena we analyze. Treating reversible kinase and phosphatase is not difficult, as shown in Section 5.1. But the algebra are often more involved.

With the above assumptions, the concentration change of E* follows a single differential equation

$$\frac{\mathrm{d}[\mathrm{E}^*]}{\mathrm{d}t} = \frac{V_1(\mathrm{E_t} - [\mathrm{E}^*])}{K_1 + \mathrm{E_t} - [\mathrm{E}^*]} - \frac{V_2[\mathrm{E}^*]}{K_2 + [\mathrm{E}^*]}, \tag{5.45}$$

in which $V_1 = k_2 K_t$ and $V_2 = k_4 \mathrm{P}_t$ are the maximal velocities of the kinase and phosphatase, $\mathrm{E_t}$, K_t, and $\mathrm{P_t}$ are the total concentrations of the substrate enzyme, the kinase and the phosphatase; $K_{-1} = (k_{-1} + k_2)/k_1$ and $K_2 = (k_{-3} + k_4)/k_3$ are the Michaelis constants of the kinase for the E and the phosphatase for the E*.

The steady-state fraction of phosphorylation, $f = [\mathrm{E}^*]/\mathrm{E_t}$, satisfies the equation $\mathrm{d}[\mathrm{E}^*]/\mathrm{d}t = 0$. Rearranging some terms, we have

$$\frac{V_1(1-f)}{K_1\mathrm{E_t} + 1 - f} - \frac{V_2 f}{K_2\mathrm{E_t} + f} = 0,$$

which yields (Goldbeter and Koshland, 1981):

$$\theta = \frac{f(K_1\mathrm{E}_t + 1 - f)}{(K_2\mathrm{E_t} + f)(1-f)}, \tag{5.46}$$

in which we let $\theta = V_1/V_2$ to represent again the activation strength.

If both kinase and phosphatase are operating in their linear, nonsaturating regimes, that is, $K_1\mathrm{E_t}$ and $K_2\mathrm{E_t} \gg 1$, then Eq. (5.46) is reduced to

$$f = \frac{\left(\frac{K_2}{K_1}\theta\right)}{1 + \left(\frac{K_2}{K_1}\theta\right)}, \tag{5.47}$$

which is a hyperbolic activation curve as shown in Fig. 5.4D. This is exactly the top curve in Fig. 5.3 with logarithmic abscissa. If, however, both enzymes are highly saturated and operating in the zeroth-order regime,

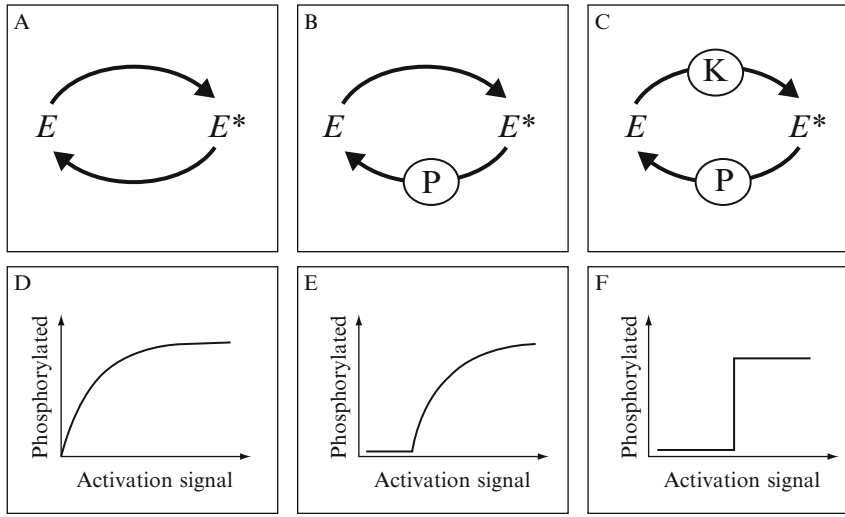

Figure 5.4 PdPC kinetics, $E \rightarrow E^* \rightarrow E$ catalyzed by kinase K and phosphatase P, can operate in different regimes: (A) Both enzymes are in their linear region if the amount of each enzyme is greater than the total substrate $E_t = [E] + [E^*]$, or E_t is less than the Michaelis constants of the enzymes. (B) The kinase is operating in the linear regime but the phosphatase is highly saturated, that is, $[E^*] \ll$the Michaelis constant of the phosphatase. The latter reaction then is zeroth order. (C) Both kinase and phosphatase are zeroth order. The corresponding steady-state levels of phosphorylation $f = [E^*]/E_t$, as function of the signal, defined as the ratio of the kinase activity to that of phosphatase, are shown in (D), (E), and (F), respectively. (D) Hyperbolic activation curve; (E) Delayed onset of activation; (F) Ultrasensitivity.

then K_1E_t, $K_2E_t \ll 1$ and Eq. (5.45) becomes $df/dt = V_1 - V_2$, where $0 \leq f \leq 1$. Therefore, its steady state is simply

$$f = \begin{cases} 0 & \theta < 1, \\ 1 & \theta > 1, \end{cases} \tag{5.48}$$

as shown in Fig. 5.4F. One can also verify this result from Eq. (5.46) by solving the quadratic equation for f. This result is known as zeroth-order ultrasensitivity (Goldbeter and Koshland, 1981).

What has not been widely discussed is when one of the enzymes is operating in the linear regime while the other in the zeroth-order regime. This gives rise to the *delayed onset*, shown in Fig. 5.4B and E (Qian and Cooper, 2008). Let us consider that the phosphatase is the one operating in zeroth-order, then $K_2E_t \ll 1$. In this case, we have the Eq. (5.46) becoming

$$f = \begin{cases} 0 & \theta \le K_1 E_t + 1, \\ 1 - \dfrac{K_1 E_t}{\theta - 1} & \theta \le K_1 E_t + 1. \end{cases} \tag{5.49}$$

We note that the activation curve in Eq. (5.49), that is, Fig. 5.4E, rises from $f = 0$ at $\theta = K_1E_t + 1$ to $f = 0.5$ at $\theta = 2K_1E_t + 1$. Hence, smaller the K_1E_t, sharper the rising. If $K_1E_t \ll 1$, Eq. (5.49) is reduced to Eq. (5.48).

In the stochastic analysis of PdPC in Qian and Cooper (2008), the three cases in Fig. 5.4A–C are called independent, semisequential, and sequential, respectively.

5.3. Substrate specificity amplification

We now focus on the PdPC with zeroth-order phosphatase and first-order kinase, as shown in Fig. 5.4B and E. Let us consider two substrates with different K_1 and K_1', for the proper and improper substrates: $K_1' > K_1$. Then because of the delayed onset characteristics, the above result suggests the ratio of the phosphorylation levels that can be very large in the appropriate range of θ (Fig. 5.5A). Quantitatively, we have

$$\frac{f}{f'} \approx \begin{cases} \dfrac{K_1'}{K_1} & \theta < K_1E_t, \\ \dfrac{(\theta - 1 - K_1E_t)(K_1'E_t + 1 - \theta)}{K_2E_t\theta(\theta - 1)} & 1 + K_1E_t < \theta < 1 + K_1'E_t, \\ \dfrac{\theta - 1 - K_{-1}E_t}{\theta - 1 - K_1'E_t} & \theta > K_1'E_t. \end{cases} \tag{5.50}$$

It is clear that the ratio has a maximum between $1 + K_1E_t$ and $1 + K_1'E_t$. In fact, if $1 \ll K_1E_t \ll K_1'E_t$, the maximum is located very near $\theta = K_1E_t$.

We thus have obtained an interesting biochemical result that is not at all intuitive: The specificity in signaling process can be regulated by the magnitude of the Michaelis constant of the phosphatase, which has *no* direct interaction with the two substrates. This could be a yet to be discovered biological function of "zeroth-order" phosphatase.

We also note that the ratio f/f' can be much greater than K_1'/K_1 (Fig. 5.5B). The selectively in a living cell needs not to be limited by the equilibrium affinity. In open chemical systems, the energy from phosphorylation reaction can amplify the specificity (Qian, 2007).

6. Summary and Challenges

6.1. A little historical reflection

When Newton originally proposed the equation of motion, $F = ma$, and combined with Hook's law for elasticity force $F = -k(x - x_0)$, there was no concept of energy. However, from analyzing the Newton's equation of motion:

$$m\frac{\mathrm{d}^2x}{\mathrm{d}t^2} = -kx, \tag{5.51}$$

Newton, and Leibniz, discovered that

$$\frac{1}{2}m\left(\frac{\mathrm{d}x}{\mathrm{d}t}\right)^2 + \frac{1}{2}kx^2 = \text{constant} \tag{5.52}$$

in the motion. The concept of kinetic energy emerged out of the idea of *vis viva*, which Leibniz defined as the product of the mass of an object and its velocity squared. Energy is a conserved quantity in mechanics. Later on, by introducing the frictional force into the equation of motion and to account for the loss of mechanical energy:

$$m\frac{\mathrm{d}^2x}{\mathrm{d}t^2} = -kx - \eta\frac{\mathrm{d}x}{\mathrm{d}t}, \tag{5.53}$$

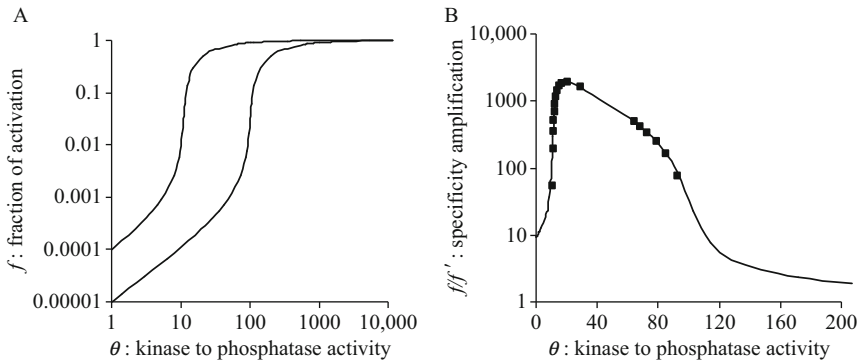

Figure 5.5 Specificity amplification in PdPC with zeroth-order phosphatase and first-order kinase. In (A) the $K_1E_t = 10$ for the upper curve and $K_1'E_t = 100$ for the lower curve following Eq. (5.46), both with $K_2E_t = 0.001$. Hence the conventional affinity difference is 10-fold. For small θ, there is a linear regime. (B) The ratio of f/f' from (A), which is about 10 for small θ, can increase up to 2000 for the optimal $\theta \approx 20$. Eventually for very large θ, $f/f' \approx 1$. The filled squares are according to approximated, analytical formula given in Eq. (5.50).

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{1}{2}m\left(\frac{\mathrm{d}x}{\mathrm{d}t}\right)^2+\frac{1}{2}kx^2\right)=-\frac{1}{2}\eta\left(\frac{\mathrm{d}x}{\mathrm{d}t}\right)^2<0, \tag{5.54}$$

Leibniz claimed that heat consisted of the random motion of the constituent parts of matter—a view shared by Newton, although it would be more than a century until this was generally accepted.

So, we see that the concept of "energy," a term now every person walking on the street uses, is a pure mathematical construction. Energy is clearly related to physical reality, but it is also a concept meaningful to any conservative dynamics which can be modeled by differential equations.

6.2. Entropy: A mathematical concept?

The situation is not different for the concept of entropy: It is clearly related to the thermal molecular systems, but it is also a concept meaningful to any stochastic dynamics.

Entropy is a mathematical concept. It is a quantity intimately associated with random dynamical systems, as we have shown in this chapter for master equations. But in fact it is much more general. For some recent accounts see Gaspard (2004), Jiang *et al.* (2004), Mackey (2003), and Qian *et al.* (2002). Just as Hamiltonian to Hamiltonian systems, and energy to conservative systems (Strogatz, 2001), when applying the stochastic dynamics theory to molecular systems at constant temperature, it is the Gibbs entropy. When applied to communication system, it is Shanon's entropy. But it could also be applied to evolutionary theory (Ao, 2008) and to economical dynamics (Chen, 2005).

At the end of the excellent text (Ben-Naim, 2007), Professor Arieh Ben-Naim discussed the nature of the Second Law and whether it can be derived. On this, I shall respectfully disagree with the author: One indeed *can* derive the Second Law of Thermodynamics, provided that one believes that the molecular physics can be represented by a mathematical theory of Markov processes. Along this line, Gibbs has already started the endeavor a century ago. One simply needs to carry on his tradition by developing a *time-dependent* ensemble theory. This might be indeed the theory of complexity one is looking for (Laughlin *et al.*, 2000; Mitchell, 2009).

REFERENCES

Antognazza, M. R. (2008). Leibniz: An Intellectual Biography. Cambridge University Press, New York.

Ao, P. (2008). Emerging of stochastic dynamical equalities and steady state thermodynamics from Darwinian dynamics. *Commun. Theor. Phys.* **49,** 1073–1090.

Bardi, J. S. (2007). The Calculus Wars: Newton, Leibniz, and the Greatest Mathematical Clash of All Time. Basic Books, New York.
Beard, D. A., and Qian, H. (2008). Chemical Biophysics: Quantitative Analysis of Cellular Systems. *Cambridge Texts in Biomedical Engineering,* Cambridge University Press, Cambridge.
Ben-Naim, A. (2007). Entropy Demystified: The Second Law Reduced to Plain Common Sence. Workd Scientific, New Jersy.
Chen, J. (2005). The Physical Foundation of Economics: An Analytical Thermodynamic Theory. World Scientific, Singapore.
De Donder, T., and Rysselberghe, P. (1936). Theory of Affinity. Stanford University Press, Palo Alto, CA.
Dill, K. A., and Bromberg, S. (2003). Molecular Driving Forces: Statistical Thermodynamics in Chemistry and Biology. Garland Science, New York.
Gaspard, P. (2004). Fluctuation theorem for nonequilibrium reactions. *J. Chem. Phys.* **120,** 8898–8905.
Goldbeter, A., and Koshland, D. E. (1981). An amplified sensitivity arising from covalent modification in biological systems. *Proc. Natl. Acad. Sci. USA* **78,** 6840–6844.
Goldstein, H. (1950). Classical Mechanics. Addison-Wesley, Reading, MA.
Hill, T. L. (1981). Proc. *Natl. Acad. Sci. USA* **78,** 5613–5617.
Hopfield, J. J. (1982). Neural networks and physical systems with emergent collective computational abilities. *Proc. Natl. Acad. Sci. USA* **79,** 2554–2558.
Howard, J. (2001). Mechanics of Motor Proteins and the Cytoskeleton. Sinauer Associates, Sunderland, MA.
Jiang, D.-Q, Qian, M., and Qian, M.-P. (2004). Mathematical Theory of Nonequilibrium Steady States: On the Frontier of Probability and Dynamical Systems. *Springer Lecture Notes in Mathematics* Vol. 1833.
Laughlin, R. B., Pines, D., Schmalian, J., Stojkovi, B. P., and Wolynes, P. G. (2000). The middle way. *Proc. Natl. Acad. Sci. USA* **97,** 32–37.
Mackey, M. C. (2003). Time's Arrow: The Origins of Thermodynamic Behaviour. Dover Publisher, New York.
Marx, K. (1992). Capital I: A Critique of Political Economy. Penguin, New York.
Mitchell, M. (2009). Complexity: A Guided Tour. Oxford University Press, New York.
Murray, J. D. (2003). Mathematical Biology I: An Introduction. 3rd ed. Springer, New York.
Qian, H. (2003). Thermodynamic and kinetic analysis of sensitivity amplification in biological signal transduction. *Biophys. Chem.* **105,** 585–593.
Qian, H. (2005). Cycle kinetics, steady-state thermodynamics and motors—A paradigm for living matter physics. *J. Phys. Cond. Matt.* **17,** S3783–S3794.
Qian, H. (2006). *J. Phys. Chem. B.* **110,** 15063–15074.
Qian, H. (2007). Phosphorylation energy hypothesis: open chemical systems and their biological functions. *Ann. Rev. Phys. Chem.* **58,** 113–142.
Qian, H. (2008). Viscoelasticity of living materials: Mechanics and chemistry of muscle as an active macromolecular system. *Mol. Cell. Biomech.* **5,** 107–117.
Qian, H., and Beard, D. A. (2005). Thermodynamics of stoichiometric biochemical networks in living systems far from equilibrium. *Biophys. Chem.* **115,** 213–220.
Qian, H., and Beard, D. A. (2006). Metabolic futile cycles and their functions: A systems analysis of energy and control. *IEE Proc. Sys. Biol.* **153,** 192–200.
Qian, H., and Cooper, J. A. (2008). Temporal cooperativity and sensitivity amplification in biological signal transduction. *Biochemistry* **47,** 2211–2220.
Qian, H., Qian, M., and Tang, X. (2002). Thermodynamics of the general diffusion process: Time-reversibility and entropy production. *J. Stat. Phys.* **107,** 1129–1141.
Segel, I. H. (1975). Enzyme Kinetics. Wiley, New York.

Shachtman, T. (2000). Absolute Zero and the Conquest of Cold. Mariner Books, Boston, MA.
Shannon, C., and Weaver, W. (1949). The Mathematical Theory of Communication. University of Illinois Press, Illinois.
Strogatz, S. H. (2001). Nonlinear Dynamics and Chaos. Perseus Books Group, New York.
Taylor, H. M., and Karlin, S. (1998). An Introduction to Stochastic Modeling. 3rd Ed. Academic Press, San Diego.