

Chapter 3

Fluctuations in Chemical Reactions

We will survey several concepts and notions related to chemical reactions at various scales and from various viewpoints. In the later chapters we will use them in the energetics of the fluctuating world.

The notion of a molecule belongs to the far from equilibrium states. Chemical reactions are then the transitions among different steady states of molecules, which often accompany the conversion of degrees of freedom between the translational degrees of freedom and the intramolecular ones.

In the survey of macroscopic reaction theory we limit ourselves to the case where the reactions are described in terms of the concentrations of the chemical components and the rate constants. Chemical equilibrium is related to the equilibrium thermodynamics. Inversely, macroscopic open systems can be described as reaction systems. Even within a macroscopic description of chemical reactions, the characteristic scale is a useful notion. We mention as examples the buffer solutions and the Michaelis–Menten kinetics.

At more microscopic scales chemical reactions are described in terms of the number of molecules (i.e., integers) of each chemical species. Stochastic processes of discrete systems are the general framework of chemical reactions on this scale. The master equation is the most often used description of discrete stochastic processes. The *detailed balance* condition is the equilibrium condition expressed by the probabilities of discrete states and the transition rates among these states. The discrete version of Langevin equation is an alternative and equivalent method to the master equation. The continuous Langevin equation (Chap. 1) can be represented as a limit of discrete processes. We take the same examples as those we have taken in the macroscopic description: $A + B \rightleftharpoons AB$, the open system, and the Michaelis–Menten kinetics. It will be useful to find the similarities and differences between the two different scales of description.

3.1 * Background of Chemical Reactions

There are different mechanisms for chemical reactions: the transition through quantum tunneling, the quantal energy injection like photo activations, the molecular collisions induced by thermal motion or by forced molecular injection, the effect of

intermediating substances like catalysts, thermal fluctuations causing large conformational changes in a protein, to mention a few. Each of these mechanisms could be best described on certain appropriate scales of space, time, or energy. Such appropriate scales may range over many orders of magnitude from one case to another. For example, quantum chemistry deals with the order of femtoseconds (10^{-12} s), while the isomerization (conformational change) of protein occurs on the order of milliseconds (10^{-3} s). In this book we limit ourselves to either macroscopic or mesoscopic descriptions where quantum mechanisms do not appear on the surface. We will begin by examining the notion of a molecule.

3.1.1 “Molecule” in Chemical Reaction Is a Nonequilibrium State with Internal Degrees of Freedom

3.1.1.1 “Molecule” as Nonequilibrium State

When one says there is a water molecule, it means there is a stable spatial aggregation of two hydrogen atoms and one oxygen atom. The notion of the macromolecule such as a polymer chain or a protein molecule implies that the aggregation of constituent atoms is maintained stably. Actually, however, no molecular state is stable forever. What we call molecule is usually a nonequilibrium state which is at best metastable or transiently stable. In other words, the (nonequilibrium) notion of the molecule is meaningful only when we are interested in timescale where the molecule maintains its identity.

The importance of the timescale is not particular to the notion of molecules: We can discuss the equilibrium thermodynamics of the glassy material if it has an extremely long though finite relaxation time. Even when we discuss the equilibrium state of a monoatomic ideal gas in a container, we assume implicitly that the container stays stable after infinitely long time when the equilibrium state of the gas is established. In other words, we limit our discussion to the timescale when the container remains in its nonequilibrium state. (This argument can be generalized: The notion of atom also requires the transient stability of the atom.)

In Boltzmann statistical mechanics, the statistical entropy of a thermodynamic state is the logarithm of the whole phase space volume which the system can visit. When the thermodynamic state is defined, the extent of the word “whole” (phase space) should be properly limited.¹ For example, we should specify which kinds of chemical reaction are admitted and which are not within a given timescale.

While such limitations of timescale do not cause problems usually, the exception is when the observation timescale and the relaxation timescale of the system reverse their relative magnitudes. For example, upon raising/lowering the temperature across the glass transition point of a material, or upon addition/depletion of the catalyst of a reaction, the ratio r of these two timescales can switch from

¹ See, Sect. 1.3.3.1.

$r \ll 1$ to $r \gg 1$ and vice versa. Such case will be discussed in detail later (Chap. 7). In this section we assume that the containers of the chemical reaction and the molecules are stable *except* through the chemical reactions which we describe explicitly.

3.1.1.2 State of Molecules

There is a characteristic timescale of environment at which a reactant molecule interacts critically with other reactant molecules or with the environment, through molecular collisions. Another timescale of the molecule is related to its internal dynamics such as vibrational and rotational motions. If the latter dynamics takes place sufficiently rapidly as compared to the former timescale, then we can justify the statistical description of each molecule, and it can be unambiguously represented by its chemical formula or molecular formula (like H_2O).

By contrast, if the time evolution of the internal state of a molecule is slower than the timescale of reactive molecular interactions, we need more parameters to characterize the internal states of the molecule. For example, the flexible polymeric chains or proteins, the deformable tethered membrane, or the soft network of gel, etc., require the conformational parameters other than their chemical formula to correctly describe the chemical reactions.

3.1.1.3 Molecular Reaction Viewed from the Degrees of Freedom

“Molecular reaction” replaces a group of transiently stable aggregated states of atoms by a new group of aggregated states. By taking the reaction, $\text{A} + \text{B} \rightarrow \text{AB}$ as an example, we can characterize the change of molecular states in two different ways.

Transfer of degrees of freedom: The translational degrees of freedom decrease from six to three. The three translational degrees of freedom are compactified. The molecule AB then possesses three internal degrees of freedom, one for vibration and two for rotation.

Correlation among translational degrees of freedom: Among the six independent translational degrees of freedom of monoatomic molecules, A and B, three of them become spatially correlated in the molecule AB due to the binding potential between the atoms. If the reaction takes place in a gas chamber or in water, this forced correlation reduces the gas pressure or the osmotic pressure, respectively.

The consequences of the forced correlation or the compaction of translational degrees of freedom are not limited to the entropic effect but there is also an energetic effect: monovalent cations could make dimers if the electrostatic intradimer repulsion is stabilized by a molecular binding force. Since the divalent cations feel less repulsion among each other than do the monovalent cations of the same charge density, the divalent cation dimers form a more dense counterionic cloud around an

anion than monovalent cations do. This is a qualitative way to understand why the overcharging around a charged colloid is more effective by multivalent counterions than the monovalent ones [1].

The stability of molecular states is due to the high free-energy barrier (relative to $k_B T$) associated with the destabilizing reactions. Since the reaction rate is mainly governed by the exponential Boltzmann factor, the reactivity is efficiently changed if the free-energy barrier is modified. This exponential dependence enables the near discrete switching on/off of reactions in inorganic and organic matter. The energetic aspect of controlling the barrier height will be discussed later (Chap. 7).

On the molecular level, the description of chemical reactions as well as open system has to incorporate the transfer of degrees of freedom. Concomitantly the energetics of chemical reaction and open system on the fluctuation level must take into account the change in degrees of freedom (see Sect. 4.2.3).

3.2 Macroscopic Description

We survey below briefly the framework of the macroscopic reaction theory of dilute solutions, using again the example of the reaction, $A + B \rightarrow AB$. The solution is assumed to be spatially homogeneous.

3.2.1 * *Law of Mass Action Relates the Rate Constants of Reaction to the Canonical Equilibrium Parameters*

3.2.1.1 Rate Equation and Rate Constant

For dilute solutions of molecules having low molecular weight, the speed of reaction depends only on the concentrations of the chemical components and the kinetic parameters called the (reaction) *rate constants*. We will represent by $[A]$, $[B]$, and $[AB]$ the concentration of the A, B, and AB molecules, respectively. The rate of production of the AB molecules by the (irreversible) reaction, $A + B \rightarrow AB$, is

$$\frac{d[AB]}{dt} = k[A][B], \quad (3.1)$$

where the parameter k is the rate constant of this reaction. The macroscopic equation for the rate of production, like (3.1), is called a rate equation. $k[A][B]$ indicates the frequency of the “collisions,” or encounter, between an A molecule and a B molecule. The dimension and magnitude of k depend on the choice of the unit of concentration, $[A]$, etc. In physical chemistry one usually uses the molar concentration, or molarity, [no. of mols of solute]/[no. of liters of solution].² In this book, however, we will adopt the following unit, unless stated otherwise explicitly:

²The use of mol in the definition is reasonable in the sense that macroscopic observers cannot count the number of solute molecules.

$$[X] \equiv \frac{(\text{no. of X molecules})}{(\text{volume in cm}^3 \text{ of solution})}. \quad (3.2)$$

We choose this unit with a view to maintain continuity with the more microscopic level discussions in later sections.

If we also take into account the reverse reaction, i.e., $A + B \rightleftharpoons AB$, we introduce another rate constant, k' , which has different dimensionality from that of k :

$$\frac{d[AB]}{dt} = k[A][B] - k'[AB]. \quad (3.3)$$

The second term on the right-hand side, $-k'[AB]$, implies that an isolated AB molecule has an average inverse lifetime, k' . The law (3.3) is valid in the limit of (i) dilute solution and (ii) near equilibrium. We will discuss a more general case of nondilute solution in Sect. 3.3.3.

3.2.1.2 Chemical Equilibrium

A reaction system is said to be closed (with respect to the chemical reactions) if (i) there is no exchange of molecules A, B, or AB between the system and the outside and also (ii) there is no mechanism to change the rate constants.³ If the above system, $A + B \rightleftharpoons AB$, is closed, the change of [A] and of [B] are given by⁴

$$d[A] = d[B] = -d[AB]. \quad (3.4)$$

Application of the zeroth law of thermodynamics to the whole system, the closed reaction system *plus* the thermal environment, implies that this isolated system will reach the thermal equilibrium after infinitely long time. The steady state of (3.3), i.e.,

$$\frac{d[AB]}{dt} = \frac{d[A]}{dt} = \frac{d[B]}{dt} = 0 \quad (3.5)$$

then gives the chemical equilibrium and satisfies

$$\frac{[AB]}{[A][B]} = \frac{k}{k'} \quad (\text{equilibrium}). \quad (3.6)$$

This type of equilibrium condition, where the powers of concentration appear in the denominator and numerator, is called the *law of mass action*. The ratio of the kinetic parameters on the right-hand side is called the *equilibrium constant*, which depends only on the thermodynamic parameters, as we will see below.

³For example, the sedimentation of [AB] would decrease k' .

⁴We omit the dt in the denominator.

If the reaction is not closed, for example, under the steady injection of A and B and the removal of AB, the stationary condition, (3.5), does not give equilibrium.

3.2.1.3 Chemical Equilibrium and Macroscopic Thermodynamics

If the law of mass action characterizes a thermal equilibrium, the relation (3.6) should be equivalent to the equilibrium condition of macroscopic thermodynamics. In the latter framework, we require the minimum of the Gibbs free energy $G(T, p, N_A, N_B, N_{AB})$ with respect to N_{AB} .⁵ This minimization yields

$$\mu_A + \mu_B = \mu_{AB}. \quad (3.7)$$

On the other hand, the chemical potential of the solute molecules in a dilute solution is

$$\mu_A = \mu_A^0 + k_B T \ln[A], \quad \text{etc.} \quad (3.8)$$

with μ_A^0 being a constant. Therefore, the equilibrium condition (3.7) is $[AB]/([A][B]) = \exp[-(\mu_{AB}^0 - \mu_A^0 - \mu_B^0)/k_B T]$. Identifying this expression with (3.6), we reach the following relation between the rate constants and the thermodynamic parameters:

$$\frac{k}{k'} = \exp\left[\frac{\mu_A^0 + \mu_B^0 - \mu_{AB}^0}{k_B T}\right]. \quad (3.9)$$

3.2.1.4 Equilibrium with a Particle Reservoir – Open System

When the reaction system, $A + B \rightleftharpoons AB$, allows for the exchange of the AB molecules with its particle reservoir, the rate equations are

$$\begin{aligned} \frac{d[AB]}{dt} &= k[A][B] - k'[AB] - k_{\text{out}}[AB] + k_{\text{in}}, \\ \frac{d[A]}{dt} &= -k[A][B] + k'[AB] = \frac{d[B]}{dt}. \end{aligned} \quad (3.10)$$

Here the exchange with the particle reservoir of [AB] is characterized by the two rate constants, $-k_{\text{out}}$ and k_{in} . The stationary condition, (3.5), yields the following two independent relations as the law of mass action:⁶

⁵Note that $N_A = [A]V$ etc., where V is the volume of the system. Under the isothermal and isobaric condition, the second law requires $\Delta(E - TS + PV) = \Delta G \leq W = 0$ for any spontaneous changes. dN_A and dN_B are dependent on dN_{AB} according to (3.4).

⁶If the particle reservoir exchanges (only or also) A molecules, the equation for $d[B]/dt$ still assures the law of mass action. If the system exchanges all the species of molecules, the law of mass action will no more hold.

$$\frac{[A][B]}{[AB]} = \frac{k'}{k}, \quad [AB] = \frac{k_{\text{in}}}{k_{\text{out}}} \quad (\text{equilibrium}). \quad (3.11)$$

At the equilibrium, the total Gibbs free-energy, $G(T, p, N_A, N_B, N_{AB}) + G_{\text{res}}(T, p, N_{AB,\text{res}})$, should be minimized under the constraints of particle conservation, $dN_A + dN_{AB} + dN_{AB,\text{res}} = 0$ and $dN_B + dN_{AB} + dN_{AB,\text{res}} = 0$. This yields⁷

$$\mu_A + \mu_B = \mu_{AB} = \mu_{AB,\text{res}}, \quad (3.12)$$

where $\mu_{AB,\text{res}}$ is the chemical potential of the particle environment of AB molecules. With (3.11) we have the following relations:

$$\frac{k}{k'} = \exp\left[\frac{\mu_A^0 + \mu_B^0 - \mu_{AB}^0}{k_B T}\right], \quad \frac{k_{\text{in}}}{k_{\text{out}}} = \exp\left[\frac{\mu_{AB,\text{res}} - \mu_{AB}^0}{k_B T}\right]. \quad (3.13)$$

Remarks

The chemical reaction theory emphasizes the transformation of the mass, but the energetic aspects (change of free energy, endothermic, or exothermic, etc.) are treated separately using thermodynamics. If we use stochastic energetics, both mass transformation and energetics are discussed on the basis of a single event of the reaction.

The chemical potential is a quantity on the level of the description where the particles are anonymous. The chemical potential (e.g., (3.8)) does not represent the free energy carried by an individual molecule. μ_A is the energetic interpretation of the relative probability of the arrival of anonymous molecule A, $\propto [A]e^{\mu_A^0/k_B T}$, using the form of the Boltzmann factor, $e^{\mu_A/k_B T}$.

3.2.2 *Large Separation of the Rate Constants Causes Different Regimes of Reaction and Rate-Limiting Processes

It often occurs that two or more reactions related to the same molecular species have widely different equilibrium constants. That the equilibrium constants depend exponentially on the chemical parameters, like μ_A^0 in (3.9) and (3.13), explain this.

Because of this aspect, we expect that a chemical reaction system can exhibit qualitatively different behaviors in different regimes. The following two simple examples demonstrate how the phenomena of different scales are treated.

⁷ We may use the method of *Lagrange multipliers*: The requirement of $d[G(x, y, z) + G_{\text{res}}(\bar{z})] = 0$ under the constraints, $d(x + z + \bar{z}) = 0$ and $d(y + z + \bar{z}) = 0$, is equivalent to the constraint-free requirement, $d[G(x, y, z) + G_{\text{res}}(\bar{z}) - \lambda_x(x + z + \bar{z}) - \lambda_y(y + z + \bar{z})] = 0$, with λ_x and λ_y being unknown, called the *Lagrange multipliers*. The parameter set, (x, y, z, \bar{z}) , stands for $(N_A, N_B, N_{AB}, N_{AB,\text{res}})$. Then $\mu_A = \lambda_x$, $\mu_B = \lambda_y$, $\mu_{AB} = \lambda_x + \lambda_y$, and $\mu_{\text{res}} = \lambda_x + \lambda_y$.

3.2.2.1 Titration and Buffer Solution

The object is to study the titration and the buffer solution of acid–base system starting from a unified framework. The solution (1ℓ in total) is prepared from a_0 mol of acid, HA, b_0 mol of a base, BOH, and pure water. The base is assumed to be strong base, so that it 100% dissociates ($\text{BOH} \rightarrow \text{B}^+ + \text{OH}^-$) into B^+ (b_0 mol) and OH^- (b_0 mol). We study how the amount of the hydronium ion $h = [\text{H}_3\text{O}^+]$ or equivalently $\text{pH} \equiv -\log_{10} h$ is related to the initial amount of the base b_0 . This relation results from the two mechanisms: the water dissociation equilibrium, $[\text{H}_3\text{O}^+][\text{OH}^-] = K_w$,⁸ or

$$h(b_0 + h - y) = K_w, \quad (3.14)$$

and the acid dissociation equilibrium, $[\text{H}_3\text{O}^+][\text{A}^-]/[\text{HA}] = K_a$, or

$$\frac{hy}{a_0 - y} = K_a, \quad (3.15)$$

where $y = [\text{A}^-] = a_0 - [\text{HA}]$, and K_w and K_a are the equilibrium constants of the water and the acid, respectively, at a given temperature. Elimination of y from (3.14) and (3.15) yields

$$b_0 - a_0 = \frac{K_w}{h} - C(h, a_0, K_a)h, \quad (3.16)$$

where $C(h, a_0, K_a) = 1 + \frac{a_0}{K_a + h}$. Equation (3.16) is called the Charlot equation. If the acid HA is also a strong acid ($K_a \gg a_0$) which dissociates 100% into ions through $\text{HA} + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{A}^-$, then $C_\infty \equiv \lim_{K_a \rightarrow \infty} C(h, a_0, K_a) = 1$. In this case the solution behaves, $a_0 - b_0 \simeq h$ for $h \gg \sqrt{K_w}$ and $b_0 - a_0 \simeq K_w/h$ for $h \ll \sqrt{K_w}$, with very narrow range of crossover, $\Delta|b_0 - a_0| \sim \sqrt{K_w}$, around the equivalence point, $b_0 = a_0$ with $h = \sqrt{K_w}$.

If the acid HA is a weak acid (not very large K_a), but if its dissociation, $\text{HA} + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{A}^-$, is much stronger than the dissociation of water ($2\text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{OH}^-$), there can arise the situation where the nondimensional parameters, $X \equiv K_w/a_0^2$ and $Y \equiv K_a/a_0$ satisfy $X \ll Y \ll 1$. Figure. 3.1 shows an example of pH vs. $b_0 - a_0$ for $a_0 = 1$, $K_w = 10^{-14}$ and $K_a = 10^{-5}$. In this case, one regime $h/K_a \ll 1$ is again the crossover between $a_0 - b_0 \simeq h/Y$ for $h \gg \sqrt{K_w K_a/a_0}$ and $b_0 - a_0 \simeq \frac{K_w}{h}$ for $(0 <) h \ll \sqrt{K_w K_a/a_0}$, across the equivalence point $h = \sqrt{K_w K_a/a_0}$ (i.e., $h/a_0 = \sqrt{XY}$). At the equivalence point, the pH is shifted toward basic by $-\frac{1}{2} \log_{10} Y$. The consistency of the assumption $h/K_a \ll 1$ is verified since $\frac{h}{K_a} = \left\{ \frac{X}{Y} \right\}^{1/2} \ll 1$ at the equivalence point.

⁸In molar unit, what would be the denominator, $[\text{H}_2\text{O}] = 55.5$, is roughly of order 1 and conventionally suppressed.

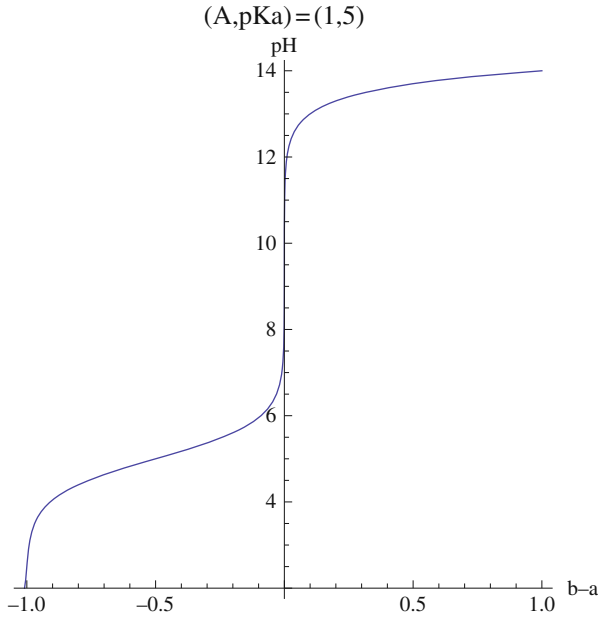


Fig. 3.1 pH vs. $b_0 - a_0$ for $a_0 = 1$, $K_w = 10^{-14}$ and $pK_a = 5$, i.e., $K_a = 10^{-5}$

The new regime, called the *buffer regime*, is $h/K_a \equiv 10^{-\text{pH} + pK_a} \sim 1$ in (3.16). If we assume $h \ll a_0$ and $\frac{K_w}{h} \ll a_0$ in (3.16), h/K_a is written as $\frac{h}{K_a} \simeq \frac{b_0 - a_0}{b_0}$. It implies that, as far as $\frac{b_0 - a_0}{b_0} \sim 1$, the pH of the solution is kept at around $\text{pH} \simeq pK_a \equiv -\log_{10} K_a$. The above assumptions are consistent since $\frac{h}{a_0} \sim \frac{K_a}{a_0} = Y \ll 1$ and $\frac{K_w}{h a_0} \sim \frac{K_w}{K_a a_0} = \frac{X}{Y} \ll 1$. The buffering regime is, therefore, realized due to the double inequalities, $X \ll Y \ll 1$.

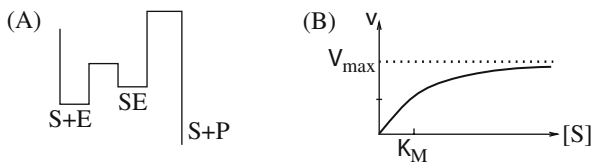
3.2.2.2 Michaelis–Menten Kinetics

Michaelis–Menten kinetics is one of the fundamental reaction schemes in biochemistry, because it describes a catalytic (enzyme) reaction and it also applies to many practical situations. We describe this kinetic scheme below and discuss the generality of this kinetics from the viewpoint of characteristic scales or the rate-limiting processes.

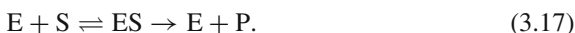
Reaction with a Catalyst

A catalyst is a chemical substance which is not consumed in the reaction but increases the rate constant of the reaction in both the forward and the backward directions by the same factor. The catalyst, therefore, does not change its equilibrium constant defined in Sect. 3.2.1.4. In biology, catalytic proteins are called the enzymes.

Fig. 3.2 (A) Schema of Michaelis–Menten reaction. (B) Rate of production v as function of substrate concentration, $[S]$. See (3.21)



A simple 1:1 reaction between a Substrate (S) molecule and a Product (P) molecule catalyzed by an Enzyme (E) is $E + S \rightleftharpoons E + P$. When we are interested in the dependence on the enzyme concentration, $[E]$, we do not simplify this scheme as $S \rightleftharpoons P$. One of the representative schemas of enzymic reaction is the Michaelis–Menten kinetics which has been introduced around 1913. The schema of Michaelis–Menten kinetics is



In this schema we assume the following circumstance, see Fig. 3.2 (A):

1. The direct reaction, $S \rightleftharpoons P$, is slow enough to be ignored.
2. There is a transition state called Enzyme–Substrate complex (ES).
3. The total concentration of the enzyme, $[E]^{tot} = [E] + [ES]$, is finite.
4. At most one substrate particle, S, can interact at any time with an enzyme particle (protein).
5. $[P]$ is much smaller than the equilibrium value, so that the backward reaction, $ES \leftarrow E + P$, can be neglected.

These hypotheses might look very particular among many other possibilities. Nevertheless we will argue later that the above schema (3.17) is rather general from the viewpoint of the timescales of reaction.

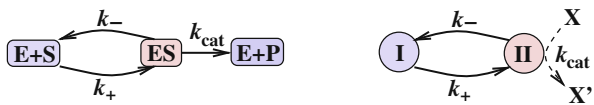
Michaelis–Menten Equation

Let us denote by k_{cat} the rate constant of the forward reaction, $ES \rightarrow E + P$. See Fig. 3.3 (*left*). We seek the rate of production,

$$\frac{d[P]}{dt} = k_{cat}[ES], \quad (3.18)$$

when the preceding step of complex formation has reached the steady state:⁹

Fig. 3.3 Michaelis–Menten reaction (*left*) and its generalized form (*right*). The change $X \rightarrow X'$ requires the transition $I \rightarrow II$



⁹This condition is often attributed to Briggs and Haldane.

$$\frac{d[\text{ES}]}{dt} = k_+[\text{E}][\text{S}] - (k_- + k_{\text{cat}})[\text{ES}] = 0. \quad (3.19)$$

This equation leads to the relation¹⁰

$$\frac{[\text{E}][\text{S}]}{[\text{ES}]} = \frac{k_- + k_{\text{cat}}}{k_+}. \quad (3.20)$$

From this equation, we eliminate [E] using $[\text{E}] = [\text{E}]^{\text{tot}} - [\text{ES}]$ and then we substitute the resulting [ES] as function of [S] into (3.18). We then obtain the desired result, which is called the Michaelis–Menten equation (See Fig. 3.2 (B)),

$$v \equiv k_{\text{cat}}[\text{ES}] = \frac{V_{\text{max}}[\text{S}]}{K_{\text{M}} + [\text{S}]}, \quad (3.21)$$

where we have introduced the maximal production rate, V_{max} , for $[\text{S}] = +\infty$, and the so-called Michaelis–Menten constant, K_{M} :

$$V_{\text{max}} \equiv k_{\text{cat}}[\text{E}]^{\text{tot}}, \quad K_{\text{M}} \equiv \frac{k_- + k_{\text{cat}}}{k_+}. \quad (3.22)$$

When $[\text{S}] = K_{\text{M}}$, we have $v = \frac{1}{2}V_{\text{max}}$. To estimate these parameters from experimental data of v and $[\text{S}]$, the sigmoidal curve, (3.21), is often replotted as the linear plot between v^{-1} and $[\text{S}]^{-1}$ or between $v^{-1}[\text{S}]$ and $[\text{S}]$.¹¹

As a model of chemical reaction, the Michaelis–Menten scheme is related to the transient state [Eyring's] theory (see, for example, [2] Chap. 28) and also to Kramer's theory [3]. The latter refined the notion of the transition state as a group of states between which the molecule diffuses. The identification of the transient state(s) in complex reactions is among contemporary topics [4].

Generality of the Michaelis–Menten Kinetics

When many enzymatic reactions are mutually linked and form a network (e.g., the metabolic network), there can be several key reactions – the rate-limiting reactions – which determines the global rate of the reactions. In order for a reaction to be the key reaction, there must not be other important bypassing or substituting reactions. Moreover, it is necessary that (i) the activation energy barrier of the reaction is high (even in the presence of enzyme) and/or (ii) the number of enzymes is limited and many substrate molecules are waiting for the unbound enzyme. The substrate S for this key reaction is a product of the preceding (upstream) reaction(s),

¹⁰ Although (3.20) takes the form of the law of mass action, the system is not in equilibrium. The exception is when $k_{\text{cat}} \ll k_-$ holds. The approximation of neglecting k_{cat} in (3.19) is called the rapid-equilibrium assumption.

¹¹ The latter representation is called the Hanes–Wolf plot.

and the product P for this key reaction is a substrate of the following (downstream) reaction(s). Thus, if the product of the upstream reaction is supplied faster than it is converted into P, then the substrate S stays among $E + S$ and ES states, and the quasi-equilibrium (rapid equilibrium), $E + S \rightleftharpoons ES$, is realized. Also, if the substrate of the downstream reaction is consumed faster than it is converted from S, then the product P has little probability to be bound to E to form ES , and the unidirectionally reaction, $ES \rightarrow E + P$, is realized. These two features are what constitute the schema of Michaelis–Menten kinetics. Therefore, the Michaelis–Menten schema describes a general feature of the key reactions. The formula (3.21) shows that the key reaction is *controlled* by the total number of the enzyme, $[E]_{\text{tot}}$.¹²

If a reaction has the substrate concentration, $[S]$, much smaller than the K_M , then this reaction cannot be controlled by $[E]_{\text{tot}}$, and the reaction is not the key reaction. If a lot of enzyme $[E]_{\text{tot}}$ is injected in a key reaction, then there would be a shortage of the substrate and the process is no more controlled by this reaction, i.e., the reaction ceases to be the key reaction. In brief, the Michaelis–Menten kinetics works when and where the reaction in question is among the key reactions in the network. In biochemical reaction network the change of the *activity* of enzymes¹³ may change dynamically the locations of the key reactions.

The notion of the key reaction described above is not limited to the bulk enzymatic reaction in solution. The production rate of the form of (3.21) is found in other conditions: for the reaction with a surface catalyst the rate of production obeys the form of (3.21). If the concentration $[S]$ is higher than K_M , then most catalyst molecules are occupied, and it limits the production rate. For crystal growth from vapor or from solution competition between bulk diffusion and surface kinetics leads to the growth velocity in the form of (3.21).

There is another interpretation of the Michaelis–Menten equation, which also explains why Michaelis–Menten-type behavior is found in a variety of situations. See Fig. 3.3 (right). If we look back to the derivation of (3.21), we find that the mathematical origin of its saturating feature is found simply in the bistable transition between the “states,” $E + S$ and ES . See Fig. 3.2. Wherever this (quasi) equilibrium to-and-fro exists, any observable linearly related to the occupied fraction of the ES state should show Michaelis–Menten type saturation.¹⁴ For example, if S and E are, respectively, the ATP-hydrolyzing motor protein and its filament, then the ATP consumption rate should obey the curve of (3.21) since ATP hydrolysis is catalyzed by the motor–filament interaction. In this case the products, ADP and inorganic phosphate (Pi), are not fragments of a motor protein.

¹²Describing the dynamics of a reaction network by focusing on the rate-limiting reactions is similar in idea to what is done in the statistical dynamics, that is, reducing dynamical variables by focusing on the slowly varying ones.

¹³i.e., The ability to function as enzyme.

¹⁴The fraction of the occupied enzyme, $[ES]/[E]_{\text{tot}}$, is $[S]/(K_M + [S])$, which saturates for $[S] \gg K_M$.

3.3 Stochastic Description

3.3.1 *Stochastic Transitions Among Discrete States Are Described by Master Equation or Discrete Langevin Equation*

Rate equations are not the fundamental equations but can be derived from more microscopic levels. In order to address the chemical reaction on more microscopic scales, we survey the framework of stochastic processes over discrete states. The master equation describes the evolution of instantaneous probabilities, as the Fokker–Planck equation does for continuous states. As the latter was derived from the Langevin equation, the master equation can be derived from the discrete Langevin equation. Gillespie algorithm is an efficient method to generate discrete stochastic processes.

We specify the class of master equations which allow *detailed balance (DB)* among the discrete states. For this class of systems the global steady state is the canonical equilibrium. The transition rates and the equilibrium probability can then be represented in terms of a potential (free-energy) landscape.

Stochastic description of chemical reactions usually uses the master equation, where the discrete states are distinguished by the number of molecules of each chemical species. The (continuous) Langevin equation can be regarded as a limit of discrete stochastic process. The condition of the detailed balance is related to the Einstein's relation.

3.3.1.1 * Basic Concepts

Discrete States

Unlike the quantum level description, where the microscopic states of a finite system are essentially discretized, we refer in this book the approximately discretized groups of continuous states as the discrete states: Suppose that the state of a system undergoes, for most of the time, small fluctuations around one of the discrete representative states and undergoes, only occasionally, rapid jumps from around a representative state to the domain of other representative state. In such cases, we can simplify the description of the evolution of the system by the use of coarse graining both in state and time. For example, if a conformational change of a protein is described as $S \rightleftharpoons P$, it implies that many substates of the protein are represented by either S or P and that the substates joining these two groups of substates are ignored.¹⁵

Hereafter we represent by S_j , etc., the discrete states of a system (obtained by the above mentioned coarse graining), where the suffix j takes, for example, an integer number or a set of integer numbers.

¹⁵ One can imagine S=coiled state and P=globular state.

State Transition and Markov Approximation

Temporal change among discrete states is called state transition. We will regard transitions as instantaneous events. That is, we ignore the time lapse of each transition. Such description presupposes that (1) in most cases the system stays in the same state for much longer time than the time of transition and (2) the time resolution of the description is coarser than the time of transition.

We further suppose that the consecutive state transitions are Markovian, that is, the statistical characteristic of the transition from the present state S_j is independent of the previous transition to this state, see Sect. 1.2.1.4. Such description presupposes that in most cases the system stays in the same state for the time long enough so that the intrastate fluctuations erase the memory of the system's previous state.

Transition Rate

We denote by $I_i = \{j\}_i$ the set of indices of the states $\{S_j\}$ that the state S_i of the system can make direct transitions.¹⁶ The so-called transition rate, $w_{i \rightarrow j}$, from the discrete state S_i to the discrete state S_j ($j \in I_i$) is defined as follows:

- Suppose that a system is in the state S_i at a time t .
- The (conditional) probability that the system makes the transition to a different state S_j during an infinitesimal time lapse, $dt (> 0)$, is $w_{i \rightarrow j} dt$.

As a result, the probability that the system remains in the same state S_i at $t + dt$ is $(1 - \sum_{j \in I_i} w_{i \rightarrow j} dt)$.

We recall the first passage time, introduced in Sect. 1.3.3.3: The transition from the state i to the other state can correspond to the exit from a basin Ω of a potential energy $U(x)$. This was the idea of Kramers to calculate the transition rate [3].¹⁷ The average first passage time (FPT) is related to $(\sum_{j \in I_i} w_{i \rightarrow j})^{-1}$. To assess the individual transition rate, $w_{i \rightarrow j}$, we will need to solve the first passage problem under constraints. In the context of FPT, the Markov approximation amounts to the neglect of the initial position dependence of the first passage time.

3.3.1.2 * Statistical Approach – Master Equation

Probability Flux

The transition rate $w_{i \rightarrow j}$ characterizes the redistribution of the (conditional) probability from the state S_i to S_j per unit of time. We can generalize this notion to the case where we find a system in the state S_i with the probability of P_i at present time. Then the redistribution of the probability through all the possible transitions during infinitesimal time, $dt (> 0)$, constitutes a network of fluxes of probabilities. Between

¹⁶ By definition, $i \notin I_i$.

¹⁷ A review [5] surveys many papers after [3] up to 1990.

an arbitrary pair of states, S_i and S_j , there is the flow of probability $P_j w_{i \rightarrow j}$ from S_i to S_j and $P_i w_{j \rightarrow i}$ from S_j to S_i . We call the net flow of the probability per unit of time the (net) probability flux and denote it by $J_{i \rightarrow j} (= -J_{j \rightarrow i})$:

$$J_{i \rightarrow j} = P_i w_{i \rightarrow j} - P_j w_{j \rightarrow i} = -J_{j \rightarrow i}. \quad (3.23)$$

For later convenience, we complement the definitions; $J_{i \rightarrow j} \equiv 0$ ($\forall j \notin I_i$), especially, $J_{i \rightarrow i} \equiv 0$.

For a finite time interval, Δt , the redistribution of the probabilities from S_i to S_j corresponds to many different types of state transitions, such as $S_i \rightarrow S_k \rightarrow S_j$ or $S_i \rightarrow S_j \rightarrow S_i \rightarrow S_j$, in addition to the direct one. In the limit of $\Delta t \rightarrow 0$, however, all the indirect transitions have probabilities of higher order of Δt , and the redistribution of the probability is described only by the direct transitions, $J_{i \rightarrow j}$.

Master Equation

Let us denote by $P_i(t)$ the probability to find the system at time t in the state S_i . Given the concept of the probability flux (3.23), the redistributed probabilities $\{P_i(t + dt)\}$ should satisfy

$$P_i(t + dt) = P_i(t) - \sum_j J_{i \rightarrow j} dt.$$

Then we have the following evolution equation for $\{P_i(t)\}$ called the *master equation*:

$$\frac{dP_i(t)}{dt} = - \sum_j J_{i \rightarrow j}, \quad (3.24)$$

where the sum runs for all states, S_j .¹⁸ Because of the identity, $J_{j \rightarrow i} = -J_{i \rightarrow j}$, the total probability, $\sum_i P_i(t)$, is conserved: $\frac{d}{dt} \sum_i P_i(t) = 0$. Different approximation methods to deal with the master equation are found in, for example, the textbooks [6, 7] or monographs [8, 9].

Steady State

The steady state (or the stationary state) of the master equation is defined such that $dP_j(t)/dt = 0$ for every state, S_j . The steady state does *not* imply the flux-free state: $J_{i \rightarrow j} = 0$. A simplest model may be the three-state system with the transition rates being $w_{1 \rightarrow 2} = w_{2 \rightarrow 3} = w_{3 \rightarrow 1} \equiv w > 0$ and $w_{2 \rightarrow 1} = w_{3 \rightarrow 2} = w_{1 \rightarrow 3} \equiv w' > 0$

¹⁸The expression (3.24) has the same structure as the equation of continuity or the mass conservation, where the sum on the right-hand side is the divergence of the flux.

($w \neq w'$). The steady state of this model is $P_1 = P_2 = P_3 = 1/3$ but the probability flux is nonzero; $J_{1 \rightarrow 2} = J_{2 \rightarrow 3} = J_{3 \rightarrow 1} = (w - w')/3$.

Convergence to a Steady State

It is often observed the situation where the evolution of the probabilities $\{P_j(t)\}$ is convergent to a nonequilibrium steady state, like the above simple example. The convergence to an equilibrium state has long been understood using variational inequality about the entropy, $-\sum_j P_j \ln P_j$, under appropriate constraints (on energy, volume, etc.) [10]. Recently, variational inequality has been developed also for the nonequilibrium steady states. It is the minimization of the so-called the Kullback–Leibler distance or the relative entropy (see, for example, [11]). For two sets of normalized probabilities, $\mathbf{P} \equiv \{P_j\}$ and $\mathbf{Q} \equiv \{Q_j\}$ ($j = 1, \dots, n$), we denote by $D(\mathbf{P} \parallel \mathbf{Q})$ the Kullback–Leibler distance of \mathbf{P} relative to \mathbf{Q} and define as follows:

$$D(\mathbf{P} \parallel \mathbf{Q}) \equiv \sum_{i=1}^n P_i \ln \frac{P_i}{Q_i} (\geq 0). \quad (3.25)$$

The continuous version of this quantity has been introduced in Sect. 1.2.3.2, where the nonnegativity of this quantity has been shown.¹⁹ When the time-discretized probability \mathbf{P} converges to the steady-state probability \mathbf{Q} , the $D(\mathbf{P} \parallel \mathbf{Q})$ monotonically decreases to 0. Below is a brief derivation. The technical details are given in Appendix A.3.1.

1. If the time and the states are discretized, the evolution of the probability \mathbf{P} by the master equation can be formally written as a *Markov chain*, i.e., the discrete-time discrete state Markov process,²⁰

$$\mathbf{P} \equiv \{P_i\} \mapsto \mathbf{K}\mathbf{P} \equiv \left\{ \sum_{j=1}^n K_{ij} P_j \right\} \quad (i = 1, \dots, n), \quad (3.26)$$

where the $n \times n$ matrix $\mathbf{K} \equiv \{K_{ij}\}$ ($i, j = 1, \dots, n$) has nonnegative components, $K_{ij} \geq 0$, and satisfies the sum rule, $\sum_{i=1}^n K_{ij} = 1$ for $j = 1, \dots, n$. In order to recover the continuous time version, we identify $\mathbf{P}(t + dt) = \mathbf{K}\mathbf{P}(t)$, where $\mathbf{P}(t + dt) = \{P_i(t + dt)\}$ ($i = 1, \dots, n$) and $\mathbf{K} = 1 + \mathcal{O}(dt)$.

2. With this Markov chain, the following inequality holds:

$$D(\mathbf{P} \parallel \mathbf{Q}) \geq D(\mathbf{K}\mathbf{P} \parallel \mathbf{K}\mathbf{Q}). \quad (3.27)$$

¹⁹Despite the word “distance,” this quantity is not symmetric; $D(\mathbf{P} \parallel \mathbf{Q}) \neq D(\mathbf{Q} \parallel \mathbf{P})$.

²⁰For the Markov process, see Sect. 1.2.1.4.

The proof is given in Appendix A.3.1.²¹

3. Suppose that \mathbf{Q} is a steady state of this Markov chain, $K\mathbf{Q} = \mathbf{Q}$. Then (3.27) implies

$$D(\mathbf{P} \parallel \mathbf{Q}) \geq D(K\mathbf{P} \parallel \mathbf{Q}) \quad (K\mathbf{Q} = \mathbf{Q}). \quad (3.28)$$

4. If the Markov chain, $\{\mathbf{P}, K\mathbf{P}, K^2\mathbf{P}, \dots\}$, converges to this steady state \mathbf{Q} , then $D(K^m\mathbf{P} \parallel \mathbf{Q})$ must decrease monotonically to 0.

The inequality (3.27) can be interpreted in the context of Stein’s lemma [11], which states the following: Given n events obeying the i.i.d. probability \mathbf{P} , the chance of mistaking \mathbf{P} for another probability \mathbf{Q} is given by the following formula of LDP (see Sect. 1.1.2.3): $\sim \exp[-nD(\mathbf{P} \parallel \mathbf{Q})]$. According to this lemma, the inequality (3.27) implies that the pair $K\mathbf{P}$ and $K\mathbf{Q}$ is less distinct as compared to the pair \mathbf{P} and \mathbf{Q} , and, therefore, there is more chance of mistaking.

Notice that, if a system does not tend to a steady state, the above result does not apply directly. For example, the time evolution of (x, p) by a Hamiltonian $H(x, p)$ is a Markov process. But its evolution starting from a definite initial condition, $P(x, p, 0) = \delta(X - x(0))\delta(P - p(0))$, does not attain any steady state.

In conclusion, the variational principle of the steady state is not a unique property of the equilibrium distribution. Which aspects of the equilibrium thermodynamics are conserved in the nonequilibrium steady states is the question under active field research. See, for example, [12–15].

3.3.1.3 * Single-Process Approach I – Discrete Langevin Equation

In order to motivate the introduction of discrete Langevin equation, we recall that the Fokker–Planck equation gives the evolution of ensemble probability at time t while the Langevin equation generates a single realization of stochastic process. The former can be derived by the latter, and the latter can be deduced from the former. Similar duality of description is widely found in physics

$$\begin{aligned} \text{Heisenberg picture} &\longleftrightarrow \text{Schrödinger picture of quantum mechanics} \\ \text{Lagrange picture} &\longleftrightarrow \text{Euler picture of hydrodynamics} \\ \text{Langevin equation} &\longleftrightarrow \text{Fokker–Planck equation} \\ \text{Discrete Langevin equation} &\longleftrightarrow \text{Master equation} \end{aligned}$$

In the above the left-hand side follows some observables, while the right-hand side observes at a fixed point. As the white Gaussian noise was the elementary source of Langevin equation, the stochastic process called the Poisson process/noise plays an elementary role in the discrete Langevin equation. Poisson noise is also the base of the Gillespie algorithm (see below). We, therefore, start by the definition of Poisson noise.

²¹ That $K\mathbf{P}$ approaches $K\mathbf{Q}$ does not imply the uniformization of \mathbf{P} and \mathbf{Q} by the Markov evolution, K .

Poisson Noise

A particular realization of Poisson noise $\hat{\zeta}(\cdot)$ is as follows:

$$\zeta(t) = \sum_{\alpha} \delta(t - t_{\alpha}), \quad (3.29)$$

where $\delta(z)$ is the Dirac delta function and $\{t_{\alpha}\}$ with $t_{\alpha} < t_{\alpha+1}$ represents the time of spike events, which take place randomly. The spike events are a Markov processes and, therefore, characterized only by the mean rate of spiking per unit of time, w . Within a very small time interval, $(t, t + \Delta t]$, the normalized probability for having n spikes is given by the Poisson distribution:

$$P \left[\int_t^{t+\Delta t} \zeta(s) ds = n \right] = \frac{e^{-w\Delta t}}{n!} (w\Delta t)^n. \quad (3.30)$$

For $\hat{n} \equiv \int_t^{t+\Delta t} \hat{\zeta}(s) ds$ we can verify $\langle \hat{n} \rangle = w\Delta t$. We generalize this definition to all the time slices, and we allow for the dependence of the mean spiking rate $w(a)$ on the external parameter, a . When a is varied as a function of time, $\langle \hat{\zeta}(t) \rangle = w(a(t))$.²²

If $\hat{\zeta}_1(t)$ and $\hat{\zeta}_2(t)$ are two independent Poisson noises, we can identify $\hat{\zeta}_1(t)\hat{\zeta}_2(t) = 0$ within any integration over time t . The reason is that, for a given time interval, $(t, t + \Delta t]$, the probability that *both* processes give rise to at least one spike is $\mathcal{O}(\Delta t^2)$. In the limit of $\Delta t \rightarrow 0$ such events are negligible (i.e., measure 0). Hereafter we often omit “” for stochastic processes for simplicity of notation.

To apply the Poisson process for transition between discrete states, we assign i.i.d. Poisson process to each distinct transition:

$$\hat{n}_{i,j}(t, t + \Delta t) = \int_t^{t+\Delta t} \zeta_{i,j}(s) ds, \quad (3.31)$$

and $\zeta_{i,j}(s)$ are independent Poisson noises with $\langle \zeta_{i,j}(t) \rangle = w_{i \rightarrow j}(a(t))$.²³

We denote, following [16], the states that the system can take by the base vectors $|i\rangle$, etc., i is a discrete index. These states can depend on the system's parameter a . We introduce also the dual base vectors, $\langle i|$, etc., so that $\langle i|j\rangle = \delta_{ij}$ for the same parameter a .

By $|i(t)\rangle$ we denote the state of the system at time t . $i(t)$ is among the index mentioned above. We define that, unless the system's state undergoes transition, $\frac{\partial}{\partial t} |i(t)\rangle = 0$ even if the system's parameter a depends on time.

²² We can verify the following formula for the characteristic function:

$\langle e^{i\phi\hat{n}} \rangle = e^{(e^{i\phi} - 1)w\Delta t}$. The characteristic functional of the Poisson noise $\hat{\zeta}(\cdot)$ is

$\langle e^{i \int_0^t \phi(t') \zeta(t') dt'} \rangle = \exp \left[\int_0^t (e^{i\phi(t')} - 1) w(a(t')) dt' \right]$, where $\phi(t)$ is an arbitrary smooth real function.

²³ The characteristic function $\langle e^{i \int_0^t \phi_{i,j}(t') \zeta_{i,j}(t') dt'} \rangle$ is equal to

$\exp \left[\int_0^t (e^{i\phi_{i,j}(t')} - 1) w_{i \rightarrow j}(a(t')) dt' \right]$.

Using the above notation, the discrete Langevin equation is as follows:

$$\frac{d}{dt}|i(t)\rangle = \sum_j (|j\rangle - |i(t)\rangle) \cdot \zeta_{i(t),j}(t), \quad (3.32)$$

where $\frac{d}{dt}|i(t)\rangle \equiv (|i(t+dt)\rangle - |i(t)\rangle)/dt$, and the multiplicative Poisson noise, $\zeta_{i(t),j}(t)$, obeys (3.31). The symbol “ \cdot ” means the Itô-type multiplication: The vector $|i(t)\rangle$ on the right-hand side is nonanticipating with respect to the variation of $\zeta_{i(t),j}(t)$.

In order to see how (3.32) works, let us assume that the first future spike in the Poisson noise among $\{\zeta_{i(t),j}(t)\}$ is at $t = t^*$ with $j = j^*$. Then the integration of (3.32) from the present time t up to $t^* + 0$ yields

$$|i(t^*)\rangle - |i(t)\rangle = (|j^*\rangle - |i(t)\rangle) \times 1,$$

where the last factor 1 comes from the time integration of $\delta(t - t^*)$. We then update the system's state to $|i(t^*)\rangle = |j^*\rangle$.

Another confirmation is that (3.32) reproduces the master equations (3.24) and (3.23). We denote the probability for the state $|i\rangle$ at the time t by $P_j(t) \equiv \langle \delta_{j,i(t)} \rangle$ with $\delta_{j,i(t)} = \langle j|i(t)\rangle$. Then we have

$$\begin{aligned} \frac{dP_j}{dt} &= \sum_{\ell} \langle (\delta_{j,\ell} - \delta_{j,i(t)}) \cdot \zeta_{i(t),\ell}(t) \rangle \\ &= \sum_{\ell} \sum_k \langle (\delta_{j,\ell} - \delta_{j,i(t)}) \delta_{k,i(t)} \cdot \zeta_{k,\ell}(t) \rangle \\ &= \sum_k [P_k w_{k \rightarrow j}(a(t)) - P_j w_{j \rightarrow k}(a(t))]. \end{aligned} \quad (3.33)$$

Equation (3.32) is analogous to the Langevin equation and the characteristic functional of its noise $\xi(t)$. Gillespie has proposed an approximate approach with finite Δt and then coarse grained it to have a Langevin equation [17].

3.3.1.4 * Single-Process Approach II – Gillespie Algorithm

The discrete Langevin equation (3.32) is not common in the literature. But we actually solve this when we simulate the master equation (3.24). From practical viewpoint, the temporal discretization of (3.32) is not a very efficient method, especially when the transitions occur rarely. A better idea is to focus on the waiting time, Δt^* ($0 \leq \Delta t < \infty$), with which a system ceases to stay the present state S_i to make the *first* transition to the new state S_{j^*} (“event driven method”). With this

idea Gillespie [18–20] formulated an efficient simulation algorithm to generate the particular realizations of (3.32). It consists of the following two steps:

- (1) We take a sample of the set of independent random variables, $\{\hat{y}_j\}_{j \in I_i}$, which are uniformly distributed on the domain, $[0, 1]$. From a sample $\{y_j\}_{j \in I_i}$, we define $\{\tau_j\}_{j \in I_i}$ such that $e^{-w_{i \rightarrow j} \tau_j} \equiv y_j$.
- (2) We define Δt^* as the minimum among $\{\tau_j\}_{j \in I_i}$ and identify j^* so that τ_{j^*} gives this minimum of $\{\tau_j\}_{j \in I_i}$.²⁴

The derivation is a little technical but at the same time pedagogical. We, therefore, summarize its outline below. The key quantities are

$p_{ii}(\Delta t)$: the probability that the system stays continuously in the state between the time t and $t + \Delta t$.

$p_{ij}(\Delta t)$ ($j \in I_i$): the probability that the system has ceased to stay in the state S_i to make the *first* transition to the state S_j between the time t and $t + \Delta t$.

By definition, the initial conditions for p_{ii} and p_{ij} are

$$p_{ii}(0) = 1, \quad p_{ij}(0) = 0 \quad (j \in I_i), \quad (3.34)$$

and they should obey the following evolution equations:

$$\frac{dp_{ii}(\Delta t)}{d\Delta t} = -p_{ii}(\Delta t) \sum_{j \in I_i} w_{i \rightarrow j}, \quad \frac{dp_{ij}(\Delta t)}{d\Delta t} = p_{ii}(\Delta t) w_{i \rightarrow j}, \quad j \in I_i. \quad (3.35)$$

The solution for $p_{ii}(t)$ and $p_{ij}(\Delta t)$ ($j \neq i$) with any $\Delta t (\geq 0)$ are

$$p_{ii}(\Delta t) = \exp\left\{-\sum_{j'' \in I_i} w_{i \rightarrow j''} \Delta t\right\},$$

$$p_{ij}(\Delta t) = \frac{w_{i \rightarrow j}}{\sum_{j' \in I_i} w_{i \rightarrow j'}} [1 - \exp\{-\sum_{j'' \in I_i} w_{i \rightarrow j''} \Delta t\}]. \quad (3.36)$$

These probabilities satisfy the sum rule, $p_{ii}(\Delta t) + \sum_{j \in I_i} p_{ij}(\Delta t) = 1$.

We can verify that those $(\Delta t^*, j^*)$ defined by (1)–(2) reproduces (3.36). Using the rules (1)–(2), the probability corresponding to $p_{ij}(\Delta t)$ writes

$$\text{Prob}[T_j(\hat{y}_j) \leq \Delta t, \text{ and } T_{j'}(\hat{y}_{j'}) \geq T_j(\hat{y}_j) (\forall j' \in I_i)] \equiv \check{p}_{ij}(\Delta t), \quad (3.37)$$

where we defined the functions $T_j(y)$ by $e^{-w_{i \rightarrow j} T_j(y)} = y$. Using the uniform distribution of $\{\hat{y}_j\}_{j \in I_i}$, we have

²⁴ That is, $\Delta t^* = \min_{j \in I_i} \tau_j = \tau_{j^*}$.

$$\tilde{p}_{ij}(\Delta t) = \int_0^1 \theta(\Delta t - \tau(y_j)) \left\{ \prod_{j' \in I, (j' \neq j)} \left[\int_0^1 \theta(\tau(y_{j'}) - \tau(y_j)) dy_{j'} \right] \right\} dy_j,$$

where $\theta(z) = 0$ for $z < 0$ and $\theta(z) = 1$ for $z \geq 0$. The integrations are simple to do,²⁵ and we find for $\tilde{p}_{ij}(\Delta t)$ the identical expression $p_{ij}(\Delta t)$ of (3.36).

3.3.1.5 *Detailed Balance and Equilibrium

Detailed balance adds stringent conditions on the steady state of master equation. The unique steady state with detailed balance can be regarded as a thermal equilibrium state. The equilibrium probability is reconstructed using the detailed balance conditions, and the set of rate constants that enable the equilibrium state have simple interpretations in terms of the free-energy landscape.

State of Detailed Balance

We consider the steady state of a master equation that satisfies more stringent conditions:

$$J_{i \rightarrow j} = 0, \quad \text{for } \forall i, \forall j \text{ (detailed balance)} \quad (3.38)$$

or, equivalently,

$$P_i w_{i \rightarrow j} = P_j w_{j \rightarrow i}, \quad \text{for } \forall i, \forall j \text{ (detailed balance)}. \quad (3.39)$$

We call such steady state the state of detailed balance. Whether a system has the state of detailed balance depends on the transition rates because there are more equations $\{J_{i \rightarrow j} = 0\}$ than the number of components of $\{P_j\}$.

*Equilibrium State of Master Equation

We call the steady state of master equation the equilibrium state if this state satisfies the detailed balance. As mentioned in Sect. 3.3.1.4, not all steady states satisfy detailed balance. Even if the probabilities $\{P_i(t)\}$ evolving according to a master equation converge to a unique state irrespective of the initial condition $\{P_i(t_{\text{init}})\}$ we cannot call it the equilibrium state of the master equation by analogy with (the first law of) macroscopic thermodynamics.

This restriction is required by the compatibility with thermodynamic laws. Below is its demonstration: if a system has a steady state which does not satisfy (3.38), the probability fluxes $\{J_{i \rightarrow j}\}$ can be written as a nontrivial superposition of *circulations of probability flux*. Each of the circulations consists of at least three discrete

²⁵ We use the formula $\sum_{j' \in I, (j' \neq j)} \frac{w_{i \rightarrow j'}}{w_{i \rightarrow j}} + 1 = \frac{1}{w_{i \rightarrow j}} \sum_{j' \in I} w_{i \rightarrow j'}$.

states, say $S_2 \rightarrow S_3 \rightarrow S_7 \rightarrow S_2$, and we can assign on it a constant flux, e.g., $J_{2 \rightarrow 3} = J_{3 \rightarrow 7} = J_{7 \rightarrow 2} \neq 0$. From such steady-state circulation, we can conceive a hypothetical machine that interacts selectively with the states, $\{S_2, S_3, S_7\}$. This machine could “rotate” in one direction because of the broken symmetry of the flux on these three states. Thus we can extract some systematic work, for example, to wind a string under a load using the rotation of this machine. Now if this steady state were the thermodynamic equilibrium, the machine would be a perpetual machine of the second kind (see Sect. 2.1.2), and this is contradiction to the second law of thermodynamics. Therefore, a steady state violating the detailed balance cannot correspond to a thermal equilibrium state.

* Reconstruction of Equilibrium Probabilities

If a unique steady state of the master equation satisfies detailed balance, we can find easily the equilibrium probabilities, $\{P_j^{\text{eq}}\}$. Below is the protocol:

1. We choose arbitrarily a state, S_i , as a reference.
2. We derive all the P_j^{eq} using (3.39), i.e., $P_j^{\text{eq}} = \frac{w_{i \rightarrow j}}{w_{j \rightarrow i}} P_i^{\text{eq}}$. In case that $w_{j \rightarrow i} = 0$ for some j , we can determine P_j^{eq} indirectly by applying the chain of equalities of (3.39). The presence of a unique steady state assures that it is feasible.
3. Once all the values of P_j^{eq} are determined relative to P_i^{eq} , the normalization condition, $\sum_j P_j^{\text{eq}} = 1$, determines the value of P_i^{eq} .

* Representation of Transition Rates

Suppose that a system with n states, $\{S_1, \dots, S_n\}$, has a unique state of detailed balance. Let us establish the balance sheet for the number of unknown parameters and the number of conditions. There are $n(n-1)$ parameters of the transition rates and n parameters of the equilibrium probabilities. The constraints of the type (3.39) impose $n(n-1)/2$ conditions. An additional constraint is the normalization of the probabilities. There remains, therefore, $[n(n+1)/2 - 1]$ degrees of freedom.²⁶ We can write these degrees of freedom in a physically appealing manner [21–24]:

- $F_j/k_B T$: “free-energy levels (per $k_B T$).” They amount to $(n-1)$ degrees of freedom, where (-1) is due to the arbitrariness of an additive constant.²⁷
- $\Delta_{i,j}/k_B T$: “activation free energies (per $k_B T$)” having the symmetry, $\Delta_{i,j} = \Delta_{j,i}$. They amount to $[n(n-1)/2 - 1]$ degrees of freedom, where (-1) is due to the arbitrariness of an additive constant.²⁸
- ν : the unique “attempting frequency.” One degree of freedom.

²⁶ The calculation is $[n(n-1) + n] - [n(n-1)/2 + 1] = n(n+1)/2 - 1$.

²⁷ In chemistry, one can regard F_j as the Gibbs free energy under isobaric condition, rather than Helmholtz free energy.

²⁸ The last additive constant can be chosen independently of the one for $\{F_j/k_B T\}$, see the remark after (3.40).

The above parameterization allows us to represent both $\{P_j^{\text{eq}}\}$ and $\{w_{i \rightarrow j}\}$ in the context of the thermal activation-assisted transition in a free-energy landscape.

$$P_j^{\text{eq}} = \frac{e^{-F_j/k_B T}}{\sum_i e^{-F_i/k_B T}}, \quad w_{i \rightarrow j} = \nu \exp \left[-\frac{\Delta_{i,j} - F_i}{k_B T} \right]. \quad (3.40)$$

The arbitrariness in both $\Delta_{i,j}$ and F_i can be absorbed by the pre-exponential factor, ν .²⁹

The above expression of the transition rates, $\{w_{i \rightarrow j}\}$, provides the following intuitive picture [21–24] (see Fig. 3.4): A system in the state S_i has (free) energy F_i . This system attempts to make a state transition to any other state with a common frequency, ν . Because of the (free) energy barrier of activation ($\Delta_{i,j} - F_i$), the probability of a successful attempt for the transition $S_i \rightarrow S_j$ is the Boltzmann factor, $e^{-(\Delta_{i,j} - F_i)/k_B T}$. Note that the purely kinetic parameters $\Delta_{i,j}$ do not appear in the equilibrium probabilities.

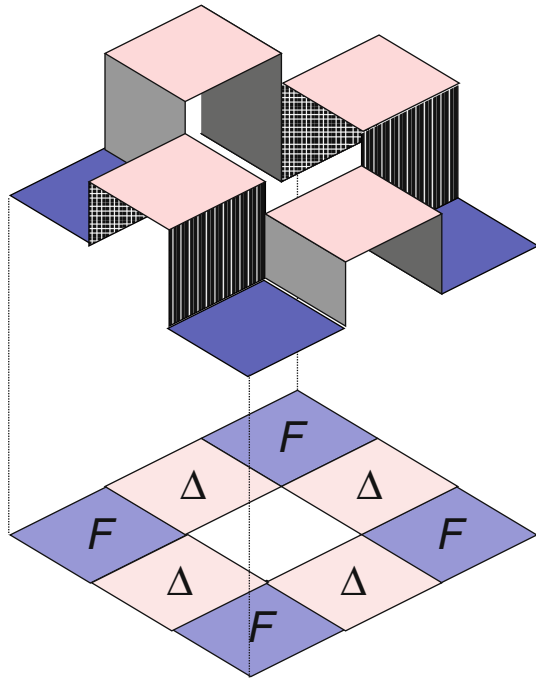


Fig. 3.4 Interpretation of (3.40). The squares on the corners represent the free-energy levels, F_i , while the plateaus between the nearest states represent the barriers, $\Delta_{i,j}$

²⁹ Once we fix the ν 's value, the difference $\Delta_{i,j} - F_i$ has a physical meaning of the activation barrier and contains no arbitrary additive constants.

Nonequilibrium Processes

Once the transition rates are fixed using the detailed balance condition of equilibrium, we can proceed to study the master equation under nonequilibrium conditions. This implies several different things:

Transient nonequilibrium states: Keeping the transition rates of the form (3.40) unchanged, we study the relaxation of the probabilities $P_j(t)$ starting from nonequilibrium initial ones. Also we solve the discrete Langevin equation with these transition rates and look for stochastic processes on the state space.

Nonequilibrium settings I: We may vary F_j 's, $\Delta_{i,j}$'s, or $k_B T$ as function of time *in* the transition rates of (3.40). In this case, the instantaneous equilibrium distribution and the landscape picture are still valid according to (3.40). The $P_j(t)$ evolves toward a temporary equilibrium state, although there can be a lag of relaxation.

Nonequilibrium settings II: We modify each *activation barrier*, $\Delta_{i \rightarrow j}^{\text{act}} \equiv \Delta_{i,j} - F_i$, disregarding the DB conditions, based on physical arguments.

In fact each activation barrier often has a physical justification of its own, independent of the compatibility with the global equilibrium states. It is like that the macroscopic rate constant k for the reaction $A+B \rightarrow AB$ can be used either in (3.3) or in (3.1), which is far from equilibrium. Therefore, we can combine these transition rates to build up a reaction network having nonequilibrium steady states. A simple example is given in Sect. 3.3.3.3

Since the number of combinations of $[i \rightarrow j]$, i.e., $n(n-1)$, is more than the degrees of freedom left by the DB condition, $n(n+1)/2 - 1$, the modified transition rates can no more be represented by a single-valued landscape like Fig. 3.3. The system now allows steady-state circulations of probability flux.³⁰

Relation between the transient nonequilibrium states and the nonequilibrium settings II: When we model the chemical coupling schematized by Fig. 2.7, we can model either the whole closed system, i.e., the chemical engine plus the four particle reservoirs, or the chemical engine as an open system.

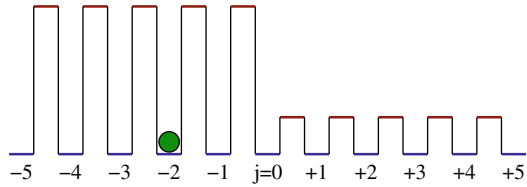
The former viewpoint is not very practical but formally simple: we assume the transition rates satisfying detailed balance. The global landscape is fixed like in Fig. 2.8. The nonequilibrium process is regarded as a transient process toward the equilibrium of the whole closed system.

The latter viewpoint is more practical but we must use the nonequilibrium settings of type II. The reservoirs' states are no more taken into account, and only the chemical potentials enter as a parameter for the chemical engine.

In the former formal point of view, the system's evolution is relaxing and downhill on the average. In the latter point of view, the chemical engine makes a stochastic cyclic transitions in its (reduced) state space.

³⁰One may imagine the Escher staircase.

Fig. 3.5 Landscape with inhomogeneous barrier heights. See the text



Simple Example – Will Particles Be Stagnant in the Region of Small Diffusion Coefficient?

Suppose that a system can take the states S_j ($j = 0, \pm 1, \dots, \pm N$) and that the nonzero transition rates only between j and $j + 1$ ($-N \leq j < N$). Figure 3.5 shows the case that $F_j = 0$ for all j , $\Delta_{j,j+1} = W$ for $-N \leq j < 0$, and $\Delta_{j,j+1} = w$ for $0 \leq j < N$ with $w < W$. The general argument above tells that this system has an equilibrium state with detailed balance, and the equilibrium probability is uniform, $P_j^{eq} = (2N + 1)^{-1}$. Nevertheless, might we not expect that the system spends more time in the left region ($j < 0$), where the diffusion takes more time? The key to avoid this trap is to be aware of the opposing effects to this argument. The state $S_{j=0}$ situated between the high barrier W to the left and the low barrier w to the right. If the system is in this state, the (conditional) probability of the transition $S_0 \rightarrow S_{-1}$ is smaller than that of the transition $S_0 \rightarrow S_{+1}$. Therefore, the chance that the system enters into the $j < 0$ states is relatively small, though the residence time in $j < 0$ states are relatively large. In equilibrium, these two effects exactly cancel.

3.3.1.6 Langevin Equation as a Limit of Discrete Process

Transition Rate of Langevin Equation

The Langevin equation can be regarded as the limit of a discrete process, where the states are infinitely finely distinguished and the transitions are allowed to occur only among the “nearby” states. (The Fokker–Planck equation is, therefore, a limit of the master equation.³¹) Below we demonstrate how the transition rate is obtained for the overdamped Langevin equation.

Let us write the Langevin equation in the form of SDE, see Sect. 1.2.1.1:

$$dx_t = -\frac{1}{\gamma} \frac{dU(x_t)}{dx_t} dt + \sqrt{2D} dB_t, \tag{3.41}$$

where we denote by x_t the value of x at time t and D is the diffusion coefficient. The probability density for x_t is $\langle \delta(x - x_t) \rangle$. Then the conditional probability density for $x_{t+dt} = x_t + dx_t$, given that $x = x_t$ at t , is $\langle \delta(x - x_t) \delta(x' - x_{t+dt}) \rangle / \langle \delta(x - x_t) \rangle$. For $x \neq x'$, this conditional density gives the flow of probability to x' within the time dt . Therefore, the transition rate $w_{x \rightarrow x'}$ should be related to this density through

³¹The derivation uses the technique called the Kramers–Moyal expansion. See, for example, [3, 25, 26, 7, 8].

$$\frac{\langle \delta(x - x_t) \delta(x' - x_{t+dt}) \rangle}{\langle \delta(x - x_t) \rangle} = \delta(x - x') + w_{x \rightarrow x'} dt. \quad (3.42)$$

To evaluate the left-hand side, we develop $\delta(x' - x_{t+dt})$ around $\delta(x' - x_t)$ (Sect. 1.2.2.4) using (3.41) and the Itô formula (1.58).³² The result is

$$w_{x \rightarrow x'} = \frac{1}{\gamma} \frac{dU(x)}{dx} \delta'(x' - x) + D \delta''(x' - x). \quad (3.43)$$

Detailed Balance Condition and Einstein Relation

We can verify that the equilibrium state, $\mathcal{P}^{\text{eq}}(x) \propto e^{-U(x)/k_B T}$, is the state of detailed balance *if* the diffusion coefficient satisfies the Einstein relation, $D = k_B T / \gamma$. As (3.43) includes the derivatives of the δ -function, what corresponds to (3.39) should be expressed by the integral form:

$$\int dx \int dx' f(x) [\mathcal{P}^{\text{eq}}(x) w_{x \rightarrow x'} - \mathcal{P}^{\text{eq}}(x') w_{x' \rightarrow x}] g(x') = 0, \quad (3.44)$$

where $f(x)$ and $g(x')$ are arbitrary functions of good properties.³³ A straightforward integrations by parts of (3.44) with (3.43) leads to $D = k_B T / \gamma$.

Detailed Balance and Fluctuation–Dissipation (FD) Relation

In Sect. 1.3.1.2 we have seen that the Einstein relation is related also to the fluctuation–dissipation relation. In general, stochastic processes satisfying the detailed balance condition have equilibrium state distribution, and their fluctuations and linear responses obey the fluctuation–dissipation (FD) relation.

For the processes breaking the detailed balance condition, several generalization of the fluctuation–dissipation relation have been formulated [27, 28], and also the discrepancy from the (true) fluctuation–dissipation relation has been related to the heat generation described [29–31]. The latter points will be discussed in the part II.

3.3.2 Stochasticity of Molecule Numbers in the Chemical Reaction Can Be Described by Discrete Master Equation

The method described in the previous section is used to describe the stochastic aspect of chemical reaction. We shall take up the same examples as before, $A + B \rightleftharpoons AB$. The object here is to know the relation between macroscopic and

³²Note that $\delta(x' - x_t)$ has nonanticipating property with respect to dB_t .

³³For example, we assume that they are derivable arbitrary many times and are decaying faster than any power of x for $|x| \rightarrow \infty$ (Schwartz space).

stochastic parameters, and see how the number of molecular species are distributed at equilibrium.

3.3.2.1 Number State Representation

Fluctuations are unavoidable if we describe a chemical reaction with the resolution of the (integer) number of molecular species. Suppose that the reaction, $A+B \rightleftharpoons AB$, occurs in a closed container at the temperature T , where the total number of atoms A and atoms B is fixed at N_A^{tot} and N_B^{tot} , respectively. The number of AB molecule, N_{AB} , is then sufficient to characterize the state of the system, because the numbers of the other molecules, A or B, are given as $N_A = N_A^{\text{tot}} - N_{AB}$ or $N_B = N_B^{\text{tot}} - N_{AB}$, respectively. The system has, therefore, $\min\{N_A^{\text{tot}}, N_B^{\text{tot}}\} + 1$ discrete states. Below we shall use N_{AB} to represent the state, $S_{N_{AB}}$, unless confusions arise. On this level of description, we do not distinguish the individuality of the atoms to define the states, nor their orientations and other internal degrees of freedom. But still the description is more detailed than the macroscopic description of Sect. 3.2. The (number) concentrations, $[A]$, etc., in macroscopic description are readily given as $\langle N_A \rangle / V$, etc., where V (in liter) is the volume of the system.

3.3.2.2 Transition Rates and the Rate Constant

Transition Rates

We consider for a moment only the forward reaction, $A + B \rightarrow AB$, or in stochastic term, the state transition of $N_{AB} \rightarrow (N_{AB} + 1)$. In the stochastic description, we assume the following simple model for the transition rate, $w_{N_{AB} \rightarrow N_{AB}+1}$:

$$w_{N_{AB} \rightarrow N_{AB}+1} = k \frac{N_A N_B}{V}, \quad (3.45)$$

where k is a constant independent of the number of molecules or volume. The approximation leading to (3.45) is that every A molecule and B molecule is distributed randomly in the volume V and that the chance to find a pair of A and B molecule within an atomic distance is $\propto \frac{N_A N_B}{V}$ up to the relative error of $\mathcal{O}(N_A/V, N_B/V)$. The factor k should include the activation factor, or the probability that a collision between an A and a B molecules leads to the formation of an AB molecule.

Rate Constant

We will relate the transition rate $w_{N_{AB} \rightarrow N_{AB}+1}$ to the rate constant of the macroscopic description of the reaction, described in Sect. 3.2.1.1. If the state transition, $N_{AB} \rightarrow (N_{AB} + 1)$, occurs the probability $w_{N_{AB} \rightarrow N_{AB}+1} dt$ for an infinitesimal time dt , N_{AB} should increase approximately by $w_{N_{AB} \rightarrow N_{AB}+1} dt$, that is $dN_{AB}/dt \simeq w_{N_{AB} \rightarrow N_{AB}+1} = k N_A N_B / V$, where we have used (3.45). Dividing each part of this equation by V , we have

$$\frac{d[\text{AB}]}{dt} \simeq \frac{w_{N_{\text{AB}} \rightarrow N_{\text{AB}}+1}}{V} = k[\text{A}][\text{B}]. \quad (3.46)$$

The rightmost the equation is of the same form as the formula for the macroscopic reaction. Therefore, we identify the coefficient k in (3.45) with the rate constant of the reaction, $\text{A} + \text{B} \rightarrow \text{AB}$.

Next we take into account the backward state transition, $(N_{\text{AB}} + 1) \rightarrow N_{\text{AB}}$, also. This corresponds to the reaction $\text{AB} \rightarrow \text{A} + \text{B}$. We assume that the transition rate, $w_{N_{\text{AB}}+1 \rightarrow N_{\text{AB}}}$, is proportional to the number of AB molecules *before* the transition, therefore,

$$w_{N_{\text{AB}}+1 \rightarrow N_{\text{AB}}} = k'(N_{\text{AB}} + 1), \quad (3.47)$$

where a positive constant, k' , is independent of the number of molecules or volume. It is justified if the dissociation occurs in individual AB molecules. By approximately identifying this transition rate with a contribution to $-dN_{\text{AB}}/dt$, we obtain the

$$\frac{d[\text{AB}]}{dt} \simeq k[\text{A}][\text{B}] - k'[\text{AB}]. \quad (3.48)$$

We, therefore, identify the coefficient k' in (3.47) with the rate constant of the reaction, $\text{AB} \rightarrow \text{A} + \text{B}$.

Remark: Extensivity of the Transition Rate

The frequency of the transition $N_{\text{AB}} \rightarrow N_{\text{AB}} + 1$ has an extensive character that is proportional to the size of the system. Therefore, the time defined, for example, by $(w_{N_{\text{AB}} \rightarrow N_{\text{AB}}+1})^{-1}$ has nothing to do with the reaction mechanism of individual molecules.

In order that the modeling as a Markov process be a good approximation, the subsequent transitions, for example, $N_{\text{AB}} \rightarrow N_{\text{AB}} + 1$ and $N_{\text{AB}} + 1 \rightarrow N_{\text{AB}} + 2$ should be uncorrelated. If the reacting solution is dilute, successive transitions occur at distant spatial locations in the volume, and the Markov approximation is justified, however, large is the transition rate, $w_{N_{\text{AB}} \rightarrow N_{\text{AB}}+1}$. That the inverse transition rates scale with V^{-1} is the basis of the van Kampen's expansion method of the master equation [32, 8].

If the nature of chemical reaction is such that two consecutive transitions, e.g., $N_{\text{AB}} \rightarrow N_{\text{AB}} + 1$ and $N_{\text{AB}} + 1 \rightarrow N_{\text{AB}} + 2$, are strongly correlated on the molecular level, then we can better define the reaction as $2\text{A} + 2\text{B} \rightleftharpoons 2\text{AB}$ and define the state transition as $N_{\text{AB}} \rightarrow N_{\text{AB}} + 2$.

3.3.2.3 Probability Fluxes and the Master Equation

Probability Flux of Stochastic Chemical Reaction

We denote by $P(N_{AB}, t)$ ($0 \leq N_{AB} \leq \min\{N_A^{\text{tot}}, N_B^{\text{tot}}\}$) the probability that the systems in the state N_{AB} at time t . Applying the definition of probability flux, (3.23), the probability flux of the reaction is given as follows:

$$\begin{aligned} J_{N_{AB} \rightarrow N_{AB}+1} &\equiv P(N_{AB}, t)w_{N_{AB} \rightarrow N_{AB}+1} - P(N_{AB} + 1, t)w_{N_{AB}+1 \rightarrow N_{AB}} \\ &= -J_{N_{AB}+1 \rightarrow N_{AB}}. \end{aligned} \quad (3.49)$$

Master Equation of Stochastic Chemical Reaction

With the above probability flux, the master equation for $P(N_{AB}, t)$ is written as

$$\frac{dP(N_{AB}, t)}{dt} = J_{N_{AB}-1 \rightarrow N_{AB}} - J_{N_{AB} \rightarrow N_{AB}+1}. \quad (3.50)$$

The normalization of the probabilities:

$$\sum_{n=0}^{\min\{N_A^{\text{tot}}, N_B^{\text{tot}}\}} P(n, t) = \text{const}. \quad (3.51)$$

can be verified by (3.50) at all time t .

Substitution of the expressions of the transition rates, (3.45) and (3.47), we have

$$\begin{aligned} \frac{\partial P(N_{AB})}{\partial t} &= k \frac{(N_A + 1)(N_B + 1)}{V} P(N_{AB} - 1, t) \\ &- \left\{ k' N_{AB} + k \frac{N_A N_B}{V} \right\} P(N_{AB}, t) + k'(N_{AB} + 1)P(N_{AB} + 1, t). \end{aligned} \quad (3.52)$$

Equation (3.52) includes macroscopic reaction equation for $[AB]$, i.e., for $\langle N_{AB} \rangle = \sum_{n=0}^{\min\{N_A^{\text{tot}}, N_B^{\text{tot}}\}} n P(n, t)$. See, for example, [7–9] for the methods to derive the macroscopic equation from (3.52).

3.3.2.4 Equilibrium Properties

State of Detailed Balance

The steady state of (3.52) satisfying the detailed balance (DB) imposes the condition

$$J_{N_{AB} \rightarrow N_{AB}+1} = 0, \quad 0 \leq N_{AB} < \min\{N_A^{\text{tot}}, N_B^{\text{tot}}\}$$

under fixed values of N_A^{tot} and N_B^{tot} . This condition gives the probabilities of the equilibrium state:

$$P(N_{AB}, t = \infty) = \mathcal{N} \frac{\tilde{N}_A^{N_A}}{N_A!} \frac{\tilde{N}_B^{N_B}}{N_B!} \frac{\tilde{N}_{AB}^{N_{AB}}}{N_{AB}!} \equiv P^{eq}(N_{AB}), \quad (3.53)$$

where \mathcal{N} is the normalization constant, and the three parameters, $(\tilde{N}_A, \tilde{N}_B, \tilde{N}_{AB})$ are solutions to the following three equations:

$$\frac{(\tilde{N}_A v_0/V)(\tilde{N}_B v_0/V)}{(\tilde{N}_{AB} v_0/V)} = \frac{k'}{k}, \quad \tilde{N}_A + \tilde{N}_{AB} = N_A^{\text{tot}}, \quad \tilde{N}_B + \tilde{N}_{AB} = N_B^{\text{tot}}, \quad (3.54)$$

where v_0 is a constant with the dimension of volume. The formula (3.53) looks apparently the product of three independent Poisson distributions. In fact, these distributions are not independent for the closed system, because of the constraints $N_A = N_A^{\text{tot}} - N_{AB}$ and $N_B = N_B^{\text{tot}} - N_{AB}$. Equation (3.54) gives a function of the single variable, N_{AB} .

Nevertheless the form of the product of Poisson distributions is the consequence of only the DB condition, whether or not the system is closed. When the number of N_A and N_B is adjustable by their particle environments, (3.53) describes the true product of Poisson distributions.

Law of Mass Action

The constraint (3.54) suggests already a law of mass action at equilibrium. In fact, when the system is macroscopic, the equilibrium state of master equation (3.53) includes the law of mass action (3.6), that is, $[A][B]/[AB] = k'/k$.

Since (3.54) has a form of law of mass action, we need only to show that the parameters \tilde{N}_A , \tilde{N}_B , and \tilde{N}_{AB} are the values of N_A , N_B , and N_{AB} , respectively, when $P_{\text{eq}}(N_{AB})$ is the maximum respect to N_{AB} . It can be done using the technique of logarithmic derivative.³⁴ Thus, through the relation (3.54) the equilibrium state (3.53) includes the law of mass action (3.6).

Chemical Potential

In order to see how the chemical potential is interpreted in this simple reaction scheme, $A + B \leftrightarrow AB$, we will compare the result of $P^{eq}(N_{AB})$ with the prediction from statistical mechanics.

We define μ_A^0 , μ_B^0 , and μ_{AB}^0 as the free energies of *individual* molecules, A, B, and AB, respectively, which reflect the effect of the kinetic energies and the internal degrees of freedom of each molecule in the form of the free energy:

$$\mu_M^0 = -k_B T \ln z_M \quad (M = A, B, AB), \quad (3.55)$$

³⁴ We require $\partial[\ln P_{\text{eq}}(N_{AB})]/\partial N_{AB} = 0$. Denoting by $\{N_A^*, N_B^*, N_{AB}^*\}$ the numbers $\{N_A, N_B, N_{AB}\}$ at the maximum of the probability, and using the Stirling formula, $n! \sim n^n e^{-n}$, we have the equality $(N_A^*/\tilde{N}_A)(N_B^*/\tilde{N}_B)(N_{AB}^*/\tilde{N}_{AB})^{-1} = 1$. The last equation implies $N_A^* = \tilde{N}_A$, etc.

where z_M are the partition functions of a molecular species M .³⁵ These free energies can depend on the temperature. We then assign to each state of the system, N_{AB} ($\leq \min\{N_A^{\text{tot}}, N_B^{\text{tot}}\}$), the following “potential energy”:

$$U(N_{AB}) = N_A \mu_A^0 + N_B \mu_B^0 + N_{AB} \mu_{AB}^0,$$

where $N_A \equiv N_A^{\text{tot}} - N_{AB}$ and $N_B \equiv N_B^{\text{tot}} - N_{AB}$.³⁶ We then write down the canonical (configurational) partition function of the form of $\sum e^{-U(N_{AB})/k_B T}$. We have

$$\frac{Z(T, V, N_A^{\text{tot}}, N_B^{\text{tot}})}{N_A^{\text{tot}}! N_B^{\text{tot}}!} = \sum_{N_{AB}=0}^{\min\{N_A^{\text{tot}}, N_B^{\text{tot}}\}} \frac{\alpha_A^{N_A} \alpha_B^{N_B} \alpha_{AB}^{N_{AB}}}{N_A! N_B! N_{AB}!}, \quad (3.56)$$

where $\alpha_M \equiv (V/v_1)e^{-\frac{\mu_M^0}{k_B T}}$, and v_1 is a constant. The factorials come from the combinatorial number, $N_A^{\text{tot}} C_{N_A} \times N_B^{\text{tot}} C_{N_B} \times N_{AB}!$, for forming N_{AB} of AB molecules out of N_A^{tot} of A molecules and N_B^{tot} of B molecules. According to the statistical mechanics of Gibbs, we can identify each term in the sum on the right-hand side of (3.56) with the relative probability. This probability has exactly the form of (3.53), except for a factor of normalization. Therefore, we find

$$\alpha_M = \tilde{N}_M.$$

Combining this result with (3.54) we have³⁷

$$\exp \left\{ \frac{\mu_{AB}^0 - \mu_A^0 - \mu_B^0}{k_B T} \right\} = \frac{k'}{k}. \quad (3.57)$$

We have thus recovered the result of macroscopic thermodynamics, (3.9), and (3.55) gives the microscopic meaning for μ_A^0 , μ_B^0 , and μ_{AB}^0 .

Remark : Origin of the Combinatorial Factor

Looking back to the origin of the formula (3.53), we see that the combinatorial factor $N_A!$, etc., has nothing to do with the particle-wave duality of quantum physics. A statistical mechanical description of the open system also gives a similar combinatorial factor. We will come back to this point in Sect. 5.2.1.5.

³⁵ Strictly speaking, z_M is made nondimensional by a factor related to the atomic specific volumes.

³⁶ The relation between the “potential energy” and the landscape representation (Sect. 3.3.1.5) will be discussed in the next Sections.

³⁷ We put $v_0 = v_1$.

3.3.3 Stochastic Open System Is a Class of Stochastic Chemical Reaction System

3.3.3.1 Chemical Potential of the Reservoir

The formula (3.40) gives a landscape representation of the transition rates that satisfy detailed balance. We apply this schema to the system which consists of an open subsystem (open system, for short) *and* a particle reservoir between which molecules of species A are exchanged. See Fig. 3.6 (A). For simplicity, no chemical reactions are assumed to occur within the open system, although the generalization is easy. The only “reaction” is, therefore, the migration between the system (Sys) and the reservoir (Res):



This is a simple model of physical adsorption of molecule A, where the system (S) is a 2D substrate with a “volume” V .

Following the protocol of Sect.3.3.2, we build up the master equation of this model.

1. The state of the system is distinguished by the number of particles in the open system, $N_A \equiv N$.
2. The transition rate $w_{N \rightarrow N+1}$ represents the average rate at which a particle enters the open system, while $w_{N+1 \rightarrow N}$ reflects the rate at which any one particle in the open system leaves for the environment. We will not assume the properties of dilute solutions, but leave the transition rates very general [33].
3. The probability flux is $J_{N \rightarrow N+1} = P_N w_{N \rightarrow N+1} - P_{N-1} w_{N-1 \rightarrow N}$.
4. The master equation for P_N is then

$$\frac{dP_N}{dt} = -J_{N \rightarrow N+1} - J_{N \rightarrow N-1}. \quad (3.59)$$

5. We assume that the system is in equilibrium. We then impose the detailed balance condition (3.40). It relates $w_{N \rightarrow N+1}$ with $w_{N+1 \rightarrow N}$:

$$w_{N+1 \rightarrow N} = w_{N \rightarrow N+1} \exp \left[\frac{F_{N+1} - F_N}{k_B T} \right]. \quad (3.60)$$

6. In order to relate the stochastic description with the macroscopic description, we introduce $\langle N \rangle \equiv \sum_N N P_N$ and $\langle w_{N \rightarrow N+1} \rangle \equiv \sum_N w_{N \rightarrow N+1} P_N$, etc.

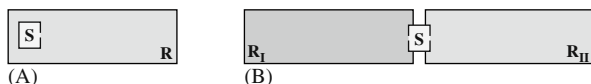


Fig. 3.6 (A) A system consisting of an open subsystem, S, and a reservoir, R. (B) A system consisting of an open subsystem, S, and two reservoirs, R_I and R_{II}

Then by the direct calculation, (3.59) gives³⁸

$$\frac{d\langle N \rangle}{dt} = \langle w_{N \rightarrow N+1} \rangle - \langle w_{N+1 \rightarrow N} \rangle. \quad (3.61)$$

The relation (3.60) is not very convenient because F_N concerns the whole system. By a physical argument we will rewrite $(F_{N+1} - F_N)$ in terms of chemical potential. We assume that the coupling between the open system and the reservoir is short-ranged so that the free energy is additive: $F_N = F_N^{\text{sys}} + F_{N^{\text{tot}}-N}^{\text{res}}$ + (indep. of N), where N^{tot} is the total number of particles in the whole system (SUR), and the last term represents the interface between the open system and the environment. The chemical potentials of the open system and the reservoir are defined, respectively, by $\mu \equiv \partial F_N^{\text{sys}} / \partial N$ and $\mu^{\text{res}} \equiv \partial F_{N^{\text{res}}}^{\text{res}} / \partial N^{\text{res}}$. Then we have

$$F_{N+1} - F_N = \mu - \mu^{\text{res}}. \quad (3.62)$$

Then we find the following relation between the transition rates:

$$w_{N+1 \rightarrow N} = w_{N \rightarrow N+1} \exp \left[\frac{\mu - \mu^{\text{res}}}{k_B T} \right]. \quad (3.63)$$

In combining with (3.61) we have the following formula:

$$\frac{d\langle N \rangle}{dt} = \langle w_{N \rightarrow N+1} \rangle \left(1 - \exp \left[\frac{\mu - \mu^{\text{res}}}{k_B T} \right] \right).$$

Or using $[A] = \langle N \rangle / V$,

$$\frac{d[A]}{dt} = k_{\text{in}}([A]) \left(1 - \exp \left[\frac{\mu([A]) - \mu^{\text{res}}}{k_B T} \right] \right), \quad (3.64)$$

where

$$k_{\text{in}}([A]) = \langle w_{N \rightarrow N+1} \rangle / V. \quad (3.65)$$

Unlike the law of mass action, (3.64) allows the rate $(d[A]/dt)$ to depend on $[A]$ in nonlinear manner. In the van der Waals model of fluids, μ depends on $[A]$ in a sigmoidal way. As a result, there can be several equilibrium concentrations $[A]$ satisfying $\mu([A]) = \mu^{\text{res}}$ for certain value(s) of μ^{res} . This leads to the phase changes between the cooperative adsorption phase and the dilute adsorption phase.³⁹ In

³⁸ We supposed that the distribution of P_N vs. N is sharply peaked around $N = \langle N \rangle (\gg 1)$ and ignored the errors of order $o(\langle N \rangle)$.

³⁹ The stable equilibria should satisfy $\partial(\mu([A]) - \mu^{\text{res}}) / \partial [A] > 0$.

addition to the multi-equilibria, formula (3.64) describes the relaxation and hysteresis of the concentration [A].

3.3.3.2 Butler–Volmer Equation

The above result includes the so-called Butler–Volmer equation in electrochemistry [34] as a special case. Knowing that the transition rates are extensive (see Remark of Sect. 3.3.2.2) and that ν in (3.40) can absorb the global additive constants in $\Delta_{N,N+1}$'s and in F_N 's, we choose $\nu = \tilde{\nu} V$. Then we can assume that $\Delta_{N,N+1} - F_N$ and $\Delta_{N,N+1} - F_{N+1}$ as well as $\tilde{\nu}$ are nonextensive, i.e., of $\mathcal{O}(V^0)$. Therefore, the weighed average of these two barrier height

$$\psi \equiv \Delta_{N,N+1} - (\alpha_+ F_N + \alpha_- F_{N+1}), \quad \alpha_+ + \alpha_- = 1, \quad (3.66)$$

is also of $\mathcal{O}(V^0)$ for arbitrary choice of α_+ ($= 1 - \alpha_-$). Then (3.61) with (3.40) can be rewritten using this ψ and the chemical potentials of (3.62):

$$\frac{d}{dt} \left(\frac{\langle N \rangle}{V} \right) = \tilde{\nu} \exp \left[-\frac{\psi + \alpha_- (\mu - \mu^{\text{res}})}{k_B T} \right] - \tilde{\nu} \exp \left[-\frac{\psi - \alpha_+ (\mu - \mu^{\text{res}})}{k_B T} \right]. \quad (3.67)$$

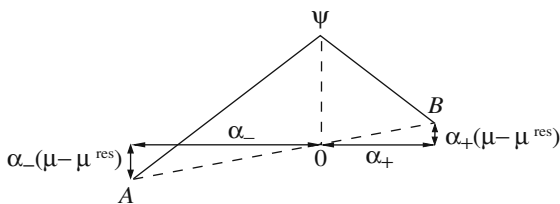
This form (3.67) is called Butler–Volmer equation.

The Butler–Volmer equation has been proposed by geometrical considerations (see textbook, e.g., [34] (p.1048), or recent articles [35, 36]), which is summarized in Fig. 3.7. Recently [37] proposed to use μ derived from a Cahn-Hilliard-type chemical free energy functional [38] so as to include the effect of inhomogeneous concentration. However, the above derivation implies that the experimental fitting with Butler-Volmer equation per se justifies no particular geometrical models of the adsorption because (3.67) is general: α_+ can be arbitrary, even negative, and this ψ can depend on the concentrations $\langle N \rangle / V$ or on the temperature. α_{\pm} can even depend on the kinetic parameters of the system. Therefore, it is only when α_{\pm} have separate justification that the geometrical representation Fig. 3.7 is meaningful.

3.3.3.3 Nonequilibrium Open System

When we constructed the Langevin equation, we have used the equilibrium state of the system to determine the relation (Einstein relation) between the viscous friction coefficient, γ , and the strength of random thermal force, b . Once the relation,

Fig. 3.7 Graphical representation of the “activation free energies,” $\psi \pm \alpha_{\mp} (\mu - \mu^{\text{res}})$. The levels of the “valleys” A and B are different by $\mu - \mu^{\text{res}}$



$b = \gamma k_B T$, is obtained, we use the Langevin equation for the various situations including nonequilibrium conditions.

In the case of discrete stochastic processes, what we first determined using the equilibrium state, or the conditions of detailed balance (DB), was the *relation* between the transition rates, $w_{i \rightarrow j}$, and the physical parameters. In Sect. 3.3.1.5 we saw that if the transition rates are consistent with an equilibrium state, they can be formally represented in terms of ν , $\Delta_{i,j}$, F_j , and $k_B T$ (see (3.40)). After that, we related this formal result to the physical parameters, such as μ , μ^{Res} , or k_{in} , in a concrete case (see (3.63) and (3.65)).

As we discussed in Sect. 3.3.1.5,⁴⁰ we can then develop physical arguments and modify each transition rate so that those rates are applicable also in nonequilibrium conditions. Below we show how it is practically done in a modeling of nonequilibrium steady states: We consider an open system, S, and the two particle reservoirs, R_I and R_{II}, with which the system can exchange molecules, A. See Fig. 3.6 (B). We generalize the schema (3.58) to



and denote the state of the whole system by the number of particles in the system, $N \equiv N_A$, and that in the reservoir R_I, $N' \equiv N_A^{\text{Res-I}}$. (Note that the number of particles in reservoir R_{II}, $N_A^{\text{Res-II}}$ depends on N and N').

The transitions we consider are

$(N, N') \rightarrow (N \pm 1, N' \mp 1)$: migration of an A molecule between S and R_I.

$(N, N') \rightarrow (N \pm 1, N')$: migration of an A molecule between S and R_{II}.

One of the easiest ways of modeling the transition rates for these transitions is to consider the special case where one of the two reservoirs is practically inaccessible due to an extremely high energy barrier between the system and the reservoir. We can then use the previous results (3.63) and (3.65) for the transition rates for the migration with the reservoir which is not blocked. A physical hypothesis that we take here is that the transition rates between the system and a reservoir are unchanged whether or not the migration with the other reservoir is blocked.⁴¹ If this is a good approximation, we can repeat the same argument by exchanging the blocked reservoir and unblocked one, we obtain the following model:

$$\begin{aligned} w_{(N,N') \rightarrow (N+1,N'-1)} &\simeq k_{\text{in}}^{\text{Res-I}} V, \\ w_{(N,N') \rightarrow (N-1,N'+1)} &= w_{(N,N') \rightarrow (N+1,N'-1)} \exp \left[\frac{\mu - \mu^{\text{Res-I}}}{k_B T} \right], \end{aligned}$$

⁴⁰ See *Nonequilibrium settings II*.

⁴¹ Such a hypothesis is *not* always plausible. For example, some proteins might function so that the accessibility to the system is exclusive, called *alternative access model* [39]. (cf. *Exchange of binding* in Sect. 7.2.1.4.)

$$\begin{aligned}
 w_{(N,N') \rightarrow (N+1,N')} &\simeq k_{\text{in}}^{\text{Res-II}} V, \\
 w_{(N,N') \rightarrow (N-1,N')} &= w_{(N,N') \rightarrow (N+1,N')} \exp \left[\frac{\mu - \mu^{\text{Res-II}}}{k_{\text{B}} T} \right]. \quad (3.69)
 \end{aligned}$$

We recall the note on the *Relation between the transient nonequilibrium states and the nonequilibrium settings II* (Sect. 3.3.1.5). If we describe the process in the whole (N, N') space, we may construct a landscape that matches the above transition rates. (In fact the state space is separated into slices according to the total number of particles.) But it is not a practical description. We rather use a (reduced) representation where we look at only the open system and regard the particle environments as stationary reservoirs. Then each line of (3.69) represents the rate of entrance from R_I , of departure to R_I , entrance from R_{II} , and of departure to R_{II} , respectively. Here the chemical potential μ depends on N .

On the macroscopic level, the equation for $[A]$ corresponding to (3.64) is

$$\frac{d[A]}{dt} = k_{\text{in}}^{\text{Res-I}} \left[1 - e^{\frac{\mu - \mu^{\text{Res-I}}}{k_{\text{B}} T}} \right] + k_{\text{in}}^{\text{Res-II}} \left[1 - e^{\frac{\mu - \mu^{\text{Res-II}}}{k_{\text{B}} T}} \right], \quad (3.70)$$

where μ , $k_{\text{in}}^{\text{Res-I}}$, and $k_{\text{in}}^{\text{Res-II}}$ are functions of the concentration $[A]$ in the system. Under nonequilibrium condition, $\mu^{\text{Res-I}} > \mu^{\text{Res-II}}$, the value of $[A]$ in the steady-state solution is determined by solving (3.70) with $d[A]/dt = 0$.

3.3.3.4 Stochastic Michaelis–Menten Kinetics

The merit and at the same time demerit of the Poisson distribution is that it is governed by only one parameter. Its variance, therefore, adds no new information to the knowledge of the average value. It is not the case when the discrete states are, for example, binary $\{0, 1\}$. In that case the stochastic level observation and description of chemical reactions bring more information than the rate constants. As an example, we will again take up the Michaelis–Menten kinetics (3.17), i.e., $E + S \rightleftharpoons ES \rightarrow E + P$ (see Sect. 3.2.2.2). We will show that, from the stochastic data of the slow process, $ES \rightarrow E + P$, we can extract the parameter of the fast process, $E + S \rightleftharpoons ES$.

Parameters of the Single-Enzyme Michaelis–Menten Kinetics [40, 41]

We introduce several stochastic parameters characterizing a particular event of the release of the product P from a single enzyme, E (see Fig. 3.8).

$t_v^{(k)}$: The k th ($1 \leq k \leq n$) time interval of the free enzyme E .

$t_r^{(k)}$: The k th ($1 \leq k \leq n$) time interval of the complex ES .

n : The times of the reaction, $E + S \rightarrow ES$, at which the product release, $ES \rightarrow E + P$, occurs.

t_p : The period between the last product release and the present product release:

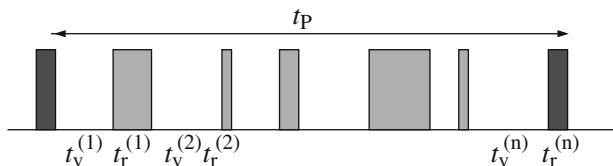


Fig. 3.8 Temporal “data” of single-enzyme reaction of Michaelis–Menten type. Each black [gray] bar denotes the complex ES which dissociates into E+P [E+S], respectively. The gaps between the bars denote the free enzyme E

$$t_P = \sum_{k=1}^n (t_r^{(k)} + t_v^{(k)}). \quad (3.71)$$

Setup of Problem

We suppose that one can only observe the events of the product release, that is the sequence of t_P . Also we assume that one can do the observation with different values of the substrate concentration, $[S]$. We introduce a Markov model which contains the following statistical parameters:

T_v^{-1} : The transition rate of the formation of the complex ES.

κ : The coefficient such that $T_v^{-1} = \kappa[S]$.

T_r^{-1} : The transition rate of the termination of the complex ES.

q : The probability of the production, $ES \rightarrow E + P$, from the state ES.

Our goal is to determine as many parameters as possible from the observation.

Result: Informations Obtained from Stochastic Data

By the analysis using the probability of individual events, we have the following relations:

$$\frac{1}{\langle t_P \rangle} = \frac{\frac{1-q}{T_r} [S]}{\frac{1}{\kappa T_r} + [S]} \quad (3.72)$$

and

$$\frac{\langle t_P \rangle}{\langle t_P \rangle^2 - 2\langle t_P^2 \rangle} = \kappa[S] + \frac{1}{T_r}. \quad (3.73)$$

For the derivation, see Appendix A.3.2. The first result (3.72) is the rate of production per enzyme. This could have also been obtained from the macroscopic production rate, v , of (3.21) if we knew the total molar concentration of the enzyme,

$[E]^{\text{tot}}$. By contrast, the second result, (3.73), contains intrinsically the information of the stochastic data. From the data of $\langle t_p \rangle$ and $\langle t_p^2 \rangle$ for various concentrations of the substrate, $[S]$, the formulas (3.72) and (3.73) allow us to obtain the three constants, κ , and T_r^{-1} , and q . Especially, $\langle n \rangle = (1 - q)^{-1}$ is obtained.

3.4 Discussion

We have analyzed chemical reactions using two levels of descriptions, macroscopic deterministic and continuous description and mesoscopic stochastic and discrete description. The latter description includes the former as a result of coarse graining. But if the total number of a molecular species is not large, the coarse-grained description is not valid.

Even the discrete stochastic description may not be valid if the transition rate depends strongly on the parameters which are not represented by the chemical formula, such as the orientations or configurations of participating molecules and the internal states of solvent molecules. For example, a rapid water exchange between the hydration shell of a molecule and the surrounding fluid water is beyond the description of the previous sections.

Depending on what spatiotemporal scale is decisively important for the reaction rate, we should choose different methods, such as the Langevin equation, molecular dynamics simulation, or density functional description. Except for the full quantum descriptions of whole atoms and electrons, we always ignore some details as rapidly (often said “adiabatically”) following degrees of freedom, but the justification of such hypothesis – separation of fast and slow degrees of freedom – is often done a posteriori by the comparison of model results with experimental observations.

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