

Mathematical Theory of Cellular Dynamics

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CHAPTER 1

Introduction

A *mathematical theory* of any subject, by definition, is an interdisciplinary study between pure mathematics and the subject area. Whether it is taught in an applied mathematics program or as a theory course in the subject area is not an intellectual matter, but rather a result of historical development and academic preference. In physics, knowledge are delivered almost exclusively using mathematical language; this is not so in biology. One also notices that the teaching of physics and many engineering classes, such as in mechanical engineering, electrical engineering, chemical engineering, etc., are very different. The former is much more focused on concepts, ideas, and *principles*, while the latter is on more realistic subjects with greater detailed knowledge. Viewed through this perspective, we see that biological science has yet to differentiate into its "mathematical" and "engineering" specialties. In our opinion, the highly acclaimed textbook *Physical Biology of the Cell* [19] has made a major contribution toward defining the latter; and the current little book is an attempt to introduce the former.

A piece of good applied mathematics always has two components: mathematical techniques that are expressed in equations and formulas, and their "interpretations" that can also be called "narratives", which is just a fancier word for story-telling. Some of you might be surprised to hear I say this: This is because most applied mathematics one traditionally learns are about *simple* not *complex systems* to which biological problems belong. It is on this issue of "simple vs. complex" that you are required to read two important articles, one by P. W. Anderson [2] and another by J. J. Hopfield [11].

Simple systems and problems have relatively straightforward representations in terms of mathematics, while complex ones are often poorly represented by mathematics; most times an effective representation itself is yet to be discovered. It is not an overstatement to say that representation is almost everything. Consider this problem: Can 32384732572057 be divided by 7? This is not an easy task. But 32384732572057 is nothing but 6551501601656455 in base-7; and obviously it can not.

One interesting lesson from the mathematical theory of quantum physics is that what happens and what can be observed are two very different things: What happens in a quantum system is represented by an abstract function in a Hilbert space H ; changing with time, as described by Schrödinger's

equation, is completely independent of what are the observables, which are represented by self-adjoint operators on the H [29]. It turns out, Kolmogorov's notions of a probability space and random variables, as the foundation of the modern mathematical theory of probability, have a very similar characteristic [14]: The latter is *measurable functions* defined on the former, called a *measurable space*, whose existence and dynamics are completely independent of any random variable, e.g., observables.*

A careful look shows us that the confidence one derives from exact sciences is often from the certainties in mathematics. This is even more true for complex systems. Isaac Newton understood this earlier and better than anyone else [9].

The theory of cellular dynamics establishes a mathematical foundation for analytical studies of cells. Its intellectual significance resides in its ability to "mathematically explain" how inanimate molecules collectively give rise to behavior and functions of a living cell; bridging physics and biology through chemistry and applied mathematics. While we focus on the biology of cells, the methods and ideas are applicable to other complex biological systems. This is explained in ...

We start our discussion by closely scrutinizing every statement. Let us start with parsing the title of this book, "cellular dynamics" | "Why cell? What is "dynamics"?"

1.1 Cell

There are several reasons why we pick cell as the central theme for a mathematical understanding of biological systems in general [1]: First, it is considered as the fundamental building blocks of all biology; things smaller than that, say a protein molecule, is also very complex, at least to atomic physicists, but it is no longer a really living organism. Yet, a cell shares a great deal of similarities with the much smaller protein, as well as the much bigger cancerous tissue. Therefore, cell can be used as an archetype for studying complex living systems consisting of populations of individuals with multiple scales [6].

Studying protein is a subject of chemistry; a protein contains atoms; and there are only about 110 some types of atoms in the periodic table, most of them do not even show up in a protein. One of the approaches to study protein is molecular dynamics (MD), which represents each atom in a protein molecule and its surrounding water molecules as point masses that follow Newton's equations of motions [15].

For a given measurable space, there are infinite many possible observables. Only when the set of all possible outcome is finite, there exists *holographic* random variables with maximum entropy.

Studying tumorous tissue is a subject of cancer biology; it contains heterogeneous cells. Non-genetic heterogeneity among cancer cells in a tumor and their potential of phenotype switching have made this area one of the most exciting new frontiers of cancer biology [3].

Studying a cell is the subject of cell biology; a typical bacterial cell contains more than 4,000 proteins, while mammals, including humans, require upwards of 100,000 different proteins. The number of copies of a particular protein ranges from less than a hundred to a more than a million (c.f., actin in myocytes) [8].

Cell theory is one of the fundamental organization principles in essentially all life sciences. One of its main statements is "life comes from life" which, in the post-genomic era, is exclusively interpreted as DNA is replicated from DNA - one key step in the central dogma of molecular biology. Cells, as the basic unit of structures and functions, divide the inanimate materials in biochemistry and living organisms.

1.2 Dynamics

What is dynamics? If t represents time and x is a certain measurement, is observed $x(t) = 5 \sin(t)$ a dynamics? The answer is "no". $x(t)$ is a function of time; but it does not represent a *dynamical system*. On the other hand, $d^2x(t)/dt^2 = -x(t)$, to which one can easily verify that $5 \sin(t)$ is a solution, is a dynamics. The difference is profound: From the differential equation, e.g., a dynamic rule, we see that knowing $x(0)$ alone is not sufficient for predicting all the $x(t)$, $t \geq 0$. However, knowing both $x(0)$ and $dx(0)/dt$ is sufficient. The dynamic description contains a great deal of generalizations and predictions in connection to the observed data, $5 \sin(t)$. One of the important consequences of thinking dynamically is to know the potential of many other behaviors yet to be observed: According to Newton's mathematical theory there is Halley's Comet; this is certainly not contained in Kepler's laws.

The dynamical description of nature can be understood as a two-by-two grids. On the one axis: Mathematical models are based on either data or mechanisms; and on the other axis: it is expressed in terms of deterministic and stochastic mathematical descriptions.

The most significant example of a deterministic dynamic model based on data is perhaps Kepler's three laws of planetary motion. Developing stochastic-process models based on big data is the subject of statistics. Research on bioinformatics, ecology, econometrics, etc. are this kind. Analyzing deterministic differential or difference equations based on mechanisms has been the central theme of applied mathematics. For example the study of nonlinear wave. Finally, studying stochastic dynamics based on mechanisms has been very important to mathematical biology and it is a growing new direction in current applied mathematics.

1.2.1 *Nonlinear, stochastic dynamics as a new paradigm*

What is modern science? Elementary and high-school students are constantly being told that science is about "observations" and "experiments". But we all know that those are only the very first steps: Exact science is also a *narrative* written in terms of *mathematics*. Lord Kelvin once said: "When you can measure what you are speaking about, and express it in numbers, you know something about it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts advanced to the stage of science." [28]

The *nonlinear, stochastic dynamics* offers a new mathematical framework toward dynamics that encompass both deterministic and statistical aspects of modeling. But it offers more. Perhaps one of the most important insights is the emergence of *rare events* which has infinitesimal probability to occur in a short time, but it will occur with probability 1 on a much longer time scale, or with a precise percentage among a large population. Rare events cannot be understood by neither classical deterministic mathematics nor normal statistics. The only tool we know of is by mechanistic stochastic modeling.[†]

Cancers, ecological catastrophes, stock market crashes, and sociopolitical revolutions are all rare events. It is these rare events that are truly *unpredictable* in the classical sense, giving the appearance of *free will*. Hopfield called it *dynamic symmetry breaking*. James Clerk Maxwell has said "It is manifest that the existence of unstable conditions renders impossible the prediction of future events, if our knowledge of the present state is only approximate, and not accurate. ... At these (unstable) points, influences whose physical magnitude is too small to be taken account of by a finite being, may produce results of the greatest importance. All great results produced by human endeavour depend on taking advantage of these singular states when they occur." [20] The *singular* state Maxwell referred to is called a transition state in chemistry and it is associated with a "checkpoint" in current cell biology verbiage.

1.3 Some philosophical thoughts

[†] One of the profound insights from the probability theory of rare events is that in a very complex nonlinear system, uncertainty about a rare event is only in the "when" while the "how" is almost completely deterministic, in terms of the sequence of events leading to its occurrence.

CHAPTER 2

Mechanics and Chemistry

We distinguish a mechanical representation of the world in terms of point masses with positions and momenta and the chemical representation of the world in terms of population densities of different individuals, each with an internal dynamics that is very complex. The internal dynamics are so complex that they appear as intrinsically stochastic; yet at the population level they follow statistical laws in their syntheses, degradations, diffusion, and interactions.

	Mechanics	Chemistry
representation	spatial coordinates	number densities
key concept	point masses	elementary reactions
dynamics	$m_i \frac{d^2 x_i}{dt^2} = F_i(\mathbf{x})$	$\frac{dx_i}{dt} = \sum_{j=1}^N j_i R_j^+(\mathbf{x}) - R_j^-(\mathbf{x})$
cause	forces with vector addition	reaction rates with additive fluxes
example	$F(x) = -kx$	$I + S \xrightarrow{k_f} 2I, S \xrightarrow{k_p} R$
potential condition	$F_i(\mathbf{x}) = -\frac{\partial U(\mathbf{x})}{\partial x_i}$	$\frac{R_j^+(\mathbf{x})}{R_j^-(\mathbf{x})} = \exp \left(\sum_{i=1}^N \frac{\partial G(\mathbf{x})}{\partial x_i} \right)$
energy law	mechanical energy conservation	chemical energy balance
thermodynamics	$S = -k_B \ln \Omega(E)$	Chapter 5
mechanism	Newton's theory is "fundamental", or Verlinde's theory?	elementary reaction, one at a time; mechanical and stochastic theories

2.1 Consequences of Newton's theory of mechanics

Following Newton's equation of motion, we have

$$\begin{aligned} m_i \frac{dx_i}{dt} \frac{d^2 x_i}{dt^2} &= F_i(\mathbf{x}) \frac{dx_i}{dt}; \\ \frac{m_i}{2} \frac{d}{dt} v_i^2(t) &= F_i(\mathbf{x}) v_i(t); \\ \frac{1}{2} \frac{d}{dt} \mathbf{p}(t) \cdot \mathbf{v}(t) &= \mathbf{F}(\mathbf{x}(t)) \cdot \mathbf{v}(t); \end{aligned} \quad (2.1)$$

in which $p_i = m_i v_i$ are called the momentum of the i^{th} point mass. Then, we have

$$\frac{d}{dt} \underbrace{\frac{\mathbf{p}(t) \cdot \mathbf{v}(t)}{2}}_{\text{kinetic energy}} - \underbrace{\int_{t_0}^t \mathbf{F}(\mathbf{x}(s)) \cdot d\mathbf{x}(s)}_{\text{mechanical work}} = 0; \quad (2.2)$$

The right-hand-side term in (2.1) is called mechanical power; it is the rate of mechanical work. If the force $\mathbf{F}(\mathbf{x}) = -\nabla_{\mathbf{x}} U(\mathbf{x})$ has a potential function, then (2.2) becomes the more familiar

$$\frac{d}{dt} \frac{\mathbf{p}(t) \cdot \mathbf{v}(t)}{2} + U(\mathbf{x}(t)) = 0; \quad (2.3)$$

2.1.1 Hamiltonian dynamics

$$\frac{dx}{dt} = \frac{\partial H(x; y)}{\partial y}; \quad \frac{dy}{dt} = -\frac{\partial H(x; y)}{\partial x}; \quad (2.4)$$

The $H(x; y)$ is conserved.

2.1.2 The mechanical theory of heat

Let us consider $H(x; y; \epsilon)$ which also contains a parameter ϵ . So one naturally interested in how a Hamiltonian dynamics depends on the ϵ . In particular, what is the long-time behavior. We recognize that the long time behavior is a continuous motion on a H -level set, determined by the initial value of H . Therefore, long-time, *thermodynamic* state of a mechanical system is a state of motion; the entire level set $H(x; y; \epsilon) = E$.

Introducing the notion of generalized force and work due to a change in ϵ :

$$dW = \frac{\partial H}{\partial \epsilon} d\epsilon = F d\epsilon; \quad (2.5)$$

We shall return to this notion later. Then, if the $\Omega(E)$ is the phase volume contained by, or the surface area of, the level set $H(x; y) = E$, then

let $S(E; \gamma) = \ln \Omega(E; \gamma)$ and one has $E = E(S; \gamma)$:

$$dE = \frac{\partial E}{\partial S} dS + \frac{\partial E}{\partial \gamma} d\gamma \quad (2.6)$$

$$\left| \frac{\partial E}{\partial S} \right|_{\gamma} = T \quad \left| \frac{\partial E}{\partial \gamma} \right|_S = F$$

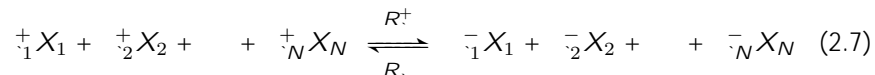
$$T dS = dQ \quad F d\gamma = dW$$

Therefore, there is an energy conservation for all different value of γ , through work $dW = F d\gamma$ and heat $dQ = T dS$. This is the *First Law of Thermodynamics*. This derivation of Eq. 2.6 is Helmholtz-Boltzmann's mechanical theory of heat.

Beyond predicting conservation of mechanical energy and deriving the First Law, one should note that while Newton's equation of motion $m_i d^2 x_i / dt^2 = F_i(\mathbf{x})$ is considered to be a natural law that is widely valid, it is not very useful until one knows the right-hand-side $F_i(\mathbf{x})$ as functions of \mathbf{x} . For a complex system, this is a daunting task. In the case of molecular dynamics of proteins, it tooks many scientists and fifty years to develop several usable *force fields*: AMBER (assisted model building and energy refinement), CHARMM (chemistry at Harvard molecular mechanics), GROMOS (Groningen molecular simulation), to name a few that are well-known [15]. Even with such a major and concerted effort of an entire research community, there are still criticisms that the mechanical approach might be irrelevant to certain key aspects of protein dynamics and functions, c.f., folding or ligand binding [16].

2.2 Consequences of the chemical kinetic equations

A chemical or biochemical reaction system can be represented in term of N species and M reactions. The k^{th} reversible chemical reaction



has two set of *stoichiometric coefficients* $\nu_k^+; \nu_k^-; 1 \leq k \leq M; 1 \leq i \leq N$.

We shall assume the reaction vessel is rapidly stirred, hence it is well-mixed in space. Under this assumption, the system will have no spatial inhomogeneity. Then because of the conservation of atoms and molecules, the change of number density, i.e., concentration of the i^{th} chemical species in the system (2.7) follows the

$$\frac{dx_i(t)}{dt} = \sum_{k=1}^M \nu_i^+ R_k^+(\mathbf{x}) - \nu_i^- R_k^-(\mathbf{x}) \quad (2.8)$$

where $x_i(t)$ is the concentration of chemical species X_i at time t , $1 \leq i \leq N$, $\nu_i^+ = \nu_i^- = \nu_i$.

We shall point out that the validity of Eq. 2.8 for a chemical kinetic system is just as sound and wide as Newton's equation for the mechanical motions

of a system of particles. Yet, just as discussed for Newton's equation, without explicitly knowing more about the right-hand-side of (2.8), it is nearly useless. To be useful, one needs to further assume the functional forms of $R^\pm(\mathbf{x})$ in terms of the $\mathbf{x} = (x_1; x_2; \dots; x_N)$.

2.2.1 Waage-Guldbergs law of mass action

One of the widely used functional form for $R^\pm(\mathbf{x})$ is known as the Law of Mass Action, which states that each elementary chemical reaction has an instantaneous rate, i.e., the number of reactions per unit time, that is proportional to

2.2.3 Gibbs potential condition

The Gibbs potential condition given in (2.10) can be written as

$$\begin{aligned} \sum_{i=1}^N x_i \frac{\partial G(\mathbf{x})}{\partial x_i} &= \ln \frac{R_j^+(\mathbf{x})}{R_j^-(\mathbf{x})} \\ &= \frac{\ln R_j^+(\mathbf{x})}{R_j^+(\mathbf{x})} - \frac{\ln R_j^-(\mathbf{x})}{R_j^-(\mathbf{x})} R_j^+(\mathbf{x}) - R_j^-(\mathbf{x}) : \end{aligned} \quad (2.12)$$

Then the chemical kinetic equation (2.8) becomes

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^M \gamma_i (R_j^+(\mathbf{x}) - R_j^-(\mathbf{x})) = \sum_{k=1}^M D_{ik}(\mathbf{x}) \frac{\partial G(\mathbf{x})}{\partial x_k}; \quad (2.13)$$

in which symmetric, semi-positive definite matrix

$$D_{ik}(\mathbf{x}) = \sum_{j=1}^M \gamma_j \frac{R_j^+(\mathbf{x}) - R_j^-(\mathbf{x})}{\ln R_j^+(\mathbf{x}) - \ln R_j^-(\mathbf{x})} \gamma_k. \quad (2.14)$$

When the $R_j^+; R_j^- = jR^+ - R^-j$ for each and every reversible reaction j , the term inside () becomes $\frac{1}{2} (R^+(\mathbf{x}) + R^-(\mathbf{x}))$. In stoichiometric network kinetics, the term in (2.14) has been called *biochemical conductance* [24].

We note that from a simple minded calculus standpoint, the ODE system (2.8) is a gradient system if and only if there exists a potential function $U(\mathbf{x})$ such that

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^M \gamma_j (R_j^+(\mathbf{x}) - R_j^-(\mathbf{x})) = \frac{\partial U(\mathbf{x})}{\partial x_i}. \quad (2.15)$$

The equation in (2.13), however, suggests two complications: There is the \mathbf{x} -dependent factor $D_{ij}(\mathbf{x})$ and it is actually a tensor. They correspond to deeper mathematical differences, in terms of *change of measure* and dynamics on a *manifold* [26], between mechanical motions in space and chemical kinetics on a graph.

2.2.4 Gibbs potential of ideal solution and the law of mass action

From the textbook on chemical thermodynamics, the Gibbs potential for an ideal solution, in $K_B T$ unit, has the form:

$$G(\mathbf{x}) = \sum_{j=1}^N x_j \left(\frac{\mu_j^0}{K_B T} + \ln x_j \right) - 1 : \quad (2.16)$$

It is easy to verify that this function is consistent with the Gibbs potential condition and Waage-Guldbergs law of mass action:

$$\ln \frac{R^+(\mathbf{x})}{R^-(\mathbf{x})} = \ln \frac{k^+}{k^-} \sum_{j=1}^N \nu_j^+ - \sum_{j=1}^N \nu_j^- \ln x_j = - \sum_{j=1}^N \nu_j \frac{\partial G(\mathbf{x})}{\partial x_j} ;$$

in which $\nu_j = \nu_j^- - \nu_j^+$.

CHAPTER 3

Stochastic Theory of Elementary Reactions

3.1 Exponential distribution for a rare event

Let us consider an event that can occur at any time. Let $P(t)$ be the probability it has not occurred yet at time t . If everything is time-homogeneous, e.g., stationary, and the probabilities of the event not occurring in time intervals $[0; t]$ and $[t; t + \Delta t]$ are independent, then $P(t + \Delta t) = P(t)P(\Delta t)$. If the event is rare, that is within a short Δt time, the probability to occur is $\lambda \Delta t$, and not occur is $1 - \lambda \Delta t$, where $\lambda \Delta t \ll 1$. Then

$$\begin{aligned} P(t + \Delta t) &= P(t)P(\Delta t) \\ &= P(t)(1 - \lambda \Delta t); \end{aligned} \quad (3.1a)$$

$$\begin{aligned} P(t + \Delta t) - P(t) &= -\lambda P(t) \Delta t; \\ \frac{dP(t)}{dt} &= -\lambda P(t); \end{aligned} \quad (3.1b)$$

The equality in (3.1a) is based on the assumption that the event occurs at anytime uniformly and independently. We give several counter examples:

- 1) The time a mosquito "feels hungry and starts to hunt". In this case, the "event" occurs with increasing λ in time since the hungry sensation increases with time; there is an urgency.
- 2) The first arrival at a shop that posts a "on sale" sign. In this case, the event is likely not a "rare" since people coming to the doorstep in "cluster".
- 3) ...

3.1.1 Essential properties of exponential distributions

If we use T to denote the random variable for the waiting time for the event to occur, then T has a cumulative distribution function (cdf) $F_T(t) = 1 - e^{-\lambda t}$ and probability density function (pdf) $f_T(t) = \lambda e^{-\lambda t}$. The expected value and variance of T are

$$E[T] = \int_0^{\infty} t f_T(t) dt = \frac{1}{\lambda}; \quad (3.2)$$

$$\text{Var } T = \int_0^\infty t^2 E[T]^{-2} f_T(t) dt = E[T^2] - E[T]^2 = \frac{1}{\lambda^2}; \quad (3.3)$$

One of the most important properties of an exponential distribution is *memoryless*:

$$\Pr(T > t + s | T > t) = \frac{\int_t^\infty f_T(s) ds}{\int_t^\infty f_T(s) ds} = \frac{e^{-\lambda(t+s)}}{e^{-\lambda t}} = e^{-\lambda s} = \Pr(T > s); \quad (3.4)$$

which is independent of t . Here is a weird story in connection to this mathematical result:

You and your lazy brother doing experiments on measuring the time distribution for the radioactive decay of certain nucleus. You arrive at the laboratory at 7:00am, take the nuclear material out of a freezer and use a Geiger counter to record clicks, which represent the time of each radioactive decay event of one nucleus. Your brother shows up at 9:00am, and starts recording on the same material using his own Geiger counter. You expected your brother to observe a roughly two-hours shorter mean time. But amazingly, when all are done, you and your brother get a same result.

If there are N independent rare events, each follows an exponential distribution with rate λ_i , then the time for the first event to occur, irrespective of which, also follows an exponential distribution. In fact, the time for the first event is $T_* = \min(T_1, T_2, \dots, T_N)$, where T_k is the waiting time for the k^{th} event. Then the cumulative distribution function (cdf)

$$\begin{aligned} F_T(t) &= \Pr(T_* < t) = 1 - \Pr(T_* > t) \\ &= 1 - \Pr(T_1 > t, T_2 > t, \dots, T_N > t) \\ &= 1 - e^{-\lambda_1 t} e^{-\lambda_2 t} \dots e^{-\lambda_N t} = 1 - e^{-\lambda_* t}; \end{aligned} \quad (3.5)$$

where $\lambda_* = \lambda_1 + \lambda_2 + \dots + \lambda_N$. Therefore,

$$f_T(t) = \frac{d}{dt} F_T(t) = \lambda_* e^{-\lambda_* t}; \quad (3.6)$$

Specifically, if all the T_k are i.i.d. with rate λ , then the rate parameter for T_* is $N\lambda$. The first one to occur is N times faster.

Now think about N runners: Do you expect the first one to reach the finishing line sooner with a larger N , especially the time is inversely proportional to N ?

3.2 Poisson process

We now consider the repeated occurrence of a "rare" event. Note, the term "rare" here is no longer a synonym for "occasional"; it is now a mathematical

concept for an event that occurs with exponential waiting time. Let $P_n(t)$ the probability that at time t , there have been n occurrences of the event. Then

$$\begin{aligned} P_n(t + \Delta t) &= P_n(t)P_0(\Delta t) + P_{n-1}(t)P_1(\Delta t) + P_{n-2}(t)P_2(\Delta t) + \\ &= P_n(t)(1 - \lambda\Delta t) + P_{n-1}(t)\lambda\Delta t + o(\Delta t); \\ \frac{dP_n(t)}{dt} &= P_n(t) - P_{n-1}(t); \end{aligned} \quad (3.7)$$

Being rare, the probability of two events to occur within the time Δt is $o(\Delta t)$. Therefore, noting that $P_0(0) = 1$ and $P_n(0) = 0$ for all $n \geq 1$, we have

$$P_n(t) = \frac{(\lambda t)^n}{n!} e^{-\lambda t}. \quad (3.8)$$

3.2.1 Counting process, point process, and renewal process

If we let $N(t)$ to denote the number of event has occurred at time t , then $N(t)$ is an integer-valued random variable with probability distribution

$$\Pr \{N(t) = n\} = \frac{(\lambda t)^n}{n!} e^{-\lambda t}. \quad (3.9)$$

There is another way to represent the same process with recurrent events: The time at which the k^{th} event occurs, T_k . We then have

$$\begin{aligned} F_{T_n}(t) &= \Pr \{T_n < t\} = \Pr \{N(t) > n\} = \sum_{m=n+1}^{\infty} \frac{(\lambda t)^m}{m!} e^{-\lambda t}; \\ f_{T_n}(t) &= \frac{d}{dt} F_{T_n}(t) = \sum_{m=n+1}^{\infty} \frac{m(\lambda t)^{m-1}}{(m-1)!} e^{-\lambda t} \\ &= \sum_{m=n+1}^{\infty} \frac{(\lambda t)^{m-1}}{(m-1)!} e^{-\lambda t} = \frac{(\lambda t)^n}{n!} e^{-\lambda t}. \end{aligned} \quad (3.10)$$

This is a Gamma distribution. Therefore, a Poisson process has a counting representation $N(t)$, $t \geq 0$, and a point-process representation T_k , $k \geq 1$.

Gamma distributed T_{n+1} is actually the sum of T_n and an independent X with exponential distribution $f_X(t) = \lambda e^{-\lambda t}$. To show this, let us denote $T_n + X = Y$, then

$$f_Y(t) = \int_0^t f_{T_n}(s) f_X(t-s) ds = \int_0^t \frac{(\lambda s)^n}{n!} e^{-\lambda s} \lambda e^{-\lambda(t-s)} ds = \frac{(\lambda t)^{n+1}}{(n+1)!} e^{-\lambda t} = f_{T_{n+1}}(t).$$

Therefore, T_n can be understood as the sum of n i.i.d. exponentially distributed $X^{(1)}, X^{(2)}, \dots, X^{(n)}$.

$$T_n = X^{(1)} + X^{(2)} + \dots + X^{(n)}. \quad (3.11)$$

Eq. 3.11 gives a Poisson process a third representation as a *renewal process* generated by an exponential waiting time for the next renewal.

As we shall show in Sec. 3.6, Poisson process plays a fundamental role in the theory of mesoscopic chemical reaction kinetics in terms of Delbrück-Gillespie processes.

3.3 Three theorems

Theorem 1 If X_1, X_2, \dots, X_n are n i.i.d. positive random variables with probability density function $f_X(x)$, with $f_X(0) \neq 0$, and let

$$X_* = n \min \{X_1, X_2, \dots, X_n\}$$

Then,

$$\lim_{n \rightarrow \infty} f_{X_*}(x) = e^{-x};$$

where $\lambda = f_X(0)$.

Theorem 2 (Khinchin) If $T_k^{(1)}, T_k^{(2)}, \dots, T_k^{(n)}$ are n i.i.d. renewal processes with waiting time distribution $f_T(x)$, then the superposition of the n renewal processes has an exponential waiting time for the next event in the limit of $n \rightarrow \infty$, with rate parameter $nE^{-1}[T]$.

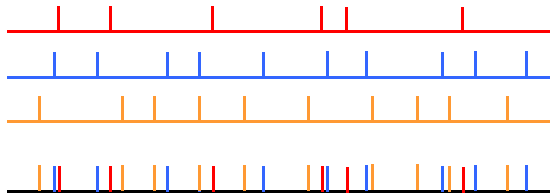


Figure 3.1 If the red, orange, and blue point processes represent the renewal events of light bulbs for 3 different sockets, then the fourth row is the combined point process for all the bulb changes. It is the superposition of the three individual processes. With more and sockets, a statistical law emerges.

Theorem 3 (Kramers) See Fig. 3.2, and more detailed in Chapter 8.

3.4 Markov processes

Let $X(t)$ be a Markov process with a discrete state space \mathcal{S} and continuous time t . Then the probability of the system in state $i \in \mathcal{S}$ at time t is

$$\frac{dp_i(t)}{dt} = \sum_{j \in \mathcal{S}} p_j(t)q_{ji} - p_i(t)q_{ij}; \quad (3.12)$$

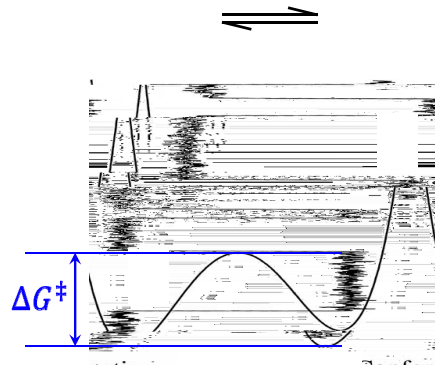


Figure 3.2 The mathematical description of a chemical reaction of a single molecule. It is an emergent statistical law of a large number of discrete, stochastic reactions. $k_1 \propto e^{-\Delta G^\ddagger/k_B T}$. Similarly, k_2 has its own activation barrier height. According to this description, the ratio k_1/k_2 becomes independent of the barrier.

in which q_{ij} is the transition rate from state i to state j , with exponential waiting time distribution. If we express the $p_i(t)$ as a row vector $\mathbf{p}(t) = (p_1; p_2; \dots)$, then Eq. 3.12 can be written as

$$\frac{d\mathbf{p}(t)}{dt} = \mathbf{p}\mathbf{Q}; \quad \mathbf{Q} = \begin{matrix} & \begin{matrix} \text{O} & \text{X} & & & 1 \end{matrix} \\ \begin{matrix} \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \end{matrix} & \begin{matrix} q_{1j} & q_{12} & q_{13} & & \\ j \in \mathcal{S}; \neq 1 & \text{X} & & & \\ q_{21} & q_{2j} & q_{23} & & \\ j \in \mathcal{S}; \neq 2 & \text{X} & & & \\ q_{31} & q_{32} & q_{3j} & & \\ j \in \mathcal{S}; \neq 3 & & & & \\ \vdots & \vdots & \vdots & & \ddots \end{matrix} \end{matrix} \quad (3.13)$$

We note that the \mathbf{Q} matrix have all the off-diagonal elements being positive, and the sum of each and every row being 0. They are the defining properties of a *Markov transition probability rate matrix*. Note the word "rate".

The solution to the vector-matrix equation (3.13) is

$$\mathbf{p}(t) = \mathbf{p}(0) \exp \mathbf{Q}t; \quad \text{or} \quad \mathbf{p}(t + \Delta t) = \mathbf{p}(t) \exp \mathbf{Q}\Delta t \quad (3.14)$$

The matrix $e^{\mathbf{Q}t}$ can have a very clear probabilistic interpretation: It contains all the conditional probability

$$\Pr[X(t) = j | X(0) = i] = e^{\mathbf{Q}t}_{ij} \quad (3.15)$$

This matrix is called Markov transition probability matrix. Each and every element of the matrix is now a probability, between 0 and 1. More importantly,

the sum of every row is unity:

$$\begin{aligned} \sum_{j \in \mathcal{S}} e^{\mathbf{Q}t}_{ij} &= \sum_{j \in \mathcal{S}} \sum_{k=0}^{\infty} \frac{\mathbf{Q}^k}{k!}_{ij} = \sum_{k=0}^{\infty} \sum_{j \in \mathcal{S}} \frac{\mathbf{Q}^k}{k!}_{ij} \\ &= \sum_{j \in \mathcal{S}} \frac{\mathbf{Q}^0}{0!}_{ij} = \sum_{j \in \mathcal{S}} \mathbf{I}_{ij} = 1 \quad \forall i \in \mathcal{S}; \end{aligned}$$

in which \mathbf{I} is the identity matrix.

More importantly, a Markov process is characterized by the probability of any *trajectory*, in terms of a joint probability:

$$\begin{aligned} \Pr \{X(0) = i_0; X(t_1) = i_1; X(t_2) = i_2; \dots; X(t_n) = i_n\} \\ = p_{i_0}(0) e^{\mathbf{Q}t_1}_{i_0 i_1} e^{\mathbf{Q}t_2}_{i_1 i_2} \dots e^{\mathbf{Q}t_n}_{i_{n-1} i_n}; \end{aligned} \quad (3.16)$$

in which $t_k = t_k - t_{k-1}$.

The equation in (3.12) and (3.13) is known as a master equation, or a Kolmogorov forward equation, for a discrete state, continuous time Markov process. Its solution gives the transition probability matrix $e^{\mathbf{Q}t}$ for the Markov process.

3.5 Stationary distribution and stationary process

All the elements of matrix $\mathbf{P}(t) = e^{\mathbf{Q}t}$ are non-negative. One of the fundamental theorems on square positive matrix is the Perron-Frobenius theorem, which states that $\mathbf{P}(t)$ has its largest eigenvalue being 1, and its corresponding eigenvector is non-negative. In fact, it is easy to see that the right eigenvector associated with eigenvalue 1 is simply $(1; 1; \dots)^T$. It is also the eigenvector of \mathbf{Q} with eigenvalue 0. More effort are needed to obtain the corresponding left eigenvector $\pi = (\pi_1; \pi_2; \dots)$.

A Markov process is said to be irreducible if it is possible to get to any state from any state. For such Markov process, its \mathbf{Q} , thus the $\mathbf{P}(t)$, has a unique eigenvalue 1, and its π_i are strictly positive. Then for any initial probability distribution $\mathbf{p}(0)$:

$$\lim_{t \rightarrow \infty} \mathbf{p}(0) e^{\mathbf{Q}t} = \pi; \quad (3.17)$$

Note if $\mathbf{p}(0)$ is normalized, then π is normalized. The distribution $(\pi_1; \pi_2; \dots)$ therefore is called the *stationary distribution* of the Markov process. It is unique.

A stationary Markov process has its initial distribution π . Thus for all time $\mathbf{p}(t) = \pi$. This is a highly, highly abstract concept. For each and every realization, of course, $X(t)$ still jumps around. An process started from $t = -1$ is necessarily stationary.

3.5.1 Solution to the master equation

According to the theory of linear, homogeneous ordinary differential equation with constant coefficients, the solution to Eq. 3.13 can be expressed in terms of the eigenvalues and eigenvectors of \mathbf{Q} . In fact, if we denote its eigenvalues $\lambda_0 = 0; \lambda_1; \lambda_2; \dots$, where all λ 's except λ_0 are negative, and corresponding left, row eigenvectors $\mathbf{v}_0 = (v_0; v_1; v_2; \dots)$ and right column eigenvectors $\mathbf{u}_0 = (1; \dots; 1)^T; \mathbf{u}_1; \mathbf{u}_2; \dots$, then

$$e^{\mathbf{Q}t} = \mathbf{u}_0 \mathbf{u}_0^T + \mathbf{u}_1 \mathbf{u}_1^T e^{\lambda_1 t} + \mathbf{u}_2 \mathbf{u}_2^T e^{\lambda_2 t} + \dots \quad (3.18)$$

Note, each \mathbf{u} is a column vector, so the $\mathbf{u}_0 \mathbf{u}_0^T$ is a matrix. We see that when $t \rightarrow \infty$,

$$e^{\mathbf{Q}t} = \mathbf{u}_0 \mathbf{u}_0^T \quad (3.19)$$

This proves Eq. 3.17. That is, for any initial distribution $\mathbf{p}(0)$,

$$\mathbf{p}(t) = \mathbf{p}(0) e^{\mathbf{Q}t} \quad (3.20)$$

if the zero eigenvalue is unique.

3.5.2 Time correlation function of an observable

Let the state space of a Markov process be \mathcal{S} , and a measurement $x(t)$ for state $i \in \mathcal{S}$. Then through $X(t)$ one can observe the stochastic process $X(t)$. If the $X(t)$ is stationary, the correlation function of x is defined as

$$\begin{aligned} G(\tau) &= \text{cov}(x(t); x(t+\tau)) = E[x(t)x(t+\tau)] - E[x(t)]E[x(t+\tau)] \\ &= \sum_{i,j,k \in \mathcal{S}} x(i)x(k) e^{\lambda_i \tau} e^{\lambda_j \tau} \sum_{j \in \mathcal{S}} x(j) \mathbf{u}_j^T \mathbf{u}_i \\ &= \sum_{j,k \in \mathcal{S}} x(j)x(k) e^{\lambda_j \tau} e^{\lambda_k \tau} \sum_{j \in \mathcal{S}} x(j) \mathbf{u}_j^T \mathbf{u}_k \end{aligned} \quad (3.21)$$

How to estimate this statistical quantity from data? Let $f_n/n = 0; 1/2; \dots; Ng$ be a time series measurements with uniform time interval g . Then one can estimate the correlation function according to

$$\hat{G}(n) = \frac{1}{N+1} \sum_{j=0}^N X_j^{n+1} - \sum_{j=0}^N X_j^n; \quad (3.22)$$

in which \hat{G} is the estimated expected value

$$= \frac{1}{N+1} \sum_{i=0}^N X_i^n. \quad (3.23)$$

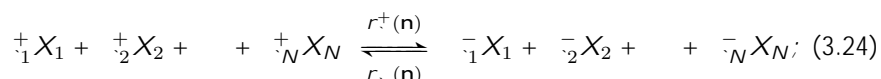
Note that $\hat{G}(0)$ is an estimated variance. Averaging using the stationary process $X(t)$ is equal to the expected value according to the stationary distribution $f^s(g)$. This is called *ergodicity*.

3.5.3 What is a "quantum collapse"?

Why did I said that the notion of a stationary process is highly abstract?

3.6 Delbrück-Gillespie processes of chemical reaction kinetics

A chemical or biochemical reaction is *elementary* if its occurrence follows an exponential distribution, with the rate r being the function of the numbers of all the reactants, $\mathbf{n} = (n_1; n_2; \dots; n_N)$, as well as the volume of the reaction vessel V . Then for a system of reactions



its kinetics is an integer-value, continuous-time Markov process $\mathbf{n}(t)$ whose master equation

$$\frac{dp_V(\mathbf{n}; t)}{dt} = \sum_{i=1}^M \left[p_V(\mathbf{n} - \mathbf{v}_i; t) r_i^+(\mathbf{n} - \mathbf{v}_i) - p_V(\mathbf{n}; t) r_i^-(\mathbf{n}) \right] + p_V(\mathbf{n}; t) r_i^+(\mathbf{n}) - p_V(\mathbf{n} + \mathbf{v}_i; t) r_i^-(\mathbf{n} + \mathbf{v}_i); \quad (3.25)$$

in which $\mathbf{v}_i = (v_{i1}; v_{i2}; \dots; v_{iN})$. Eq. 3.25 is called a *chemical master equation* (CME).

Let us now further consider discrete, individual events of the M possible reversible reactions in Eq. (3.24), one at a time. The Delbrück-Gillespie process (DGP) description of chemical kinetics assumes that the j^{th} reaction occurs

following an exponential time, with rate parameter

$$\begin{aligned} r_j^+(\mathbf{n}) &= k_j^+ V \sum_{i=1}^M \frac{n_i!}{(n_i - j_i^+)! V^{j_i^+}} A_i; \\ r_j^-(\mathbf{n}) &= k_j^- V \sum_{i=1}^M \frac{n_i!}{(n_i - j_i^-)! V^{j_i^-}} A_i; \end{aligned} \quad (3.26)$$

in which the k_j^\pm are the same proportional constants as in Eq. 2.9. Note $r(\mathbf{n})$ has the dimension of $[\text{time}]^{-1}$, while $R(\mathbf{x})$ in Eq. 2.9 can have a dimension of $[\text{time}]^{-1}[\text{volume}]^{-1}$.

According to Theorem 1, among all the possible $2M$ independent reactions, the first reaction that occurs also follows an exponential time, with the rate being the sum of the $2M$ reactions:

$$\sum_{j=1}^{2M} r_j^+(\mathbf{n}) + r_j^-(\mathbf{n}) : \quad (3.27)$$

In fact, among the i.i.d. T_1, T_2, \dots, T_n , all exponentially distributed with respective rate parameters $\lambda_1, \lambda_2, \dots, \lambda_n$, the probability of the smallest one being T_k is

$$\begin{aligned} \Pr(T^* = T_k) &= \Pr(T_k \leq \min_{i \neq k} T_i) \\ &= \frac{\lambda_k}{\lambda_1 + \dots + \lambda_n}. \end{aligned} \quad (3.28)$$

More importantly,

$$\begin{aligned} \Pr(T^* = T_k; T^* \leq t) &= \Pr(T_k \leq t; T_{k-1} \leq T_k; T_{k+1} \leq T_k; \dots; T_n \leq T_k) \\ &= \int_0^t \lambda_k e^{-\lambda_k t_k} \prod_{i=1, i \neq k}^n \int_0^{t_k} \lambda_i e^{-\lambda_i t_i} dt_i dt \\ &= \int_0^t \lambda_k e^{-\lambda_k t_k} \prod_{i=1, i \neq k}^n \int_0^{t_k} \lambda_i e^{-\lambda_i t_i} dt_i dt \\ &= \frac{\lambda_k}{\lambda_1 + \dots + \lambda_n} e^{-(\lambda_1 + \dots + \lambda_n)t}. \end{aligned} \quad (3.29)$$

This means the following important fact: The random time of the smallest one among $fT_k g$, and the probability of which one, are independent.

3.6.1 Random time-changed Poisson representation

The stochastic trajectory of the DGP can be expressed in terms of the Poisson processes:

$$n_j(t) = n_j(0) + \sum_{i=1}^M \gamma_j(Y^{\pm}) \int_0^t r_j^{\pm}(\mathbf{n}(s)) ds \quad ; \quad (3.30)$$

in which $Y^{\pm}(t)$ and $Y^{\mp}(t)$ are 2ⁿ independent standard Poisson processes with mean $E(Y^{\pm}(t)) = t$.

We see that in the limit of $\mathbf{n} \rightarrow 1$ and $V \rightarrow 1$, but $\mathbf{n}=V \rightarrow \mathbf{x}$,

$$r_j^+(\mathbf{n}) \rightarrow k_j^+ V^{\gamma_j^+} \frac{n_j^{\gamma_j^+}}{V^{\gamma_j^+}} = k_j^+ V^{\gamma_j^+} x_j^{\gamma_j^+} = V R_j^+(\mathbf{x}). \quad (3.31)$$

Similarly, $r_j^-(\mathbf{n}) \rightarrow V R_j^-(\mathbf{x})$. $r(\mathbf{n})$ is widely called a *propensity* in stochastic simulations community.

3.6.2 Kurtz's macroscopic limit

We now consider $V \rightarrow 1$ and finite concentration of species i : $x_i(t) = n_i(t)/V$. We note if the rate is very large, then a Poisson process $Y(t) \sim t$, with negligible standard deviation on the order of \sqrt{t} . Therefore, in the limit of $V; n_i(t) \rightarrow 1$, Eq. 3.30 becomes

$$x_i(t) = x_i(0) + \sum_{j=1}^M \gamma_j \int_0^t R_j^{\pm}(\mathbf{x}(s)) ds. \quad (3.32)$$

This is, of course, exactly the integral form of the ordinary differential equation in (2.8). Therefore, the DGP is not an alternative theory to the classical, deterministic kinetics and the Law of Mass Action, but a more complete theory that covers both small, mesoscopic, and large, macroscopic, biochemical reaction systems.

3.7 General population dynamics

We give two examples to show that one can "map" chemical kinetics to more general population dynamics, such as those in ecology and infectious disease epidemics.

3.7.1 Predator and prey system

Let $z(t)$ be the population density of a predator at time t and $x(t)$ be the population density of a prey at the same time. Then the simplest predator-

prey dynamics is

$$\begin{aligned} \frac{dx}{dt} &= x - xz; \\ \frac{dz}{dt} &= y + xz; \end{aligned} \quad (3.33)$$

The detailed analysis of the nonlinear dynamics can be found in many textbooks on mathematical biology or differential equations.

Let us now consider the following chemical reaction system:



According to the Law of Mass Action, the concentrations of X and Y , with fixed concentrations of A and B being a and b :

$$\frac{dx}{dt} = k_1 a x - k_2 x y; \quad \frac{dy}{dt} = k_2 x y - k_3 y; \quad (3.35)$$

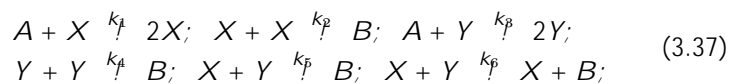
Therefore, we see that dynamics of an ecological predator-prey system is remarkable similar to that of a chemical reaction system with autocatalysis.

3.7.2 A competition model

Let us now consider another widely studied ecological dynamics with competition:

$$\begin{aligned} \frac{dN_1}{dt} &= r_1 N_1 - a_1 N_1^2 - b_{21} N_1 N_2; \\ \frac{dN_2}{dt} &= r_2 N_2 - a_2 N_2^2 - b_{12} N_2 N_1. \end{aligned} \quad (3.36)$$

Can one "design" a chemical reaction that yields an identical system of differential equation? Without loss of generality, let us assume that $b_{12} > b_{21}$.



which, according to the Law of Mass Action,

$$\begin{aligned} \frac{dx}{dt} &= (k_1 a) x - k_2 x^2 - k_5 x y; \\ \frac{dy}{dt} &= (k_3 a) y - k_4 y^2 - (k_5 + k_6) x y; \end{aligned} \quad (3.38)$$

If we identify x, y with N_1, N_2 , and

$$(k_1 a) \equiv r_1; \quad k_2 \equiv a_1; \quad k_5 \equiv b_{21}; \quad (k_3 a) \equiv r_2; \quad k_4 \equiv a_2; \quad (k_5 + k_6) \equiv b_{12};$$

then Eq. (3.38) is the same as Eq. (3.36). Note that the last reaction, $X + Y \rightarrow X + B$, is introduced to represent $b_{12} > b_{21}$.

A close inspection of the system of chemical reactions in (3.37) indicates that the overall reaction is $2A \rightarrow B$. Since all the each and every reaction is irreversible, there can be no chemical equilibrium. Rather, the system eventually reaches a *nonequilibrium steady state* in which there is a continuous chemical flux converting $2A$ to B .

Mesoscopic Thermodynamics of Markov Processes

We have seen how by merely introducing mathematically the notion of entropy, $S = k_B \ln \dots$, L. Boltzmann was able to "derive" the equation for the First Law of Thermodynamics from Newtonian mechanics. We particularly point out the significance of the k_B , Boltzmann's constant: To a mathematician, it has no consequence; but to a physicist, it made the mathematical concept connected to reality: $k_B = 1.3807 \times 10^{-23} \text{ J K}^{-1}$, joules per kelvin. $k_B T$ is energy where T is the absolute temperature.

4.1 Entropy balance equation

We consider a Markov process $X(t)$ with discrete state space \mathcal{S} and transition probability rate q_{ij} , $i, j \in \mathcal{S}$. We further assume that $X(t)$ is irreducible and $q_{ij} \neq 0$ if and only if $q_{ji} \neq 0$. The first assumption implies the existence of a unique, positive π , and the second assumption means one can introduce terms like $(q_{ij} - q_{ji})$, as we shall do below.

The Shannon entropy of a Markov process at time t is defined as

$$S(\mathbf{p}(t)) = - \sum_{i \in \mathcal{S}} p_i(t) \ln p_i(t) \quad (4.1)$$

We then have

$$\begin{aligned} \frac{d}{dt} S(\mathbf{p}(t)) &= - \sum_{i \in \mathcal{S}} \frac{dp_i(t)}{dt} \ln p_i(t) = - \sum_{i, j \in \mathcal{S}} p_i q_{ji} - p_j q_{ji} \ln p_i \\ &= - \frac{1}{2} \sum_{i, j \in \mathcal{S}} p_i q_{ji} - p_j q_{ji} \ln \frac{p_i}{p_j} \\ &= - \frac{1}{2} \sum_{i, j \in \mathcal{S}} p_i q_{ji} - p_j q_{ji} \ln \frac{p_i q_{ij}}{p_j q_{ji}} - \frac{1}{2} \sum_{i, j \in \mathcal{S}} p_i q_{ji} - p_j q_{ji} \ln \frac{q_{ij}}{q_{ji}} \quad (4.2) \end{aligned}$$

We note the first term in (4.2) is non-negative. If you had some knowledge in elementary chemistry, you will recognize that the first logarithmic term

is remarkably similar to \dot{S}_{p} , and the second logarithmic term is remarkably similar to \dot{S}_{e} , of a unimolecular chemical reaction. We shall call the first term instantaneous *entropy production rate*, e_p . The second term then is related to *entropy exchange*. In the theory of nonequilibrium thermodynamics, the latter is often related to heat exchange rate divided by temperature, $h_{\text{ex}}=T$:

$$\frac{d}{dt} S(\mathbf{p}(t)) = e_p - \frac{h_{\text{ex}}}{T}; \quad (4.3a)$$

$$e_p(\mathbf{p}) = \frac{1}{2} \sum_{i,j \in \mathcal{S}} (p_i q_{ji} - p_j q_{ji}) \ln \frac{p_i q_{ij}}{p_j q_{ji}} \geq 0; \quad (4.3b)$$

$$\frac{h_{\text{ex}}(\mathbf{p})}{T} = \frac{1}{2} \sum_{i,j \in \mathcal{S}} (p_i q_{ji} - p_j q_{ji}) \ln \frac{q_{ij}}{q_{ji}}; \quad (4.3c)$$

Equation (4.3a) is known, and will be called, entropy balance equation. In physics, it originates from the Second Law of Thermodynamics and Clausius inequality. Since in our Markov theory, the notion of temperature does not exist, we let $T = 1$. This seems to imply that the Markov theory is a theory about *isothermal* systems and processes.

In L. Onsager's theory of irreversible thermodynamics, entropy production rate is the sum of many terms, each represents an irreversible process, in the form of "thermodynamic flux \times thermodynamic force". This implies that $(p_i q_{ij} - p_j q_{ji})$ can be considered as a flux, and $\ln(p_i q_{ij} / p_j q_{ji})$ can be identified as a force. One example of Onsager's theory is "electrical current \times voltage" = power, which can be written as $I \times V$.

With this intuition, we introduce the very important notion of *detailed balance* in Markov processes.

4.2 Detailed balance and reversibility

There is a more general subclass of Markov processes that is particularly important and interesting: its stationary distribution satisfies $\pi_i q_{ij} = \pi_j q_{ji}$, $\forall i, j \in \mathcal{S}$. This is known as *detailed balance*. It is a property of the \mathbf{Q} .

Theorem 4 *An irreducible Markov process with \mathbf{Q} matrix has a detailed balanced stationary distribution if and only if for every sequence of distinct states $i_0, i_1, \dots, i_{n-1}, i_n \in \mathcal{S}$:*

$$q_{i_0 i_1} q_{i_1 i_2} \dots q_{i_{n-1} i_n} q_{i_n i_0} = q_{i_1 i_0} q_{i_2 i_1} \dots q_{i_n i_{n-1}} q_{i_0 i_n}. \quad (4.4)$$

The equation in (4.4) is called Kolmogorov cycle condition. The Theorem 4 implies that detailed balance is actually a possible property of a \mathbf{Q} matrix.

Proof. The necessity: From detailed balance, we have

$$1 = \prod_{k=0}^{n-1} \frac{q_{i_k i_{k+1}}}{q_{i_{k+1} i_k}} \cdot \frac{q_{i_n i_0}}{q_{i_0 i_n}} = \prod_{k=0}^{n-1} \frac{q_{i_k i_{k+1}}}{q_{i_{k+1} i_k}} \cdot \frac{q_{i_n i_0}}{q_{i_0 i_n}},$$

which yields relation (4.4).

The sufficiency: From (4.4), introducing a set of positive, normalized values for each and every state $i \in \mathcal{S}$, π_i as:

$$\frac{\pi_i}{\pi_j} = \frac{q_{j i_1} q_{i_1 i_2} \dots q_{i_{n-1} i}}{q_{i_1 j} q_{i_2 i_1} \dots q_{i i_{n-1}}} = \frac{q_{j i}}{q_{i j}}.$$

Then

$$\sum_{i, j \in \mathcal{S}} \pi_j q_{ji} - \pi_i q_{ij} = \sum_{i, j \in \mathcal{S}} \pi_i q_{ij} \left(\frac{j q_{ji}}{i q_{ij}} - 1 \right) = 0.$$

Therefore, $\pi_i q_{ij}$ is a stationary solution to the master equation. Since the normalized stationary solution is unique, $\pi_i = \pi_i$, thus, $\pi_i q_{ij} = \pi_j q_{ji}$, $\forall i, j \in \mathcal{S}$. \square

Theorem 5 *The following six statements about an irreducible Markov process with matrix \mathbf{Q} are equivalent.*

(i) *Its stationary distribution satisfies detailed balance: $\pi_i q_{ij} = \pi_j q_{ji}$, $\forall i, j \in \mathcal{S}$.*

(ii) *Any path connecting states i and j : $i = i_0, i_1, i_2, \dots, i_n = j$, has a path independent*

$$\ln \frac{q_{i_0 i_1}}{q_{i_1 i_0}} + \ln \frac{q_{i_1 i_2}}{q_{i_2 i_1}} + \dots + \ln \frac{q_{i_{n-1} i_n}}{q_{i_n i_{n-1}}} = \ln \pi_n - \ln \pi_0. \quad (4.5)$$

(iii) It describes a time reversible stationary Markov process.

(iv) Its \mathbf{Q} matrix satisfies Kolmogorov cycle condition for every sequence of states.

(v) There exists a positive diagonal matrix $\mathbf{\Pi}$ such that matrix $\mathbf{Q}\mathbf{\Pi}$ is symmetric.

(vi) Its stationary process has zero entropy production rate.

Proof. (i) \Rightarrow (ii):

Using (i) we have

$$\ln \frac{q_{i_0 i_1}}{q_{i_1 i_0}} + \ln \frac{q_{i_1 i_2}}{q_{i_2 i_1}} + \dots + \ln \frac{q_{i_{n-1} i_n}}{q_{i_n i_{n-1}}} \quad (4.6a)$$

$$= \ln \frac{i_0 q_{i_0 i_1}}{i_1 q_{i_1 i_0}} + \ln \frac{i_1 q_{i_1 i_2}}{i_2 q_{i_2 i_1}} + \dots + \ln \frac{i_{n-1} q_{i_{n-1} i_n}}{i_n q_{i_n i_{n-1}}} + \ln i_n - \ln i_0$$

$$= \ln i_n - \ln i_0. \quad (4.6b)$$

This means the term in (4.6a) is independent of the path; it is completely determined by the initial state $i = i_0$ and final state $j = i_n$.

Statement (ii) is similar to the path-independent work in a conservative force field, which implies the existence of a potential function. In this discrete case, (4.6) indicates that the potential function is the minus logarithm of the stationary distribution. Equilibrium probability distribution is the exponential function of a potential energy is known as Boltzmann's law in statistical mechanics.

(ii) \Rightarrow (iii):

Equation (4.6) is equivalent to

$$i_0 q_{i_0 i_1} q_{i_1 i_2} \dots q_{i_{n-1} i_n} = i_n q_{i_n i_{n-1}} \dots q_{i_2 i_1} q_{i_1 i_0},$$

which implies

$$i_0 p_{i_0 i_1}(t_1) p_{i_1 i_2}(t_2) \dots p_{i_{n-1} i_n}(t_n) = i_n p_{i_n i_{n-1}}(t_n) \dots p_{i_2 i_1}(t_2) p_{i_1 i_0}(t_1);$$

where $p_{ij}(t) = e^{\mathbf{Q}t}_{ij}$. This means for stationary $X(t)$, and $t_k = \sum_{j=1}^N \delta_{kj}$,

$$k = 1, 2, \dots, n;$$

$$\Pr \{X(0) = i_0; X(t_1) = i_1; X(t_2) = i_2; \dots; X(t_n) = i_n\} =$$

$$\Pr \{X(0) = i_n; X(t_n) = i_{n-1}; X(t_{n-1}) = i_{n-2}; \dots; X(t_n - t_1) = i_1; X(t_n) = i_0\}.$$

That is, the process $X(t)$ is time reversible: Its statistical behaviors are identical when observed forward or backward in time.

(iii) \Rightarrow (i):

Reversible Markov process has joint distribution $p_{ij}(t) = p_{ji}(t)$ for any t . Therefore,

$$\begin{aligned} e^{\mathbf{Q}t} p_{ij} &= e^{\mathbf{Q}t} p_{ji}; \\ p_{ij} + q_{ij}t + \frac{t^2}{2}(\mathbf{Q}^2)_{ij} &= p_{ji} + q_{ji}t + \frac{t^2}{2}(\mathbf{Q}^2)_{ji}; \\ p_{ij} + q_{ij}t + \frac{t}{2}(\mathbf{Q}^2)_{ij} &= p_{ji} + q_{ji}t + \frac{t}{2}(\mathbf{Q}^2)_{ji}. \end{aligned}$$

Letting $t = 0$ we have $p_{ij} = p_{ji}$.

(ii) \Rightarrow (iv):

We simply choose $i = j$, then statement (ii) becomes statement (iv).

(iv) \Rightarrow (i):

This is contained in Theorem 4.

(i) \Leftrightarrow (v):

Simply choose the positive diagonal matrix $\mathbf{\Pi} = \text{diag}(p_1, p_2, \dots)$. Conversely, if there exists a set of positive numbers p_i such that $p_i q_{ij} = p_j q_{ji}$, then it is an eigenvector of \mathbf{Q} with eigenvalue 0. Therefore since \mathbf{Q} has a unique eigenvalue 0, the normalized

$$P_i = \frac{p_i}{\sum_{k \in \mathcal{S}} p_k} = p_i;$$

(i) \Leftrightarrow (vi):

The entropy production rate is defined in (4.3b):

$$e_p = \frac{1}{2} \sum_{i,j \in \mathcal{S}} (p_i q_{ji} - p_j q_{ij}) \ln \frac{p_i q_{ij}}{p_j q_{ji}};$$

in which every term inside the summation $(p_i q_{ji} - p_j q_{ij}) \ln \frac{p_i q_{ij}}{p_j q_{ji}} = 0$. Therefore, the entire sum is zero if and only if when $p_i q_{ji} - p_j q_{ij} = 0$. This is detailed balance. \square

In thermodynamics, a stationary system, with fluctuations, is said to be at equilibrium if it has a detailed balance. If not, then it is called a nonequilibrium steady state (NESS). An equilibrium steady state has no sense of direction in time; it is time reversible. Theorem 5 suggests that in such a system, any sequence of events that occurs will have equal probability to "de-occur": Nothing can be really accomplished in a system at equilibrium.

From statement (ii), one naturally thinks of $\ln p_i$ as an "internal energy function" of the state i . Then Eq. 4.5 becomes a kind of conservation of internal energy and heat: The left-hand-side of (4.5) is the amount of heat released when system moves along the path $i_0; i_1; \dots; i_n$, and the right-hand-side of (4.5) is the internal energy difference between the state i_0 and i_n .

Because statement (v), \mathbf{Q} is similar to a symmetric matrix:

$$-\frac{1}{2}\mathbf{Q}^{-\frac{1}{2}} = \frac{1}{2}\mathbf{Q}^T - \frac{1}{2} = -\frac{1}{2}\mathbf{Q}^{-\frac{1}{2}T};$$

all eigenvalues of \mathbf{Q} are real. There is no kinetic oscillation in a system with detailed balance.

Equilibrium systems are well-understood through the theory of equilibrium statistical mechanics and thermodynamics. There is currently no widely accepted theory of nonequilibrium statistical mechanics or thermodynamics.

A living cell, even when it is considered as in a stationary process, is not an equilibrium system; it has positive entropy production. As we shall show in Chapter ??, biochemical reactions in a cell are not detailed balanced.

4.2.1 Free energy

Markov systems with detailed balanced stationary p_i has another important property. With detailed balance, let us now revisit the entropy exchange h_d in (4.3c):

$$\frac{h_d}{T} = \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_i q_{ji} - p_j q_{ji} \ln \frac{q_{ij}}{q_{ji}} = \frac{d}{dt} \sum_{i \in \mathcal{S}} p_i(t) \ln p_i; \quad (4.7)$$

If we identify $\ln p_i$ as the potential energy of state i , then

$$\bar{E}(t) = \sum_{i \in \mathcal{S}} \ln p_i p_i(t) \quad (4.8)$$

is the mean potential energy of the entire system at time t . Then the entropy balance equation (4.3a) can be re-written as

$$\frac{d}{dt} \bar{E}(t) - TS(t) = -T e_p \mathbf{p} \leq 0; \quad (4.9)$$

The term inside () is known in thermodynamics as free energy. It is known that for an isothermal system with temperature T , the Second Law of Thermodynamics states that its free energy never increases, and its decreasing rate is the same as the entropy production rate times the T .

Only systems with a uniform $p_i = C$ have $dS/dt = 0$: The Second Law of Thermodynamics widely known among laypersons.

4.3 Free energy balance equation

Eqs. 4.8 and 4.9 suggest a mathematical definition, in the context of a general, irreducible Markov process with or without detailed balance, of a *generalized free energy*

$$F[\mathbf{p}] = \sum_{i \in \mathcal{S}} p_i \ln \frac{p_i}{i} : \quad (4.10)$$

In information theory, the quantity in (4.10) is called relative entropy or Kullback-Leibler divergence. It is a "nicer" quantity than entropy in the thermodynamic theory of Markov processes with detailed balance.

Concerning the $F[\mathbf{p}]$ in (4.10), since $\ln x = x - 1$, we first have

$$\begin{aligned} F[\mathbf{p}] &= \sum_{i \in \mathcal{S}} p_i \ln \frac{p_i}{i} = \sum_{i \in \mathcal{S}} p_i \ln \frac{i}{p_i} \\ &\quad - \sum_{i \in \mathcal{S}} p_i \frac{i}{p_i} + 1 = \sum_{i \in \mathcal{S}} i - p_i = 0 : \end{aligned} \quad (4.11)$$

Furthermore we have

$$\begin{aligned} \frac{d}{dt} F[\mathbf{p}(t)] &= \sum_{i \in \mathcal{S}} \frac{dp_i(t)}{dt} \ln \frac{p_i(t)}{i} = \sum_{i,j \in \mathcal{S}} p_j q_{ji} - p_i q_{ij} \ln \frac{p_i}{i} \\ &= \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_j q_{ji} - p_i q_{ij} \ln \frac{p_i}{i} - \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_i q_{ij} - p_j q_{ji} \ln \frac{p_j}{j} \\ &= \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_j q_{ji} - p_i q_{ij} \ln \frac{j q_{ji}}{i q_{ij}} - e_p[\mathbf{p}(t)] : \end{aligned} \quad (4.12)$$

The first term in (4.12) is clearly zero if detailed balance holds true. It is not zero in general, however. Interestingly,

$$\begin{aligned} \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_j q_{ji} - p_i q_{ij} \ln \frac{j q_{ji}}{i q_{ij}} &= \sum_{i,j \in \mathcal{S}; i \neq j} p_i q_{ij} \ln \frac{j q_{ji}}{i q_{ij}} \\ &\quad - \sum_{i,j \in \mathcal{S}; i \neq j} p_i q_{ij} \frac{j q_{ji}}{i q_{ij}} + 1 = \sum_{i,j \in \mathcal{S}} \frac{j q_{ji} p_i}{i} - p_i q_{ij} \\ &= \sum_{i \in \mathcal{S}} \frac{p_i}{i} \sum_{j \in \mathcal{S}} j q_{ji} - \sum_{i,j \in \mathcal{S}} p_i q_{ij} = 0 - 0 = 0 : \end{aligned} \quad (4.13)$$

Therefore, the generalized free energy $F[\mathbf{p}]$ satisfies its own balance equation:

$$\frac{d}{dt}F[\mathbf{p}(t)] = E_{in} - e_p; \quad (4.14a)$$

$$E_{in}[\mathbf{p}] = \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_i q_{ij} - p_j q_{ji} \ln \frac{i q_{ij}}{j q_{ji}} \geq 0; \quad (4.14b)$$

$$e_p[\mathbf{p}] = \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_i q_{ji} - p_j q_{ji} \ln \frac{p_i q_{ij}}{p_j q_{ji}} \geq 0; \quad (4.14c)$$

Eq. 4.14a is a "nicer" equation than Eq. 4.3a: Because both E_{in} and e_p are non-negative, the former has a very legitimate energetic interpretation: *A Markov system's free energy changes with time, with an energy input rate (source) term E_{in} and an energy dissipation rate (sink) term e_p . The energy left the system is considered as "wasted", thus entropy production.*

4.4 Two mesoscopic thermodynamic laws of Markov processes

In addition to the generalized free energy balance equation (4.14a), one further has:

$$\begin{aligned} \frac{d}{dt}F[\mathbf{p}(t)] &= \frac{1}{2} \sum_{i,j \in \mathcal{S}} p_j q_{ji} - p_i q_{ij} \ln \frac{p_i - j}{i p_j} = \sum_{i,j \in \mathcal{S}} p_j q_{ji} \ln \frac{p_i - j}{i p_j} \\ &\quad - \sum_{i,j \in \mathcal{S}} p_j q_{ji} \frac{p_i - j}{i p_j} + 1 = \sum_{i \in \mathcal{S}} \frac{p_i}{i} \sum_{j \in \mathcal{S}} j q_{ji} - \sum_{i,j \in \mathcal{S}} p_j q_{ji} = 0; \end{aligned} \quad (4.15)$$

So the generalized free energy is also non-increasing even for general Markov processes without detailed balance.

The balance equation (4.14a) bears a remarkable resemblance to the First Law of Thermodynamics, and the Eq. 4.15 has been widely considered as the Second Law of Thermodynamics. Together, Markov processes provide a rigorous mathematical representation for the theory of thermodynamics.

CHAPTER 5

From Mesoscopic to Emergent Macroscopic Chemical Thermodynamics

In the macroscopic limit, when $V/\mathbf{n} \rightarrow 1$ in Eq. 3.25 with $\mathbf{n}=V = \mathbf{x}$, we have

$$p_V(\mathbf{x}; V; t) \rightarrow V^{-1} f(\mathbf{x}; t); r^\pm(\mathbf{n}) \rightarrow V R^\pm(\mathbf{x}); \quad (5.1)$$

and the CME (3.25) becomes

$$\begin{aligned} \frac{\partial f(\mathbf{x}; t)}{\partial t} &= \sum_{i=1}^M \frac{f(\mathbf{x}; t) R^+(\mathbf{x}) - f(\mathbf{x} - \mathbf{e}_i; t) R^+(\mathbf{x} - \mathbf{e}_i)}{1=V} \\ &\quad - \sum_{i=1}^M \frac{f(\mathbf{x} + \mathbf{e}_i; t) R^-(\mathbf{x} + \mathbf{e}_i) - f(\mathbf{x}; t) R^-(\mathbf{x})}{1=V} \\ &= \sum_{i=1}^M \left(R^+(\mathbf{x}) - R^-(\mathbf{x}) \right) \frac{\partial f(\mathbf{x}; t)}{\partial x_i} \end{aligned} \quad (5.2)$$

In terms of the method of characteristics, this first-order partial differential equation implies

$$\frac{dx_i}{dt} = \sum_{i=1}^M \left(R^+(\mathbf{x}) - R^-(\mathbf{x}) \right) \quad (5.3)$$

which is exactly Eq. 2.8. This is a heuristic demonstration of what is known as Kurtz's theorem, which proves mathematically that the Markov process $\mathbf{n}_V(t)$ defined by the CME (3.25) approaches to the solution of (5.3) in the macroscopic limit. Note that this is the same result as what we have already obtained in Sec. 3.6.2 using the random time-changed Poisson representation for the Delbrück-Gillespie processes.

In the theory of probability, a stochastic object converging to a deterministic one is called *law of large numbers*:

$$V p_V(\mathbf{z}; V; t) \rightarrow \delta(\mathbf{z} - \mathbf{x}(t))$$

Since the Dirac- function on the right-hand-side is not a nice, continuous

function of \mathbf{z} , the convergence must be not *uniform* for all \mathbf{z} . For this type of results, one usually can further ask the rate of convergence, characterized by a *large-deviation rate function* in the form of

$$\phi(\mathbf{x}; t) = \lim_{V \rightarrow \infty} \frac{\ln p_V(\mathbf{x}; V; t)}{V}; \quad (5.4)$$

In other words, for very large V ,

$$p_V(\mathbf{x}; V; t) \sim e^{-V \phi(\mathbf{x}; t)}; \quad (5.5)$$

Eq. 5.5 is known as WKB ansatz. If we substitute this expression into Eq. 3.25, then we obtain:

$$\frac{\partial \phi(\mathbf{x}; t)}{\partial t} = \sum_{i=1}^M e^{V \phi(\mathbf{x}; t)} \frac{\hbar}{e^{-V \phi(\mathbf{x} - \mathbf{r}_i; t)} R^+(\mathbf{x} - \mathbf{r}_i; V)} - \sum_{i=1}^M \frac{\hbar}{e^{-V \phi(\mathbf{x} + \mathbf{r}_i; t)} R^-(\mathbf{x} + \mathbf{r}_i; V)};$$

Therefore,

$$\frac{\partial \phi(\mathbf{x}; t)}{\partial t} = \sum_{i=1}^M \frac{\hbar}{R^+(\mathbf{x} - \mathbf{r}_i)} e^{-\hbar \nabla \phi(\mathbf{x}; t) \cdot \mathbf{r}_i} - \sum_{i=1}^M \frac{\hbar}{R^-(\mathbf{x} + \mathbf{r}_i)} e^{-\hbar \nabla \phi(\mathbf{x}; t) \cdot \mathbf{r}_i}; \quad (5.6)$$

which can be also expressed as

$$\frac{\partial \phi(\mathbf{x}; t)}{\partial t} = \sum_{i=1}^M \frac{\hbar}{R^+(\mathbf{x} - \mathbf{r}_i)} - \sum_{i=1}^M \frac{\hbar}{R^-(\mathbf{x} + \mathbf{r}_i)} e^{-\hbar \nabla \phi(\mathbf{x}; t) \cdot \mathbf{r}_i} - \sum_{i=1}^M \frac{\hbar}{R^-(\mathbf{x} + \mathbf{r}_i)} e^{-\hbar \nabla \phi(\mathbf{x}; t) \cdot \mathbf{r}_i}; \quad (5.7)$$

We see immediately that the Gibbs potential $G(\mathbf{x})$ given in Eq. 2.10 is a stationary solution to (5.7). In fact, $G(\mathbf{x})$ makes every term inside the summary zero. This is a very special class of chemical reaction kinetic systems which reaches a chemical equilibrium in the long-time limit.

5.1 Macroscopic emergent potential

For general chemical kinetic system, let $\phi^{ss}(\mathbf{x})$ be the stationary solution to (5.7). Then, noting $R^\pm(\mathbf{x}) \geq 0$ and $e^y = 1 + y$,

$$0 = \sum_{i=1}^M \frac{\hbar}{R^+(\mathbf{x} - \mathbf{r}_i)} e^{-\hbar \nabla \phi^{ss}(\mathbf{x}) \cdot \mathbf{r}_i} - \sum_{i=1}^M \frac{\hbar}{R^-(\mathbf{x} + \mathbf{r}_i)} e^{-\hbar \nabla \phi^{ss}(\mathbf{x}) \cdot \mathbf{r}_i} - \sum_{i=1}^M \frac{\hbar}{R^-(\mathbf{x} + \mathbf{r}_i)} - \sum_{i=1}^M \frac{\hbar}{R^+(\mathbf{x} - \mathbf{r}_i)} - \hbar \nabla \phi^{ss}(\mathbf{x}); \quad (5.8)$$

This implies that for the solution to the ordinary differential equation (2.8), $\mathbf{x}(t)$:

$$\begin{aligned} \frac{d}{dt} \psi^{ss}(\mathbf{x}(t)) &= \frac{d\mathbf{x}(t)}{dt} \cdot \nabla_{\mathbf{x}} \psi^{ss}(\mathbf{x}) \\ &= \sum_{k=1}^N (R^+(\mathbf{x}) - R^-(\mathbf{x})) \cdot \nabla_{\mathbf{x}} \psi^{ss}(\mathbf{x}) \\ &= 0. \end{aligned} \quad (5.9)$$

$\psi^{ss}(\mathbf{x})$ is a "landscape" for the transient dynamics $\mathbf{x}(t)$.

5.1.1 Gibbs-Duhem equation

We have seen in Eq. 5.4 that in the limit of $V \rightarrow \infty$,

$$\lim_{V \rightarrow \infty} \frac{\ln p_V(\mathbf{x}; V; t)}{V} = \psi(\mathbf{x}; t).$$

We note that both numerator and denominator above tend to infinity; hence one can apply L'Hospital's rule:

$$\begin{aligned} \psi(\mathbf{x}; t) &= \lim_{V \rightarrow \infty} \frac{\partial \ln p_V(\mathbf{x}; V; t)}{\partial V} \\ &= \lim_{V \rightarrow \infty} \frac{\sum_{k=1}^N x_k \nabla_{x_k} \ln p_V(\mathbf{x}; V; t)}{V} \\ &= \sum_{k=1}^N x_k \nabla_{x_k} \psi(\mathbf{x}; t); \quad \nabla_{x_k} \psi(\mathbf{x}; t) = \frac{\partial \psi(\mathbf{x}; t)}{\partial x_k}. \end{aligned} \quad (5.10)$$

Eq. 5.10 is known as the Gibbs-Duhem equation in chemical thermodynamics.

5.2 Macroscopic emergent thermodynamics

What happens to the free energy balance equation (4.14a) and the three mesoscopic quantities, generalized free energy $F[\mathbf{p}]$, entropy production rate $e_p[\mathbf{p}]$, and energy input rate $E_{in}[\mathbf{p}]$?

Based on Eqs. 5.1 and 5.5, we have

$$\frac{F[\mathbf{p}]}{V} \rightarrow \psi^{ss}(\mathbf{x}); \quad (5.11a)$$

$$\frac{d\psi^{ss}(\mathbf{x})}{dt} = \text{cmf}(\mathbf{x}) - \psi(\mathbf{x}); \quad (5.11b)$$

$$\frac{e_p[\mathbf{p}]}{V} \rightarrow \psi(\mathbf{x}) = \sum_{k=1}^N (R^+(\mathbf{x}) - R^-(\mathbf{x})) \ln \frac{R^+(\mathbf{x})}{R^-(\mathbf{x})}; \quad (5.11c)$$

$$\frac{E_{in}[\mathbf{p}]}{V} - \text{cmf}(\mathbf{x}) = \sum_{j=1}^M R^+_j(\mathbf{x}) - R^-_j(\mathbf{x}) \ln \frac{R^+_j(\mathbf{x})}{R^-_j(\mathbf{x})} e^{-\sum_{i=1}^N \nabla_{\mathbf{x}}^i \cdot \mathbf{ss}^i(\mathbf{x})} ; \quad (5.11d)$$

in which $\sum_{j=1}^M R^+_j(\mathbf{x}) - R^-_j(\mathbf{x})$ is the macroscopic entropy production rate density; and $\text{cmf}(\mathbf{x})$ is chemical motive force that drives a nonequilibrium chemical reaction system. For closed, non-driven chemical reaction systems, $\text{cmf}(\mathbf{x}) = 0$.

Eqs. 5.9 and 5.11b are two emergent laws for macroscopic chemical reaction kinetics. They are valid for open, driven chemical and biochemical reaction systems.

5.2.1 Delbrück-Gillespie processes and ideal solution in equilibrium

The term "solution" in the title means an aqueous fluid with solutes. It is a chemical term which has nothing to do with an answer to a mathematical problem. Eq. 5.11d indicates that for a chemical reaction system in equilibrium,

$$\sum_{j=1}^M R^+_j{}^{eq}(\mathbf{x}) = \ln \frac{R^+_j(\mathbf{x})}{R^-_j(\mathbf{x})} ; \quad (5.12)$$

This is the Gibbs potential condition in Sec. 2.2.3. For systems with detailed balance, therefore, $\sum_{j=1}^M R^+_j{}^{eq}(\mathbf{x})$ is the Gibbs potential for macroscopic chemical equilibrium.

If a M -dimensional vector $\mathbf{v} = (v_1, v_2, \dots, v_M)$ satisfies

$$\sum_{j=1}^M v_j R^+_j = 0 ; \quad (5.13)$$

for all $i, 1 \leq i \leq N$, then \mathbf{v} represents a reaction cycle, a set of reaction fluxes, together there is a perfect balance of the concentrations of all the chemical species:

$$\frac{dx_i}{dt} = \sum_{j=1}^M v_j R^+_j = 0 ; \quad (5.14)$$

Eq. 5.12 implies that for any such \mathbf{v} ,

$$\sum_{j=1}^M v_j \ln \frac{R^+_j(\mathbf{x})}{R^-_j(\mathbf{x})} = \sum_{j=1}^M v_j \sum_{i=1}^N \nabla_{\mathbf{x}}^i \cdot \mathbf{ss}^i(\mathbf{x}) = 0 ; \quad (5.15)$$

In chemistry, this equation is known as Wegscheider-Lewis cycle condition.

We now employ the Delbrück-Gillespie rate laws $r^\pm(\mathbf{n}; V)$ given in Eq. 3.26 and its macroscopic counterpart $R^\pm(\mathbf{x})$ in Eq. 2.9. Then the Wegscheider-

One can in fact introduce a "local force" for the i^{th} reversible reaction

$$X_i(\mathbf{x}) = \ln \frac{R_i^+(\mathbf{x})}{R_i^-(\mathbf{x})}; \quad (5.19)$$

Then Eq. 5.11c becomes

$$\frac{d\mathbf{x}}{dt} = \sum_{i=1}^M R_i^+(\mathbf{x}) - R_i^-(\mathbf{x}) \quad \dot{\mathbf{x}}(\mathbf{x}) = \sum_{i=1}^M X_i(\mathbf{x}) C_i(\mathbf{x}) - \dot{\mathbf{x}}(\mathbf{x}); \quad (5.20)$$

in which the chemical conductance of the i^{th} reaction is (see Eq. 2.14)

$$C_i(\mathbf{x}) = \frac{R_i^+(\mathbf{x})}{\ln R_i^+(\mathbf{x})} - \frac{R_i^-(\mathbf{x})}{\ln R_i^-(\mathbf{x})}; \quad (5.21)$$

Equations in 5.20 are known as a part of Onsager's theory of irreversible thermodynamics: entropy production is the product of "flux" "thermodynamic force", and the force and the flux are linearly related.

And Eq. 5.11d and Eq. 5.11b can be written as

$$\text{cmf}(\mathbf{x}) = \sum_{i=1}^M R_i^+(\mathbf{x}) - R_i^-(\mathbf{x}) = \nabla_{\mathbf{x}} \cdot \mathbf{r}^{ss}(\mathbf{x}) - \dot{\mathbf{x}}(\mathbf{x}); \quad (5.22)$$

$$\begin{aligned} \frac{d \cdot^{ss}(\mathbf{x})}{dt} &= \sum_{i=1}^M R_i^+(\mathbf{x}) - R_i^-(\mathbf{x}) - \nabla_{\mathbf{x}} \cdot \mathbf{r}^{ss}(\mathbf{x}) \\ &= \sum_{i=1}^M X_i(\mathbf{x}) C_i(\mathbf{x}) - \nabla_{\mathbf{x}} \cdot \mathbf{r}^{ss}(\mathbf{x}); \end{aligned} \quad (5.23)$$

A chemical kinetic system can be represented by the set of kinetic rates $R_i^{\pm}(\mathbf{x})$, or it can be represented thermodynamically by forces and transport coefficients $X_i(\mathbf{x})$; $C_i(\mathbf{x})$:

$$R_i^+(\mathbf{x}) = \frac{C_i(\mathbf{x}) \cdot \dot{\mathbf{x}}(\mathbf{x})}{e^{\Psi_i(\mathbf{x})} - 1}; \quad R_i^-(\mathbf{x}) = \frac{C_i(\mathbf{x}) \cdot \dot{\mathbf{x}}(\mathbf{x})}{1 - e^{-\Psi_i(\mathbf{x})}}; \quad (5.24)$$

and

$$\frac{d\mathbf{x}(t)}{dt} = \sum_{i=1}^M X_i(\mathbf{x}) C_i(\mathbf{x}) - \dot{\mathbf{x}}(\mathbf{x}); \quad (5.25)$$

For reaction system with zero cmf:

$$\dot{\mathbf{x}}(\mathbf{x}) = \frac{d \cdot^{ss}(\mathbf{x})}{dt} = \sum_{i=1}^M C_i(\mathbf{x}) \cdot \nabla_{\mathbf{x}} \cdot \mathbf{r}^{ss}(\mathbf{x})^2; \quad (5.26)$$

is a quadratic form with a symmetric, $N \times N$ matrix, which we have seen in Eq. 2.14,

$$\mathbf{D}(\mathbf{x}) = \sum_{i=1}^M \mathbf{C}_i^T(\mathbf{x}) \mathbf{C}_i(\mathbf{x}); \quad (5.27)$$

where \mathbf{r}_i are row vectors and \mathbf{r}_j^T are column vectors. The entry $D_{ij}(\mathbf{x})$ contains terms like $\gamma_{ij} \neq 0$: the species i is connected to species j via reaction γ_{ij} .

5.3 Hamiltonian structure and Lagrangian principle

The nonlinear partial differential equation (PDE) with first-order in $r_{\mathbf{x}}'(\mathbf{x}; t)$ in (5.7) is widely called a Hamilton-Jacobi equation (HJE):

$$\frac{\partial \psi(\mathbf{x}; t)}{\partial t} + H(\mathbf{x}; r_{\mathbf{x}}'(\mathbf{x}; t)) = 0; \quad (5.28)$$

with a Hamiltonian function

$$H(\mathbf{x}; \mathbf{y}) = \sum_{i=1}^N \mathbf{r}_i^T(\mathbf{x}) R_i(\mathbf{x}) e^{-\mathbf{y}^T \mathbf{r}_i} = \sum_{i=1}^N \mathbf{r}_i^T(\mathbf{x}) e^{-\mathbf{y}^T \mathbf{r}_i}; \quad (5.29)$$

In the advanced PDE class, it can be shown that the solution to the HJE can be constructed from the solution to the systems of ODEs

$$\frac{d\mathbf{x}(t)}{dt} = r_{\mathbf{y}} H(\mathbf{x}; \mathbf{y}); \quad \frac{d\mathbf{y}(t)}{dt} = -r_{\mathbf{x}} H(\mathbf{x}; \mathbf{y}); \quad (5.30)$$

through the method of characteristics [121, 122].

5.3.1 The probabilistic meaning of the Hamiltonian description

What is the meaning of the Hamiltonian dynamics (5.30), which is actually a $2N$ -dimensional system, double the size of the ODE in (5.3)? In classical mechanics, we know that a Hamiltonian system is equivalent to a Newton's equation, which also has a Lagrangian action principle through a minimizer. It turns out, one can introduce a scalar function through the Legendre-Fenchel transform:

$$L(\mathbf{x}; \mathbf{z}) = \sup_{\mathbf{y}} \mathbf{y}^T \mathbf{z} - H(\mathbf{x}; \mathbf{y}) = \mathbf{y}^* \mathbf{z} - H(\mathbf{x}; \mathbf{y}^*); \quad (5.31)$$

in which $\mathbf{y}^*(\mathbf{x}; \mathbf{z})$ is the root of $\mathbf{z} = \partial H(\mathbf{x}; \mathbf{y}) / \partial \mathbf{y}$. Then

$$\exp \left(-V \int_{t_0}^t L(\mathbf{x}(s); \mathbf{z}(s)) ds \right) \quad (5.32)$$

is proportional to the probability density of the trajectory $\mathbf{x}(t)$ with $\mathbf{x}(t_0) = \mathbf{x}_0$ and $\mathbf{x}(t) = \mathbf{x}_t$. The most probable trajectory $\mathbf{x}(t)$ satisfies a system of second-order ODEs, known as Euler-Lagrange equation

$$\frac{\partial L[\mathbf{x}; \mathbf{z}]}{\partial \mathbf{x}_i} - \frac{d}{dt} \frac{\partial L[\mathbf{x}; \mathbf{z}]}{\partial \dot{\mathbf{x}}_i} = 0; \quad i = 1, 2, \dots, N; \quad (5.33)$$

as a solution to the *boundary value problem*.

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In the macroscopic limit of $V \rightarrow \infty$, any trajectory $\mathbf{x}(t)$ that is not the solution to the ODE in (5.3) is nearly impossible; it is a rare event. Still, with given $\mathbf{x}(t_0) = \mathbf{x}_0$ and $\mathbf{x}(t) = \mathbf{x}_t$, a rare event is possible, and the corresponding probability is given by Eq. 5.32. With very large V , only the $\mathbf{x}(t)$ that minimizes the action in (5.32) can really occur; all the other $\mathbf{x}(t)$'s connecting \mathbf{x}_0 to \mathbf{x}_t are impossible among the nearly impossibles.

A solution to (5.3) is not a rare event; it has $L[\mathbf{x}(t); \dot{\mathbf{x}}(t)] = 0$ $\forall t$. This corresponds to the solution to (5.30) with $\mathbf{y} = \mathbf{0}$. Note that

$$\frac{d\mathbf{y}}{dt} = -\nabla_{\mathbf{x}} H(\mathbf{x}; \mathbf{0}) = \mathbf{0} \quad (\Rightarrow) \quad \mathbf{y}(t) = \mathbf{0}; \quad (5.34a)$$

$$\frac{d\mathbf{x}}{dt} = \nabla_{\mathbf{y}} H(\mathbf{x}; \mathbf{0}) = \sum_{i=1}^M \left(R_i^+(\mathbf{x}) - R_i^-(\mathbf{x}) \right) \mathbf{e}_i; \quad (5.34b)$$

and along this solution, $H[\mathbf{x}(t); \mathbf{0}] = 0$.

5.4 An example

For unimolecular reaction



with $\mathbf{e} = (-1, +1)$, and its Hamilton-Jacobi equation is

$$\frac{\partial}{\partial t} H(x_1, x_2; t) + H(x_1, x_2; \frac{\partial}{\partial x_1}, \frac{\partial}{\partial x_2}) = 0; \quad (5.36)$$

in which the Hamiltonian

$$H(x_1, x_2; y_1, y_2) = k_{+1} x_1 e^{-y_1+y_2} - k_{+1} x_1 - k_{-1} x_2 + k_{-1} x_2 e^{y_1-y_2}; \quad (5.37)$$

The Hamiltonian system of ODEs:

$$\begin{aligned} \frac{dx_1}{dt} &= -k_{+1} x_1 e^{-y_1+y_2} + k_{-1} x_2 e^{y_1-y_2} \\ \frac{dy_1}{dt} &= k_{+1} - k_{-1} e^{y_1-y_2} \\ \frac{dx_2}{dt} &= k_{+1} x_1 e^{-y_1+y_2} - k_{-1} x_2 e^{y_1-y_2} \\ \frac{dy_2}{dt} &= k_{-1} - k_{+1} e^{y_1-y_2}; \end{aligned} \quad (5.38)$$

We see that $d(x_1 + x_2)/dt = 0$. Let $z = y_1 - y_2$, then

$$\begin{aligned} \frac{dx_1}{dt} &= -k_{+1} x_1 e^{-z} + k_{-1} x_2 e^z \\ \frac{dz}{dt} &= k_{+1} - k_{-1} e^z; \end{aligned} \quad (5.39)$$

AN EXAMPLE

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in which $x_{tot} = x_1(t) + x_2(t)$. When $z = 0$, the $dx_1(t) = dt$ in (5.39) becomes the mass-action kinetics.

5.5 Maxwell relations in macroscopic thermodynamics

Let us now consider the situation where the mesoscopic probability distribution has several *extensive parameters* in addition to the volume V : $p_V(\mathbf{n}; t; \hat{\cdot}; \cdot)$. Then in the macroscopic limit we have

$$p_V(\mathbf{x}; V; t; \wedge V; \wedge V) \sim e^{-V'(\mathbf{x}; t; \wedge; \wedge)}; \quad (5.40)$$

5.6 The logics of mesoscopic dynamics

5.6.1 Some considerations based on symmetry

If we introduce two new rate functions

$$R^\pm(\mathbf{x}; \cdot) = R^\pm(\mathbf{x}) e^{\pm \frac{1}{2} \cdot \cdot}(\mathbf{x}; t); \quad (5.41)$$

then the HJE (A10) becomes

$$\frac{\partial}{\partial t} \langle \mathbf{x}; t \rangle = \langle \mathbf{x}; t \rangle \quad (5.42)$$

$$\frac{\partial}{\partial t} \langle \mathbf{x}; t \rangle = \sum_{i=1}^M \ln \frac{R^+(\mathbf{x}; \cdot)}{R^-(\mathbf{x}; \cdot)} D_{\cdot \cdot}(\mathbf{x}; \cdot) e^{\frac{1}{2} \cdot \cdot} e^{-\frac{1}{2} \cdot \cdot} \quad (5.43)$$

Let us first consider systems with detailed balance. If we denote $r_{\mathbf{x}}'(\mathbf{x}; t) = r_{\mathbf{x}}'^{eq}(\mathbf{x}) + \tilde{\cdot}(\mathbf{x}; t)$ and $\tilde{\cdot}(\mathbf{x}) = (\partial/\partial t) r_{\mathbf{x}}'(\mathbf{x}; t)$, they are, following Onsager, called thermodynamic force and thermodynamic flux, respectively. Then from Eq. 5.7

$$\begin{aligned} \frac{\partial}{\partial t} \tilde{\cdot}(\mathbf{x}) &= r_{\mathbf{x}}' \sum_{i=1}^M \ln \frac{R^+(\mathbf{x}) + R^-(\mathbf{x})}{R^+(\mathbf{x}) + R^-(\mathbf{x})} \frac{e^{-\cdot \cdot \nabla_{\mathbf{x}}' eq(\mathbf{x})}}{e^{-\cdot \cdot \nabla_{\mathbf{x}}' eq(\mathbf{x})} + 1} \\ &= \frac{1}{1 + e^{-\cdot \cdot \nabla_{\mathbf{x}}' eq(\mathbf{x})}} \frac{e^{-\cdot \cdot \nabla_{\mathbf{x}}' eq(\mathbf{x})}}{e^{-\cdot \cdot \nabla_{\mathbf{x}}' eq(\mathbf{x})} + 1} \frac{\partial}{\partial t} \tilde{\cdot}(\mathbf{x}) \end{aligned} \quad (5.44)$$

5.6.2 Onsager's linear irreversibility

If we assume the system is "near equilibrium", then one expects $\tilde{\cdot}(\mathbf{x}) \ll 1$, and it satisfies a linear equation:

$$\frac{\partial}{\partial t} \tilde{\cdot}(\mathbf{x}) = r_{\mathbf{x}}' \sum_{i=1}^M \ln \frac{R^+(\mathbf{x}) + R^-(\mathbf{x})}{R^+(\mathbf{x}) + R^-(\mathbf{x})} \tanh \frac{\cdot \cdot r_{\mathbf{x}}'^{eq}(\mathbf{x})}{2} \cdot \tilde{\cdot}(\mathbf{x}) \quad (5.45)$$

whose characteristic lines satisfy Eq. (5.3). Actually, the more interesting result is the linear perturbation $\cdot'(\mathbf{x}; t) = \cdot'^{ss}(\mathbf{x}) + u(\mathbf{x}; t)$, where $r_{\mathbf{x}} u(\mathbf{x}; t) \ll 1$:

$$\frac{\partial u(\mathbf{x}; t)}{\partial t} = \sum_{i=1}^M R^-(\mathbf{x}) e^{-\cdot \cdot \nabla_{\mathbf{x}}' ss(\mathbf{x})} - R^+(\mathbf{x}) e^{-\cdot \cdot \nabla_{\mathbf{x}}' ss(\mathbf{x}; t)} \cdot r_{\mathbf{x}} u(\mathbf{x}; t); \quad (5.46)$$

If the system is actually detailed balanced, then one has $r_{\mathbf{x}}^{ss}(\mathbf{x})$ satisfies relation ???. In this case,

$$\frac{\partial u(\mathbf{x}; t)}{\partial t} = \sum_{i=1}^M R_i^+(\mathbf{x}) - R_i^-(\mathbf{x}) = r_{\mathbf{x}} u(\mathbf{x}; t); \quad (5.47)$$

Which can and should be interpreted as Onsager's linear irreversibility with thermodynamic force \sim and thermodynamic flux \sim :

$$\frac{\partial}{\partial t} \sim(\mathbf{x}) = \sim(\mathbf{x}); \quad (5.48)$$

where \sim and \sim are related via

$$\begin{aligned} \sim(\mathbf{x}) &= r_{\mathbf{x}} \sum_{i=1}^M R_i^+(\mathbf{x}) - R_i^-(\mathbf{x}) = \sim(\mathbf{x}) \\ &= r_{\mathbf{x}} \sum_{i=1}^M R_i^+(\mathbf{x}) + R_i^-(\mathbf{x}) = \sim(\mathbf{x}) \end{aligned} \quad (5.49)$$

Which one is "near equilibrium"?

5.6.3 Local and global dynamics

The first shock.

5.6.4 Emergent behavior and a circular logic

$$u(x; y; t) = \frac{\partial}{\partial y} \frac{\partial}{\partial x}; \quad (5.50)$$

Then,

$$\begin{aligned} \frac{\partial u(x; y; t)}{\partial t} &= \frac{\partial}{\partial y} \frac{\partial}{\partial x} [k_{+1}x^{-1} e^{-u(x; y; t)} + k_{-1}y^{-1} e^{u(x; y; t)}] \\ &= k_{+1}x e^{-u(x; y; t)} \frac{\partial u}{\partial y} + k_{-1}^{-1} e^{u(x; y; t)} - k_{-1}y e^{u(x; y; t)} \frac{\partial u}{\partial y} \end{aligned} \quad (5.51)$$

5.6.5

$$\frac{\partial}{\partial t} (x; t) = H(x; \frac{\partial}{\partial x}); \quad (5.52)$$

in which

$$H(x; y) = v(x)e^y + w(x)e^{-y} - v(x) - w(x); \quad (5.53)$$

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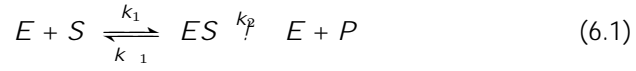
whose Hamiltonian system of ODEs are

$$\begin{aligned}\frac{dx}{dt} &= v(x)e^y - w(x)e^{-y}; \\ \frac{dy}{dt} &= v'(x) + w'(x) - v'(x)e^y - w'(x)e^{-y}.\end{aligned}\tag{5.54}$$

CHAPTER 6

Enzyme Kinetics

6.1 Double reciprocal relation and Michaelis-Menten mechanism



6.2 Quasi-steady-state approximation and singular perturbation

Using $e(t)$, $s(t)$, $c(t)$ and $p(t)$ for the concentrations of the enzyme E , substrate S , enzyme-substrate complex ES , and product P , we have

$$\frac{ds(t)}{dt} = -k_1 es + k_{-1} c; \quad (6.2a)$$

$$\frac{de(t)}{dt} = -k_1 es + k_{-1} c + k_2 c; \quad (6.2b)$$

$$\frac{dc(t)}{dt} = k_1 es - k_{-1} c - k_2 c; \quad (6.2c)$$

$$\frac{dp(t)}{dt} = k_2 c; \quad (6.2d)$$

One immediately observes

$$\frac{d}{dt} (s(t) + c(t) + p(t)) = 0; \quad \frac{d}{dt} (e(t) + c(t)) = 0; \quad (6.3)$$

They are, of course, due to the conservation of total number of molecules of S , ES , and P , s_0 , and the conservation of total number of enzyme molecules, e_0 , in the bare form E and complex form ES . Because of Eq. 6.3, there are really only two independent ODEs in (6.2):

$$\frac{ds(t)}{dt} = -k_1 e_0 s + k_1 s c + k_{-1} c; \quad (6.4a)$$

$$\frac{dc(t)}{dt} = k_1 e_0 s - k_1 c s - k_{-1} c + k_2 c; \quad (6.4b)$$

It is easy to see that the steady state of the system of ODEs is $s = c = 0$. This is expected intuitively from the chemical reaction scheme in (6.1): in the long time, all the substrate molecules becomes P , and all the enzyme molecules are in the E form. There will be no S and no ES complex.

In most biochemical problems, $e_0 \gg s_0$. Let us introduce non-dimensionalization to the equations in (6.4):

$$u = \frac{s}{s_0}; \quad v = \frac{c}{e_0}; \quad t = k_1 e_0 t; \quad (6.5)$$

Then,

$$\frac{du}{dt} = -u + uv + \frac{K_m}{q} v; \quad (6.6a)$$

$$\frac{dv}{dt} = u - uv - K_m v; \quad (6.6b)$$

in which

$$q = \frac{e_0}{s_0}; \quad K_m = \frac{k_{-1} + k_2}{k_1 s_0}; \quad q = \frac{k_2}{k_1 s_0}; \quad (6.7)$$

The initial conditions for the differential equations are $u(0) = 1$ and $v(0) = 0$.

In the limit of $q \gg 1$, $v(t)$ changes rapidly from 0 to $u - uv - K_m v = 0$ while $u(t) = 1$ has nearly change any. This occurs on the time scale of order $O(1/q)$. Therefore, we have, on the time scale $O(1)$:

$$\frac{du}{dt} = -\frac{qu}{K_m + u}; \quad (6.8)$$

6.3 Single-molecule enzymology

6.3.1 Stochastic enzyme kinetic cycle

With only a single enzyme and the concentration of S essentially constant over time, the chemical master equation (CME) is

$$\frac{dp_E(t)}{dt} = p_E k_1 S + p_{ES} (-k_{-1} + k_2); \quad (6.9a)$$

$$\frac{dp_{ES}(t)}{dt} = p_E k_1 S - p_{ES} (-k_{-1} + k_2); \quad (6.9b)$$

in which

$$p_E(t) = \Pr[n_E(t) = 1];$$

$$p_{ES}(t) = \Pr[n_E(t) = 0];$$

Note that in the Delbruck-Gillespie process, $n_E(t) + n_{ES}(t) = 1$. The stationary probability distribution

$$p_E^{ss} = \frac{k_{-1} + k_2}{k_1 S + k_{-1} + k_2}; \quad p_{ES}^{ss} = \frac{k_1 S}{k_1 S + k_{-1} + k_2}; \quad (6.10)$$

Therefore, the steady state rate of P production is

$$k_2 p_{ES}^{ss} = \frac{k_2 k_1 S}{k_1 S + k_{-1} + k_2} = \frac{k_2 S}{S + K_m}; \quad (6.11)$$

This agrees with (6.8).

6.3.2 Stochastic product arriving time, one at a time

Let $\mathbb{E}[T]$ denote the mean time from the left side of Eq. 6.1 to the right side. Then,

$$\mathbb{E}[T] = \frac{1}{k_1 s} + \frac{1}{k_{-1} + k_2} + \frac{k_2}{k_{-1} + k_2} 0 + \frac{k_{-1}}{k_{-1} + k_2} \mathbb{E}[T] \quad ; \quad (6.12)$$

From this, we solve

$$\mathbb{E}[T] = \frac{k_{-1} + k_2}{k_2 k_1 s} + \frac{1}{k_2} = \frac{k_2 k_1 s}{k_{-1} + k_2 + k_1 s}^{-1} \quad ; \quad (6.13)$$

The mean time is the reciprocal of the rate in (6.11).

The method we used to compute the $\mathbb{E}[T]$ is a part of the general theory of the *mean first passage time* problem, which will be further discussed in Chapter 8.



1-d DGP and Chemical Kinetics of Single Species

7.1 Nonlinear kinetics, stability and bifurcations

7.1.1 Saddle-node bifurcation in nonlinear dynamics

7.1.2 Cusp catastrophe

7.2 Birth-and-death process with state-dependent transition rates

With n individuals, let the rate of one birth, e.g, synthesis, production, $u(n)$, and the rate of one death, e.g., degradation, $w(n)$. Both are function of the size of the reaction vessel V . Then the CME:

$$\frac{dp_n(t)}{dt} = p_{n-1}u(n-1) - p_n[u(n) + w(n)] + p_{n+1}w(n+1): \quad (7.1)$$

Its stationary distribution can be obtained:

$$\frac{p_n^{ss}}{p_{n-1}^{ss}} = \frac{u(n-1)}{w(n)}: \quad (7.2)$$

Therefore,

$$p_n^{ss} = p_0^{ss} \prod_{k=1}^n \frac{u(k-1)}{w(k)}; \quad (7.3)$$

in which p_0^{ss} is to be determined by normalization.

As a function of discrete n , where are the peaks and troughs of the distribution? When $u(n-1) > w(n)$, p_n^{ss} increases; and when $u(n-1) < w(n)$, p_n^{ss} decreases. Therefore, the peaks and troughs are at k^* when $u(k^*-1) = w(k^*)$, when the birth rate is balanced by the death rate.

When $V \rightarrow \infty$, let us denote the number density, e.g., concentration as $x = n/V$. Then we have

$$\lim_{V \rightarrow \infty} \frac{u(xV)}{V} = \vartheta(x); \quad \lim_{V \rightarrow \infty} \frac{w(xV)}{V} = \varpi(x): \quad (7.4)$$

And, denoting $x = V^{-1}$:

$$\ln p_{xV}^{ss} = \ln p_0^{ss} + V \sum_{k=1}^{\infty} \ln \frac{u(k-1)}{w(k)} x + \int_0^x \ln \frac{\vartheta(z)}{\varpi(z)} dz + C; \quad (7.5)$$

where C is just an additive constant. Therefore,

$$\lim_{V \rightarrow \infty} \frac{\ln p_{xV}^{ss}}{V} = \vartheta'(x) = \int_0^x \ln \frac{\varpi(z)}{\vartheta(z)} dz; \quad (7.6)$$

For the solution to the corresponding macroscopic, deterministic kinetic equation

$$\frac{dx(t)}{dt} = \vartheta(x) - \varpi(x); \quad (7.7)$$

we have:

$$\begin{aligned} \frac{d}{dt} \ln p_{x(t)} &= \frac{d \vartheta'(x)}{dx} \frac{dx(t)}{dt} \\ &= \vartheta(x) - \varpi(x) \ln \frac{\varpi(x)}{\vartheta(x)} \leq 0. \end{aligned} \quad (7.8)$$

The negative value of that in Eq. (7.8) is known as *entropy production rate*.

7.3 Stochastic chemical kinetics

7.3.1 Reversible bimolecular association reaction

We now applying the stochastic chemical kinetics to a nonlinear chemical reaction in a small volume V with small number of molecules, n_A , n_B , and n_C numbers of A , B , and C :



We note that the $n_A + n_C$ and $n_B + n_C$ do not change in the reaction. Hence we can denote $n_A + n_C = n_A^0$ and $n_B + n_C = n_B^0$ as the total amount of A and B , including those in C , at the initial time. Now if we use n_C as the non-negative integer-valued random variable to describe the stochastic chemical kinetics, this simple nonlinear chemical reaction, according to DGP, is a one-dimensional birth-and-death process, with state-dependent birth and death rates $u_n = k_+ n_A n_B$ and $w_n = k_- n_C$. Then, according to Eq. (7.3), we have an equilibrium steady state distribution $p^{eq}(m) = \Pr \{n_C^{eq} = m\}$:

$$\frac{p^{eq}(m+1)}{p^{eq}(m)} = \frac{k_+(n_A^0 - m)(n_B^0 - m)}{k_-(m+1)V}; \quad (7.10)$$

in which $n_A^0 = n_A(0) + n_C(0)$ and $n_B^0 = n_B(0) + n_C(0)$. Therefore,

$$p^{eq}(m) = \frac{n_A^0! n_B^0!}{m!(n_A^0 - m)!(n_B^0 - m)!} \left(\frac{k_+}{k_- V} \right)^m; \quad (7.11)$$

where \mathcal{Z} is a normalization factor

$$\mathcal{Z} = \sum_{m=0}^{\min(n_A^0, n_B^0)} \frac{n_A^0! n_B^0!}{m!(n_A^0 - m)!(n_B^0 - m)!} = \frac{k_+}{k_- V}; \quad (7.12)$$

More importantly, by noting $n_A + n_B + n_C = n_A^0 + n_B^0 - n_C$,

$$\begin{aligned} & \ln p^{eq}(n_C) \\ &= \ln \frac{n_C! (n_A^0 - n_C)! (n_B^0 - n_C)!}{n_A^0! n_B^0!} + \text{const.} \\ &= n_A \ln \frac{n_A}{V} - n_A + n_B \ln \frac{n_B}{V} - n_B + n_C \ln \frac{n_C}{V} - n_C - n_C \ln \frac{k_+}{k_-} \\ &= n_A \ln x_A + n_B \ln x_B + n_C \ln x_C + n_C \left(\frac{n_C}{V} - \frac{n_A^0}{V} - \frac{n_B^0}{V} \right) - (n_A + n_B + n_C) \ln \frac{k_+}{k_-} \\ &= n \ln x + \text{const.} \end{aligned} \quad (7.13)$$

$x = n_A, n_B, n_C$

This agrees with Eq. 2.16, which was taken from chemical thermodynamics textbooks, and Eq. 5.17a, which is a general result we had derived.

7.3.2 Logistic model and Keizer's paradox

Let us now consider a still simple, but nonlinear chemical reaction system,



Recall in standard textbooks on mathematical biology, e.g., by J. D. Murray [117], this system is introduced as a one-species ecological population growth model. It is easy to see that the ODE according to the LMA,

$$\frac{dx}{dt} = r \left(1 - \frac{x}{K} \right); \quad r = k_1 a; \quad K = \frac{r}{k_2}; \quad (7.15)$$

is the celebrated *logistic equation* in population dynamics. In the ecological context, r is known as the per capita growth rate in the absence of intra-species competition; and K is known as *carrying capacity*.

The DGP stochastic model has a *chemical master equation* for the probability of n X molecules in a reaction volume of V :

$$\frac{dp_n(t)}{dt} = u(n-1)p_{n-1} - u(n)p_n + w(n)p_n + w(n+1)p_{n+1}; \quad (7.16a)$$

in which the state-dependent birth and death rates are

$$u(n) = rn; \quad w(n) = \frac{k_2 n(n-1)}{V}; \quad (7.16b)$$

Then, according to Eq. 7.3,

$$p_0^{ss} = 1 \text{ and } p_n^{ss} = 0; \quad n \geq 1; \quad (7.17)$$

since $u(0) = 0$! In other words, according to this theory, the stationary distribution is "population extinction with probability 1". But the ODE in (7.15) says that the stable steady state is $x = K$, with $x = 0$ being an unstable steady state which is not "relevant".

This seeming disagreement between the deterministic ODE in (7.15), and stochastic dynamics described by (7.16), is known as *Keizer's paradox*.

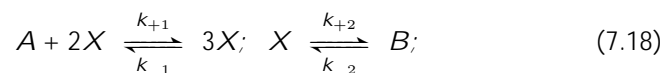
The resolution to the paradox comes in Chapter 8 below.

7.4 Nonequilibrium steady-state and chemical reaction systems driven by chemical potential difference

If a chemical reaction system reaches its chemical equilibrium, then each and every reaction in the system is in *detailed balance* with zero net flux. This puts a very strong condition on the dynamics. When a chemical reaction system has a sustained source and sink with different chemical potentials, it can not reach a chemical equilibrium. Rather, it reaches a *nonequilibrium steady state*.

Let us consider the following example.

7.4.1 Schlögl model



in which the concentrations (or chemical potentials) of A and B are sustained by an external agent. This reaction is known as *Schlögl model*, whose dynamics can be described by a single ordinary differential equation

$$\frac{dx}{dt} = k_{+1}ax^2 - k_{-1}x^3 - k_{+2}x + k_{-2}b = f(x); \quad (7.19)$$

which is a third-order polynomial. It can exhibit bistability and saddle-node bifurcation phenomenon. All of them only occur under driven condition, when $\mu_A \neq \mu_B$. Note in the chemical equilibrium: $\mu_A = \mu_A^0 + k_B T \ln a = \mu_B^0 + k_B T \ln b$, and

$$\frac{b}{a}^{eq} = \frac{k_{+1}k_{+2}}{k_{-1}k_{-2}}; \quad (7.20)$$

ODE (7.19), with its parameters $ak_{+1}k_{+2} = bk_{-1}k_{-2}$, has the right-hand-side

$$\begin{aligned} f(x) &= k_{+1}ax^2 - k_{-1}x^3 - k_{+2}x + k_{-2}b \\ &= k_{+1}ax^2 - k_{-1}x^3 - k_{+2}x + \frac{ak_{+1}k_{+2}}{k_{-1}} \\ &= x^2 + \frac{k_{+2}}{k_{-1}} - ak_{+1} - k_{-1}x : \end{aligned} \quad (7.21)$$

Therefore, the $f(x)$ has a unique fixed point at $x = x^* = ak_{+1}/k_{-1}$, the chemical equilibrium. In general, system (7.18) can exhibit chemical bistability; but this is only possible when A and B have a sufficiently large chemical potential difference. Such a sustained driving is called a *chemostat*. It is the chemical equivalence of an electric motive force, e.g., a battery.

More interestingly, when a and b satisfying (7.20), the DGP of the number of X , $n_X(t)$, is again a one-dimensional birth-and-death process, with

$$\begin{aligned} u(n) &= \frac{k_{+1}an(n-1)}{V} + k_{-2}bV \\ &= \frac{k_{+1}a}{V} n(n-1) + \frac{k_{+2}V^2}{k_{-1}} ; \end{aligned} \quad (7.22)$$

$$\begin{aligned} w(n+1) &= \frac{k_{-1}(n+1)n(n-1)}{V^2} + k_{+2}(n+1) \\ &= \frac{k_{-1}(n+1)}{V^2} n(n-1) + \frac{k_{+2}V^2}{k_{-1}} : \end{aligned} \quad (7.23)$$

Therefore, the stationary distribution, according to Eq. (7.3),

$$p_n^{ss} = C \frac{V^{n-1}}{k_{-1}(n+1)V^2} = \frac{n}{n!} e^{-n} ; \quad = \frac{k_{+1}aV}{k_{-1}} : \quad (7.24)$$

This is a Poisson distribution, with expected value being $\langle n_X^{eq} \rangle = \dots$. Therefore, the expected concentration is $x^* = (k_{+1}a/k_{-1})$.

7.5 The law of large numbers — Kurtz' theorem

7.5.1 Diffusion approximation and Kramers-Moyal expansion

Starting with the master equation in (7.1), let us consider a partial differential equation for a continuous density function $f(x; t)dx = p_{VX}(t)$ where $x = nV^{-1}$, $\dot{x} = V^{-1}$,

$$\begin{aligned}
\frac{\partial f(x; t)}{\partial t} &= V \frac{dp_{Vx}(t)}{dt} \\
&= \frac{1}{dx} [f(x+dx; t)u(x+dx) - f(x; t)u(x)] + w(x) \\
&\quad + f(x+dx; t)w(x+dx) \\
&= \frac{\partial}{\partial x} [f(x+dx; t)u(x+dx) - f(x; t)u(x)] + \frac{\partial}{\partial x} [f(x+dx; t)w(x+dx)] \\
&\quad + \frac{\partial}{\partial x} [f(x; t)u(x)] + \frac{\partial}{\partial x} [f(x; t)w(x)] + \frac{w(x) + u(x)}{2V} f(x; t) + \dots
\end{aligned} \tag{7.25}$$

in which

$$\lim_{V \rightarrow \infty} \frac{u(Vx)}{V} = u(x); \quad \lim_{V \rightarrow \infty} \frac{w(Vx)}{V} = w(x); \tag{7.26}$$

its pdf $f_Y(y; t)$ satisfies

$$\frac{\partial f_Y(y; t)}{\partial t} = \frac{\partial}{\partial y} \frac{\partial}{\partial y} \frac{W(x(t)) + U(x(t))}{2} f_Y(y; t) \quad (7.30)$$

We see both the diffusion "coefficient" and the drift are themselves time dependent. It can be shown that the solution to this equation is a Gaussian process.

7.6 Diffusion's dilemma

Truncating the Eq. (7.25) after the second order, it has a stationary distribution

$$\frac{1}{V} \ln \hat{F}_Y^{st}(y) = 2 \int \frac{W(x) - U(x)}{U(x) + W(x)} dx = \chi(x) \quad (7.31)$$

On the other hand, according to Eq. 7.6,

$$\chi'(x) = \ln \frac{W(x)}{U(x)} \quad (7.32)$$

Is it possible Eqs. (7.31) and (7.32) are actually the same? We notice that both has identical local extrema:

$$\frac{d}{dx} \chi(x) = 2 \frac{W(x) - U(x)}{W(x) + U(x)} = 0 \quad \Leftrightarrow \quad W(x) = U(x) \quad (7.33)$$

In fact, the curvature at a local extremum are identical:

$$\begin{aligned} \frac{d^2}{dx^2} \chi(x) \Big|_{U=W} &= 2 \frac{W'(x) - U'(x)}{W(x) + U(x)} = \frac{W'(x) - U'(x)}{U(x)} \\ &= \frac{d^2}{dx^2} \chi'(x) \Big|_{U=W} \end{aligned} \quad (7.34)$$

However, it can be shown, via an example, that the global minima of the $\chi(x)$ and $\chi'(x)$ can be different!

The Kramers-Moyal expansion is not mathematically valid. The reason is that the scaling for obtaining a law of large numbers (LLN) and the scaling for obtaining a central limit theorem (CLT) are different: To have a non-trivial LLN means a zero variance in the latter; and to have a non-trivial CLT means a divergent LLN, if the LLN is finite. The mathematically correct theory for the DGP, therefore, yields a time-dependent central limit theorem. In stochastic physics, this is known as van Kampen's ϵ -expansion.



CHAPTER 8

Phase Transition, Mesoscopic Phenomena, and Multiple Scales

The result in Sec. 7.1 is only valid for finite time: We have first taken the limit of $V \rightarrow 1$ and obtained an ODE for the dynamics, and then studied the long-time behavior of the ODE, e.g., its fixed points. One of the most important features of a nonlinear ODE is the breakdown of ergodicity: The long-time behavior is dependent upon the initial condition; it is not unique. On the other hand, we have shown that the long-time behavior of the stochastic kinetics, for any finite V , is ergodic. There is a unique stationary distribution $p_V^{ss}(n)$. To understand this stark contrast between the two limiting behaviors: V tending to infinity following $t \rightarrow 1$ and V tending to infinity preceding $t \rightarrow 1$, we use the solvable 1-d models as examples. Here we will be able to explicitly compute the exact stationary distribution and its large deviation properties. When this is discussed in the context of saddle-node bifurcation, the Landau's theory of phase transition arises. A key new result in this discussion is Kramers' theory for barrier crossing.

8.1 Mean first passage time (MFPT)

We consider a one-dimensional diffusion process with probability density function following the Kolmogorov forward equation

$$\frac{\partial f(x; t)}{\partial t} = \frac{\partial^2 f(x; t)}{\partial x^2} + \frac{\partial}{\partial x} U'(x) f(x; t); \quad (8.1)$$

where $x \in \mathbb{R}$. Now let us consider $x \in [a; b]$ where $x = a$ is a reflecting boundary and $x = b$ is absorbing, and one is interested in the mean time, $\mathbb{E}[T_{fp}]$, the diffusion process takes from $x = a$ to $x = b$ for the very first time. This problem is known as *mean first-passage time*. To compute this, one needs to first know the probability of random time of first arriving at $x = b$, starting at $x = a$.

Let $(x; t|z)$ be the probability density function remaining inside $[a; b]$ at time t , starting at $x = z \in [a; b]$. Clearly, $(x; t|z)$ satisfies the Eq. (8.1), with

boundary condition

$$\frac{d^2}{dx^2} \psi(x; t) + U'(x) \psi(x; t) = 0; \quad \psi(b; t) = 0; \quad (8.2)$$

and initial condition $\psi(x; t|z) = \psi(x; z)$. More importantly,

$$\frac{\partial}{\partial t} \psi(x; t|z) = \frac{\partial^2}{\partial z^2} \psi(x; t|z) - U'(z) \frac{\partial}{\partial z} \psi(x; t|z). \quad (8.3)$$

This is the Kolmogorov backward (partial differential) equation. Then the remaining total probability

$$\int_a^b \psi(x; t|z) dx = \Pr(T_{fp} > t) \quad (8.4)$$

where T_{fp} is the random first passage time. Therefore,

$$\begin{aligned} \mathbb{E}[T_{fp}(z)] &= \int_0^\infty t f_{fp}(t) dt = \int_0^\infty t dF_{fp}(t) \\ &= \int_0^\infty t \Pr(T_{fp} > t) dt \\ &= \int_0^\infty \int_a^b \psi(x; t|z) dx dt. \end{aligned} \quad (8.5)$$

Therefore,

$$\begin{aligned} &\frac{\partial^2}{\partial z^2} \mathbb{E}[T_{fp}(z)] - U'(z) \frac{\partial}{\partial z} \mathbb{E}[T_{fp}(z)] \\ &= \int_a^b \int_0^\infty t \frac{\partial}{\partial t} \psi(x; t|z) dx dt \\ &= \int_a^b dx \int_{t=0}^\infty t \frac{\partial}{\partial t} \psi(x; t|z) dt \\ &= \int_a^b dx \int_0^\infty \psi(x; t|z) dt = \int_0^\infty \Pr(T_{fp} > t) dt = 1. \end{aligned} \quad (8.6)$$

Eq. (8.6), together with boundary conditions

$$\frac{d\mathbb{E}[T_{fp}(z)]}{dz} \Big|_{z=a} = 0; \quad \mathbb{E}[T_{fp}(b)] = 0;$$

solves the *mean first passage time* problem.

8.2 Kramers' theory

The inhomogeneous differential equation (8.6) can be solved in terms of integrals. Let us denote $\mathbb{E}[T_{fp}(z)] = \tau(z)$. Then,

$$\frac{d}{dz} \left(\frac{\tau'(z)}{U'(z)} \right) = -1; \quad (8.7)$$

where $\phi'(z)$ is the derivative of $\phi(z)$ with respect to z . Noting that $\phi'(a) = 0$, we have

$$\phi'(z) = \frac{1}{\phi'(a)} \int_a^z \exp \left(-\frac{U(z) - U(y)}{\phi'(a)} \right) dy; \quad (8.8)$$

Integration again, we have an exact result

$$\phi(z) = \frac{1}{\phi'(a)} \int_a^z \int_a^y \exp \left(-\frac{U(z) - U(y)}{\phi'(a)} \right) dy dz; \quad (8.9)$$

8.2.1 Asymptotic evaluation of an integral

If the potential function $U(x)$ has two energy wells, located at $x = x_0 > a$ and $x = b$, which are separated by an energy barrier located at x^\ddagger , then in the triangle domain of (x, y) for the double integral of (8.9) has a maximum at $x = x^\ddagger$ and $y = x_0$. The exponent of the integrand of (8.9), near this maximum, can be expressed as

$$U(x) - U(y) = U(x^\ddagger) - U(x_0) + \frac{1}{2} U''(x^\ddagger) (x - x^\ddagger)^2 + U''(x_0) (y - x_0)^2 + \dots; \quad (8.10)$$

Therefore, if $k_B T$ is very small and following Laplace's method for integrals, one has

$$\begin{aligned} (a) \quad & \frac{1}{\phi'(a)} \int_a^z \int_a^y \exp \left(-\frac{U(x) - U(y)}{\phi'(a)} \right) dy dz \\ &= \frac{1}{\phi'(a)} \int_a^z \int_{-\infty}^a \exp \left(-\frac{U(x) - U(y)}{\phi'(a)} \right) dy dz \\ &= \frac{2}{\phi'(a) \phi''(x^\ddagger) \phi''(x_0)} \exp \left(-\frac{U(x^\ddagger) - U(x_0)}{\phi'(a)} \right); \end{aligned} \quad (8.11)$$

However for a discrete DGP, as we have discussed in Sec. 7.6, the diffusion approximation is not a fully legitimate mathematical representation for large but finite V . Whether the landscape $\psi(x)$ can be used, as the $U(x)$ in the Kramers' formula, to compute the MFPT for a DGP in the limit of $V \rightarrow 1$ is still a question.

In this section, we directly formulate the MFPT for the discrete birth-and-death process in Sec. 7.2. Let us assume n_0 be a reflecting boundary and n_1 be the absorbing boundary for the DGP $n(t)$. We shall denote the random first passage time, by $T(n_0)$ where n_0 is the initial value of process $n(t)$, and its expected value $\mathbb{E}[T(n_0)] = \tau_{n_0}$. Then τ_n satisfies the equation

$$\tau_n = \frac{1}{u(n) + w(n)} + \frac{u(n) \tau_{n+1} + w(n) \tau_{n-1}}{u(n) + w(n)}, \quad (8.12)$$

which can be re-arranged into

$$\mathcal{L}^* \tau = \mathbf{1}, \quad \text{where } \mathcal{L}^* \tau_n = u(n) \tau_{n+1} - u(n) \tau_n + w(n) \tau_n - w(n) \tau_{n-1} = -1. \quad (8.13)$$

One should observe the close similarity between this difference equation and the differential Eq. 8.6. In terms of matrix representation, the middle part of (8.13) is the adjoint of

$$\mathcal{L} p = \mathbf{0}, \quad \text{where } \mathcal{L} p_n = p_{n-1} u(n-1) - p_n u(n) + p_n w(n) - p_{n+1} w(n+1). \quad (8.14)$$

Introducing $s_n = p_{n+1} - p_n$, we have Eq. 8.13 expressed in terms of a first order difference equation for s_n :

$$u(n) s_n - w(n) s_{n-1} = -1, \quad (8.15)$$

with boundary condition at n_0 : $s(n_0) = 0$.

The solution to (8.15) can be obtained using the method of variation of parameters for inhomogeneous linear equations:

$$s_n = \sum_{k=n_0}^n \frac{1}{w(k)} \prod_{j=0}^{k-1} \frac{u(j)}{w(j)} \prod_{i=0}^3 \frac{w(i)}{u(i)}. \quad (8.16)$$

Thus,

$$\tau_n = \sum_{m=n+1}^{\infty} s_m = \sum_{m=n+1}^{\infty} \sum_{k=n_0}^m \frac{1}{w(k)} \prod_{j=0}^{k-1} \frac{u(j)}{w(j)} \prod_{i=0}^3 \frac{w(i)}{u(i)}. \quad (8.17)$$

Interestingly, the τ_n in (8.17) can be expressed in terms of the stationary solution to (8.14), given in (7.3):

$$\tau_n = \sum_{m=n+1}^{\infty} \frac{p_m^{ss}}{w(m) p_m^{ss}}. \quad (8.18)$$

Recognizing the V dependence of the stationary distribution p_n^{ss} and $w(n)$,

we have an asymptotic approximation to (8.18):

$$xV = \int_x^{x_1} \frac{dz}{W(z)} e^{\int_z^{x_1} V(y) dy} \quad (8.19)$$

This equation should be compared and contrasted with Eq. 8.9.

8.3.1 Gambler's ruin problem

The gambler's ruin problem is a discrete time step Markov chain, and with a probability p to win a bet of a \$1, and $q = 1 - p$ to loss it, the game ends when the player reaching N or lossing all. Let the u_n be the probability of eventually winning, starting with n ; and let τ_n be the MFPT for the duration of the game. Then we have

$$u \text{ or } \tau$$

a reflecting boundary condition at $n = 0$. In this case, we have

$$n = \frac{p}{(q-p)^2} \frac{q}{p}^N - \frac{q}{p}^{n^{\#}} - \frac{N}{q} \frac{n}{p}; \quad (8.26)$$

Now if $q > p$, then this time is about

$$n \approx \frac{p}{(q-p)^2} \frac{q}{p}^N \quad (8.27)$$

which is independent of n , the initial value. The $\ln n / N \ln(q/p)$, which is the "barrier height" in the landscape language: The stationary probability distribution is $p_n^{ss} / (p=q)^N$, and

$$\ln n / N = \ln p_N^{ss} + \ln p_0^{ss}; \quad (8.28)$$

8.4 Thermodynamic limit and global minimum of $\psi(x)$

8.5 Exchange of limits: $\beta \rightarrow 0$ and $t \rightarrow 1$

Cellular Biochemical Dynamics, I: Gene Regulatory Networks

9.1 The central dogma of molecular biology

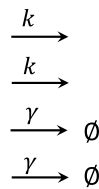


Figure 9.1 *Transcription (mRNA polymerization reaction) and translation (protein biosynthesis reaction) are two fundamental processes in the central dogma of molecule biology. Both mRNA and protein molecules are continuously being degraded inside a living cell.*

9.1.1 Deterministic dynamics

According to the macroscopic, well-mixed mass-action kinetic description, the central dogma shown in Fig. 9.1 can be represented by a system of two ODEs

$$\frac{dx(t)}{dt} = k_1 - \gamma_1 x; \quad (9.1a)$$

$$\frac{dy(t)}{dt} = k_2 x - \gamma_2 y; \quad (9.1b)$$

in which $x(t)$ represents the concentration of mRNA, and $y(t)$ the concentration of protein, at time t . The parameters $k_1 = k_1^o[\text{DNA}][\text{NTP}]$ and $k_2 = k_2^o[\text{AA}]$.

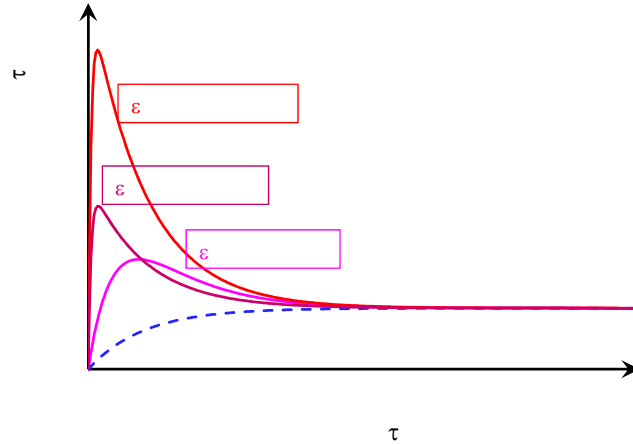


Figure 9.2 Protein concentration, $v(\tau)$, according to Eq. 9.3b, with $v(0) = 0$, $u(0) = 3$ (purple and burgundy) and 6 (red), and $\epsilon = 0.05$ (burgundy and red) and 0.5 (purple). Blue dashed line is the outer solution in (9.3b).

The system of ODE in (9.1) can be non-dimensionalized into

$$\frac{du(\tau)}{d\tau} = 1 - u; \quad (9.2a)$$

$$\frac{dv(\tau)}{d\tau} = \frac{u}{\epsilon} - v; \quad (9.2b)$$

in which $u = (k_2/k_1)x$, $v = (k_1/k_2)y$, $\tau = k_1 t$, and $\epsilon = k_2/k_1$. The solution to (9.2) can be explicitly obtained as:

$$u(\tau) = u(0)e^{-\tau} + 1; \quad (9.3a)$$

$$v(\tau) = \underbrace{\frac{v(0) - 1}{\epsilon} e^{-\tau} + 1}_{\text{outer solution}} + \underbrace{\frac{u(0)}{\epsilon} \frac{1 - e^{-\tau}}{\tau}}_{\text{inner solution}}; \quad (9.3b)$$

If $\epsilon \ll 1$, then the system in (9.1) is a singularly perturbed ODE system in which $u(\tau)$ are very fast, thus the $v(\tau)$ has a fast component and a slow component. According to the perturbation theory of differential equations [111], the fast and slow components can be analytically obtained as the so-called inner and outer solutions respectively.

Fig. 9.2 shows with $v(0) = 0$, $v(\tau)$ has a transient "burst". The amplitude of the transient burst increases with increasing $u(0)$. The figure also suggests that the amplitude increases with decreasing ϵ . To understand this result, we note that the term inside $f - g$ in (9.3b) is responsible for the transient. It

can be easily verified that function

$$\frac{1}{1 - e^{-t}} e^{-t} = e^{-t} / (1 - e^{-t})$$

reaches its maximum at $t^* = -\ln 2$. It has the largest amplitude 1 when $t = 0$. In this case,

$$\lim_{t \rightarrow 0} \frac{1}{1 - e^{-t}} e^{-t} = \begin{cases} 0 & t = 0 \\ e^{-t} & t > 0 \end{cases}$$

The limit is a discontinuous function of t .

9.1.2 Goodwin's model and self-regulating gene expression

Goodwin's model [112] is a more elaborate version of the kinetics in (9.2), with mRNA (x), its gene product, an enzyme with concentration y , and the substrate of the enzyme, S , with concentration z . The S regulates the transcription process that produces the mRNA:

$$\frac{dx(t)}{dt} = k_1(z) - \delta_1 x; \quad (9.4a)$$

$$\frac{dy(t)}{dt} = k_2 x - \delta_2 y; \quad (9.4b)$$

$$\frac{dz(t)}{dt} = k_3 y - \delta_3 z; \quad (9.4c)$$

If function $k_1(z)$ is an decreasing function of z , then we say the S is an repressor of the transcription, and the interaction between the S and transcription process is a *negative feedback*. If the $k_1(z)$ is an increasing function of z , then this is a *positive feedback* and the S is a promoter of the transcription.

The steady states of the system (9.4) are the roots of

$$k_1(z) - \frac{\delta_1 \delta_2 \delta_3}{k_2 k_3} z = 0; \quad (9.5)$$

If $k_1(z)$ is a strict non-increasing function of z , then there will be only one steady state to the kinetic system. One such example is

$$k_1(z) = \frac{V}{K + z^n}; \quad (9.6)$$

On the other hand, if $k_1(z)$ is an increasing function of z , then the kinetic system could exhibit multi-stability. Note that while a negative feedback has only one steady state, it could be unstable. This implies a limit cycle oscillation. For example, when $n > 8$ in (9.6) [117].

9.2 Stochastic gene expression without feedback and transcription burst

In terms of the stochastic DGP, the kinetic system in Fig. 9.1 has a state space $(m; n)$ representing the copy numbers of mRNA and protein inside a cell, with the transition rates shown in Fig. 9.3, below.

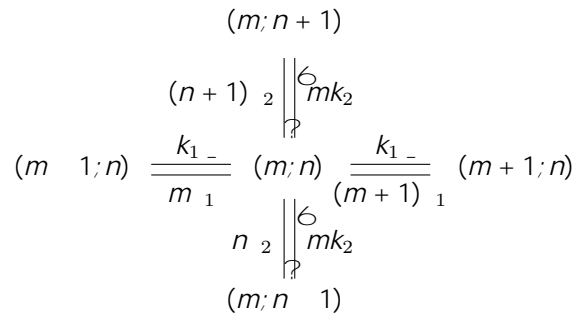


Figure 9.3 The state transition diagram for the DGP representing the biochemical reactions in the central dogma of molecule biology, shown in Fig. 9.1. $k_1 = k_1^0 \times \text{DNA concentration} \times \text{nucleotide concentration}$; $k_2 = k_2^0 \times \text{amino acids concentration}$.

The CME for the joint distribution of number of mRNA and protein in the system at time t , $p_{MP}(m; n; t) = \Pr\{M(t) = m; P(t) = n\}$, is

$$\begin{aligned}
 & \frac{dp(m; n; t)}{dt} \\
 &= k_1 p(m-1; n) - p(m; n) \frac{k_1}{m} + k_2 m p(m; n-1) - p(m; n) \frac{k_2 n}{m} + (m+1)p(m+1; n) \\
 &+ (n+1)p(m; n+1) :
 \end{aligned} \tag{9.7}$$

The mRNA copy number has a steady state marginal distribution

$$p_M(m) = \frac{(k_1)^m}{m!} e^{-k_1} \tag{9.8}$$

The distribution for protein number is rather complex. One limiting case is the negative binomial distribution (see Sec. 9.2.2),

$$p_P(n) = \frac{(n+r-1)!}{n! (r-1)!} b^r (1-b)^{n-r} \tag{9.9}$$

with $b = k_2/(k_1 + k_2)$ and $r = k_1/k_2$. This distribution characterizes "transcription burst" based on high-resolution measurements, with single-molecule sensitivity, on single cells. Negative binomial distribution is also called Polya

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distribution, whose probability generating function (PGF) is

$$1 - \frac{b}{1-b} s = 1 - r s : \quad (9.10)$$

The distribution in (9.9) has been widely intuitively interpreted as follows: One mRNA has an exponentially distributed lifetime, with mean value $\frac{1}{r}$

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under the condition $U_1(1) = 1$. We see that if $k_2 = 0$, then $U_1(s)$ is indeed the generating function for a geometric distribution with parameter $\rho = \frac{k_1}{1+k_1}$:

$$\sum_{n=0}^{\infty} s^n \rho^n (1-\rho) = \frac{1-\rho}{1-s\rho} = \frac{1}{1+k_1(s-1)}.$$

For $k_2 \neq 0$, denoting

$$\phi(s) = \int_0^s \frac{k_2(s-1)}{2(1-s)} ds = \frac{1}{2} \ln(s-1) - \frac{k_2 s}{2}. \quad (9.15)$$

Then,

$$\begin{aligned} U_1(s) &= e^{-\phi(s)} = C + \frac{1}{2} \int_0^s \frac{e^{-\phi(z)}}{z-1} dz \\ &= \frac{1}{2} (s-1)^{-\frac{1}{2}} e^{-\frac{k_2}{2}(s-1)} \int_0^{s-1} z^{-\frac{1}{2}-1} e^{-\frac{k_2}{2}z} dz, \end{aligned} \quad (9.16)$$

with $C = 0$ to satisfy $U(1) = 1$. $U_1(s) = 1$ if $k_2 = 0$ as expected.

The above method can be generalized to total M copies of mRNA. When $k_1 = 0$ and initial condition $p(m; n; 0) = \delta_{mM} \delta_{n0}$, we have the CME (9.7):

$$\begin{aligned} \frac{dp(m; n; t)}{dt} &= -m-1 + k_2 p(m; n) + 1(m+1)p(m+1; n) \\ &\quad + mk_2 p(m; n-1) - 2 np(m; n) - (n+1)p(m; n+1); \end{aligned} \quad (9.17)$$

in which $0 \leq m \leq M$. Introducing the generating function

$$G_m(s) = \sum_{n=0}^{\infty} s^n \int_0^{\infty} p(n; m; t) dt; \quad (9.18)$$

which satisfy

$$\begin{aligned} \sum_{m=0}^M (m-k_2(s-1)) \frac{dG_m(s)}{ds} &= -1(m+1)G_{m+1}(s); \\ \sum_{m=0}^M M(k_2(s-1)) \frac{dG_M(s)}{ds} &= 1; \end{aligned} \quad (9.19)$$

in which $1 \leq m < M$. Then $U_M(s) = \sum_{m=0}^M G_m(s)$ is the generating function for the distribution of the number of protein copy numbers when *all* the M copies of mRNA are degraded. In terms of the $\phi(s)$ function defined in (9.15), the solution to this system of equations is

$$G_M(s) = \frac{e^{-M\phi(s)}}{2} \int_0^s \frac{e^{M\phi(z)}}{z-1} dz; \quad (9.20a)$$

$$G_m(s) = \frac{e^{-m\phi(s)}}{2} \int_0^s \frac{e^{m\phi(z)}}{z-1} (m+1)G_{m+1}(z) dz; \quad (9.20b)$$

The $U_M(s) \notin U_1^M(s)$ in general! However, when $\gamma_2 = 0$, we have

$$\begin{aligned} U_M(s) &= \sum_{n=0}^{\infty} G_1(s) = \frac{\sum_{n=0}^{\infty} \frac{2}{n!} G_2(s)}{\sum_{n=0}^{\infty} \frac{1}{n!} k_2(s-1)^n} = \frac{\sum_{n=0}^{\infty} \frac{3}{n!} G_3(s)}{[\sum_{n=0}^{\infty} \frac{1}{n!} k_2(s-1)^n]^2} = \\ &= \frac{\sum_{n=0}^{\infty} \frac{M}{n!} G_M(s)}{[\sum_{n=0}^{\infty} \frac{1}{n!} k_2(s-1)^n]^{M-1}} = U_1^M(s); \end{aligned} \quad (9.21)$$

In the presence of protein degradation, the total number of proteins when all the M copies of mRNA are gone is not the same as the sum of the remaining proteins when each one of the mRNA is gone.

9.2.2 Stationary and transient protein distribution with bursting biosynthesis

We now consider protein synthesis can be "instantaneous" with bursts that come with a Poisson rate k_1 , each with a geometric distribution for the protein numbers. The master equation for the probability of having n number of protein at time t then is

$$\begin{aligned} \frac{dp(n; t)}{dt} &= -\gamma_2 (n+1)p(n+1) - np(n) \\ &+ k_1(1-b) \sum_{n=0}^{\infty} b^n p(n) - \sum_{n=0}^{\infty} b^n p(n); \end{aligned} \quad (9.22)$$

in which $b = \frac{k_2}{1+k_2} < 1$. The corresponding PGF $G_P(s; t)$ satisfies

$$\frac{\partial G_P(s; t)}{\partial t} = -\gamma_2(1-s) \frac{\partial G_P(s)}{\partial s} + k_1 \frac{sb}{1-sb} G_P(s); \quad (9.23)$$

Therefore, the stationary distribution for protein has its generating function

$$\begin{aligned} G_P^{ss}(s) &= \exp \int_{\gamma_2}^{\gamma_2 s} \frac{b}{1-zb} dz \\ &= \exp \left[\frac{k_1}{\gamma_2} \ln \frac{bs-1}{b-1} \right] = \frac{1-b}{1-bs}^r; \end{aligned} \quad (9.24)$$

in which $r = \frac{k_1}{\gamma_2}$. This proves Eq. 9.11.

One can also solve the Eq. 9.23 and obtain the time-dependent transient distribution for the protein:

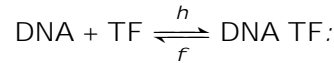
$$G_P(s; t) = (1-s)e^{-\gamma_2 t} G_P^{ss}(s); \quad (9.25)$$

in which $(1-s)$ is determined by the PGF for the initial distribution $p(n; 0)$. That is,

$$G_P(s; t) = G_P(1) (1-s)e^{-\gamma_2 t}; 0 \leq \frac{1+k_2(1-s)e^{-\gamma_2 t}}{1+k_2(1-s)}^r; \quad (9.26)$$

9.3 Gene regulatory network with feedbacks

When a transcription factor (TF) is regulating its own gene expression, a feedback loop is formed. In this case, the single DNA molecule inside a cell undergoes the biochemical reaction



We shall call the bare DNA o -state and DNA bound with the TF on-state. Fig. 9.4 gives the state transition diagram for the DGP.

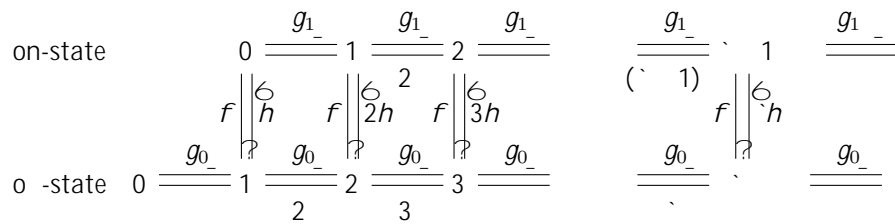


Figure 9.4 O -state and on-state represent the unbound and bound state of the single copy of DNA (gene) with a TF. f denote the copy of free TF. Monomeric TF binds DNA with on-rate constant h and o -rate constant f . Binding reduces the copy number of free TF by 1. TF biosynthesis rate is g_1 and g_0 when the gene is bound and unbound, respectively. TF degradation rate is f .

When $f = h = 0$, the steady state distribution for the protein copy numbers in both on- and o -states are Poissonian:

$$p_P(n|i) = \frac{(g_i)^n}{n!} e^{-g_i}; \quad (9.27)$$

where $i = 0$ for o - and $i = 1$ for on-state, respectively. The modal value of a Poisson distribution is at its mean value g_i . Therefore, for very different g_i the two modal values can be very different. For a very small f and h , the probability distribution for the protein is simply

$$\begin{aligned} p_P(n) &= \frac{f p_P(n|0) + g_0 h p_P(n|1)}{f + g_0 h} \\ &= \frac{-n}{n!} \frac{f g_0^n e^{-g_0} + g_0 h g_1^n e^{-g_1}}{f + g_0 h}; \end{aligned} \quad (9.28)$$

which has two modal values approximately at g_0 and g_1 .

On the other extreme, if the f and h are very large, that is the TF binding-unbinding to DNA are much faster than the protein biosynthesis and degradation, then there is a mean g value at each n , the total protein copies:

$$g(n) = \frac{f g_0 + n h g_1}{f + n h}; \quad - (n) = n \frac{f + h(n-1)}{f + n h}; \quad (9.29)$$

then the protein copy number distribution is

$$p_P(n) = C \prod_{i=1}^n \frac{\bar{g}(i-1)}{\bar{\gamma}(i)} = \frac{C}{n!} \frac{g_1}{n!} \prod_{i=1}^n \frac{[f g_0 = (h g_1)] + (i-1)}{(f=h) + (i-1)}; \quad (9.30)$$

where C is a normalization factor. This is a uni-modal distribution with an intermediate modal value.

Note that the macroscopic ODE dynamics, in a test tube with a large number of DNA molecules with concentration $x(t)$ at time t ($0 \leq x \leq 1$), is

$$\begin{aligned} \frac{dx(t)}{dt} &= h y (1-x) - f x; \\ \frac{dy(t)}{dt} &= g_0 (1-x) + g_1 x - y; \end{aligned} \quad (9.31)$$

in which $y(t)$ is the concentration of protein at time t . $g_1 < g_0$ means the TF is its own gene expression repressor and the feedback is negative. $g_1 > g_0$ means the TF is its own gene expression enhancer and the feedback is positive. In the latter case, the two null-clines for the ODE system are

$$y_1(x) = \frac{f x}{h(1-x)}; \quad y_2(x) = g_0(1-x) + g_1 x; \quad (9.32)$$

Both $y_1(x)$ and $y_2(x)$ are increasing functions of x ; $y_1(x)$ is a convex function and $y_2(x)$ is linear. There is only a single intersection $x^* \in (0;1]$. The macroscopic fixed point is located at (x^*, y^*) in which y^* is the positive root of

$$y^2 + \frac{f}{h} \frac{g_1}{y} - \frac{f g_0}{h} = 0;$$

We note this is the same equation as $\bar{g}(n) = \bar{\gamma}(n)$, both are given in (9.29). Therefore, the macroscopic kinetics is closer to the rapid TF-binding scenario, with the term $g_0(1-x) + g_1 x$ in Eq. 9.31 representing the law of large numbers. Therefore there is no bistability according to the ODE model. The bimodality in the stochastic model is a consequence of single copy of DNA. This phenomenon is called *stochastic bistability*, in contrast to *nonlinear bistability*.

Treating the protein concentration $y(t)$ as a deterministic dynamic variable, and the single DNA as a two-state Markov process, the hybrid system is called an ODE with Markov switching [113, 116], or a random evolution [114], or a piecewise deterministic Markov process (PDMP) [115].

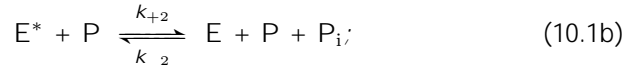
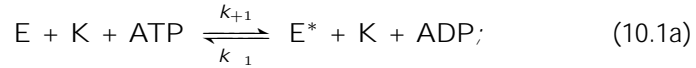
9.3.1 Walczak-Onuchic-Wolynes resonance



Cellular Biochemical Dynamics, II: Signaling Networks

10.1 Phosphorylation-dephosphorylation signaling

Intracellular regulations are carried out in major part by the phosphorylation and dephosphorylation of functional enzymes, or the exchange of proteins bound to GDP for GTP. In the former case, say for an enzyme E:



in which K, called a kinase, is the enzyme to the phosphorylation reaction, and P, called a phosphatase, is the enzyme to the dephosphorylation reaction. The substrates of enzymes K and P are themselves enzymes, E and E*, respectively. ATP, ADP, and P_i stand for adenosine triphosphate, adenosine diphosphate, and inorganic phosphate.

In the second case, one has a very similar kinetic scheme:



in which GEF is an enzyme called guanine nucleotide exchange factors, and GAP is another enzyme called GTPase-activating protein. The enzyme E in the reaction 10.2b is called a GTPase that catalyzes the hydrolysis of GTP to GDP + P_i.

Assume all the biochemical species in (10.1) are kept at constant concentrations except E and E*, we have

$$\frac{dx}{dt} = k_{+1}KT + k_{-2}PP_i(1-x) - k_{-1}KD + k_{+2}P x \quad (10.3)$$

where x(t) is the fraction of E* at time t, K, T, D, P, and P_i are the corresponding concentrations of K, ATP, ADP, P, and P_i.

The steady state level of protein E phosphorylation according to the system (10.1) is

$$x^{ss} = \frac{k_{+1}KT + k_{-2}PP_i}{k_{+1}KT + k_{-2}PP_i + k_{-1}KD + k_{+2}P} = \frac{+}{+ + - + 1}; \quad (10.4)$$

in which

$$= \frac{k_{+1}KT}{k_{+2}P}; \quad = \frac{k_{+1}k_{+2}T}{k_{-1}k_{-2}DP_i}; \quad = \frac{k_{-2}P_i}{k_{+2}}; \quad (10.5)$$

The parameter is called an "activation parameter" which increases with increasing kinase (K) and decreasing phosphatase (P). In represents the amount of phosphorylation energy in an ATP hydrolysis reaction. When = 1, the Eq. 10.4 becomes

$$x^{ss} = \frac{+}{(+ +) 1 + 1} = \frac{+}{+ 1}. \quad (10.6)$$

Note in this case the x^{ss} is completely independent of ! *No phosphorylation energy, no cellular signaling.* The two forms of the enzyme E and E* are in a chemical equilibrium. To a chemist, it is widely known that the amount of enzyme to a reaction, the kinase and the phosphatase in this case, can not change a chemical equilibrium. The amount of enzyme can only change the "kinetics" of a reaction.

For $\neq 1$, the x^{ss} in (10.6) represents not a chemical equilibrium, but a *nonequilibrium steady state*. The rate of entropy production, in $k_B T$ units, is

$$\left(\frac{K k_{+1}k_{+2}T - k_{-1}k_{-2}DP_i P}{k_{+1}KT + k_{-2}PP_i + k_{-1}KD + k_{+2}P} \right) \ln : \quad (10.7)$$

The term in f g is the number of ATP hydrolysis per unit time.

10.2 Zeroth-order ultrasensitivity

In the kinetic equation (10.3), we have assumed that both the phosphorylation reaction (10.1a) and dephosphorylation reaction (10.1b) are operating in the linear regime of their respective enzymes. If this is not a valid assumption, then instead of Eq. 10.3, we follow Briggs-Haldane kinetics:

$$\frac{dx}{dt} = \frac{V_1^+ \frac{1}{K_K} x - V_1^- \frac{x}{K_K^*}}{1 + \frac{x}{K_K^*} + \frac{1}{K_K} x} - \frac{V_2^+ \frac{x}{K_P^*} - V_2^- \frac{1}{K_P} x}{1 + \frac{x}{K_P^*} + \frac{1}{K_P} x}; \quad (10.8)$$

in which K_K and K_K^* are the Michaelis constants of the kinase for E and E*, respectively; and K_P and K_P^* are the Michaelis constant of the phosphatase for

E and E*. Among the eight parameters, the Haldane equation, a generalized detailed balance condition, states that

$$\frac{V_1^+ K_K^*}{K_K V_1^-} = \frac{K_P V_2^+}{V_2^- K_P^*} \quad (10.9)$$

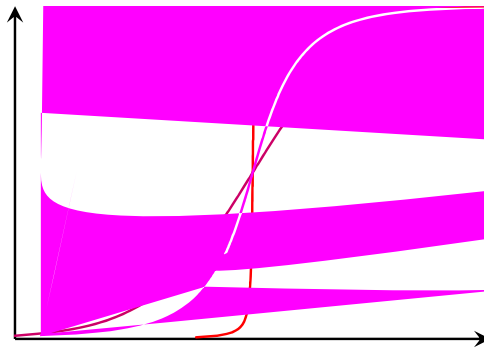


Figure 10.1 Steady state level of phosphorylation according to Eq. 10.12. The values in the parentheses are $(\frac{K_K}{K_K^*}, \frac{K_P}{K_P^*})$. A discontinuous step function arises in the limit of both being zero.

The steady state x^* satisfies

$$x = \frac{V_1^+ (1-x)}{K_K + 1 + \frac{K_K}{K_K^*} (1-x)} = \frac{K_P V_2^+ (1-x)}{K_P^* + x + \frac{K_P}{K_P^*} (1-x)} \quad (10.10)$$

in which

$$\frac{V_1^+}{V_2^+} = \frac{V_2^- K_P^*}{K_P V_1^-}$$

If all the K 's are very large, then Eq. 10.11 is reduced to (10.4), in which should be identified as $K_P^* = K_K$. On the other hand, if all the K 's are small, then

$$x = \frac{V_1^+ (1-x)}{1 + x + \frac{K_K}{K_K^*} (1-x)} = \frac{K_P V_2^+ (1-x)}{x + \frac{K_P}{K_P^*} (1-x)} \quad (10.11)$$

In this case, both the kinase and the phosphatase are operating under zeroth order, saturated condition. In particular, if $\frac{K_K}{K_K^*} \rightarrow 0$ and $\frac{K_P}{K_P^*} \rightarrow 1$, then

$$1 - \frac{K_K}{K_K^*} = 1 - \frac{K_P^*}{K_P} x^2 + 1 - \frac{2 K_P^*}{K_P} x + \frac{K_P^*}{K_P} = 0 \quad (10.12)$$

Fig. 10.1 shows that with decreasing $K_K = K_K^*$ and $K_P^* = K_P$, the transition curve according to Eq. 10.12 becomes sharper, known as *ultrasensitivity*. In the limit of $K_K = K_K^* = K_P^* = K_P = 0$, $x^{ss} = 0$ for $x < 1$ and $x^{ss} = 1$ for $x > 1$.

10.3 Multiple steps signaling cascade

The phosphorylation and dephosphorylation biochemical reactions are the molecular processes that carry out the step-after-step delivery of cellular information. They often form a "signaling cascade" as shown in Fig. 10.2. One well-known example is the MAPK (mitogen activated protein kinase) pathway.

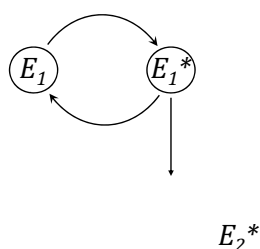


Figure 10.2 A signaling cascade consisting of three phosphorylation-dephosphorylation cycles. The activation of enzyme E_1 is considered to the "upstream" of E_2 , to which the activation of E_3 is considered as a "down-stream" step. An activated enzyme serves as the catalyst for its down-stream biochemical reaction.

$$\frac{dx_1}{dt} = k_1(x_N)(1 - x_1) - k_{-1}(x_N)x_1; \quad (10.13a)$$

$$\frac{dx_2}{dt} = k_2x_1(1 - x_2) - k_{-2}x_2; \quad (10.13b)$$

$$(10.13c)$$

$$\frac{dx_N}{dt} = k_Nx_{N-1}(1 - x_N) - k_{-N}x_N; \quad (10.13d)$$

To obtain the steady state, we note

$$\frac{1}{x_k} = 1 + \frac{k}{k} \frac{1}{x_{k-1}}; \quad (10.14)$$

then,

$$\begin{aligned} \frac{1}{x_N} &= 1 + \frac{N}{N} x_{N-1}^{-1} = 1 + \frac{N}{N} \left(1 + \frac{N-1}{N-1} x_{N-2}^{-1} \right) \\ &= 1 + \sum_{k=0}^{N-2} \frac{N-k}{N-k} + \frac{N}{N} \frac{N-1}{N-1} \frac{1}{2} \frac{1(x_N)}{1(x_N)}; \end{aligned} \quad (10.15)$$

Therefore, denoting

$$A = \frac{N}{N} \frac{N-1}{N-1} \frac{1}{2}; \quad B = \sum_{k=0}^{N-2} \frac{N-k}{N-k}; \quad (10.16)$$

$A, B > 0$, we have

$$\frac{1(x_N)}{1(x_N)} - \frac{Ax_N}{1 + (1+B)x_N} = 0; \quad (10.17)$$

This equation should be compared with the Eq. 9.5 from the Goodwin's model for the central dogma in Sec. 9.1.2. Again, we see that if $1(x) = 1(x)$ is a decreasing function of x , representing a negative feedback, then (10.17) has a unique root.

10.4 Enzyme mediated biochemical activation and temporal cooperativity

The notion of cooperativity is one of the most important concept in equilibrium biochemistry and equilibrium statistical physics. Allosteric cooperativity is a cornerstone of molecular biophysics. We now focus on a single step in Fig. 10.2: how does an enzyme E_k catalyze the transformation of E_{k+1} ? We are particularly interested in the case when both the numbers of molecules of E_k and E_{k+1} are small.

In Sec. 4.14c we have discussed the case of single enzyme with a large number of substrate molecules and derived the Michaelis-Menten kinetic equation based on the mean first passage time.



CHAPTER 11

**Chemical Oscillations and Stochastic
Circulation**



CHAPTER 12

Mechanics Revisited

The 20th century physicists have already shown that the movement of point masses in the microscopic world is not deterministic; they follow quantum mechanical rules, which has a probabilistic interpretation. Let us take this insight as our starting point for a nonlinear, stochastic dynamic theory of mechanical motions. We assume the space at the very microscopic level is a three-dimensional discrete lattice with spacing ℓ . Then the stochastic movement of a single point mass is simply represented by six transition rates in $x; y; z$ directions:

$$u_1^\pm(\mathbf{n}); u_2^\pm(\mathbf{n}); u_3^\pm(\mathbf{n}) \quad (12.1)$$

in which $\mathbf{n} = (n_1; n_2; n_3)$. The corresponding master equation for the probability is

$$\frac{dp(\mathbf{n}; t)}{dt} = \sum_{k=1,2,3} \left[p(\mathbf{n} - \mathbf{e}_k; t) u_k^+(\mathbf{n} - \mathbf{e}_k) - p(\mathbf{n}; t) u_k^-(\mathbf{n}) \right] \quad (12.2)$$

in which $\mathbf{e}_1 = (1; 0; 0)$, $\mathbf{e}_2 = (0; 1; 0)$, and $\mathbf{e}_3 = (0; 0; 1)$.

The transition rates are related to the ℓ in such a way that in the limit of $\ell \rightarrow 0$,

$$\lim_{\ell \rightarrow 0} \ell u_k^\pm(\mathbf{x}; \ell) = R(\mathbf{x}) + T_k^\pm(\mathbf{x}) + O(\ell^2); \quad (12.3)$$

the difference between u_k^+ and u_k^- at a given \mathbf{n} disappears in the macroscopic limit, in an isotropic space. Furthermore, $R(\mathbf{x}) = R$ independent of \mathbf{x} for a homogeneous space with translational symmetry. Then we have a HJE:

$$\frac{\partial}{\partial t} \langle \mathbf{x}; t \rangle + H(\mathbf{x}; \nabla_{\mathbf{x}} \langle \mathbf{x}; t \rangle) = 0; \quad (12.4)$$

with Hamiltonian function

$$H(\mathbf{x}; \mathbf{y}) = 2R \cosh y_1 + \cosh y_2 + \cosh y_3 - 3; \quad (12.5)$$

and Hamiltonian dynamics:

$$\frac{dx_i}{dt} = 2R \sinh y_i; \quad \frac{dy_i}{dt} = 0; \quad (12.6)$$

Therefore,

$$\frac{d^2 x_i}{dt^2} = -2R \cosh y_i \frac{dy_i}{dt} = 0. \quad (12.7)$$

This is Newton's first law of motion. One actually notices that for small y_i :

$$H(\mathbf{x}; \mathbf{y}) \approx R (y_1^2 + y_2^2 + y_3^2) :$$

$$\frac{d\mathbf{x}(t)}{dt} = \bigotimes_{i=1;2;3} T_i^+(\mathbf{x}) - T_i^-(\mathbf{x}) \quad (12.8)$$
$$\ln \frac{R_k^+(\mathbf{x})}{R_k^-(\mathbf{x})} = \frac{@' SS(\mathbf{x})}{@X_k}; \quad (12.9)$$
$${}^{ss}(\mathbf{x}) = \lim_{\rightarrow 0} \ln \mathbf{x} = ; \quad (12.10)$$

We have seen in Chapter ?? that the ratio $\ln(q_{ij}=q_{ji})$ can be interpreted as the heat exchange in the transition $i \rightarrow j$. When $q_{ij} = q_{ji}$, the transition is considered adiabatic. We now apply this idea to mechanics, and assume that for any \mathbf{n} , $u_k^+(\mathbf{n}) \rightarrow u_k^-(\mathbf{n})$, which is a statement of isotropic space. But there is a tiny difference $u_k^+(\mathbf{n}) - u_k^-(\mathbf{n}) = u_k^+(\mathbf{n}); u_k^-(\mathbf{n})$, and we shall call

quantum heat exchange associated with the microscopic spatial movement. Then Eq. 12.9 implies that $r_{\mathbf{x}} \rightarrow 1$, and the HJE becomes

in which vector $\mathbf{V} = (V_1; V_2; V_3)$, with $V_k(\mathbf{x}) = R_k^+(\mathbf{x}) - R_k^-(\mathbf{x})$ and matrix

$$D(\mathbf{x}) = \frac{1}{2} \sum_{k=1:2:3}^X \tau_k R_k^+(\mathbf{x}) + R_k^-(\mathbf{x}) \quad k \quad x_j/F10 \quad 5ec5J/F69 \quad 986 \quad Tf \quad 5. \quad 8$$

$$H(\mathbf{x}; \mathbf{y}) = \mathbf{V}(\mathbf{x}) - \mathbf{y} + \mathbf{y} \mathbf{D}(\mathbf{x}) \mathbf{y} \quad (12.16)$$

with Hamiltonian system

$$\frac{d\mathbf{x}}{dt} = \mathbf{V}(\mathbf{x}) + 2\mathbf{D}(\mathbf{x})\mathbf{y}; \quad \frac{d\mathbf{y}}{dt} = -\nabla_{\mathbf{x}} [\mathbf{V}(\mathbf{x}) - \mathbf{y} + \mathbf{y} \mathbf{D}(\mathbf{x}) \mathbf{y}] \quad (12.17)$$

If the \mathbf{y} is very large, and $d\mathbf{y} \approx \mathbf{y}$, then,

$$\frac{d\mathbf{x}}{dt} = 2\mathbf{D}(\mathbf{x})\mathbf{y}; \quad \frac{d\mathbf{y}}{dt} = -\nabla_{\mathbf{x}} \mathbf{y} \mathbf{D}(\mathbf{x}) \mathbf{y} \quad (12.18)$$

The second equation is essentially the Newton's law with a potential function defined as $U(\mathbf{x}) = \mathbf{y} \mathbf{D}(\mathbf{x}) \mathbf{y}$.

If we further assume that

$$\frac{d}{dt} \ln \frac{R_k^+(\mathbf{x})}{R_k^-(\mathbf{x})} = \frac{r_{\mathbf{x}} R_k^+(\mathbf{x})}{R_k^+(\mathbf{x})} - \frac{r_{\mathbf{x}} R_k^-(\mathbf{x})}{R_k^-(\mathbf{x})} \frac{d\mathbf{x}(t)}{dt} \quad (12.19)$$

and

$$\frac{d^2 \mathbf{x}(t)}{dt^2} = \sum_{k=1,2,3} \frac{d\mathbf{x}(t)}{dt} \left(r_{\mathbf{x}} R_k^+(\mathbf{x}) - r_{\mathbf{x}} R_k^-(\mathbf{x}) \right) : \quad (12.20)$$

are

12.1 Symmetric diffusion and Schrödinger's equation

Let us consider the Kolmogorov's forward and backward equations for a diffusion process with $D(\mathbf{x})$ and gradient drift $\mathbf{b}(\mathbf{x}) = D(\mathbf{x}) r U(\mathbf{x})$:

$$\frac{\partial f(\mathbf{x}; t)}{\partial t} = \mathcal{L} f = r D(\mathbf{x}) r f(\mathbf{x}; t) + r U(\mathbf{x}) f(\mathbf{x}; t) ; \quad (12.21)$$

$$\frac{\partial u(\mathbf{x}; t)}{\partial t} = \mathcal{L}^* u = r D(\mathbf{x}) r u(\mathbf{x}; t) - r U(\mathbf{x}) r u(\mathbf{x}; t). \quad (12.22)$$

We know the forward equation has a stationary distribution $f^{ss}(\mathbf{x}) = \exp U(\mathbf{x}) = D$. Introducing a symmetric operator

$$\begin{aligned} \mathcal{L} &= e^{\frac{U(\mathbf{x})}{2}} \mathcal{L} e^{-\frac{U(\mathbf{x})}{2}} (\mathbf{x}) \\ &= e^{\frac{U(\mathbf{x})}{2}} r D(\mathbf{x}) r e^{-\frac{U(\mathbf{x})}{2}} (\mathbf{x}) + r U(\mathbf{x}) e^{-\frac{U(\mathbf{x})}{2}} (\mathbf{x}) \\ &= e^{\frac{U(\mathbf{x})}{2}} r D(\mathbf{x}) \frac{1}{2} (x) r U(x) e^{-\frac{U(\mathbf{x})}{2}} + e^{-\frac{U(\mathbf{x})}{2}} r (\mathbf{x}) \\ &= r D(\mathbf{x}) r (\mathbf{x}) + \frac{r D(\mathbf{x}) r U}{2} - \frac{r U D(\mathbf{x}) r U}{4} (\mathbf{x}) \\ &= e^{-\frac{U(\mathbf{x})}{2}} \mathcal{L}^* e^{\frac{U(\mathbf{x})}{2}} (\mathbf{x}) : \end{aligned} \quad (12.23)$$

We see that the \mathcal{L} is a Schrödinger operator $r D(\mathbf{x}) r - E(\mathbf{x})$ with potential energy function

$$E(\mathbf{x}) = \frac{r U(\mathbf{x}) D(\mathbf{x}) r U(\mathbf{x})}{4} - \frac{r D(\mathbf{x}) r U(\mathbf{x})}{2}. \quad (12.24)$$

Note the $r U(\mathbf{x}) r U(\mathbf{x})$ appears also in the HJE:

$$H(x; y) = \mathbf{y} D \mathbf{y} + \quad (12.25)$$



From Cellular Dynamics to Evolutionary Stable Strategy and Back

We now introduce an alternative mathematical theory which is widely employed in evolution theory and ecological dynamics: the theory of *evolutionary stable strategy* (ESS). This approach is based on a very different kind of mathematical tools: nonlinear optimizations rather than dynamical systems. However, we would like to present this approach in the general framework of cellular dynamics.

We shall use cancer cell growth as a metaphor. Let us assume there is a pre-genetic stage of carcinogenesis for a cell: Its biochemical and gene regulatory networks lead to two very different cellular attractors: one goes through cell division and one does not. Let us further assume that a cell that remains dormant has a very low death rate, d_1 , over a given time period T . On the other hand, the cell that goes into division gives rise to two cells but faces a higher death rate $d_2 > d_1$.

Let's say a cell population has fixed fractions p_1 and $p_2 = (1 - p_1)$ being in the dormant and growing states. Then the simplest mathematical model one has is

$$\frac{du}{dt} = (p_1 d_1 + p_2(b - d_2)) u; \quad (b; d_1; d_2; p_1; p_2 \geq 0) \quad (13.1)$$

where $u(t)$ is the population of the "cancer cell in the pre-genetic stage", and b is the doubling, or birth, rate of the cells in the growing state.

The dynamics that follows Eq. (13.1) is simple exponential increasing or decreasing depending on the *net growth rate* $r \triangleq ((1 - p_1)(b - d_2) - p_1 d_1) > 0$ or $r < 0$. Then the formal answer to the question "what is the choice of p_1 such that the cancer will appear?" is

$$\begin{aligned} & \begin{cases} p_1 > 1 \\ p_1 < 0 \\ p_1 < \frac{b - d_2}{d_1 - d_2 + b} \end{cases} \quad \text{if} \quad \begin{cases} b < d_2 - d_1; \\ d_2 - d_1 < b < d_2; \\ b > d_2; \end{cases} \end{aligned} \quad (13.2)$$

Therefore, it is impossible for pre-cancer cells to survive if $b < d_2$. If $b > d_2$, then there is a "strategy" for the cancer to have a right value of p_1 to "survive":

$p_2 > \frac{d_1}{d_1 - d_2 + b}$; and the optimal strategy is $p_2 = 1$ which gives the maximum growth rate $(b - d_2)$.

The above model is certainly not realistic; but it gives us a sense of how to think about "life-history strategies" in the context of cancer cell dynamics. What we would like to do next is to develop a stochastic view of the above problem, and to see how questions like such can be turned into many useful "predictions".

13.1 Discrete versus continuous times

Differential equations for population dynamics such as (13.1) assume a large population size and the population $u(t)$ having real, continuous values. However, when dealing with early cancer development, these assumptions are not warranted. There is a significant stochastic element in the early stage of carcinogenesis, and the cell population should be counted in integers.

First, let us see an important difference between a generation-by-generation view and the continuous growth view of a population:

$$u(t + \Delta t) = u(t); \quad \dot{u} = e^{r\Delta t}; \quad (13.3)$$

here we assume that the time for a generation is Δt . The population increases or decreases depending on $r > 1$ or $r < 1$. Then following the same argument for the strategy in the previous section, we have

$$u(t + \Delta t) = p_1 e^{-d_1 \Delta t} + p_2 e^{(b-d_2) \Delta t} u(t); \quad (13.4)$$

One should immediately note that this result is very different from what is expected based on Eq. (13.1):

$$u(t + \Delta t) = u(t) e^{(-p_1 d_1 + p_2 (b-d_2)) \Delta t}. \quad (13.5)$$

The strategy for p_1 will also be different

$$\begin{aligned} p_1 &> 1 && \text{if } b < d_2 - d_1; \\ p_1 &< 0 && \text{if } d_2 - d_1 < b < d_2; \\ p_1 &< \frac{e^{(b-d_2)\Delta t} - 1}{e^{(b-d_2)\Delta t} - e^{-d_1\Delta t}} && \text{if } b > d_2; \end{aligned} \quad (13.6)$$

How does one explain this result? The answer to this question is very simple: If you have two different growth possibilities r_1 and r_2 for investment, you always invest in the two by two separated pots of money, rather than continuously mixing the two pots:

$$e^{p_1 r_1 + p_2 r_2} = p_1 e^{r_1} + p_2 e^{r_2}; \quad (13.7)$$

This is known as Jensen's inequality; it is because the function e^x is a convex function.

13.2 Life-history strategies in fluctuating environments

It turns out that the birth rate b , death rates d_1 and d_2 above are all fluctuating over space and time. Therefore, one needs to consider the consequence of this important effect. Let us consider discrete time steps:

$$u_{n+1} = \lambda u_n; \quad (13.8)$$

where the $\lambda = e^{r\Delta t} > 0$, the Δt being the time step, i.e., the generation time.

(a) We first consider the scenario of λ has a temporal stationary fluctuation: For each step, λ_n follows an independent identical distribution $f(\lambda)$. Then,

$$u_n = u_0 \exp \sum_{i=0}^{n-1} \ln \lambda_i; \quad (13.9)$$

In the limit of $n \rightarrow \infty$, we have the term inside the parenthesis

$$\frac{1}{n} \sum_{i=0}^{n-1} \ln \lambda_i \xrightarrow[n \rightarrow \infty]{} \int_{-\infty}^{\infty} (\ln x) f(x) dx \triangleq h \ln \lambda \quad (13.10)$$

according to the Law of Large Numbers. Therefore, asymptotically we have

$$u_n = u_0 e^{(h \ln \lambda)n}; \quad (13.11)$$

Note that Eq. (13.11) is different from $u_n = u_0 h \lambda^n$. We note that

$$h \ln \lambda < \ln h \lambda; \quad (13.12)$$

This is known as Jensen's inequality.

Let us assume that the critical size of cancer detection is u^* . Then according to the simple stochastic model, we can obtain the distribution for the "random time of detection" N is:

$$u^* = u_0 \exp \sum_{i=1}^N \ln \lambda_i; \quad (13.13)$$

Let us denote the critical r^* :

$$r^* = \frac{1}{t} \ln \frac{u^*}{u_0}; \quad (13.14)$$

and cumulative probability distribution for random variable r

$$F(x) = \int_{-\infty}^x f_r(z) dz; \quad f'(x) = \int_x^{+\infty} f_r(z) dz; \quad (13.15)$$

Therefore,

$$\begin{aligned} \Pr fN = 1g &= \int_{-\infty}^{+\infty} f_r(x) dx = f'_r(r^*); \\ \Pr fN = 2g &= \int_{-\infty}^{+\infty} f_r(x) dx \int_{-\infty}^{+\infty} f_r(y) dy = \int_{-\infty}^{+\infty} f_r(x) f'_r(r^* - x) dx; \\ \Pr fN = 3g &= \int_{-\infty}^{+\infty} f_r(x) dx \int_{-\infty}^{+\infty} f_r(y) dy f'_r(r^* - y); \end{aligned}$$

One can also estimate the distribution of N :

$$\bar{N} = \frac{1}{r} \ln \frac{u^*}{u_0}; \quad (13.16)$$

where \bar{N} is a function of the random variable r .

HOMEWORK 1: *Compute the distribution of N exactly, and compare with the distribution for the approximated \bar{N} given in Eq. (13.16).*

(b) We now consider the case of $u = e^{r\Delta t}$ has a spatical heterogeneity, but constant over time at a fixed location.

HOMEWORK 2: *Find the probability distribution for the N according to the spatical herterogeneous r .*

13.3 Population dynamics and frequency dynamics

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Entropic Force and Rectified Brownian Motion

Let us consider a diffusion process with that is restricted within interval $[a; b]$, with reflecting boundary condition at a and absorbing boundary condition at b , and initially $f(x; 0) = \delta(x - a)$.

Then, we have

$$\frac{\partial f(x; t)}{\partial t} = D \frac{\partial^2 f(x; t)}{\partial x^2}; \quad (14.1a)$$

with

$$\frac{\partial f(x; t)}{\partial x} \Big|_{x=a} = 0; \quad f(b; t) = 0; \quad f(x; 0) = \delta(x - a); \quad (14.1b)$$

The solution to the partial differential equation $f(x; t)$ tends to zero in the limit of $t \rightarrow \infty$. The "missing probability" is located at $x = b$. Hence one can write the "total probability" as

$$f_{tot}(x; t) = f(x; t) + \int_a^b f(z; t) dz = \delta(x - b); \quad (14.2)$$

It is easy to check that

$$\int_a^b f_{tot}(x; t) dx = 1; \quad (14.3)$$

and the apparent "velocity" of the partial movement

$$\begin{aligned} & \frac{d}{dt} \int_a^b x f_{tot}(x; t) dx \\ &= D \int_a^b x \frac{\partial^2 f(x; t)}{\partial x^2} dx - b \frac{d}{dt} \int_a^b f(z; t) dz \\ &= D \int_a^b x \frac{\partial^2 f(x; t)}{\partial x^2} dx \\ &= D \int_a^b \frac{\partial f(x; t)}{\partial x} dx \\ &= D [f(a; t) - f(b; t)] \end{aligned} \quad (14.4)$$

Now let us consider a steady state problem. We replace the reflecting boundary condition at a to $f(a; t) = f_a$.

14.0.1

Within t time, the change in "total probability" associated with interval $[a; b]$ is

$$\frac{df_{tot}(x; t)}{dt} = \frac{df(x; t)}{dt} + D \left[\frac{\partial f(x; t)}{\partial x} \right]_a^{(x=a)} - D \left[\frac{\partial f(x; t)}{\partial x} \right]_b^{(x=b)}; \quad (14.5)$$

Let us consider

$$\begin{aligned} \frac{\overline{x(t)}}{t} &= \frac{aD \left[\frac{\partial f(x; t)}{\partial x} \right]_a - bD \left[\frac{\partial f(x; t)}{\partial x} \right]_b + \int_a^b x \frac{df(x; t)}{dt} dx}{\int_a^b f(t; x) dx} \\ &= \frac{aD \left[\frac{\partial f(x; t)}{\partial x} \right]_a - bD \left[\frac{\partial f(x; t)}{\partial x} \right]_b + D \int_a^b x \frac{\partial f(x; t)}{\partial x} dx}{\int_a^b f(t; x) dx} \\ &= \frac{D \left[f(a; t) - f(b; t) \right]}{\int_a^b f(t; x) dx} = \frac{D \left[\frac{\partial \ln f(x; t)}{\partial x} \right]_a^b}{\int_a^b f(t; x) dx} \quad (14.6) \end{aligned}$$

Now consider diffusion with a drift V :

$$\frac{\partial f(x; t)}{\partial t} = D \frac{\partial^2 f(x; t)}{\partial x^2} + \frac{\partial}{\partial x} [V(x) f(x; t)] \quad (14.7)$$

Then,

$$\begin{aligned} \frac{\overline{x(t)}}{t} &= \frac{aD \left[\frac{\partial f(x; t)}{\partial x} \right]_a - bD \left[\frac{\partial f(x; t)}{\partial x} \right]_b + \int_a^b x \frac{df(x; t)}{dt} dx}{\int_a^b f(x; t) dx} \\ &= \frac{D \left[f(a; t) - f(b; t) \right] + \int_a^b x \frac{\partial}{\partial x} [V(x) f(x; t)] dx}{\int_a^b f(x; t) dx} \\ &= \frac{D + aV(a) f(a; t) - D + bV(b) f(b; t) + \int_a^b V(x) f(x; t) dx}{\int_a^b f(x; t) dx} \quad (14.8) \end{aligned}$$

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Further Readings

Chapter 1

Chapter 2

Chapter 3

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APPENDIX A

A Field Equation Formalism of Ecological Population Dynamics

Given a population network in terms of stoichiometric coefficients ν_i and kinetic rate laws

$$\frac{dx}{dt} = \sum_{i=1}^M R^+_i(x) - R^-_i(x) \quad ; \quad (A1)$$

we have a generalized Gibbs potential $\psi(x)$ satisfying

$$\begin{aligned} \frac{d}{dt} \psi(x(t)) &= \frac{dx(t)}{dt} \cdot \nabla_x \psi(x) \\ &= \sum_{i=1}^M R^+_i(x) - R^-_i(x) \cdot \nabla_x \psi(x) \\ &= \sum_{i=1}^M R^+_i(x) - R^-_i(x) \ln \frac{R^+_i(x)}{R^-_i(x)} e^{-\nabla_x \psi(x)} \cdot x(t) \quad ; \quad (A2) \end{aligned}$$

in which

$$x(t) = \sum_{i=1}^M R^+_i(x) - R^-_i(x) \ln \frac{R^+_i(x)}{R^-_i(x)} = 0 \quad (A3)$$

We now study the first term in (A2):

$$\begin{aligned} &\sum_{i=1}^M R^+_i(x) - R^-_i(x) \ln \frac{R^+_i(x)}{R^-_i(x)} e^{-\nabla_x \psi(x)} \\ &= \sum_{i=1}^M R^+_i(x) \ln \frac{R^+_i(x)}{R^-_i(x)} e^{-\nabla_x \psi(x)} + R^-_i(x) \ln \frac{R^-_i(x)}{R^+_i(x)} e^{-\nabla_x \psi(x)} \\ &\quad \sum_{i=1}^M R^+_i(x) - 1 \frac{R^-_i(x)}{R^+_i(x)} e^{-\nabla_x \psi(x)} + R^-_i(x) \ln 1 - \frac{R^+_i(x)}{R^-_i(x)} e^{-\nabla_x \psi(x)} \\ &= \sum_{i=1}^M R^+_i(x) - 1 e^{-\nabla_x \psi(x)} + R^-_i(x) - 1 e^{-\nabla_x \psi(x)} = 0 \quad ; \quad (A4) \end{aligned}$$

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Therefore, if we have a \eld equation"

$$\frac{\partial \rho(\mathbf{x}; t)}{\partial t} = \sum_{i=1}^M R_i^+(\mathbf{x}) - 1 - e^{-\beta \nabla \cdot \mathbf{x}'}(\mathbf{x}; t) + R_i^-(\mathbf{x}) - 1 - e^{-\beta \nabla \cdot \mathbf{x}'}(\mathbf{x}; t) \quad (A5)$$

Then, its steady state solution $\rho^{ss}(\mathbf{x})$ will satisfy an energy balance equation with source and sink:

$$\frac{d}{dt} \rho^{ss}(\mathbf{x}(t)) = E_{in}[\mathbf{x}] - E_{out}[\mathbf{x}] \quad (A6)$$

in which both $E_{in}[\mathbf{x}]$ and $E_{out}[\mathbf{x}]$ are non-negative.

So what is the logic relationship between this equation and the kinetic equation? First, one can obtain the latter in the limit of $\beta \rightarrow \infty$. In this case, Eq. A5 becomes

$$\frac{\partial \rho(\mathbf{x}; t)}{\partial t} = \sum_{i=1}^M R_i^-(\mathbf{x}) - R_i^+(\mathbf{x}) - \nabla \cdot \mathbf{x}'(\mathbf{x}; t) \quad (A7)$$

which implies the rate equation (A1). In this way of thinking,

Now for systems with

$$\frac{d}{dt} \rho^{ss}(\mathbf{x}(t)) = 0 \quad (A8)$$

we call it conservative ecology [example? LV system?] Then, there is an "energy conservation"; but more importantly, a ???

Let $k_1 k_2 k_3 = A$ and $k_{-1} k_{-2} k_{-3} = B$ both A and B are giving. This gives
 $k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}$ as well as

$$\ln \frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} :$$

The entropy production over the 3-state cycle is

$$\frac{A - B}{k_3 k_{-1} + k_{-2} k_{-1} + k_2 k_3 + k_1 k_{-2} + k_{-3} k_{-2} + k_3 k_1 + k_2 k_{-3} + k_{-1} k_{-3} + k_1 k_2} \ln \frac{A}{B} ; \quad (A9)$$

To minimize this is to maximize the denominator. We know

$$\frac{k_3 k_{-1} + k_{-2} k_{-1} + k_2 k_3 + k_1 k_{-2} + k_{-3} k_{-2} + k_3 k_1 + k_2 k_{-3} + k_{-1} k_{-3} + k_1 k_2}{A}$$

$$= k_3 k_{-1} + k_{-2} k_{-1} + k_2 k_3 + k_1 k_{-2} + k_{-3} k_{-2} + k_3 k_1 + k_2 k_{-3} + k_{-1} k_{-3} + k_1 k_2$$

In our research, we have obtained the following equation:

$$\frac{\partial'(\mathbf{x};t)}{\partial t} = \sum_{i=1}^M R^+(\mathbf{x}) \frac{1}{1 - e^{-\nabla \mathbf{x}'(\mathbf{x};t) \cdot \mathbf{i}}} + R^-(\mathbf{x}) \frac{1}{1 - e^{-\nabla \mathbf{x}'(\mathbf{x};t) \cdot \mathbf{i}}} \quad (A10)$$

in which $\mathbf{x} \in \mathbb{R}^N$, in the first quadrant. $R^\pm(\mathbf{x})$, $1 \leq i \leq M$, are $2M$ non-negative scalar functions, and \mathbf{i} are M integer-valued N -dimensional vectors.

It is widely believed that the equation (A10) and the following (A11):

$$\frac{\partial'(\mathbf{x};t)}{\partial t} = r'(\mathbf{x}) - \mathbf{D}(\mathbf{x})r'(\mathbf{x}) + \mathbf{V}(\mathbf{x}) \quad (A11)$$

in which $\mathbf{V}(\mathbf{x}) : \mathbb{R}^N \rightarrow \mathbb{R}^N$ is a vector field, and $\mathbf{D}(\mathbf{x})$ is a positive definite matrix, are in the same class of nonlinear PDE. In particular, someone told me that the (A11) has a Riemannian structure while (A10) has a Finsler structure.

But based on earlier David's comments, even the (A11) having a Riemannian structure is not for sure and obvious?