Mathematical Theory of Cellular Dynamics

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CHAPTER 1

Introduction

A mathematical theory of any subject, by de nition, 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 di erent. 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 di erentiate 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 de ning 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. Hop eld [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 e ective 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 di erent things: What happens in a quantum system is represented by an abstract function

in a Hilbert space H; changing with time, as described by Schrodinger's

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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* de ned 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 con dence 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 signi cance 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]: Frist, 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 pupulations 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.

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Studying tumorous tissue is a subject of cancer biology; it contains heterogenous 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 di erent 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 di erence is profound: From the di erential equation, e.g., a dynamic rule, we see that knowing x(0) alone is not su cient for predicting all the x(t), t = 0. However, knowing both x(0) and dx(0)=dt is su cient. 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 signi cant example of a deterministic dynamic model based on data is perhaps Kepler's three laws of planetary motion. Developing stochasticprocess models based on big data is the subject of statistics. Research on bioinformatics, ecology, econometrics, etc. are this kind. Analyzing deterministic di erential or di erence 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.

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1.2.1 Nonlinear, stochastic dynamics as a new paradigm

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What is modern science? Elemetary 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 rst steps: Exact science is also a *narra-tive* 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 scarely, in your thoughts advanced to the stage of science." [28]

The *nonlinear, stochastic dynamics* o ers a new mathematical framework toward dynamics that encompass both deterministic and statistical aspects of modeling. But it o ers more. Perhap one of the most important insights is the emergence of *rare events* which has in nitesimal 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 craches, and sociopolitical revolutions are all rare events. It is these rare events that are truly *unpredicatable* in the classical sense, giving the appearance of *free will*. Hop eld called it *dynamic symmetry breaking*. Jame 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, in uences whose physical magnitude is too small to be taken account of by a nite 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

^y 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 di erent 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, di usion, and interactions.

	Mechanics	Chemistry	
representation	spatial coordinates	number densities	
key concept	point masses	elementary reactions	
dynamics	$m_i \frac{\mathrm{d}^2 x_i}{\mathrm{d} t^2} = F_i \mathbf{x}$	$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_{i=1}^{\mathcal{M}} j_i R_j^+(\mathbf{x}) R_j^-(\mathbf{x})$	
cause	forces with vector addition	reaction rates with additive uxes	
example	F(x) = kx	I + S ^k 2I, S ^k R	
potential condition	$F_i(\mathbf{x}) = -\frac{\mathscr{Q}U(\mathbf{x})}{\mathscr{Q}X_i}$	$\frac{R_j^+(\mathbf{x})}{R_j^-(\mathbf{x})} = \exp \sum_{i=1}^{N} \frac{\partial G(\mathbf{x})}{\partial x_i}$	
energy law	mechanical energy conservation	chemical energy balance	
thermodynamics	$S = \ln (E)$	Chapter 5	
mechanism	Newton's theory is \fundamental", or Verlinde's theory?	elementary reaction, one at a time; mechanical and stochastic theories	

MECHANICS AND CHEMISTRY

2.1 Consequences of Newton's theory of mechanics

Following Newton's equation of motion, we have

$$m_{i} \frac{\mathrm{d}x_{i}}{\mathrm{d}t} \quad \frac{\mathrm{d}^{2}x_{i}}{\mathrm{d}t^{2}} = F_{i}(\mathbf{x}) \frac{\mathrm{d}x_{i}}{\mathrm{d}t};$$

$$\frac{m_{i}}{2} \frac{\mathrm{d}}{\mathrm{d}t} v_{i}^{2}(t) = F_{i}(\mathbf{x}) v_{i}(t);$$

$$\frac{1}{2} \frac{\mathrm{d}}{\mathrm{d}t} \mathbf{p}(t) \quad (t) = \mathbf{F} \mathbf{x}(t) \mathbf{v}(t); \qquad (2.1)$$

in which $p_i = m_i v_i$ are called the momentum of the *i*th point mass. Then, we have 7

$$\frac{\mathrm{d}}{\mathrm{d}t} \frac{\mathbf{p}(t) \mathbf{v}(t)}{\left| \frac{2}{\sqrt{2}} \right|^{2}} \qquad \mathbf{F} \mathbf{x}(s) \quad \mathrm{d}\mathbf{x}(s) = 0.$$
(2.2)
kinetic energy
$$\frac{t_{0}}{\mathrm{mechanical work}}$$

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

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

2.1.1 Hamiltonian dynamics

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{@H(x;y)}{@y}; \quad \frac{\mathrm{d}y}{\mathrm{d}t} = -\frac{@H(x;y)}{@x}; \quad (2.4)$$

The H(x; y) is conserved.

2.1.2 The mechanical theory of heat

Let us consider $H(x; y; \cdot)$ which also contains a parameter . So one naturally interested in how a Hamiltonian dynamics depends on the . 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 $H(x; y; \cdot) = E$.

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

$$dW = \frac{@H}{@} d F d :$$
 (2.5)

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

CONSEQUENCES OF THE CHEMICAL KINETIC EQUATIONS

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

$$dE = \frac{\overset{@E}{=}}{\underset{TdS=dQ}{\overset{@E}{=}}} dS + \frac{\overset{@E}{=}}{\underset{Fd}{\overset{@E}{=}}} d: \qquad (2.6)$$

Therefore, there is an energy conservation for all di erent value of , through work dW = F d and heat dQ = TdS. 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 fty years to develop several usable *force elds*: AMBER (assisted model building and energy re nement), 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 e ort 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 th reversible chemical reaction

$$+_{1}X_{1} + +_{2}X_{2} + + +_{N}X_{N} \xleftarrow{R^{+}}_{R} -_{1}X_{1} + -_{2}X_{2} + + -_{N}X_{N} (2.7)$$

has two set of stoichiometric coe cients f_{k}^+ ; $\bar{f}_{k}^ M_i$ 1 k Ng.

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

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = \frac{\mathcal{M}}{1-1} \quad \forall i \quad R^+_{\cdot}(\mathbf{x}) \quad R^-_{\cdot}(\mathbf{x})$$
(2.8)

where $x_i(t)$ is the concentration of chemical species X_i at time t, 1 = i = N, $y_i = -\frac{1}{2} = -\frac{1}{2}$.

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

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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

CONSEQUENCES OF THE CHEMICAL KINETIC EQUATIONS112.2.3 Gibbs potential condition

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

$$\overset{\mathcal{N}}{\underset{i=1}{\overset{j_i \longrightarrow G(\mathbf{x})}{@X_i}} = \ln \frac{R_j^+(\mathbf{x})}{R_j^-(\mathbf{x})} = \frac{\ln R_j^+(\mathbf{x}) \ln R_j^-(\mathbf{x})}{R_j^+(\mathbf{x}) R_j^-(\mathbf{x})} R_j^+(\mathbf{x}) R_j^-(\mathbf{x}) : (2.12)$$

Then the chemical kinetic equation (2.8) becomes

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = \frac{\mathcal{M}}{\sum_{i=1}^{k}} r_i R^+(\mathbf{x}) R^-(\mathbf{x}) = \frac{\mathcal{M}}{\sum_{k=1}^{k-1}} D_{ik}(\mathbf{x}) \frac{\mathscr{Q}G(\mathbf{x})}{\mathscr{Q}x_k}; \qquad (2.13)$$

in which symmetric, semi-positive de nite matrix

$$D_{ik}(\mathbf{x}) = \bigvee_{i=1}^{\mathcal{M}} \gamma_i \frac{R_{\gamma}^+(\mathbf{x}) - R_{\gamma}^-(\mathbf{x})}{\ln R_{\gamma}^+(\mathbf{x}) - \ln R_{\gamma}^-(\mathbf{x})} \gamma_k$$
(2.14)

When the R^+ ; $R^ jR^+$ R^-j for each and every reversible reaction `, 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

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = \sum_{i=1}^{M} e_i R^+(\mathbf{x}) R^-(\mathbf{x}) \qquad \frac{\mathscr{O}U(\mathbf{x})}{\mathscr{O}x_i} : \qquad (2.15)$$

The equation in (2.13), however, suggests two complications: There is the xdependent factor $D_{ij}(\mathbf{x})$ and it is actually a tensor. They correspond to deeper mathematical di erences, 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_BT unit, has the form:

$$G(\mathbf{x}) = \sum_{j=1}^{N} x_j \quad {}_{j}^{o} + \ln x_j \quad 1 : \qquad (2.16)$$

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

$$\ln \frac{R^+_{\cdot}(\mathbf{x})}{R^-_{\cdot}(\mathbf{x})} = \ln \frac{k^+_{\cdot}}{k^-_{\cdot}} \frac{X^{\prime}}{j} + \frac{1}{j} - \frac{1}{j} \ln x_j = \frac{1}{j} \frac{@G(\mathbf{x})}{@x_j}$$

in which $y_j = \frac{1}{j} + \frac{1}{j}$.

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 occured yet at time *t*. If everything is time-homogeneous, e.g., stationary, and the probabilities of the event not occurs in time intervals [0; t]and [t; t +] are independent, then P(t +) = P(t)P(). If the event is rare, that is within a short *t* time, the probability to occur is *t*, and not occur is 1 *t*, where o(t). Then

$$P(t + t) = P(t)P(t)$$
(3.1a)
= P(t) 1 t;
$$P(t + t) P(t) = P(t) t;$$

$$\frac{dP(t)}{dt} = P(t):$$
(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 in time since the hungry sensation increases with time; there is an urgency.

2) The rst 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) $F_T(t) = 1 e^{-t}$ and probability density function (pdf) $f_T(t) = e^{-t}$. The expected value and variance of *T* are Z_{rec}

$$E T = \int_{0}^{2} t f_{T}(t) dt = \frac{1}{2}; \qquad (3.2)$$

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Var
$$T = \int_{0}^{2-\infty} t \in T^{-2} f_T(t) dt = E T^2 = E^2[T] = \frac{1}{2}$$
: (3.3)

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

Pr
$$T$$
 $t + T$ $t = \frac{Z_{t+}^{t+}}{f_T(s)ds} = \frac{e^{-(t+)}}{e^{-t}} = e^{-} = \Pr T > ;$
 t (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 borther get a same result.

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

$$F_{T}(t) = \Pr T_{*} < t = 1 \quad \Pr T_{*} \quad t$$

= 1 \ \Pr T_{1} \ t \ \Pr T_{2} \ t \ \Pr T_{N} \ t
= 1 \ e^{-1t}e^{-2t} \ e^{-Nt} = 1 \ e^{-t} (3.5)

where $_* = _1 + _2 + _ + _N$. Therefore,

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

Speci cally, if all the T_k are i.i.d. with rate , then the rate parameter for T_* is N. The rst one to occur is N times faster.

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

3.2 Poisson process

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

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

$$P_{n}(t + t) = P_{n}(t)P_{0}(t) + P_{n-1}(t)P_{1}(t) + P_{n-2}(t)P_{2}(t) + = P_{n}(t)(1 t) + P_{n-1}(t) t + o(t); \frac{dP_{n}(t)}{dt} = P_{n}(t) P_{n-1}(t);$$
(3.7)

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

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

3.2.1 Counting process, point process, and renewal process

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

Pr
$$N(t) = n = \frac{(t)^n}{n!} e^{-t}$$
: (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

$$F_{T_n}(t) = \Pr T_n < t = \Pr N(t) > n = \frac{\bigotimes}{m=n} \frac{(t)^m}{m!} e^{-t};$$

$$f_{T_n}(t) = \frac{d}{dt} F_{T_n}(t) = \frac{\bigotimes}{m=n} \frac{mt^{m-1}}{(m-1)!} \frac{\frac{m+1}{t^m}t^m}{m!} e^{-t}$$

$$= \frac{\bigotimes}{m=n-1} \frac{\frac{m+1}{t^m}t^m}{m!} \frac{\bigotimes}{m=n} \frac{\frac{m+1}{t^m}t^m}{m!} e^{-t} = \frac{nt^{n-1}}{(n-1)!}e^{-t} (3.10)$$

This is a Gamma distribution. Therefore, a Poisson process has a counting representation N(t), $t \ge \mathbb{R}^+$, and a point-process representation T_k , $k \ge \mathbb{N}$.

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

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

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

$$T_n = X^{(1)} + X^{(2)} + X^{(n)}:$$
(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.

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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 Delbruck-Gillespie processes.

3.3 Three theorems

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

$$X_* = n \quad \min X_1; X_2; \quad ; X_n :$$

Then,

$$\lim_{n \to \infty} f_X(x) = e^{-x};$$

where $= f_X(0)$.

Theorem 2 (*Khinchin*) If $T_k^{(1)}$, $T_k^{(2)}$, , $T_k^{(n)}$ 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! = 1, 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 di erent sockets, then the fourth row is the combined point process for all the bulb changs. 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 \mathscr{S} and continuous time *t*. Then the probability of the system in state $i \mathscr{2S}$ at time *t* is

$$\frac{\mathrm{d}p_i(t)}{\mathrm{d}t} = \sum_{j \in \mathscr{S}}^{X} p_j(t)q_{j\,i} \quad p_i(t)q_{ij} \quad (3.12)$$



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. $k_1 \propto e^{-\Delta G^Z/k_BT}$. 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

$$\frac{d\mathbf{p}(t)}{dt} = \mathbf{p}\mathbf{Q}; \quad \mathbf{Q} = \begin{bmatrix} 0 & X & & & & 1 \\ q_{1j} & q_{12} & q_{13} & & & \\ j \in \mathscr{S}; \neq 1 & X & & & \\ q_{21} & q_{2j} & q_{23} & & \\ j \in \mathscr{S}; \neq 2 & X & & \\ q_{31} & q_{32} & q_{3j} & & \\ j \in \mathscr{S}; \neq 3 & & \\ \vdots & \vdots & \vdots & \ddots \\ \end{cases}$$
(3.13)

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

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

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

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

$$\Pr^{\cap} X(t) = j \ X(0) = i^{\circ} = e^{\mathbf{Q}t} \qquad (3.15)$$

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,

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ī.

the sum of every row is unity:

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

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

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

$$= p_{i_0}(0) e^{\mathbf{Q}_1} e^{\mathbf{Q}_2} e^{\mathbf{Q}_n} (3.16)$$

in which $\cdot = t \cdot t_{-1}$.

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 $(1/t)^{T}$. It is also the eigenvector of \mathbf{Q} with eigenvalue 0. More e ort are needed to obtain the corresponding left eigenvector $= (1/t)^{T}$.

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 $_{i}$ are strictly positive. Then for any initial probability distribution $\mathbf{p}(0)$:

$$\lim_{t \to \infty} \mathbf{p}(0)e^{\mathbf{Q}t} = \qquad (3.17)$$

Note if $\mathbf{p}(0)$ is normalized, then is normalized. The distribution $\begin{pmatrix} 1 & 2 \\ 2 & 2 \end{pmatrix}$ therefore is called the *stationary distribution* of the Markov process. It is unique.

A stationary Markov process has its initial distribution . Thus for all time $\mathbf{p}(t) = .$ 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.

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3.5.1 Solution to the master equation

According to the theory of linear, homogeneous ordinary di erential equation with constant coe cients, 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 eigenvales $_0 = 0; _1; _2; _$, where all 's except $_0$ are negative, and corresponding left, row eigenvectors $\mathbf{v}_0 = .; \mathbf{v}_1; \mathbf{v}_2; _$ and right column eigenvectors $\mathbf{u}_0 = (1; ...; 1)^T; \mathbf{u}_1; \mathbf{u}_2;$, then

$$e^{\mathbf{Q}t} = \mathbf{u}_{0}/\mathbf{u}_{1}/ \qquad \begin{bmatrix} e^{0} & 0 & 0 & \mathbf{v}_{0} \\ 0 & e^{-t} & 0 & \mathbf{v}_{0} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ddots & \vdots \end{bmatrix} \begin{pmatrix} \mathbf{v}_{0} \\ \mathbf{v}_{1} \\ \mathbf{v}_{2} \\ \mathbf{v}_{1} \\ \mathbf{v}_{1} \\ \mathbf{v}_{2} \\ \mathbf{v}_{2} \\ \mathbf{v}_{1} \\ \mathbf{v}_{2} \\ \mathbf{v}_{2} \\ \mathbf{v}_{1} \\ \mathbf{v}_{2} \\ \mathbf{v}_{2} \\ \mathbf{v}_{2} \\ \mathbf{v}_{1} \\ \mathbf{v}_{2} \\ \mathbf{v}_{$$

Note, each **u** is a column vector, so the \mathbf{u}_0 ; \mathbf{u}_1 ; is a matrix. We see that when $t \neq 1$,

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

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

if the zero eigenvalue is unique.

3.5.2 Time correlation function of an observable

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

$$G() = \text{cov} (t); (t +) = E (t) (t +) E^{2}[]
= \begin{pmatrix} \times \\ i;j;k\in\mathscr{S} \end{pmatrix} (j) (k) i e^{Qt} ij e^{Q} jk \begin{pmatrix} \otimes \\ j \in \mathscr{S} \end{pmatrix} (j) j^{A} \\ = \begin{pmatrix} \times \\ j;k\in\mathscr{S} \end{pmatrix} (j) (k) j e^{Q} jk \begin{pmatrix} \otimes \\ j \in \mathscr{S} \end{pmatrix} (j) j^{A} : (3.21)$$

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

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$$\hat{G}(n) = \frac{1}{N n + 1} \int_{j=0}^{N-n} j \qquad j + n \qquad (3.22)$$

in which is the estimated expected value

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

Note that \hat{G} (0) is an estimated variance. Averging using the stationary process X(t) is equal to the expected value according to the stationary distribution f 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 occurence 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

$$+ \frac{1}{2}X_1 + \frac{1}{2}X_2 + + \frac{1}{2}N_N \xrightarrow{r_{\star}^+(\mathbf{n})}_{T_{\star}^-(\mathbf{n})} - \frac{1}{2}X_1 + \frac{1}{2}X_2 + + \frac{1}{2}N_N \xrightarrow{r_{\star}^+(\mathbf{n})}_{T_{\star}^-(\mathbf{n})}$$
(3.24)

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

$$\frac{\mathrm{d}\rho_{V}(\mathbf{n};t)}{\mathrm{d}t} = \frac{p_{V}(\mathbf{n},t)r_{*}^{+}(\mathbf{n},t)r_{*}^{+}(\mathbf{n},t)}{p_{V}(\mathbf{n};t)r_{*}^{-}(\mathbf{n},t)}$$

$$i$$

$$p_{V}(\mathbf{n};t)r_{*}^{+}(\mathbf{n}) + p_{V}(\mathbf{n},t)r_{*}^{-}(\mathbf{n},t)$$

$$i$$
(3.25)

in which $\gamma = (\gamma_1; \gamma_2; \dots; \gamma_N)$ 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 Delbruck-Gillespie process (DGP) description of chemical kinetics assumes that the j^{th} reaction occurs

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following an exponential time, with rate parameter

$$r_{j}^{+}(\mathbf{n}) = k_{j}^{+} V \overset{\forall @}{=} \frac{n \cdot !}{(n \cdot j^{+})! V^{j^{+}} A};$$

$$r_{j}^{-}(\mathbf{n}) = k_{j}^{-} V \overset{\forall @}{=} \frac{n \cdot !}{(n \cdot j^{-})! V^{j^{+}} A};$$

$$(3.26)$$

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

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

$$\sum_{j=1}^{M} r_{j}^{+}(\mathbf{n}) + r_{j}^{-}(\mathbf{n}) : \qquad (3.27)$$

In fact, among the i.i.d. T_1 ; T_2 ; ; T_n , all exponentially distributed with respective rate parameters 1; 2; ; n, the probability of the smallest one being T_k is

Pr
$$T^* = T_k = \Pr^n T_k \min T_1; ; T_{k-1}; T_{k+1}; ; T_n^o$$

= $\frac{k}{1+r_n};$ (3.28)

More importantly,

$$\Pr_{n} T^{*} = T_{k}; T^{*} \quad t$$

$$= \Pr_{n} T_{1} \quad T_{k}; \quad ; T_{k-1} \quad T_{k}; T_{k} \quad t; T_{k+1} \quad T_{k}; T_{n} \quad T_{k};$$

$$= \frac{Z_{\infty}}{k} e^{-kt_{k}} \quad e^{-$$

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

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3.6.1 Random time-changed Poisson representation

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

$$n_{j}(t) = n_{j}(0) + \sum_{i=1}^{M} r_{i}^{+} r_{i}^{+} \mathbf{n}(s) ds \qquad Y_{i}^{-} \sum_{i=1}^{L} r_{i}^{-} \mathbf{n}(s) ds \qquad (3.30)$$

in which $Y_{\cdot}^{+}(t)$ and $Y_{\cdot}^{-}(t)$ are 2` independent standard Poisson processes with mean $E(Y_{\cdot}^{\pm}(t)) = t$.

We see that in the limit of $n \neq 7$ and $V \neq 7$, but $n=V \neq x$,

$$r_{j}^{+}(\mathbf{n}) / k_{j}^{+} V \bigvee_{i=1}^{\gamma} \frac{n_{i}}{V} = k_{j}^{+} V \bigvee_{i=1}^{\gamma} x_{i}^{j} = V R_{j}^{+}(\mathbf{x}):$$
 (3.31)

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

3.6.2 Kurtz's macroscopic limit

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

$$x_{i}(t) = x_{i}(0) + \sum_{i=1}^{M} \sum_{j=1}^{L} R^{+}_{s} \mathbf{x}(s) \qquad R^{-}_{s} \mathbf{x}(s) \qquad ds: \qquad (3.32)$$

This is, of course, exactly the integral form of the ordinary di erential 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-

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0

prey dynamics is

$$\stackrel{O}{\gtrless} \frac{dx}{dt} = x \quad xz;$$

$$\stackrel{O}{\Rightarrow} \frac{dz}{dt} = y + xz;$$
(3.33)

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

Let us now consider the following chemical reaction system:

$$A + X \stackrel{k_1}{\sim} 2X; X + Y \stackrel{k_2}{\sim} 2Y; Y \stackrel{k_3}{\sim} B;$$
 (3.34)

The according to the Law of Mass Action, the concentrations of X and Y, with xed concentrations of A and B being a and b:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k_1 a x \quad k_2 x y; \quad \frac{\mathrm{d}y}{\mathrm{d}t} = -k_3 y + k_2 x y; \quad (3.35)$$

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:

$$\stackrel{O}{\gtrless} \quad \frac{dN_1}{dt} = r_1 N_1 \quad a_1 N_1^2 \quad b_{21} N_1 N_2;$$

$$\stackrel{\aleph}{\longrightarrow} \quad \frac{dN_2}{dt} = r_2 N_2 \quad a_2 N_2^2 \quad b_{12} N_2 N_1;$$

$$(3.36)$$

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

which, according to the Law of Mass Action, $\overset{8}{8}$

$$\stackrel{\sim}{\gtrless} \quad \frac{\mathrm{d}x}{\mathrm{d}t} = (k_1 a)x \quad k_2 x^2 \quad k_5 x y;$$

$$\stackrel{\geq}{\Rightarrow} \quad \frac{\mathrm{d}y}{\mathrm{d}t} = (k_3 a)y \quad k_4 y^2 \quad (k_5 + k_6) x y;$$
(3.38)

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

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

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A close inspection of the system of chemical reactions in (3.37) indicates that the overall reaction is $2A \ B$. 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 ux converting 2A to B.

CHAPTER 4

Mesoscopic Thermodynamics of Markov Processes

We have seen how by merely introducing mathematically the notion of entropy, $S = k_B \ln \alpha$, L. Boltzmann was able to \derive" the equation for the First Law of Thermodynamics from Newtonian mechanics. We particularly point out the signi ance 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: $k_B = 1.3807 \quad 10^{-23} \mathcal{J} \quad \mathcal{K}^{-1}$, 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 \mathscr{S} and transition probability rate q_{ij} , $i; j \ \mathscr{S}$. We further assume that X(t) is irreducible and $q_{ij} \ne 0$ if and only if $q_{ji} \ne 0$. The rst assumption implies the existence of a unique, positive , 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 de ned as

$$S \mathbf{p}(t) = \bigwedge_{i \in \mathscr{S}} p_i(t) \ln p_i(t):$$
(4.1)

We then have

$$\frac{\mathrm{d}}{\mathrm{d}t}S \mathbf{p}(t) = \frac{X}{\substack{i \in \mathscr{S} \\ i \in \mathscr{S}}} \frac{\mathrm{d}p_i(t)}{\mathrm{d}t} \ln p_i(t) = \frac{X}{\substack{i:j \in \mathscr{S} \\ i:j \in \mathscr{S}}} p_i q_{j\,i} \quad p_j q_{j\,i} \quad \ln p_i$$

$$= \frac{1}{2} \frac{X}{\substack{i:j \in \mathscr{S} \\ i:j \in \mathscr{S}}} p_i q_{j\,i} \quad p_j q_{j\,i} \quad \ln \frac{p_i}{p_j}$$

$$= \frac{1}{2} \frac{X}{\substack{i:j \in \mathscr{S} \\ i:j \in \mathscr{S}}} p_i q_{j\,i} \quad p_j q_{j\,i} \quad \ln \frac{p_i q_{ij}}{p_j q_{j\,i}} \quad \frac{1}{2} \frac{X}{\substack{i:j \in \mathscr{S} \\ i:j \in \mathscr{S}}} p_i q_{j\,i} \quad \ln \frac{q_{ij}}{q_{j\,i}}$$
(4.2)

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

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, and the second logarithmic term is remarkably is remarkably similar to ^o, of a unimolecular chemical reaction. We shall call the rst term similar to 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, $h_{ex}=T$:

$$\frac{\mathrm{d}}{\mathrm{d}t}S \mathbf{p}(t) = e_p \frac{h_{ex}}{T}; \qquad (4.3a)$$

$$e_{p} \mathbf{p} = \frac{1}{2} \sum_{i:j \in \mathscr{S}} p_{i}q_{ji} p_{j}q_{ji} \ln \frac{p_{i}q_{ij}}{p_{j}q_{ji}} \quad 0; \quad (4.3b)$$

$$\frac{h_{ex} \mathbf{p}}{T} = \frac{1}{2} \sum_{i:j \in \mathscr{S}}^{X} p_i q_{ji} p_j q_{ji} \ln \frac{q_{ij}}{q_{ji}} : \qquad (4.3c)$$

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 \thermodynamics ux thermodynamic force". This implies that $(p_i q_{ij} \quad p_j q_{ji})$ can be considered as a ux, 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 voltage"

= power, which can nroc2namir11.955 Td4 Tfknegtiov27(er.]TJ 0 -11.543 Td [(INoe)-367 (II)-2467the)-27

DETAILED BALANCE AND REVERSIBILITY

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 satis es $_{i}q_{ij} = _{j}q_{ji}$, 8i; j 2 S. This is known as *detailed balance*. It is a property of the .

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

$$q_{i_0i_1}q_{i_1i_2} \quad q_{i_{n-1}i_n}q_{i_ni_0} = q_{i_1i_0}q_{i_2i_1} \quad q_{i_ni_{n-1}}q_{i_0i_n}:$$
(4.4)

ī

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

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

which yields relation (4.4).

The su ciency: From (4.4), introducing a set of positive, normalized values for each and every state $i 2 \mathscr{S}_{i}$, *i* as:

$$\frac{i}{j} = \frac{q_{j;i_1}q_{i_1i_2}}{q_{i_1;j}q_{i_2i_1}} = \frac{q_{i_{n-1};i}}{q_{i_{n-1}}} = \frac{q_{ji}}{q_{ij}}:$$

Then

$$\begin{array}{ccc} \times & & \\ & & \\ i j q_{j i} & i q_{i j} & = & \\ & & \\ i j \in \mathscr{S} & & \\ i q_{i j} & \frac{j q_{j i}}{i q_{i j}} & 1 & = 0. \end{array}$$

Therefore, $f_{i}g$ is a stationary solution to the master equation. Since the normalized stationary solution is unique, i = i, thus, $iq_{ij} = jq_{ji} 8i; j 2 S$.

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

(i) Its stationary distribution satis es detailed balance: $_{i}q_{ij} = _{j}q_{ji}$, $8i; j \ge \mathcal{S}$.

(ii) Any path connceting states i and j: i i_0 ; i_1 ; i_2 ; ; i_n j, has a path independent

$$\ln \frac{q_{i_0 i_1}}{q_{i_1 i_0}} + \ln \frac{q_{i_1 i_2}}{q_{i_2 i_1}} + \ln \frac{q_{i_{n-1} i_n}}{q_{i_n i_{n-1}}} = \ln_{i_n} \ln_{i_0}$$
(4.5)

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(iii) It de nes a time reversible stationary Markov process.

(iv) Its **Q** matrix satis es Kolmogorov cycle condition for every sequence of states.

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

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

Proof. (*i*)) (*ii*):

Using (i) we have

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

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

$$= \ln i_n \quad \ln i_0: \tag{4.6b}$$

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

Statement (*ii*) is similar to the path-independent work in a conservative force eld, 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*)) (*iii*):

Equation (4.6) is equivalent to

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

which implies

$$i_{0}p_{i_{0}i_{1}}(1)p_{i_{1}i_{2}}(2) \quad p_{i_{n-1}i_{n}}(n) = i_{n}p_{i_{n}i_{n-1}}(n) \quad p_{i_{2}i_{1}}(2)p_{i_{1}i_{0}}(1);$$

where $p_{ij}() = e^{\mathbf{Q}}_{ij}$. This means for stationary X(t), and $t_k = \sum_{i=1}^{k} k = 1:2$: :n:

$$\Pr^{(n)} X(0) = i_0; X(t_1) = i_1; X(t_2) = i_2; \quad ; X(t_n) = i_n^{(n)} = \prod_{n=1}^{(n)} X(t_n) = i_{n-1}; X(t_n + t_{n-1}) = i_{n-2}; \quad ; X(t_n + t_1) = i_1; X(t_n) = i_0^{(n)}$$

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

DETAILED BALANCE AND REVERSIBILITY

(*iii*)) (*i*):

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

$$i \ e^{\mathbf{Q} t} \ _{ij} = j \ e^{\mathbf{Q} t} \ _{ji};$$

$$i \ _{ij} + q_{ij} t + \frac{t^2}{2} (\mathbf{Q}^2)_{ij} = j \ _{ji} + q_{ji} t + \frac{t^2}{2} (\mathbf{Q}^2)_{ji}$$

$$i \ _{qij} + \frac{t}{2} (\mathbf{Q}^2)_{ij} = j \ _{qji} + \frac{t}{2} (\mathbf{Q}^2)_{ji} :$$

Letting t = 0 we have $_{i}q_{ii} = _{i}q_{ii}$.

(*ii*)) (*iv*):

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

(*iv*)) (*i*):

This is contained in Theorem 4.

(*i*) (*v*):

Simply choose the positive diagonal matrix $\mathbf{\Pi} = \text{diag}(\begin{array}{cc} 1; & 2; \\ 1; & 2; \end{array})$. Conversely, if there eixts a set of positive numbers $f_{i}g$ such that $\begin{array}{cc} _{i}q_{ij} = & _{j}q_{ji}$, then it is an eigenvector of \mathbf{Q} with eigenvalue 0. Therefore since \mathbf{Q} has a unique eigenvalue 0, the normalized

$$\frac{i}{k \in \mathscr{S}^{k}} = i$$

(*i*) () (*vi*):

The entropy production rate is de ned in (4.3b):

$$e_p = \frac{1}{2} \frac{X}{\substack{i: i \in \mathscr{A}}} \quad iq_{ji} \quad jq_{ji} \quad \ln \quad \frac{iq_{ij}}{jq_{ji}} \quad ;$$

in which every term inside the summation $({}_{i}q_{ji} {}_{ji}q_{ji}) \ln({}_{i}q_{ji} {}_{ji}q_{ji}) 0$. Therefore, the entire sum is zero if and only if when ${}_{i}q_{ji} {}_{ji}q_{ji} {}_{ji} {}_{ji} {}_{0}$. This is detailed balance.

In thermodynamics, a stationary system, with uctuations, is said to be at equilibrum 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 reversibe. 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.

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From statement (*ii*), one naturally thinks of In $_i$ 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 ; $;i_n$, and the right-hand-side of (4.5) is the internal energy di erence between the state i_0 and i_n .

Because statement (v), **Q** is similar to a symmetrix matrix:

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

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

Equilibrium systems are well-undestood 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 well shall show in Chapter **??**, biochemical reactions in a cell are not detailed balanced.

4.2.1 Free energy

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

$$\frac{h_d}{T} = \frac{1}{2} \sum_{\substack{i:j \in \mathscr{S} \\ i \in \mathscr{S}}}^{\times} p_i q_{j\,i} \quad p_j q_{j\,i} \quad \ln \quad \frac{q_{ij}}{q_{j\,i}} = \frac{d}{dt} \sum_{\substack{i \in \mathscr{S} \\ i \in \mathscr{S}}}^{\times} p_i(t) \ln \quad i : \quad (4.7)$$

If we identify In , as the potential energy of state *i*, then

$$\overline{E}(t) = \bigwedge_{\substack{i \in \mathscr{S} \\ i \in \mathscr{S}}} \ln_i p_i(t)$$
(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

$$\frac{\mathrm{d}}{\mathrm{d}t} \ \overline{E}(t) \quad TS(t) = Te_p \mathbf{p} \quad 0.$$
(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 i = C have dS=dt 0: The Second Law of Thermodynamics widely known among laypersons.
FREE ENERGY BALANCE EQUATION

4.3 Free energy balance equation

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

$$F \mathbf{p} = \underset{i \in \mathscr{S}}{\times} p_i \ln \frac{p_i}{i}$$
 : (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 rest have

$$F \mathbf{p} = \frac{\times}{\substack{i \in \mathscr{S} \\ i \in \mathscr{S}}} p_i \ln \frac{p_i}{i} = \frac{\times}{\substack{i \in \mathscr{S} \\ i \in \mathscr{S}}} p_i \ln \frac{i}{p_i}$$

$$\times p_i \frac{i}{p_i} = 1 = \frac{\times}{\substack{i \in \mathscr{S} \\ i \in \mathscr{S}}} p_i = 0: \quad (4.11)$$

Furthermore we have

$$\frac{\mathrm{d}}{\mathrm{d}t}F\mathbf{p}(t) = \frac{\times}{\substack{i\in\mathscr{S}\\ i\in\mathscr{S}}} \frac{\mathrm{d}p_i(t)}{\mathrm{d}t}\ln\frac{p_i(t)}{i} = \frac{\times}{\substack{i:j\in\mathscr{S}\\ i:j\in\mathscr{S}}} p_j q_{ji} p_i q_{ij} \ln\frac{p_i}{i}$$
$$= \frac{1}{2} \frac{\times}{\substack{i:j\in\mathscr{S}\\ i:j\in\mathscr{S}}} p_j q_{ji} p_i q_{ij} \ln\frac{p_{ij}}{i} \frac{p_{ij}}{i} e_p \mathbf{p}(t) : \quad (4.12)$$

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

$$\frac{1}{2} \bigotimes_{i;j \in \mathscr{S}} p_j q_{ji} \quad p_i q_{ij} \quad \ln \quad \frac{j q_{ji}}{i q_{ij}} = \bigotimes_{\substack{i:j \in \mathscr{S}: i \neq j \\ i:j \in \mathscr{S}: i \neq j \\ i \neq j$$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}F\mathbf{p}(t) = E_{in} e_{p}; \qquad (4.14a)$$

$$E_{in} \mathbf{p} = \frac{1}{2} p_i q_{ij} p_j q_{ji} \ln \frac{1}{j} q_{ji} 0; \quad (4.14b)$$

$$e_p \mathbf{p} = \frac{1}{2} \sum_{\substack{i:j \in \mathscr{S} \\ i:j \in \mathscr{S}}} p_i q_{ji} p_j q_{ji} \ln \frac{p_i q_{ij}}{p_j q_{ji}} \quad 0: \quad (4.14c)$$

Eq. 4.14a is a \nicer" equation than Eq. 4.3a: Because both E_{in} and e_p are nonnegative, 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:

$$\frac{\mathrm{d}}{\mathrm{d}t}F \mathbf{p}(t) = \frac{1}{2} \sum_{\substack{i:j \in \mathscr{S} \\ i:j \in \mathscr{S}}}^{X} p_j q_{j\,i} p_i q_{j\,j} \ln \frac{p_{i\,j}}{ip_j} = \sum_{\substack{i:j \in \mathscr{S} \\ i:j \in \mathscr{S}}}^{X} p_j q_{j\,i} \ln \frac{p_{i\,j}}{ip_j}$$

$$\times p_j q_{j\,i} \frac{p_{i\,j}}{ip_j} 1 = \sum_{\substack{i \in \mathscr{S} \\ i \in \mathscr{S}}}^{X} \frac{p_i}{i} \sum_{\substack{j \in \mathscr{S} \\ j \in \mathscr{S}}}^{X} p_j q_{j\,i} = 0: (4.15)$$

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: $\mathbf{n} \neq -7$ in Eq. 3.25 with $\mathbf{n} = V = \mathbf{x}$, we have $p_V(\mathbf{x}V;t) / V^{-1}f(\mathbf{x};t); r^{\pm}(\mathbf{n}) / VR^{\pm}(\mathbf{x});$ (5.1)

and the CME (3.25) becomes

$$\frac{@f(\mathbf{x};t)}{@t} \qquad , \qquad \underbrace{\frac{f(\mathbf{x};t)R^{+}(\mathbf{x}) \quad f(\mathbf{x} \quad \cdot = V;t)R^{+}(\mathbf{x} \quad \cdot = V)}{1=V}}_{\substack{i=1\\ f(\mathbf{x} + \cdots = V;t)R^{-}(\mathbf{x} + \cdots = V) \quad f(\mathbf{x};t)R^{-}(\mathbf{x})}{1=V}}_{\substack{i=1\\ f(\mathbf{x} + \cdots = V;t)R^{-}(\mathbf{x} + \cdots = V) \quad f(\mathbf{x};t)R^{-}(\mathbf{x})}{1=V}}_{\substack{i=1\\ f(\mathbf{x};t)}{i=1}} \qquad \underbrace{\frac{e}{e_{X_{i}}} \quad e}_{\substack{i=1\\ e = 1}} \quad \underbrace{\frac{e}{e_{X_{i}}} \quad e}_{\substack{i=1\\ e = 1}} \quad e}_{\substack{i=1\\ e = 1}} \quad \underbrace{\frac{e}{e_{X_{i}}} \quad e}_{\substack{i=1\\ e = 1}} \quad e}_{\substack{i=1\\ e = 1} \quad e}_{\substack{i=1\\ e = 1}} \quad e}_{\substack{i=1\\ e = 1}} \quad e}_{\substack{i=1\\ e = 1} \quad e}_{\substack{i=1\\ e$$

In terms of the method of characteristics, this rst-order partial di erential equation implies

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_{i=1}^{M} \gamma_i R^+_i(\mathbf{x}) R^-_i(\mathbf{x}) ; \qquad (5.3)$$

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 $\mathbf{n}_V(t)$ de ned 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 Delbruck-Gillespie processes.

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

$$V \rho_V(\mathbf{z}V;t)$$
 ! $\mathbf{z} \mathbf{x}(t)$:

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

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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

$$'(\mathbf{x};t) = \lim_{V \to \infty} \frac{\ln p_V(\mathbf{x}V;t)}{V} :$$
 (5.4)

In other words, for very large V,

$$p_V(\mathbf{x}V;t) + e^{-V'(\mathbf{x};t)}$$
: (5.5)

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

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} \quad e^{V'(\mathbf{x};t)} \stackrel{\text{M}}{=} e^{-V'(\mathbf{x}-\cdots-\mathbf{x}=V;t)} R^+_{\mathbf{x}}(\mathbf{x} \cdots =V)$$

$$\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{\mathbf{x}=1}{\stackrel{x$$

Therefore,

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} = \frac{\mathcal{M}' \cap \mathcal{R}^+(\mathbf{x})}{\sum_{i=1}^{n}} R^+(\mathbf{x}) \stackrel{h}{1} e^{-\nabla \mathbf{x}'(\mathbf{x};t)} + R^-(\mathbf{x}) \stackrel{h}{1} e^{-\nabla \nabla \mathbf{x}'(\mathbf{x};t)};$$
(5.6)

which can be also expressed as

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} = \frac{\mathcal{M}}{\sum_{i=1}^{n}} R^+(\mathbf{x}) \quad R^-(\mathbf{x})e^{-\cdots\nabla_{\mathbf{x}}'(\mathbf{x};t)} \stackrel{\text{i}}{=} 1 \quad e^{\cdots\nabla_{\mathbf{x}}'(\mathbf{x};t)} : \quad (5.7)$$

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 'ss(x) be the stationary solution to (5.7). Then, noting $R^{\pm}(\mathbf{x}) = 0$ and $e^y = 1 + y$,

$$0 = \frac{\mathcal{H} \cap h}{R^{+}(\mathbf{x})} e^{-\nabla \mathbf{x}' \cdot ss(\mathbf{x})} + R^{-}(\mathbf{x}) e^{-\nabla \nabla \mathbf{x}' \cdot ss(\mathbf{x})} = \frac{1}{2}$$

$$R^{-}(\mathbf{x}) R^{+}(\mathbf{x}) \cdot \Gamma_{\mathbf{x}}' \cdot ss(\mathbf{x}) = (5.8)$$

$$R^{-}(\mathbf{x}) = 1$$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}, \mathrm{ss} \mathbf{x}(t) = \frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} \quad r_{\mathbf{x}}, \mathrm{ss}(\mathbf{x})$$

$$= \frac{\mathcal{M}}{\mathcal{R}^{+}(\mathbf{x})} \quad \mathcal{R}^{-}(\mathbf{x}) \quad r_{\mathbf{x}}, \mathrm{ss}(\mathbf{x})$$

$$\stackrel{'=1}{\underset{0:}{\overset{\circ}{=}}} 0: \quad (5.9)$$

' $^{ss}(\mathbf{x})$ 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 $V \neq -1$,

$$\lim_{V\to\infty}\frac{\ln p_V(\mathbf{x}\,V;\,t)}{V} = \,'\,(\mathbf{x};\,t):$$

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

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

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

$$\frac{d' ss(\mathbf{x})}{dt} = cmf(\mathbf{x}) \quad (\mathbf{x}); \quad (5.11b)$$

$$\frac{e_{\rho}[\mathbf{p}]}{V} \quad (\mathbf{x}) = \frac{\mathcal{M}}{\sum_{i=1}^{r}} R^{+}(\mathbf{x}) \quad R^{-}(\mathbf{x}) \quad \text{In} \quad \frac{R^{+}(\mathbf{x})}{R^{-}(\mathbf{x})} \quad (5.11c)$$

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

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

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 Delbruck-Gillespie processes and ideal solution in equilibrium

The term \solution" in the title means an aqueous uid 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,

$$\Gamma_{\mathbf{x}}'^{eq}(\mathbf{x}) = \ln \frac{R^+(\mathbf{x})}{R^-(\mathbf{x})} : \qquad (5.12)$$

This is the Gibbs potential condition in Sec. 2.2.3. For systems with detailed balance, therefore, $'^{eq}(\mathbf{x})$ is the Gibbs potential for macroscopic chemical equilibrium.

If a *M*-dimensional vector
$$\mathbf{v} = (v_1; v_2; ...; v_M)$$
 satis es
 $\bigvee_{i=1}^{M} v_{i-1} = 0;$ (5.13)
 $\sum_{i=1}^{n-1} v_{i-1} = 0;$

for all i, 1 N, then **v** represents a reaction cycle, a set of reaction uxes, together there is a perfect balance of the concentrations of all the chemical species:

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_{i=1}^{M} v_i v_i = 0.$$
(5.14)

Eq. 5.12 implies that for any such $v_{,}$

$$\bigvee_{\mathbf{x}=1}^{\mathcal{M}} \mathbf{v} \cdot \ln \frac{\mathbf{R}^+(\mathbf{x})}{\mathbf{R}^-(\mathbf{x})} = \bigvee_{\mathbf{x}=1}^{\mathcal{M}} \mathbf{v} \cdot \mathbf{r}_{\mathbf{x}} \cdot \mathbf{eq}(\mathbf{x}) = 0.$$
(5.15)

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

We now employ the Delbruck-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-

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One can in fact introduce a \local force" for the `th reversible reaction

$$\mathbf{r}(\mathbf{x}) = -\ln \frac{R^+(\mathbf{x})}{R^-(\mathbf{x})} \qquad (5.19)$$

Then Eq. 5.11c becomes

$$\mathbf{(x)} = \begin{array}{c} \mathbf{X} \\ \mathbf{X} \\$$

in which the chemical conductance of the `th reaction is (see Eq. 2.14)

$$C_{\cdot\cdot}(\mathbf{x}) = \frac{R_{\cdot}^{+}(\mathbf{x}) \quad R_{\cdot}^{-}(\mathbf{x})}{\ln R_{\cdot}^{+}(\mathbf{x}) \quad \ln R_{\cdot}^{-}(\mathbf{x})}$$
(5.21)

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

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

$$\operatorname{cmf}(\mathbf{x}) = \bigwedge_{i=1}^{M} R^{+}(\mathbf{x}) \quad R^{-}(\mathbf{x}) \quad r_{\mathbf{x}}^{i \, SS}(\mathbf{x}) \quad r(\mathbf{x}) ; \quad (5.22)$$

$$\frac{d' ss(\mathbf{x})}{dt} = \overset{\mathcal{M}}{\underset{i=1}{\overset{r}{\mathsf{s}}}} R^+_{\cdot}(\mathbf{x}) \quad R^-_{\cdot}(\mathbf{x}) \quad \overset{r}{\mathsf{s}} r^{*}_{\mathbf{x}}(\mathbf{x})$$
$$= \overset{\mathcal{M}}{\underset{i=1}{\overset{r}{\mathsf{s}}}} (\mathbf{x}) C \cdot (\mathbf{x}) \quad \overset{r}{\mathsf{s}} r^{*}_{\mathbf{x}}(\mathbf{x}): \quad (5.23)$$

A chemical kinetic system can be reprented by the set of kinetic rates $R^{\pm}(\mathbf{x})$, or it can be represented thermodynamically by forces and transport coecients (\mathbf{x}) ; $C_{2}(\mathbf{x})$:

$$R^{+}_{\cdot}(\mathbf{x}) = \frac{C_{\cdot\cdot}(\mathbf{x}) - (\mathbf{x})}{e^{\Psi \cdot (\mathbf{x})} - 1}; \quad R^{-}_{\cdot}(\mathbf{x}) = \frac{C_{\cdot\cdot}(\mathbf{x}) - (\mathbf{x})}{1 - e^{-\Psi \cdot (\mathbf{x})}}; \quad (5.24)$$

and

$$\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = \sum_{i=1}^{\mathcal{M}} C \cdot (\mathbf{x}) \cdot (\mathbf{x}): \qquad (5.25)$$

For reaction system with zero cmf:

$$(\mathbf{x}) = \frac{\mathsf{d}' \,^{ss}(\mathbf{x})}{\mathsf{d}t} = \sum_{i=1}^{M} C_{i}(\mathbf{x}) + \mathcal{F}_{\mathbf{x}}' \,^{ss}(\mathbf{x})^{-2}; \quad (5.26)$$

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

$$D(\mathbf{x}) = \sum_{i=1}^{N} C_{i}(\mathbf{x}) \quad (5.27)$$

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where f_{ij} are row vectors and $\frac{T}{2}$ are column vectors. The entry $D_{ij}(\mathbf{x})$ contains terms like $f_{ij} \neq 0$: the species *i* is connected to species *j* via reaction \hat{f}_{ij} .

5.3 Hamiltonian structure and Lagrangian principle

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

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} + H \mathbf{x}; \mathcal{L}_{\mathbf{x}}'(\mathbf{x};t) = 0;$$
(5.28)

with a Hamiltonian function

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

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

through the method of characteristics [121, 122].

5.3.1 The probabilistic meaning of the Hamiltonian description

What is the meaning of the Harmiltonian dynamics (5.30), which is actually a 2*N*-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 throug a minimizer. It turns out, one can introduce a scalar function through the Legendre-Fenchel transform:

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

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

$$\exp V \int_{t_0}^{L} \mathbf{x}(s) \mathbf{x}(s) \, \mathrm{d}s \qquad (5.32)$$

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 $\mathbf{x}(t)$ satis es a system of secondorder ODEs, known as Euler-Langrange equation

$$\frac{\mathscr{Q}\mathcal{L}[\mathbf{x};\mathbf{x}]}{\mathscr{Q}\mathbf{x}_{i}} \quad \frac{\mathrm{d}}{\mathrm{d}t} \quad \frac{\mathscr{Q}\mathcal{L}[\mathbf{x};\mathbf{x}]}{\mathscr{Q}\underline{x}_{i}} = 0; \quad i = 1;2; \quad ;N; \quad (5.33)$$

as a solution to the *boundary value problem*.

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In the macroscopic limit of $V \neq 1$, any trajectory $\mathbf{x}(t)$ that is not the solution to the ODE in (5.3) is nearly impossible; it is 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 $L[\mathbf{x}(t);\mathbf{x}(t)] = 0$ 8t. This correspinds to the solution to (5.30) with $\mathbf{y} = \mathbf{0}$. Note that

$$\frac{\mathrm{d}\mathbf{y}}{\mathrm{d}t} = \Gamma_{\mathbf{x}} H \mathbf{x}; \mathbf{0} = \mathbf{0} \quad () \quad \mathbf{y}(t) = \mathbf{0}; \tag{5.34a}$$

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \Gamma_{\mathbf{y}} H \mathbf{x} / \mathbf{0} = \overset{\text{M}}{\underset{i=1}{\overset{\text{result}}{\longrightarrow}}} R^+_{\mathbf{x}}(\mathbf{x}) R^-_{\mathbf{x}}(\mathbf{x}) / (5.34b)$$

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

5.4 An example

For unimolecular reaction

$$X_1 \xrightarrow[k_{-1}]{k_{-1}} X_2; \tag{5.35}$$

= (1; +1), and its Hamilton-Jacobi equation is

$$\frac{\mathscr{Q}'(x_1;x_2;t)}{\mathscr{Q}t} + H \quad x_1;x_2; \frac{\mathscr{Q}'}{\mathscr{Q}x_1}; \frac{\mathscr{Q}'}{\mathscr{Q}x_2} = 0; \qquad (5.36)$$

in which the Hamiltonian

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

The Hamiltonian system of ODEs:

$$\frac{dx_{1}}{dt} = k_{+1}x_{1}e^{-y_{1}+y_{2}} + k_{-1}x_{2}e^{y_{1}-y_{2}}$$

$$\frac{dy_{1}}{dt} = k_{+1} 1 e^{-y_{1}+y_{2}}$$

$$\frac{dx_{2}}{dt} = k_{+1}x_{1}e^{-y_{1}+y_{2}} k_{-1}x_{2}e^{y_{1}-y_{2}}$$

$$\frac{dy_{2}}{dt} = k_{-1} 1 e^{y_{1}-y_{2}} :$$
(5.38)

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

$$\stackrel{\otimes}{\geq} \frac{dx_{1}}{dt} = k_{+1}x_{1}e^{-z} + k_{-1}x_{tot} + x_{1}e^{z}$$

$$\stackrel{\otimes}{\sim} \frac{dz}{dt} = k_{+1} + 1 + e^{-z} + k_{-1}(1 + e^{z});$$
(5.39)

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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.

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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 $V: p_V(\mathbf{n}; t; \cdot; \cdot)$. Then in the macroscopic limit we have

$$p_{V}(\mathbf{x}V;t, \wedge V; \wedge V) \quad e^{-V'(\mathbf{x};t, \hat{\gamma})};$$
(5.40)

5.6 The logics of mesoscopic dynamics

5.6.1 Some considerations based on symmetry

If we introduce two new rate functions

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

then the HJE (A10) becomes

$$(\mathbf{x};t) = \mathcal{F}_{\mathbf{x}}'(\mathbf{x};t) \tag{5.42}$$

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} = \frac{\mathcal{M}}{\sum_{i=1}^{n}} \ln \frac{\mathcal{R}^+(\mathbf{x};\cdot)}{\mathcal{R}^-(\mathbf{x};\cdot)} D_{\mathcal{N}}(\mathbf{x};\cdot) e^{\frac{1}{2}} \cdots e^{-\frac{1}{2}} (5.43)$$

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

$$\frac{\mathscr{Q}}{\mathscr{Q}t} \sim (\mathbf{x}) = \mathcal{V}_{\mathbf{x}} \stackrel{\forall \mathcal{M}}{\underset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset{i=1}{\overset$$

5.6.2 Onsager's linear irreversibility

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

$$\frac{\mathscr{Q}}{\mathscr{Q}t} (\mathbf{x}) = \Gamma_{\mathbf{x}} \left(\begin{array}{c} \mathcal{M} \\ \mathcal{M} \\ \vdots = 1 \end{array} \right) + R^{+}(\mathbf{x}) + R^{-}(\mathbf{x}) \quad \text{tanh} \quad \frac{\Gamma_{\mathbf{x}} (\mathscr{Q}(\mathbf{x}))}{2} \quad (\mathbf{x}) :$$

$$(5.45)$$

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

$$\frac{\mathscr{Q}U(\mathbf{x};t)}{\mathscr{Q}t} = \bigvee_{i=1}^{\mathcal{M}} R^{-}(\mathbf{x})e^{-\cdots\nabla_{\mathbf{x}}i^{ss}(\mathbf{x})} R^{+}(\mathbf{x})e^{-\cdots\nabla_{\mathbf{x}}i^{ss}(\mathbf{x};t)} \cdots \Gamma_{\mathbf{x}}U(\mathbf{x};t):$$
(5.46)

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

$$\frac{\mathscr{Q}(\mathbf{x};t)}{\mathscr{Q}t} = \sum_{i=1}^{\mathcal{M}} R^+_{\mathbf{x}}(\mathbf{x}) \quad R^-_{\mathbf{x}}(\mathbf{x}) \quad r_{\mathbf{x}} u(\mathbf{x};t):$$
(5.47)

Which can and should be interpreted as Onsager's linear irreversibility with thermodynamic force $\,\tilde{}\,$ and thermodynamic $\,$ ux $\,\tilde{}\,$:

$$\frac{\mathscr{Q}}{\mathscr{Q}t} \sim (\mathbf{x}) = \sim (\mathbf{x}); \qquad (5.48)$$

where \sim and \sim are related via

Which one is \near equilibrium"?

5.6.3 Local and global dynamics

The rst shock.

5.6.4 Emergent behavior and a circular logic

$$u(x; y; t) = \frac{\mathscr{Q}'}{\mathscr{Q}y} \quad \frac{\mathscr{Q}'}{\mathscr{Q}x}:$$
 (5.50)

Then,

$$\frac{\mathscr{Q}u(x;y;t)}{\mathscr{Q}t} = \frac{\mathscr{Q}}{\mathscr{Q}y} \quad \frac{\mathscr{Q}}{\mathscr{Q}x} \quad \overset{h}{k_{+1}x} \quad 1 \quad e^{-u(x;y;t)} \quad + k_{-1}y \quad 1 \quad e^{u(x;y;t)} \quad i$$
$$= k_{+1}xe^{-u(x;y;t)} \quad \frac{\mathscr{Q}u}{\mathscr{Q}y} + k_{-1} \quad 1 \quad e^{u(x;y;t)} \quad k_{-1}ye^{u(x;y;t)} \quad \frac{\mathscr{Q}u}{\mathscr{Q}y} \quad (5.51)$$

5.6.5

$$\frac{\mathscr{Q}'(x;t)}{\mathscr{Q}t} = H \quad x; \frac{\mathscr{Q}'}{\mathscr{Q}x} \quad ; \tag{5.52}$$

in which

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

44 EMERGENT MACROSCOPIC CHEMICAL THERMODYNAMICS whose Hamiltonian system of ODEs are

$$\frac{dx}{dt} = v(x)e^{y} \quad w(x)e^{-y};$$

$$\frac{dy}{dt} = v'(x) + w'(x) \quad v'(x)e^{y} \quad w'(x)e^{-y};$$
(5.54)

CHAPTER 6

Enzyme Kinetics

6.1 Double reciprocal relation and Michaelis-Menten mechanism

$$E + S \underset{k_{-1}}{\overset{k_1}{\underset{k_{-1}}{\longrightarrow}}} ES \overset{k_2}{\stackrel{P}{\stackrel{}}} E + P \tag{6.1}$$

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

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

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

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

$$\frac{\mathrm{d}p(t)}{\mathrm{d}t} = k_2 c: \tag{6.2d}$$

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):

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

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

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

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

Then,

$$\frac{\mathrm{d}u}{\mathrm{d}} = u + uv + K_m \quad q \quad v; \tag{6.6a}$$

$$\frac{\mathrm{d}v}{\mathrm{d}} = u \quad uv \quad K_m v; \tag{6.6b}$$

in which

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

The initial conditions for the di erential equations are u(0) = 1 and v(0) = 0. In the limit of ! 0, v() changes rapidly from 0 to $u uv K_m v = 0$ while u() = 1 has nearly change any. This occurs on the time scale of order O(). Therefore, we have, on the time scale O(1):

$$\frac{\mathrm{d}u}{\mathrm{d}} = -\frac{qu}{K_m + u}$$
(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

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

$$\frac{d\rho_{ES}(t)}{dt} = \rho_E k_1 s \quad \rho_{ES} k_{-1} + k_2 ; \qquad (6.9b)$$

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

$$p_E^{\rm SS} = \frac{k_{-1} + k_2}{k_1 s + k_{-1} + k_2}; \quad p_{ES}^{\rm SS} = \frac{k_1 s}{k_1 s + k_{-1} + k_2}; \tag{6.10}$$

Therefore, the steady state rate of P production is

$$k_2 p_{ES}^{SS} = \frac{k_2 k_1 s}{k_1 s + k_{-1} + k_2} = \frac{k_2 s}{s + K_m}$$
(6.11)

This agrees with (6.8).

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6.3.2 Stochastic product arriving time, one at a time

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

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

From this, we solve

$$\mathbb{E}[T] = \frac{k_{-1} + k_2}{k_2 k_1 s} + \frac{1}{k_2} = \frac{k_2 k_1 s}{k_{-1} + k_2 + k_1 s} \stackrel{-1}{:}$$
(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 rst passage time* problem, which will be further discissed in Chapter 8.

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CHAPTER 7

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:

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

Its stationary distribution can be obtained:

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

Therefore,

$$p_n^{SS} = p_0^{SS} \frac{\sqrt{n}}{k=1} \frac{u(k-1)}{w(k)}$$
 (7.3)

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

As a function of discrete *n*, where are the peaks and toughs 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 $V \neq 1$, let us denote the number density, e.g., concentration as x = n = V. Then we have

$$\lim_{V \to \infty} \frac{u(xV)}{V} = u(x); \quad \lim_{V \to \infty} \frac{w(xV)}{V} = w(x); \quad (7.4)$$

50 1-D DGP AND CHEMICAL KINETICS OF SINGLE SPECIES And, denoting $x = V^{-1}$:

$$\ln p_{XV}^{SS} = \ln p_0^{SS} + V \bigvee_{k=1}^{XV} \ln \frac{u(k-1)}{w(k)} \times V \bigvee_{0}^{Z} \ln \frac{\dot{u}(z)}{\dot{w}(z)} dz + C; \qquad (7.5)$$

where C is just an additive constant. Therefore,

$$\lim_{V \to \infty} \frac{\ln p_{XV}^{ss}}{V} = '(x) = \int_{0}^{L} \ln \frac{\psi(z)}{\hat{u}(z)} dz.$$
(7.6)

For the solution to the corresponding macroscopic, deterministic kinetic equation

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \mathcal{U}(x) \quad \mathcal{W}(x); \tag{7.7}$$

we have:

$$\frac{d}{dt}' x(t) = \frac{d'(x)}{dx} \frac{dx(t)}{dt}$$
$$= \hat{u}(x) \hat{w}(x) \ln \frac{\hat{w}(x)}{\hat{u}(x)} = 0.$$
(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:

$$A + B \xrightarrow[k]{k+} C: \tag{7.9}$$

We note that the $n_A + n_C$ and $n_B + n_C$ do not change in the reaction. Hence we can denote $n_A + n_C = n_A^o$ and $n_B + n_C = n_B^o$ as the total amount of Aand B, including those in C, at the initial time. Now if we use n_C as the nonnegative integer-valued random variable to describe the stochastic chemical kinetics, this simple nonlinear chemical reaction, according to DGP, is a onedimensional 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 $p^{eq}(m) = \Pr n_C^{eq} = m$:

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

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

$$p^{eq}(m) = \frac{-1}{m!(n_A^o - m)!(n_B^o - m)!} \frac{k_+}{k_- V}$$
(7.11)

where is a normalization factor

$$() = \frac{\min(\mathcal{Q}^{o}_{A}; n^{o}_{B})}{m=0} \frac{n^{o}_{A}! n^{o}_{B}! m}{m!(n^{o}_{A} m)!(n^{o}_{B} m)!}; = \frac{k_{+}}{k_{-}V} : (7.12)$$

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

$$\ln p^{eq}(n_{C}) = \ln \frac{n_{C}}{n_{C}!(n_{A}^{o} - n_{C})!(n_{B}^{o} - n_{C})!} + \text{const.}$$

$$= n_{A} \ln \frac{n_{A}}{V} - n_{A} + n_{B} \ln \frac{n_{B}}{V} - n_{B} + n_{C} \ln \frac{n_{C}}{V} - n_{C} - n_{C} \ln \frac{k_{+}}{k_{-}}$$

$$= n_{A} \ln x_{A} + n_{B} \ln x_{B} + n_{C} \ln x_{C} + n_{C} - \frac{n_{C}}{C} - \frac{n_{A}}{A} - \frac{n_{B}}{B} - (n_{A} + n_{B} + n_{C})$$

$$= n_{A} - \frac{n_{A}}{V} - \frac{n_{$$

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,

$$A + X \stackrel{k_1}{!} 2X; X + X \stackrel{k_2}{!} B;$$
 (7.14)

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,

$$\frac{dx}{dt} = r \ 1 \quad \frac{x}{K} \quad x; \quad r = k_1 a; \quad K = \frac{r}{k_2}; \tag{7.15}$$

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 $n \ge n$ molecules in a reaction volume of V:

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

in which the state-dependent birth and death rates are

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

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Then, according to Eq. 7.3,

$$p_0^{ss} = 1$$
 and $p_n^{ss} = 0$; $n = 1$; (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 a 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 ux. This puts a very strong condition on the dynamics. When a chemical reaction system has a sustained source and sink with di erent 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 Schlogl model

$$A + 2X \xrightarrow[k_{-1}]{k_{-1}} 3X; X \xrightarrow[k_{-2}]{k_{-2}} B; \qquad (7.18)$$

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

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k_{+1}ax^2 \quad k_{-1}x^3 \quad k_{+2}x + k_{-2}b = f(x); \tag{7.19}$$

which is a third-order polynomial. It can exhibit bistability and saddle-node bifurcation phenomenon. All of them only occur under driven condition, when $A \notin B$. Note in the chemical equilibrium: $A = {a \atop A} + k_B T \ln a = {a \atop B} + k_B T \ln b$, and

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

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

$$F(x) = k_{+1}ax^{2} \quad k_{-1}x^{3} \quad k_{+2}x + k_{-2}b$$

$$= k_{+1}ax^{2} \quad k_{-1}x^{3} \quad k_{+2}x + \frac{ak_{+1}k_{+2}}{k_{-1}}$$

$$= x^{2} + \frac{k_{+2}}{k_{-1}} \quad ak_{+1} \quad k_{-1}x : \qquad (7.21)$$

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Therefore, the f(x) has a unique xed 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 su ciently large chemical potential di erence. Such a substained 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

$$u(n) = \frac{k_{+1}an(n-1)}{V} + k_{-2}bV$$

= $\frac{k_{+1}a}{V} n(n-1) + \frac{k_{+2}V^2}{k_{-1}}$; (7.22)

$$w(n+1) = \frac{k_{-1}(n+1)n(n-1)}{V^2} + k_{+2}(n+1)$$

= $\frac{k_{-1}(n+1)}{V^2} - n(n-1) + \frac{k_{+2}V^2}{k_{-1}}$ (7.23)

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

$$p_n^{SS} = C \frac{N^{-1}}{k_{-1}(1+1) = V^2} = \frac{n}{n!} e^{-1} ; \qquad = \frac{k_{+1}aV}{k_{-1}} ; \qquad (7.24)$$

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

7.5 The law of large numbers — Kurtz' theorem

7.5.1 Di usion approximation and Kramers-Moyal expansion

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

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$$\frac{\mathscr{C}f(x;t)}{\mathscr{C}t} = V \frac{dp_{Vx}(t)}{dt}$$

$$= \frac{1}{dx} f(x - x;t) \vartheta(x - x) - f(x;t) - \vartheta(x) + \vartheta(x) + f(x + -x;t) \vartheta(x + -x)$$

$$= \frac{\mathscr{C}}{\mathscr{C}x} f(x + -x;t) \vartheta(x + -x)$$

$$= \frac{\mathscr{C}}{\mathscr{C}x} \frac{\mathscr{C}}{\mathscr{C}x} - \frac{\vartheta(x) + \vartheta(x)}{2V} - f(x;t) - \vartheta(x) - \vartheta(x) - \vartheta(x) - \xi$$

$$(7.25)$$

in which

$$\lim_{V \to \infty} \frac{u(Vx)}{V} = \hat{u}(x); \quad \lim_{V \to \infty} \frac{w(Vx)}{V} = \hat{w}(x):$$
(7.26)

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its pdf $f_Y(y; t)$ satis es $@f_Y(y; t)$

$$\frac{f_{Y}(y;t)}{@t} = \frac{@}{@y} \frac{@}{@y} \frac{\mathscr{W}(x(t)) + \mathscr{U}(x(t))}{2} f_{Y}(y;t) \\ \mathscr{U}'(x(t)) \quad \mathscr{W}'(x(t)) \quad yf_{Y}(y;t) \stackrel{O}{:} (7.30)$$

We see both the di usion $\ce cient$ " and the drift are theyselves 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

$$\frac{1}{V} \ln \hat{f}_Y^{st}(y) = 2 \qquad \frac{\dot{w}(x) \quad \dot{u}(x)}{\dot{u}(x) + \dot{w}(x)} \quad \mathrm{d}x \quad \dot{\sim}(x): \tag{7.31}$$

On the other hand, according to Eq. 7.6,

$$f(x) = \int_{\alpha}^{\alpha} \ln \frac{\psi(x)}{\psi(x)} dx.$$
(7.32)

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

$$\frac{\mathrm{d}}{\mathrm{d}x}'(x) = 2 \quad \frac{\mathscr{W}(x)}{\mathscr{W}(x) + \mathscr{U}(x)} = 0 \quad () \quad \mathscr{W}(x) = \mathscr{U}(x): \tag{7.33}$$

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

$$\frac{\mathrm{d}^2}{\mathrm{d}x^2} \dot{\sim} (x) = 2 \frac{\vartheta'(x)}{\vartheta(x) + \vartheta(x)} = \frac{\vartheta'(x)}{\vartheta(x)} \frac{\vartheta'(x)}{\vartheta(x)}$$
$$= \frac{\mathrm{d}^2}{\mathrm{d}x^2} \dot{(x)} : \qquad (7.34)$$

However, it can be shown, via an example, that the global minimua of the 2(x) and 2(x) can be di erent!

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 di erent: To have a non-trival LLN means a zero variance in the latter; and to have a non-trival CLT means a divergent LLN, if the LLN is nite. 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 -expansion.

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CHAPTER 8

Phase Transition, Mesoscopic Phenomena, and Multiple Scales

The result in Sec. 7.1 is only valid for nite time: We have rst taken the limit of $V \neq 7$ and obtained an ODE for the dynamics, and then studied the longtime behavior of the ODE, e.g., its xed points. One of the most important features of a nonlinear ODE is the breakdown of ergodicity: The long-time bahavior 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 nite V, is ergodic. There is a unique stationary distribution $p_V^{SS}(n)$. To understand this stark contrast between the two limiting behavors: V tending to ini nity following $t \neq 7$ and V tending to in nity preceding $t \neq 7$, 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 di usion process with probability density function following the Kolmogorov forward equation

$$\frac{\mathscr{Q}f(x;t)}{\mathscr{Q}t} = \frac{\mathscr{Q}^2f(x;t)}{\mathscr{Q}x^2} + \frac{\mathscr{Q}}{\mathscr{Q}x} U'(x)f(x;t) ; \qquad (8.1)$$

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

Let (x; tjz) be the probability density function remaining inside [a; b] at time t, starting at x = z 2 [a; b]. Clearly, (x; tjz) satis es the Eq. (8.1), with

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boundary condition

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

and initial condition (x; t j z) = (x - z). More importantly,

$$\frac{\mathscr{Q}(x;tjz)}{\mathscr{Q}t} = \frac{\mathscr{Q}^2(x;tjz)}{\mathscr{Q}z^2} \quad U'(z)\frac{\mathscr{Q}(x;tjz)}{\mathscr{Q}z}:$$
(8.3)

This is the Kolmogorov backward (partial di erential) equation. Then the remaining total probability Z_h n o

$$\int_{a}^{b} (x; tjz) dx = \Pr \prod_{fp}^{n} T_{fp} > t$$
(8.4)

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

$$\begin{array}{cccc} h & i & Z_{\infty} & Z_{\infty} \\ \mathbb{E} & T_{fp}(z) & = & t f_{fp}(t) dt = & t d F_{fp}(t) & 1 \\ & & {}^{0}Z_{\infty} & n & {}^{0}O \\ & = & t Pr & T_{fp} > t dt \\ & & Z_{\infty}^{0} & Z_{b} & ! \\ & = & t & (x; tjz) dx dt: \end{array}$$

$$(8.5)$$

Therefore,

$$= \begin{array}{cccc} \frac{\mathscr{Q}^{2}}{\mathscr{Q}z^{2}} & U'(z) \frac{\mathscr{Q}}{\mathscr{Q}z} & \overset{h}{\mathbb{E}} T_{fp}(z) \\ Z_{\infty} & Z_{b} \\ & tdt \\ & \frac{Z_{b}^{0}}{tdt} & \frac{\mathscr{Q}(x;tjz)}{\mathscr{Q}t} & dx \\ & z_{b}^{0} & A & t(x;tjz) \\ & t=0 \\ Z_{b}^{a} & Z_{\infty} & Z_{\infty}^{0} \\ & t=0 \\ & dx & (x;tjz)dt \\ & t=0 \\ & 0 \end{array} \begin{array}{c} (x;tjz)dt \\ & z_{b}^{0} & z_{\infty} \\ & z_{\infty} & 0 \\ & z_{\infty} & 0 \end{array}$$

Eq. (8.6), together with boundary conditions

$$\frac{\mathrm{d}\mathbb{E}[T_{f\rho}(z)]}{\mathrm{d}z} = 0; \quad \mathbb{E} \ T_{f\rho}(b) = 0;$$

solves the mean rst passage time problem.

8.2 Kramers' theory

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

$$\frac{d'(z)}{dz} - \frac{U'(z)}{dz} = -;$$
 (8.7)

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where '(z) is the derivative of (z) with respect to z. Noting that '(a) = 0, we have $1^{\frac{7}{2}}$

$$'(z) = -\frac{1}{0} \exp -\frac{U(z)}{U(y)} dy$$
: (8.8)

Integration again, we have an exact result

$$(z) = \frac{1}{2} \int_{z}^{z} \int_{a}^{b} dx \exp \frac{U(x)}{y} dy: \qquad (8.9)$$

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 localted at x^{\ddagger} , then in the triangle domain of (;y) for the double integral of (a) has a maximum at $= x^{\ddagger}$ and $y = x_0$. The exponent of the integrand of (8.9), near this maximum, can be expressed as

$$U() \quad U(y) = \begin{array}{c} U(x^{\ddagger}) & U(x_{0}) \\ \frac{1}{2} & U'' & x^{\ddagger} & x^{\ddagger}^{2} + U''(x_{0}) & y & x_{0}^{2} + \dots \end{array}$$
(8.10)

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

(a)
$$\frac{1}{-}e^{\frac{U(x^{z})-U(x_{0})}{2}} e^{-\frac{jU^{\emptyset}(x^{z})j}{2}(-x^{z})^{2}} d e^{-\frac{U^{\emptyset}(x_{0})}{2}(y-x_{0})^{2}} dy$$
$$\frac{1}{-}e^{\frac{U(x^{z})-U(x_{0})}{2}} e^{-\frac{jU^{\emptyset}(x^{z})j}{2}(-x^{z})^{2}} d e^{-\frac{U^{\emptyset}(x_{0})}{2}(y-x_{0})^{2}} dy$$
$$= \frac{2}{\frac{2}{jU''(x^{\frac{3}{2}})jU''(x_{0})}} \exp \frac{U(x^{\frac{3}{2}})-U(x_{0})}{2} (x^{\frac{3}{2}})} (x^{\frac{3}{2}}) (y-x_{0})^{2}} dy$$
(8.11)

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

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

$$_{n} = \frac{1}{u(n) + w(n)} + \frac{u(n)_{n+1} + w(n)_{n-1}}{u(n) + w(n)};$$
(8.12)

which can be re-arranged into

$$\mathscr{L}^* f_n g = u(n)_{n+1} = u(n) + w(n)_n + w(n)_{n-1} = 1:$$
 (8.13)

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

$$\mathscr{L} f p_n g = p_{n-1} u(n-1) \quad p_n u(n) + w(n) + p_{n+1} w(n+1):$$
 (8.14)

Introducing $s_n = n_{+1} \dots n_n$, we have Eq. 8.13 expressed in terms of a rst order di erence equation for s_n :

$$u(n)s_n \quad w(n)s_{n-1} = 1;$$
 (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:

$$s_n = 4 \qquad \underbrace{\times}_{k=n_0} \frac{1}{w(k)} \frac{k+1}{j=0} \frac{u(j)}{w(j)} 5 \underbrace{\times}_{i=0}^{Y} \frac{w(i)}{u(i)}$$
(8.16)

Thus,

$$n = \sum_{i=n}^{n \times -1} s_{i} = \frac{n \times -1}{4} \frac{2}{k} \times \frac{1}{w(k)} \frac{k - 1}{j = 0} \frac{u(j)}{w(j)} \frac{3}{5} \bigvee_{i=0}^{Y} \frac{w(i)}{u(i)}.$$
 (8.17)

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

$${}_{n} = \frac{\chi_{1}}{m = n + 1} \frac{p_{\cdot}^{ss}}{e_{m}} \frac{p_{\cdot}^{ss}}{w(m) p_{m}^{ss}}$$
(8.18)

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

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we have an asymptotic approximation to (8.18):

$$V = V = \frac{\sum_{x_1}^{Z} \frac{dz}{w(z)}}{x} \frac{dz}{w(z)} = \frac{\sum_{x_0}^{Z} e^{V['(z) - '(y)]} dy}{x}$$
(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 $_n$ be the MFPT for the duration of the game. Then we have

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

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

Now if $q > p_i$ then this time is about

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

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

$$\ln n / \ln p_N^{ss} + \ln p_0^{ss}:$$
 (8.28)

8.4 Thermodynamic limit and global minimum of '(x)

8.5 Exchange of limits: t = 0 and t = 1

CHAPTER 9

Cellular Biochemical Dynamics, I: Gene Regulatory Networks

9.1 The central dogma of molecular biology

$$\begin{array}{c} k \\ \hline k \\ \hline \gamma \\ \hline \gamma \\ \hline \gamma \\ \hline \gamma \\ \hline \phi \\ \hline \end{array} \phi$$

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 degradated inside a living cell.

9.1.1 Deterministic dynamics

Accoding 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

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = k_1 \qquad _1 x_2^* \tag{9.1a}$$

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = k_2 x \quad _2 y; \tag{9.1b}$$

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 $k_2 = k_2^o[\text{AA}]$.

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Figure 9.2 Protein concentration, v(), according to Eq. 9.3b, with v(0) = 0, u(0) = 3 (purple and burgundy) and 6 (red), and = 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{\mathrm{d}u(\)}{\mathrm{d}} = 1 \quad \frac{u}{2} \tag{9.2a}$$

$$\frac{\mathrm{d}v()}{\mathrm{d}} = \frac{u}{v} \quad v; \tag{9.2b}$$

in which $u = (2 = k_1)x$, $v = (1 + 2y = (k_1k_2))$, y = 2t, and $y = 2t_1$. The solution to (9.2) can be explicitly obtained as:

$$u() = u(0) e^{-i} + j$$
 (9.3a)

$$v() = v(0) = \frac{1}{\{z_{-}\}} + \frac{1}{\{z_{-}\}} + \frac{u(0)}{|z_{-}|} + \frac{1}{|z_{-}|} + \frac{u(0)}{|z_{-}|} + \frac{1}{|z_{-}|} + \frac{1}{|z_{$$

If 1, then the system in (9.1) is a singularly perturbed ODE system in which u() are very fast, thus the v() has a fast component and a slow component. According to the pertubation theory of di erential 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() has a transient \burst". The amplitude of the transient burst increases with increasing u(0). The gure also suggests that the amplitude increases with decreasing . To understand this result, we note that the term inside f = g in (9.3b) is responsible for the transient. It

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can be easily veri ed that function

$$\frac{1}{1} e^{-t} e^{-t}$$

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

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

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 enzme, S, with concentration z. The S regulates the transcription process that produces the mRNA:

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = k_1(z) \quad {}_1x; \tag{9.4a}$$

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = k_2 x \quad _2 y; \tag{9.4b}$$

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = k_3 y_{-3} z z \qquad (9.4c)$$

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

$$k_1(z) = \frac{1 \ 2 \ 3}{k_2 k_3} \quad z = 0.$$
 (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

$$k_1(z) = \frac{V}{K + z^n}$$
: (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].

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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.

$$(m; n + 1)$$

$$(n + 1)_{2} | \stackrel{6}{\longrightarrow} mk_{2}$$

$$(m - 1; n) = \frac{k_{1}}{m_{1}} (m; n) = \frac{k_{1}}{(m + 1)_{1}} (m + 1; n)$$

$$n_{2} | \stackrel{6}{\longrightarrow} mk_{2}$$

$$(m; n - 1)$$

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. $k_1 = k_1^o \times DNA$ concentration \times nucleotide concentration; $k_2 = k_2^o \times amino$ acids concentration.

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

$$\frac{dp(m;n;t)}{dt}$$

$$= k_1 p(m-1;n) p(m;n) _1 mp(m;n) (m+1)p(m+1;n)$$

$$+ k_2 m p(m;n-1) p(m;n) _2 np(m;n) (n+1)p(m;n+1) :$$

The mRNA copy number has a steady state marginal distribution

$$p_{\mathcal{M}}(m) = \frac{(k_1 = 1)^m}{m!} e^{-k_1 = 1}$$
(9.8)

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

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

with $b = k_2 = (1 + k_2)$ and $r = k_1 = 2$. This distribution characterizes \transcription burst" based on high-resolution meansurements, 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

$$1 \quad \frac{b}{1 \quad b} \ s \quad 1 \quad \frac{-r}{2}$$
(9.10)

The distribution in (9.9) has been widely intuitively interpreted as follows: One mRNA has an exponentially distributed lifetime, with mean value $\ ^-$

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under the condition $U_1(1) = 1$. We see that if $_2 = 0$, then $U_1(s)$ is indeed the generating function for a geometric distribution with parameter $p = \frac{k_2}{1+k_2}$:

$$\sum_{n=0}^{\infty} s^{n} p^{n} 1 \quad p = \frac{1}{1} \frac{p}{sp} = \frac{1}{1} \frac{1}{k_{2}(s-1)} :$$

For $_2 \neq 0$, denoting

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

Then,

$$U_{1}(s) = e^{-(s)} C + \frac{1}{2} \int_{1}^{z} \frac{e^{(z)}}{z + \frac{1}{2}} dz$$

= $\frac{1}{2} (s + 1)^{-\frac{1}{2}} e^{-\frac{k_{2}}{2}(s-1)} \int_{0}^{z} z^{-\frac{1}{2}-1} e^{-\frac{k_{2}}{2}z} dz;$ (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 $p(m; n; 0) = m_{M, n0}$, we have the CME (9.7):

$$\frac{dp(m;n;t)}{dt} = m_{1} + k_{2} p(m;n) + {}_{1}(m+1)p(m+1;n) \qquad (9.17) + mk_{2}p(m;n-1) {}_{2} np(m;n) (n+1)p(m;n+1) ;$$

in which 0 m M. Introducing the generating function

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

which satisfy

$$\overset{\text{B}}{\underset{\text{M}}{\underset{\text{M}}{s}}} \overset{\text{h}}{m} \overset{\text{i}}{k_{2}}(s \ 1) \qquad \overset{\text{i}}{_{1}} \overset{\text{G}}{G_{m}}(s) \qquad _{2} \ s \ 1 \qquad \frac{\text{d}G_{m}(s)}{\text{d}s} = \qquad _{1}(m+1)G_{m+1}(s);$$

(9.19)

in which 1 m < M. Then $U_M(s) = {}_1G_1(s)$ is the generating function for the distribution of the number of protein copy numbers when *all* the *M* copies of mRNA are degradated. In terms of the (*s*) function de ned in (9.15), the solution to this system of equations is

$$G_{M}(s) = \frac{e^{-M}(s)}{2} \sum_{i=1}^{2} \frac{e^{M}(z)}{z-1} dz; \qquad (9.20a)$$

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

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The $U_{\mathcal{M}}(s) \notin U_1^{\mathcal{M}}(s)$ in general! However, when $_2 = 0$, we have

$$U_{\mathcal{M}}(s) = {}_{1}G_{1}(s) = \frac{2 {}_{1}^{2}G_{2}(s)}{{}_{1} {}_{k_{2}}(s {}_{1})} = \frac{3 {}_{1}^{3}G_{3}(s)}{[{}_{1} {}_{k_{2}}(s {}_{1})]^{2}} =$$
$$= \frac{M {}_{1}^{M}G_{\mathcal{M}}(s)}{[{}_{1} {}_{k_{2}}(s {}_{1})]^{M-1}} = U_{1}^{M}(s):$$
(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

$$\frac{dp(n;t)}{dt} = {}_{2} (n+1)p(n+1) np(n) + k_{1}(1 b) b p(n ') b p(n ') b p(n) ; (9.22)$$

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

$$\frac{\mathscr{@}G_{\mathcal{P}}(s;t)}{\mathscr{@}t} = {}_{2}(1 \quad s)\frac{\mathscr{@}G_{\mathcal{P}}(s)}{\mathscr{@}s} + k_{1} \quad \frac{sb}{1 \quad sb} \quad G_{\mathcal{P}}(s):$$
(9.23)

Therefore, the stationary distribution for protein has its generating function $\frac{7}{7}$

$$G_{P}^{ss}(s) = \exp \frac{k_{1}}{2} \left[\frac{1}{2} - s + \frac{b}{1} - zb + dz \right]$$

= $\exp \frac{k_{1}}{2} \ln \frac{bs}{b} \left[\frac{1}{1} - zb + \frac{b}{1} - zb + \frac{b}{1} - zb + \frac{b}{1} \right]$ (9.24)

in which $r = \frac{k_1}{2}$. This proves Eq. 9.11.

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

$$G_P(s;t) = (1 \ s)e^{-2t} \ G_P^{SS}(s);$$
 (9.25)

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

$$G_P(s;t) = G_P 1 (1 s)e^{-2t}; 0 \frac{1+k_2(1 s)e^{-2t}}{1+k_2(1 s)}$$
 (9.26)

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9.3 Gene regulatory netwok with feedbacks

 g_1

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

$$DNA + TF \xrightarrow{h}_{f} DNA TF:$$

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.

 g_1

on

0

-state
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 g_1

 q_1

Figure 9.4 *O* -state and on-state represent the unbound and bound state of the single copy of DNA (gene) with a TF. ` 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 .

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

$$p_P(nji) = \frac{(g_i)^n}{n!} e^{-g_i}$$
(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 di erent g_i the two modal values can be very di erent. For a very small f and h, the probability distribution for the proteni is simply

$$p_{P}(n) = \frac{f p_{P}(n j 0) + g_{0} h p_{P}(n j 1)}{f + g_{0} h}$$
$$= \frac{-n}{n!} \frac{f g_{0}^{n} e^{-g_{0} =} + g_{0} h g_{1}^{n} e^{-g_{1} =}}{f + g_{0} h}; \qquad (9.28)$$

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 bindingunbinding 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:

$$\overline{g}(n) = \frac{fg_0 + nhg_1}{f + nh}; \quad -(n) = n \quad \frac{f + h(n - 1)}{f + nh} \quad ; \quad (9.29)$$

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then the protein copy number distribution is

$$p_P(n) = C \frac{\gamma^n}{i=1} \frac{\overline{g}(i-1)}{-(i)} = \frac{C}{n!} \quad \frac{g_1}{i=1} \quad \frac{n \gamma^n}{i=1} \frac{[fg_0 = (hg_1)] + (i-1)}{(f=h) + (i-1)}; \quad (9.30)$$

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 $t(0 \ x \ 1)$, is

$$\stackrel{\bigcirc}{\geq} \frac{\mathrm{d}x(t)}{\mathrm{d}t} = hy(1 \quad x) \quad fx;$$

$$\stackrel{>}{\geq} \frac{\mathrm{d}y(t)}{\mathrm{d}t} = g_0(1 \quad x) + g_1x \quad y;$$
(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

$$y_1(x) = \frac{f_X}{h(1-x)}; \quad y_2(x) = {}^{-1} g_0(1-x) + g_1x :$$
 (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 $x^* \ 2 \ (0,1]$. The macroscopic xed point is located at (x^*, y^*) in which y^* is the positive root of

$$y^2 + \frac{f}{h} = \frac{g_1}{2} \quad y = \frac{fg_0}{h} = 0$$

We note this is the same equation as g(n) = -(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

____| |____ CHAPTER 10

Cellular Biochemical Dynamics, II: Signaling Networks

10.1 Phosphorylatin-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:

$$E + K + ATP \xrightarrow{k_{+1}} E^* + K + ADP; \qquad (10.1a)$$

$$E^* + P \xrightarrow[k_{2}]{k_{2}} E + P + P_{i'}$$
 (10.1b)

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 second case, one has a very similar kinetic scheme:

$$E GDP + GEF + GTP \xrightarrow{q_{+1}} E GAP + GEF + GDP; (10.2a)$$

$$E GTP + GAP \xrightarrow{q_{+2}} E GDP + P_i + GAP$$
; (10.2b)

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

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

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k_{+1}KT + k_{-2}PP_{\mathrm{i}} (1 \ x) \qquad k_{-1}KD + k_{+2}P \ x \tag{10.3}$$

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 .

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

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

in which

$$=\frac{k_{+1}KT}{k_{+2}P}; \quad =\frac{k_{+1}k_{+2}T}{k_{-1}k_{-2}DP_{i}}; \quad =\frac{k_{-2}P_{i}}{k_{+2}}:$$
(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

$$x^{ss} = \frac{+}{(+)1 + \frac{1}{2}} = \frac{-}{+1}$$
 (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 phosphotase in this case, can not change a chemical equilibrium. The amount of enzyme can only change the \kinetics" of a reaction.

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

$$\frac{K k_{+1}k_{+2}T k_{-1}k_{-2}DP_{i}P}{k_{+1}KT + k_{-2}PP_{i} + k_{-1}KD + k_{+2}P} \ln z$$
(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:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{V_1^+ \frac{1}{K_K} V_1^- \frac{x}{K_K^+}}{1 + \frac{x}{K_K^+} + \frac{1}{K_K}} - \frac{V_2^+ \frac{x}{K_P^+} V_2^- \frac{1}{K_P}}{1 + \frac{x}{K_P^+} + \frac{1}{K_P}}; \quad (10.8)$$

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 phosphotase for

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 ${\sf E}$ and ${\sf E}^*.$ Among the eight parameters, the Haldane equation, a generalized detailed balance condition, states that

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

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

The steady state x^* satis es

$$= \frac{x}{1} (1 \quad x) \stackrel{h}{K_{K}} + 1 + \frac{K_{K}}{K_{K}} \quad 1 \quad x \\ 1 \quad x \quad \frac{x}{K_{P}} + x + \frac{K_{P}}{K_{P}} (1 \quad x)$$
(10.10)

in which

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

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 h i

$$= \frac{x}{h} \frac{1+x}{1+x} \frac{1+x}{K_{K}} \frac{1+x}{K_{F}} \frac{1-x}{1-x} \frac{1}{1-x} \frac{$$

In this case, both the kinase and the phosphotase are operating under zeroth order, saturated condition. In particular, if ~' 0 and ~' 7 , then

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

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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 < 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 phosphorylationdephosphorylation 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.

$$\frac{dX_1}{dt} = {}_1(X_N)(1 \quad X_1) \quad {}_1(X_N)X_1; \quad (10.13a)$$

$$\frac{dx_2}{dt} = {}_2x_1(1 \ x_2) \ {}_2x_2; \qquad (10.13b)$$

$$\frac{dx_N}{dt} = {}_N x_{N-1} \ 1 \ x_N \ {}_N x_N$$
 (10.13d)

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To obtain the steady state, we note

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

then,

$$\frac{1}{X_N} = 1 + \frac{N}{N} \quad X_{N-1}^{-1} = 1 + \frac{N}{N} \quad 1 + \frac{N-1}{N-1} \quad X_{N-2}^{-1}$$
$$= 1 + \frac{N-2}{k=0} \quad \frac{N-2}{N-2} \quad + \frac{N-1}{N-1} \quad \frac{2}{2} \quad \frac{1}{2} \quad \frac{1}{2}$$

Therefore, denoting

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

A : B > 0, we have

$$\frac{1}{1}(x_N) = \frac{Ax_N}{1 (1+B)x_N} = 0.$$
 (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 rst passage time.

____| |____ CHAPTER 11

Chemical Oscillations and Stochastic Circulation

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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 . Then the stochastic movement of a single point mass is simply represented by six transition rates in x_i y; z directions:

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

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

$$\frac{\mathrm{d}\rho(\mathbf{n};t)}{\mathrm{d}t} = \frac{\times}{\substack{k=1;2;3\\k=1;2;3}} \rho(\mathbf{n},t) u_k^+(\mathbf{n},k) p(\mathbf{n};t) u_k^-$$
i
$$\rho(\mathbf{n};t) u_k^+(\mathbf{n}) + \rho(\mathbf{n}+k;t) u_k^-(\mathbf{n}+k) i$$
(12.2)

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

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

$$\lim_{\to 0} U_k^{\pm} \mathbf{x} = = R(\mathbf{x}) + T_k^{\pm}(\mathbf{x}) + O^{-2} ; \qquad (12.3)$$

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

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} + H \mathbf{x}; \mathcal{L}_{\mathbf{x}}'(\mathbf{x};t) = 0; \qquad (12.4)$$

with Hamiltonian function

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

and Hamiltonian dynamics:

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = 2R\sinh y_i; \quad \frac{\mathrm{d}y_i}{\mathrm{d}t} = 0: \tag{12.6}$$

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Therefore,

$$\frac{\mathrm{d}^2 x_i}{\mathrm{d}t^2} = 2R \cosh y_i \quad \frac{\mathrm{d}y_i}{\mathrm{d}t} = 0. \tag{12.7}$$

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

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

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The condition above yields

$$\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = \underset{i=1:2:3}{\times} \quad i \quad T_i^+(\mathbf{x}) \quad T_i^-(\mathbf{x})$$
(12.8)

The Markov process is detail balanced if and only if the invariant measure satis es detailed balance. In this case, the su cient and necessary condition is

$$\ln \frac{R_k^+(\mathbf{x})}{R_k^-(\mathbf{x})} = \frac{\mathscr{Q}'^{SS}(\mathbf{x})}{\mathscr{Q}_{X_k}}; \qquad (12.9)$$

in which

$$S^{SS}(\mathbf{x}) = \lim_{t \to 0} \ln \mathbf{x} = c$$
 (12.10)

12.0.1 Quantum heat hypothesis

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

$$\ln \frac{u_k^+(\mathbf{n})}{u_k^-(\mathbf{n})} + \frac{2 u_k^+(\mathbf{n}) - u_k^-(\mathbf{n})}{u_k^+(\mathbf{n}) + u_k^-(\mathbf{n})}$$
(12.11)

quantum heat exchange associated with the microscopic spatial movement. Then Eq. 12.9 implies that r_x' 1, and the HJE becomes

$$\frac{\mathscr{D}'(\mathbf{x};t)}{\mathscr{D}t} = \mathbf{V}(\mathbf{x}) \quad \varGamma_{\mathbf{x}}' + \varGamma_{\mathbf{x}}' \quad \mathbf{D}(\mathbf{x}) \varGamma_{\mathbf{x}}':$$
(12.12)

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

$$D(\mathbf{x}) = \frac{1}{2} \frac{X}{k=1,2,3} \quad T \quad R_k^+(\mathbf{x}) + R_k^-(\mathbf{x}) \quad k$$

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

with Hamiltonian system

$$\frac{d\mathbf{x}}{dt} = \mathbf{V}(\mathbf{x}) + 2\mathbf{D}(\mathbf{x})\mathbf{y}; \quad \frac{d\mathbf{y}}{dt} = -\mathcal{C}_{\mathbf{x}} \quad \mathbf{V}(\mathbf{x}) \quad \mathbf{y} + \mathbf{y}\mathbf{D}(\mathbf{x})\mathbf{y} \quad (12.17)$$

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

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

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

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If we further assume that

$$\frac{\mathrm{d}}{\mathrm{d}t}\ln \frac{R_k^+(\mathbf{x})}{R_k^-(\mathbf{x})} = \frac{\Gamma_{\mathbf{x}}R_k^+(\mathbf{x})}{R_k^+} \frac{\Gamma_{\mathbf{x}}R_k^-(\mathbf{x})}{R_k^-} \frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t}$$
(12.19)

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and

$$\frac{\mathrm{d}^{2}\mathbf{x}(t)}{\mathrm{d}t^{2}} = \frac{\times}{k=1,2,3} \quad k \frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} \quad \Gamma_{\mathbf{x}} R_{k}^{+}(\mathbf{x}) \quad \Gamma_{\mathbf{x}} R_{k}^{-}(\mathbf{x}) \quad (12.20)$$

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 $b(\mathbf{x}) = D(\mathbf{x}) \cap U(\mathbf{x})$:

$$\frac{\mathscr{Q}f(\mathbf{x};t)}{\mathscr{Q}t} = \mathscr{L}f = \Gamma D(\mathbf{x}) \Gamma f(\mathbf{x};t) + \Gamma U(\mathbf{x})f(\mathbf{x};t) ; (12.21)$$
$$\frac{\mathscr{Q}U(\mathbf{x};t)}{\mathscr{Q}t} = \mathscr{L}^* u = \Gamma D(\mathbf{x}) \Gamma U(\mathbf{x};t) \Gamma U(\mathbf{x};t).(12.22)$$

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

$$\begin{aligned}
\mathscr{D} &= e^{\frac{U(\mathbf{x})}{2}} \mathscr{L}^{II} e^{-\frac{U(\mathbf{x})}{2}} (\mathbf{x})^{I} \\
&= e^{\frac{U(\mathbf{x})}{2}} \Gamma D(\mathbf{x})^{I} \Gamma e^{-\frac{U(\mathbf{x})}{2}} (\mathbf{x})^{I} + \Gamma U(\mathbf{x}) e^{-\frac{U(\mathbf{x})}{2}} (\mathbf{x})^{I} \\
&= e^{\frac{U(\mathbf{x})}{2}} \Gamma D(\mathbf{x})^{I} \frac{1}{2} (\mathbf{x}) \Gamma U(\mathbf{x}) e^{-\frac{U(\mathbf{x})}{2}} + e^{-\frac{U(\mathbf{x})}{2}} \Gamma (\mathbf{x}) \\
&= \Gamma D(\mathbf{x}) \Gamma (\mathbf{x})^{I} + \frac{\Gamma D(\mathbf{x}) \Gamma U}{2} \frac{\Gamma U D(\mathbf{x}) \Gamma U}{4} (\mathbf{x}) \\
&= e^{-\frac{U(\mathbf{x})}{2}} \mathscr{L}^{*} e^{\frac{U(\mathbf{x})}{2}} (\mathbf{x})^{I} \vdots \qquad (12.23)
\end{aligned}$$

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

$$E(\mathbf{x}) = \frac{\Gamma U(\mathbf{x}) \quad D(\mathbf{x}) \Gamma U(\mathbf{x})}{4} \quad \frac{\Gamma \quad D(\mathbf{x}) \Gamma U(\mathbf{x})}{2} : \quad (12.24)$$

Note the r U(x) r U(x) appears also in the HJE:

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

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CHAPTER 13

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 di erent 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 pregenetic stage of carcinogenesis for a cell: Its biochemical and gene regulatory networks lead to two very di erent 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 xed fractions p_1 and $p_2 = (1 \quad p_1)$ being in the dormant and growing states. Then the simplest mathematical model one has is

$$\frac{du}{dt} = (p_1d_1 + p_2(b \quad d_2)) u; \quad (b; d_1; d_2; p_1; p_2 \quad 0)$$
(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

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":

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

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

Di erential 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 signi cant stochastic element in the early stage of carcinogenesis, and the cell population should be counted in integers.

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

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

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

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

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

$$U(t + t) = U(t)e^{(-p_1d_1 + p_2(b - d_2))\Delta t}$$
(13.5)

The strategy for p_1 will also be di erent

 $\begin{array}{l} \underset{k}{\overset{\boxtimes}{\geq}} & p_1 > 1 & \text{if } & b < d_2 & d_1; \\ p_1 < 0 & \text{if } & d_2 & d_1 < b < d_2; \\ \end{array} \\ \begin{array}{l} \underset{k}{\overset{\boxtimes}{\geq}} & p_1 < \frac{e^{(b-d_2)\Delta t}}{e^{(b-d_2)\Delta t}} & e^{-d_1\Delta t} & \text{if } & b > d_2: \end{array}$ (13.6)

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

$$e^{p_1r_1+p_2r_2}$$
 $p_1e^{r_1}+p_2e^{r_2}$: (13.7)

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

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13.2 Life-histroy strategies in fluctuating environments

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

$$u_{n+1} = u_{n}$$
(13.8)

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

(a) We rst consider the scenario of has a temporal stationary uctuation: For each step, n follows an independent idential distribution f(x). Then,

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In the limit of $n \neq 1$, we have the term inside the parenthesis

$$\frac{1}{n} \bigvee_{i=0}^{\infty} \ln \left(\frac{Z}{x} \right)^{\infty} (\ln x) f(x) dx \triangleq h \ln i \qquad (13.10)$$

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

$$u_n = u_0 e^{\langle \ln \rangle n}$$
(13.11)

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

$$h \ln i \ln h i$$
: (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 t:

$$u^* = u_0 \exp \left(t \frac{v}{r_1} r \right)$$
 (13.13)

Let us denote the critical r^* :

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

and cumulative probability distribution for random variable r

$$(x) = \int_{-\infty}^{z} f_{r}(z) dz; \quad '(x) = \int_{x}^{z} f_{r}(z) dz: \quad (13.15)$$

90FROM CELLULAR DYNAMICS TO EVOLUTIONARY STABLE STRATEGY AND BACK Therefore,

$$\Pr fN = 1g = \begin{cases} Z_{+\infty} \\ F_r(x)dx = (r^*); \\ Z_{r}^{\uparrow} & Z_{+\infty} \\ F_r(x)dx & f_r(y)dy = f_r(x)(r^*)dx, \\ Z_{r}^{\uparrow} & Z_{r}^{\uparrow-x} \\ F_r(x)dx & f_r(y)dy'(r^*); \end{cases}$$

$$\Pr fN = 3g = f_r(x)dx & f_r(y)dy'(r^*);$$

One can also estimate the distribution of N:

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

where \mathcal{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 \mathbb{N} given in Eq. (13.16).

(b) We now consider the case of $= e^{r\Delta t}$ has a spatical heterogeneity, but constant over time at a xed 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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CHAPTER 14

Entropic Force and Rectified Brownian Motion

Let us consider a di usion process with that is restricted within interval [a; b], with re ecting boundary condition at a and absobing boundary condition at b, and initially $f(x; 0) = (x \ a)$.

Then, we have

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

with

$$\frac{@f(x;t)}{@x} = 0; \quad f(b;t) = 0; \quad f(x;0) = (x \ a): \quad (14.1b)$$

The solution to the partial di erential equation f(x; t) tends to zero in the limit of $t \neq -7$. The \missing probability" is located at x = b. Hence one can write the \total probability" as

$$f_{tot}(x;t) = f(x;t) + 1 \int_{a}^{Z_{b}} f(z;t) dz \quad (x \quad b):$$
(14.2)

It is easy to check that

$$Z_{b}$$

 $f_{tot}(x;t)dx = 1;$ (14.3)

and the apparent \velocity" of the partical movement

$$\frac{d}{dt} \int_{z}^{z} \int_{b}^{b} x f_{tot}(x; t) dx$$

$$= D \int_{z}^{z} \int_{a}^{b} x \frac{e^{2}f(x; t)}{e^{2}x^{2}} dx \quad b \frac{d}{dt} \int_{a}^{z} f(z; t) dz$$

$$= D \int_{a}^{z} \int_{a}^{b} \frac{e^{2}f(x; t)}{e^{2}x^{2}} dx$$

$$= D \int_{a}^{a} \frac{e^{2}f(x; t)}{e^{2}x} dx$$

$$= D \int_{a}^{z} f(z; t) f(z; t) \quad (14.4)$$

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

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

$$\frac{\mathrm{d}f_{tot}(x;t)}{\mathrm{d}t} = \frac{\mathrm{d}f(x;t)}{\mathrm{d}t} + D \quad \frac{@f(x;t)}{@x} \quad a \quad (x \quad a) \quad D \quad \frac{@f(x;t)}{@x} \quad b \quad (x \quad b):$$
(14.5)

Let us consider

$$\frac{\overline{x(t)}}{t} = \frac{aD}{a} \frac{\frac{\mathscr{O}f(x;t)}{\mathscr{O}x}}{\mathscr{O}x} = bD \frac{\mathscr{O}f(x;t)}{\mathscr{O}x} = bD \frac{\mathscr{O}$$

Now consider di usion with a drift V:

$$\frac{@f(x;t)}{@t} = D \frac{@^2 f(x;t)}{@x^2} \quad \frac{@}{@x} \quad V(x) f(x;t)$$
(14.7)

Then,

$$\frac{\overline{x(t)}}{t} = aD \frac{@f(x;t)}{@x} a bD \frac{@f(x;t)}{@x} b + \frac{Z}{a} x \frac{df(x;t)}{dt} dx$$

$$= D f(a;t) f(b;t) \frac{Z}{a} x \frac{@}{@x} V(x)f(x;t) dx$$

$$= D + aV(a) f(a;t) D + bV(b) f(b;t) + \frac{Z}{a} V(x)f(x;t) dx$$

$$\frac{aV(a)f(a;t) bV(b)f(b;t) + \frac{Z}{a} V(x)f(x;t) dx}{Z b} = \frac{Z}{b} f(x;t) dx$$

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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 coe $\$ cients $\$ \rightarrow and kinetic rate laws

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \sum_{\lambda=1}^{M} R^{+}_{\lambda}(\mathbf{x}) \quad R^{-}_{\lambda}(\mathbf{x}) \quad \boldsymbol{\gamma}$$
(A1)

we have a generalized Gibbs potential ' $\left(\mathbf{x}\right)$ satisfying

$$\frac{\mathrm{d}}{\mathrm{d}t}, \mathbf{x}(t) = \frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} \quad r_{\mathbf{x}}, \mathbf{x}(t)$$

$$= \frac{\mathcal{M}}{\mathcal{R}}, R^{+}(\mathbf{x}) \quad R^{-}(\mathbf{x}) \quad r_{\mathbf{x}}, \mathbf{x}(t)$$

$$= \frac{\mathcal{M}}{\mathcal{R}}, R^{+}(\mathbf{x}) \quad R^{-}(\mathbf{x}) \quad \ln \quad \frac{R^{+}(\mathbf{x})}{R^{-}(\mathbf{x})} e^{-\nabla \mathbf{x}, \mathbf{x}(t)} \quad \mathbf{x}(t); \quad (A2)$$

in which

$$\mathbf{x}(t) = \bigvee_{i=1}^{\mathcal{M}} R_{\cdot}^{+}(\mathbf{x}) \quad R_{\cdot}^{-}(\mathbf{x}) \quad \ln \frac{R_{\cdot}^{+}(\mathbf{x})}{R_{\cdot}^{-}(\mathbf{x})} \qquad 0:$$
(A3)

We now study the rst term in (A2):

$$\overset{\overset{\overset{}}{}}{\underset{i=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{}}{\underset{i=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{'=1}{\overset{$$

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Therefore, if we have a \ eld equation"

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} = \frac{\mathcal{M}}{\sum_{i=1}^{n}} R^+(\mathbf{x}) \quad 1 \quad e^{-\nabla \mathbf{x}'(\mathbf{x};t)} + R^-(\mathbf{x}) \quad 1 \quad e^{--\nabla \mathbf{x}'(\mathbf{x};t)} \stackrel{O}{:}$$
(A5)

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

$$\frac{\mathrm{d}}{\mathrm{d}t} \overset{ss}{=} \mathbf{x}(t) = E_{in} \mathbf{x} \qquad \mathbf{x} ; \qquad (A6)$$

in which both $E_{in}[\mathbf{x}]$ and $[\mathbf{x}]$ 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 \mathbf{x} 1. In this case, Eq. A5 becomes

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} = \frac{\mathcal{M}}{\mathcal{R}^{-}(\mathbf{x})} R^{+}(\mathbf{x}) + \mathcal{L}(\mathbf{x};t) ; \qquad (A7)$$

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

Now for systems with

$$\frac{\mathrm{d}}{\mathrm{d}t} \int \frac{\mathrm{d}s}{\mathrm{d}t} \mathbf{x}(t) = 0; \qquad (A8)$$

we call it conservative ecology [exampe? LV system?] Then, there is an \energy conservation"; but more importantly, a ???
A FIELD EQUATION FORMALISM OF ECOLOGICAL POPULATION DYNAMICS 103 Let $k_1k_2k_3 = A$ and $k_{-1}k_{-2}k_{-3} = B$ both A and B are giving. This xes

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

$$\frac{A B}{k_3k_{-1} + k_{-2}k_{-1} + k_2k_3 + k_1k_{-2} + k_{-3}k_{-2} + k_3k_1 + k_2k_{-3} + k_{-1}k_{-3} + k_1k_2} \ln \frac{A}{B}$$
(A9)

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

$$= k_3k_{-1} + k_{-2}k_{-1} + k_2k_3 + k_1k_{-2} + k_{-3}k_{-2} + k_3k_1 + k_2k_{-3} + k_{-1}k_{-3} + k_1k_2$$

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In our research, we have obtained the following equation:

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} = \frac{\mathsf{X}}{\mathsf{R}} R^+(\mathbf{x}) \mathbf{1} \quad e^{-\nabla_{\mathbf{x}}'(\mathbf{x};t)} + R^-(\mathbf{x}) \mathbf{1} \quad e^{-\nabla_{\mathbf{x}}'(\mathbf{x};t)};$$
(A10)

in which $\mathbf{x} \geq \mathbb{R}^N$, in the rst quadrant. $R^{\pm}(\mathbf{x})$, 1 M, are 2M nonnegative scalar functions, and M are M integer-valued N-dimensional vectors.

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

$$\frac{\mathscr{Q}'(\mathbf{x};t)}{\mathscr{Q}t} = \Gamma'(\mathbf{x}) \quad \mathbf{D}(\mathbf{x})\Gamma'(\mathbf{x}) + \mathbf{V}(\mathbf{x}) \quad (A11)$$

in which $\mathbf{V}(\mathbf{x}) : \mathbb{R}^N \mathbb{P} \mathbb{R}^N$ is a vector eld, and $\mathbf{D}(\mathbf{x})$ is a positive de nite 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?