Chapter 6
Stochastic Population Kinetics and Its Underlying Mathematicothermodynamics

Hong Qian

Abstract [illegible]

6.1 Introduction

[illegible] (1920–2013), [illegible] [13] [illegible] J. W. Gibbs [illegible]

H. Qian (✉)
[illegible], WA, USA
e-mail: [illegible]

[illegible] AG 2019

A. [illegible] (eds.), *The Dynamics of Biological Systems*, [illegible] 4, [illegible]g/10.1007/978-3-030-22583-4_6

[illegible] Each [illegible], e.g., a [illegible]. The [illegible]. While each [illegible], e.g., [illegible] [4] [illegible] (birth), degradation (death), [illegible] (charge [illegible]), and [illegible]. Such a [illegible] V, [illegible] Ma[illegible] [illegible].

[illegible] [17]. [illegible]. In [illegible]. We [illegible].

After [illegible] Sec. 6.9 [illegible]. The [illegible]. To [illegible] ***mathematicothermodynamics*** [illegible]. We [illegible]: The first [illegible], and the second [illegible].

Finally, [illegible] $\to \infty$ and [illegible] $V \to \infty$ [12, 26].

6.2 Probability and Stochastic Processes: A New Language for Population Dynamics

There are [illegible]: (a) [illegible] and (b) describing [illegible] (a[illegible] engineered, [illegible], ec[illegible], chemistry, ecology, physiology, ...) based on testing, established formal and empirical relations. For practical purposes, we shall call the former ***data-driven modeling*** and the latter ***mechanistically derived modeling***. Note, according to Karl Popper (1902–1994) and his philosophy of science, the only legitimate scientific activities consist of [illegible] hypotheses: [illegible] (e.g., [illegible] hypotheses) and [illegible] (e.g., modeling); and (b) models [illegible] formulated logically, mathematically, deductively.

Let us [illegible] the three [illegible] read [illegible] of the above characteristics. In Chap. 1 Hutchinson and [illegible] introduced the growth rate through a [illegible] process: if a population grows from [illegible] 100 days [illegible] 50 days, and half [illegible] 25 days. In fact, the growth rate

$$= \lim_{\Delta t \to 0} \frac{P(t+\Delta t) - P(t)}{\Delta t}.$$

[illegible] (first [illegible]) one of the [illegible] concepts of Newtonian calculus! But [illegible] a population grow? A half of a [illegible]? Clearly, [illegible] when the Δ [illegible]: *population change* can only be integer-[illegible].

Second, [illegible] a population grow [illegible] in the first 100 days and [illegible] the next 100 days? [illegible] average.

Indeed, *discreteness* and *probability* are two fundamental [illegible] population dynamics. Both have been [illegible] in the differential equation-based description of population dynamics. We [illegible] population [illegible] below. Most of the [illegible] references [1, 19, 20, 22, 23, 28, 31].

6.2.1 Brief Review of Elementary Probabilities

A ***random variable*** [illegible] a [illegible] that has a probability density function (pdf) $f_X(x)$:

$$\int_{-\infty}^{\infty} f_X(x)\,dx = 1, \qquad f_X(x) \ge 0. \tag{6.1}$$

The meaning of the $f_X(x)$ is: for infinitesimally small dx, the probability of observing $X \in (x, x+dx]$ is $f_X(x)dx$:

$$\Pr\{x < X \le x + dx\} = f_X(x)\,dx. \tag{6.2}$$

Then, the … a … e … bab… d… … of … defined a…

$$F(\;) = \mathrm{P}\{\;\leq\;\} = \int_{-\infty} (\;)\mathrm{d}\;, \text{ and } (\;) = \frac{\mathrm{d}F(\;)}{\mathrm{d}}. \tag{6.3}$$

The … ea… (… e … ec ed … a… e) and … a … a…ce of the … and… … a … ab e … he… a e

$$\langle\;\rangle = \mathbb{E}[\;] = \int_{-\infty}^{\infty} (\;)\mathrm{d}\;, \tag{6.4}$$

$$\mathrm{Va}[\;] = \mathbb{E}[(\;-\mu\;)^2] = \int_{-\infty}^{\infty} (\;-\mu\;)^2 \;(\;)\mathrm{d}\;, \tag{6.5}$$

… e … a … de… ed $\mathbb{E}[\;]$ b μ . … a… e a … e… of and… … a … ab e… a … g ea … a… e… a e e … e… a … and … a , a … ca ed Ga … . The f… e … a… he … a… da d f…

$$(\;) = \lambda \;^{-\lambda}\;, \quad \geq 0,\; \lambda > 0, \tag{6.6}$$

… ea… and … a … a…ce be…g λ^{-1} and λ^{-2}; the a e … a… a … a… da d f…

$$(\;) = \frac{1}{\sqrt{2\pi}\sigma}\;^{-(\;-\mu\;)^2/2\sigma^2}, \tag{6.7}$$

… ea… μ and … a … a…ce σ^2.

Ga … a… … a d… … … de … d… … ed; … c… d…g … a … e… [11]. I … de … d a… a c… e… e…ce of the *central limit theorem*. I … a … a … ca … e e g…g f… a a ge c… ec … of … de… ca , … de e…de… a … I… he f… …g … ec … e … a … a f… d … a … ca … ce … e … g … a … he e … a … ch e… … , b … e… a … f … e … a… … a … ca … : e … e… a d … b … ed … e be… ee… a e e e… … . I… … cha … c … de …g of … a … d … a … c… … e … a f… … he a…d… … be of …d… … a… a a a … a … e; a he … he a…d… … e of the … e e… e… ha cha…ge… he … be of …d… … a … b … e.

The be… … … d…c e e, … ege - a… ed a…d… … a … ab e… a e Be … … b… a , P… … , a…d ge… e … c [30].

6.2.2 *Radioactive Decay and Exponential Time*

Le … e … he … e… d…ffe e… … a e… a …

$$\frac{\mathrm{d}}{\mathrm{d}} = -\lambda\;, \tag{6.8}$$

where $\lambda > 0$. Th[illegible] has been introduced as a mathematical model for the remaining fraction of a radioactive material at time t

$$\frac{N(t)}{N(0)} = e^{-\lambda t}. \tag{6.9}$$

If all the atom nuclei are *identical and independent*, then

$$P\left\{\text{a nucleus remaining radioactive at time } t\right\} = e^{-\lambda t}. \tag{6.10}$$

However, if T is the random time at which the event of radioactive decay occurs, then

$$P\left\{\text{a nucleus remaining radioactive at time } t\right\} = P\left\{T \geq t\right\}. \tag{6.11}$$

T is a non-negative real-valued random variable with cumulative probability distribution $F_T(t) = P\{T \leq t\} = 1 - e^{-\lambda t}$ and probability density function $f_T(t) = \mathrm{d}F(t)/\mathrm{d}t = \lambda e^{-\lambda t}$.

What [illegible]? Why [illegible]? A good understanding of these [illegible] would provide the reader a deeper understanding of the mathematical foundation of power law dynamics and [illegible] random behavior of a large population of individuals [15].

6.2.2.1 Rare Event

Let T be the random time at which a certain event occurs. If the occurrence of such a certain event is independent in time intervals $[t_1, t_2]$ and $[t_2, t_3]$, and if its occurrence is uniform in time (e.g., [illegible]), then

$$\text{Prob. of no event occurring in } [0, t + \Delta t] = \tag{6.12}$$

$$\text{Prob. of no event occurring in } [0, t] \times \text{Prob. of no event occurring in } [t, t + \Delta t].$$

That is

$$P\left\{T > t + \Delta t\right\} = P\left\{T > t\right\} \times \text{Prob. of no event occurring in } [t, t + \Delta t].$$

Now if the probability of one such event occurring in the time interval $[t, t + \Delta t]$ is proportional to Δt, and the probability of more than one event is $o(\Delta t)$, then

$$P\left\{T > t + \Delta t\right\} = P\left\{T > t\right\} \times \left(1 - \lambda \Delta t + o(\Delta t)\right). \tag{6.13}$$

The ,

$$\frac{\mathrm{d}}{\mathrm{d}}\mathrm{P}\left\{T > \ \right\} = -\lambda \mathrm{P}\left\{T > \ \right\}, \implies F_T(\ ) = \ ^{-\lambda}. \tag{6.14}$$

E a e: The a g e f he fi e c g a e he g a eg a da .

6.2.2.2 Memoryless

O e f he a , fac defi g, e e f e e a d ed a g e

$$\frac{\mathrm{P}\left\{T \geq \ + \tau\right\}}{\mathrm{P}\left\{T \geq \ \right\}} = \frac{\ ^{-\lambda(\ +\tau)}}{\ ^{-\lambda}} = \ ^{-\lambda\tau}. \tag{6.15}$$

E a e: Y a d a b he d g e e e b e he ea e f a e e a d ed e e . E e h gh b he a c g e a he e h a e ha , h e g a c be e ac he a e a !

M e e e g , he e d a a a , he fa e he e e e c . I a he a ca e f a $T \sim \lambda \ ^{-\lambda}$ a d he a e de e de d ed, he $T^* = \ (T_1, T_2, \cdots, T\ )$ a ha a e e a d

$$\begin{aligned} \mathrm{P}\left\{T^* > \ \right\} &= \mathrm{P}\left\{T_1 > \ , \cdots, T\ > \ \right\} \\ &= \mathrm{P}\left\{T_1 > \ \right\} \times \mathrm{P}\left\{T_2 > \ \right\} \times \cdots \times \mathrm{P}\left\{T\ > \ \right\} = \ ^{-\mu}\ , \end{aligned} \tag{6.16}$$

he $\mu = \lambda_1 + \lambda_2 + \cdots + \lambda\ $. Th $\ _{T^*}(\ ) = \mu \ ^{-\mu}$.

6.2.2.3 Minimal Time of a Set of Non-Exponential i.i.d. Random Times

N c de a e f a d e $\{T\ \}$. The a e *identical, independently distributed* (d.) a d e df $\ _T(\ )$ a d a e bab d $F_T(\ )$. The $T^* = \ (T_1, T_2, \cdots, T\ )$ ha d

$$\mathrm{P}\left\{T^* > \ \right\} = \left(1 - F_T(\ )\right)\ . \tag{6.17}$$

N , c g ca ed $\hat{T}^* = \ T^*$ a d c de g be e a ge, d

$$\mathrm{P}\left\{\hat{T}^* > \ \right\} = \left(1 - F_T\left(-\right)\right) \simeq \left(-\frac{F_T'(0)}{\ } + O(\ ^{-2})\right) \to \ ^{-F_T'(0)}\ . \tag{6.18}$$

The ef[illegible] $F_T'(0) =$ [illegible] $_T(0)$ [illegible]
We [illegible] $_T(0) > 0$: [illegible]

6.2.3 Known Mechanisms That Yield an Exponential Distribution

I[illegible] (1) [illegible] a[illegible]d (2) [illegible]. F[illegible] Sec. 6.2.2.3, [illegible] T, a[illegible] $_T(0) \neq 0$, [illegible] T [illegible] (6.8) [illegible]

6.2.3.1 Khinchin's Theorem

Le[illegible] ( ). F[illegible] each [illegible] 0, $T_1, T_2, \cdots$, T, $\cdots$ [illegible] ed a *renewal process*, [illegible] $T = \sum_{\ell=1}$ $^{(\ell)}$ [illegible] $^{(\ell)}$ [illegible] ℓ a[illegible] ( ). N[illegible] a *superposition* [illegible] [3], [illegible] F[illegible]g. 6.1.

F[illegible] ( ), [illegible] e.g., [illegible] N, [illegible]

$$\mathrm{P}\left\{N \geq \ \right\} = \mathrm{P}\left\{T \leq \ \right\} = F_T(\ ) = \int_0 \ _T(\ )d \ . \qquad (6.19)$$

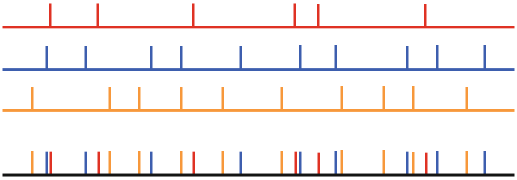

Fig. 6.1 If [illegible] 3 d[illegible] I[illegible] W[illegible]

The ef e,

$$\mathrm{P}\left\{N = \right\} = F_T\,(\;) - F_{T\;+1}(\;). \tag{6.20}$$

N f e a d c a e , a d e T^* be he a g e f he e e a , T^* a e d a e e a he . I d b d ffe e f ( ). I fac , e ha

$$\begin{aligned}\mathrm{P}\,\{T^* \leq \;\} &= \sum_{\ell=0}^{\infty} \mathrm{P}\,\left\{N = \ell\right\} \mathrm{P}\,\left\{T_{\ell+1} \leq \; + \;\right\} \\ &= \sum_{\ell=0}^{\infty} \Big(F_{T_\ell}(\;) - F_{T_{\ell+1}}(\;)\Big) F_{T_{\ell+1}}(\; + \;). \end{aligned} \tag{6.21}$$

The ef e, he bab de fi c f he a a T^*

$$_{T^*}(\;) = \frac{\mathrm{d}}{\mathrm{d}} \mathrm{P}\,\{T^* \leq \;\}. \tag{6.22}$$

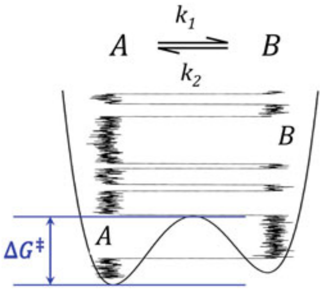

Fig. 6.2 The a e a ca de c of a che ca eac of a g e eca e. I a e e ge a ca a of a a ge be of d c e e, chas c eac $k_1 \propto e^{-\Delta G^{\ddagger}/k_BT}$

6.2.4 Population Growth

We [illegible] $\frac{d}{d} = -\lambda$ [illegible] λ: [illegible] deca[illegible]. A[illegible] $\frac{d}{d} =$ [illegible]

The [illegible] ! The[illegible] 1.2), [illegible] ( ). The[illegible], *on average the growth is 1 additional person in* $(\ \mathbb{E}[\ \ ])^{-1}$ *time*:

$$\frac{d}{d}\mathbb{E}[\ \ (\ )] = \ \mathbb{E}[\ \ (\ )]. \tag{6.25}$$

Dea[illegible] . M[illegible] J. D. M[illegible] [17] [illegible]:

$$\frac{d}{d} = \text{b[illegible]} - \text{dea[illegible]} + \text{[illegible]g a[illegible]}, \tag{6.26}$$

[illegible] ( ) [illegible] de[illegible] .

6.2.5 Discrete State Continuous Time Markov (Q) Processes

D[illegible] e Ma[illegible] Q- [illegible] A[illegible] Je[illegible] 1954 b[illegible] *A Distribution Model, Applicable to Economics* a[illegible]d [illegible] 1971 b[illegible] *Markov Chains*. I[illegible] ( ), [illegible]

$$(\ + d\ ) - \ (\ ) = \left(\sum_{\ell=1}^{N} \ _{\ell}(\ )\ _{\ell}\right) d\ , \tag{6.27}$$

[illegible] ℓ [illegible]. E[illegible]. (6.27) [illegible] a *master equation*. I[illegible] $\mathbf{P}(\ ) = \ ^{\mathbf{Q}}$ [illegible] $\mathbf{Q}$ [illegible] ≥ 0 a[illegible]d

$$= -\sum_{\neq} \ . \tag{6.28}$$

The ef e, $\mathbf{Q}$ ha each a d e e . I f e efe ed a fi e a a a e a . I ea ha h ca e, he

$$\sum^{N}_{=1} \quad ( )$$

de e de f e . The a bab c e ed e e. N e e e a a d ffe e ce be ee E . (6.26) a d (6.27): The f e a e a f a *density* ( ) h e he a e a e a f he bab f a *size* $( ) \equiv \mathrm{P}\{N( ) = \}$; he gh -ha d de f f e a a ea fi c f h e he a e ece a ea . The d e f he a e ODE e , h e e , ch h ghe ha he f e .

6.2.5.1 Kolmogorov Forward and Backward Equations

I a f , E . (6.27) ca be e e ed a $\frac{\mathrm{d}}{\mathrm{d}}\ = \mathbf{Q}$ he e $= (_1, \cdots , _N)$ a ec . Th e a ca ed *Kolmogorov forward equation*. N e c ea g he f a d e a ab he bab d b (a ec), b ab he a bab a (fi da e a) $\mathbf{P}( )$ h a a e $\mathbf{P}(0) = \mathbf{I}$. M e e e g ,

$$\frac{\mathrm{d}}{\mathrm{d}}\mathbf{P} = \mathbf{P}\mathbf{Q} = \left(\; ^{\mathbf{Q}} \right) \mathbf{Q} = \mathbf{Q}\mathbf{P}. \tag{6.29}$$

Th a d ffe e d ffe e a e a :

$$\frac{\mathrm{d}}{\mathrm{d}} = \sum_{\ell=1}^{N} \ \ell \ \ell, \tag{6.30}$$

h ch ca ed *Kolmogorov backward equation*. If $\{\pi \}$ a a a bab d b , e.g., he ,

$$\sum_{\ell=1}^{N} \pi_\ell \ \ell = 0, \qquad = 1, 2, \cdots , N,$$

he he he bac a d e a , ( ) ha he a e f

$$\sum^{N}_{=1} \quad ( )\pi$$

be g de e de f e , e.g., a c e ed a .

The K f a d a d bac a d e a a ha e a he e a e . Le ( ) a d ( ) be a f a d e a d ffe e a d (0) a d (0). The

$$\frac{d}{d}\sum_{=1}^{N} ( ) \left(\frac{( )}{( )}\right) \le 0. \qquad (6.31)$$

O e ec a ca e f h ch de , he ch ce f $( ) = \pi$, $\pi > 0\,\forall$.

S a e a K g bac a d e a , ( ) a d ( ) d ffe e a c d (0) a d (0), e ec e , ha e

$$\frac{d}{d}\sum_{=1}^{N} \left(\pi\ ( )\right) \left(\frac{( )}{( )}\right) \le 0. \qquad (6.32)$$

O e ec a ca e f he ch g $( ) \equiv 1$. The a E . (6.32) ca ed a *H*-fi c ; he a E . (6.31) ca ed e a e e , K bac Le b e d e ge ce f a he , f ee e e g h ca che . The e e ha e a dee ca f he ec d a f he d a c .

6.3 Theory of Chemical and Biochemical Reaction Systems

A ge e a e e e a f c e che ca eac e

$$\nu_1 \ _1 + \nu_2 \ _2 + \cdots \nu \longrightarrow \kappa_1 \ _1 + \kappa_2 \ _2 + \cdots \kappa \ . \qquad (6.33)$$

$1 \le \ \le$. The e a e ec e a d eac $(\nu\ , -\kappa\ )$ a e ca ed *stoichiometric coefficients*, he e a e a ec he eac . I a b ade e e, a eac a e f e e .

6.3.1 Differential Equation and Nonlinear Dynamics

Beca e f he c e a f a e ,

$$\frac{d}{d} = \sum_{=1} (\kappa\ - \nu\ )\hat{\varphi}\ (\mathbf{x}) \qquad (6.34)$$

where x_j is the concentration of chemical species j, $1 \leq j \leq N$, and

$$\hat{\varphi}_\ell(\mathbf{x}) = x_1^{\nu_{\ell 1}} x_2^{\nu_{\ell 2}} \cdots x_N^{\nu_{\ell N}} \tag{6.35}$$

is called the instantaneous flux of the ℓth reaction. $\mathbf{x} = (x_1, x_2, \cdots, x_N)$. Eq. (6.34) is called a rate equation and Eq. (6.35) is called *the law of mass action* (LMA).

6.3.2 Delbrück-Gillespie Process (DGP)

Let us now consider probabilistically the discrete, individual reactive events of the reversible reactions in Eq. (6.33), one at a time. The DGP assumes that the ℓth reaction occurs following an exponentially distributed waiting time, with rate parameter

$$\varphi_\ell(\mathbf{X}) = k_\ell V \prod_{j=1}^{N} \left(\frac{n_j!}{(n_j - \nu_{\ell j})! V^{\nu_{\ell j}}} \right), \tag{6.36}$$

where the n_j is the number of the jth chemical species being X_j. Note $\varphi_\ell(\mathbf{X})$ has the dimension of $[\text{time}]^{-1}$.

$$= \int^{\infty} \lambda \quad {}^{-\lambda} \quad \prod_{\ell=1,\ell\neq} \left(\int^{\infty} \lambda_\ell \quad {}^{-\lambda_\ell \ell} \mathrm{d} \quad {}_\ell \right)$$

$$= \left(\frac{\lambda}{\lambda_1 + \cdots + \lambda} \right) \quad {}^{-(\lambda_1+\cdots+\lambda\ )} . \tag{6.39}$$

Th ea he f g a fac : he a e a g $\{T\ \}$ g e a d a ab e : $T^* \equiv$ $\{T\ \}$ a d $^* \equiv$ a g $\{T\ \}$; he a e T^* a d he de * a e a ca de e de .

6.3.3 Integral Representations with Random Time Change

6.3.3.1 Poisson Process

A a da d P ce ( ) a ege -a ed, c e Ma ce h d b

$$\mathrm{P}\left\{ \ (\ ) = \ \right\} = \frac{}{!} \ ^{-} . \tag{6.40}$$

A P ce ha b h a *point process* e e a , $T_1, T_2, \cdots, T$, a d a *counting process* e e a ( ). The f e a e ea -a ed, d c e e- e Ma ce h de e de c e e a d $T_{+1} - T$ e e a d b ed h a e 1.

6.3.3.2 Random Time Changed Poisson Representation

I e f P ce e he cha c a ec f a DGP e e g he ege be f he eo e , a e ,

$$(\ ) = \ (0) + \sum_{=1} \left(\kappa \ - \nu \ \right) \quad \left(\int_0 \varphi \left(\mathbf{X}(\ ) \right) \mathrm{d} \ \right) \tag{6.41}$$

h ch φ ($\mathbf{X}$) g e (6.36). We ha e ab ed he a , a b h he b f a e f eo e, a E . (6.33), a d be he eac e . We ee ha he f $\mathbf{X} \to \infty$ a d $V \to \infty$,

$$\varphi \ (\mathbf{X}) \to \quad V \prod_{\ell=1} \left(\frac{\ell}{V} \right)^{\nu\ \ell} = \quad V \prod_{\ell=1} \ {}_\ell^{\nu\ \ell} = V \hat{\varphi} \ (\mathbf{x}). \tag{6.42}$$

φ ($\mathbf{X}$) a ca ed he *propensity* f he h eac .

6.3.4 Birth-and-Death Process with State-Dependent Transition Rates

6.3.4.1 One-Dimensional System

$$(6.43)$$

$$(6.44)$$

$$(6.45)$$

$$(6.46)$$

Consider a population with n subpopulations $\mathbf{x} = (x_1, x_2, \cdots, x_n)$, and $x_i \geq 0$. In the absence of migration, if we denote the per capita growth rate $r_i = b_i - d_i$, then

$$\frac{dx_i}{dt} = r_i x_i. \tag{6.48}$$

For simplicity, we assume that both the per capita birth rate b_i and death rate d_i are constants. Then the per capita growth rate for the entire population, which is also the mean per capita growth rate,

$$\bar{r} = \frac{\sum_{i=1}^{n} \frac{dx_i}{dt}}{\sum_{i=1}^{n} x_i} = \frac{\sum_{i=1}^{n} r_i x_i}{\sum_{i=1}^{n} x_i}, \quad x_i \geq 0. \tag{6.49}$$

Then,

$$\frac{d\bar{r}(\mathbf{x})}{dt} = \left[\frac{\sum_{i=1}^{n} r_i^2 x_i}{\sum_{i=1}^{n} x_i} - \left(\frac{\sum_{i=1}^{n} r_i x_i}{\sum_{i=1}^{n} x_i} \right)^2 \right]. \tag{6.50}$$

We note that the term inside $[\cdots]$ on the right-hand side is never negative:

$$\frac{\sum_{i=1}^{n} r_i^2 x_i}{\sum_{i=1}^{n} x_i} - \left(\frac{\sum_{i=1}^{n} r_i x_i}{\sum_{i=1}^{n} x_i} \right)^2 = \frac{\sum_{i=1}^{n} x_i \left(r_i - \bar{r} \right)^2}{\sum_{i=1}^{n} x_i} \geq 0. \tag{6.51}$$

In fact, it is exactly the variance of r_i among the different subpopulations. Therefore, $\bar{r}$ always moves toward the maximum among r_i. This is the mathematical essence of the ideas of both Adam Smith, on economics, and Charles Darwin, on natural selection. In fact, the term $[\cdots]$ in Eq. (6.50) has been identified by R. A. Fisher, the British statistician and evolutionary biologist, as the growth of fitness due to natural selection [6]. Here is a piece from Smith's *magnum opus* An Inquiry into the Nature and Causes of the Wealth of Nations (1776):

> As every individual, therefore, endeavours as much as he can both to employ his capital in the support of domestic industry, and so to direct that industry that its produce may be of the greatest value; every individual necessarily labours to render the annual revenue of the society as great as he can. He generally, indeed, neither intends to promote the public interest, nor knows how much he is promoting it. By preferring the support of domestic to that of foreign industry, he intends only his own security; and by directing that industry in such a manner as its produce may be of the greatest value, he intends only his own gain, and he is in this, as in many other cases, led by an invisible hand to promote an end which was no part of his intention. Nor is it always the worse for the society that it was no part of it. By pursuing his own interest he frequently promotes that of the society more effectually than when he really intends to promote it. I have never known much good done by those who affected to trade for the public good. It is an affectation, indeed, not very common among merchants, and very few words need be employed in dissuading them from it.

6.5 Ecological Dynamics and Nonlinear Chemical Reactions: Two Examples

6.5.1 Predator and Prey System

Le ( ) be he a de f a eda a e a d ( ) be he a de f a e a he a e e. The he e eda - e d a c [17]

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}} = \alpha \quad - \beta \quad , \\ \frac{\mathrm{d}}{\mathrm{d}} = -\gamma \quad + \delta \quad . \end{cases} \tag{6.52}$$

The de a ed a a f he ea d a c ca be f d a e b a he a ca b g d ffe e a e a [17].

Le c de he f g che ca eac e :

$$A + \quad \xrightarrow{1} 2 \quad , \quad + \quad \xrightarrow{2} 2 \quad , \quad \xrightarrow{3} B. \tag{6.53}$$

The acc d g he LMA, he c ce a f a d h fi ed c ce a- f A a d B be g a d :

$$\frac{\mathrm{d}}{\mathrm{d}} = {}_1 \quad - {}_2 \quad , \quad \frac{\mathrm{d}}{\mathrm{d}} = - {}_3 \quad + {}_2 \quad . \tag{6.54}$$

The ef e ee ha d a c f a ec g ca eda - e e a - ab e a ha f a che ca eac h a ca a [16]: he fi eac (6.53) e e a e g e g a a ca a f he eac $A \to$. A ec e ha a ea he b h de f a che ca eac ca ed a *catalyst*.

6.5.2 A Competition Model

Le c de a he de d ed ec g ca d a c h c e [17]:

$$\begin{cases} \frac{\mathrm{d}N_1}{\mathrm{d}} = {}_1N_1 - {}_1N_1^2 - {}_{21}N_1N_2, \\ \frac{\mathrm{d}N_2}{\mathrm{d}} = {}_2N_2 - {}_2N_2^2 - {}_{12}N_2N_1. \end{cases} \tag{6.55}$$

Ca e de g a e f che ca eac ha e d a de ca e f d ffe e a e a ? W f ge e a , e a e ha $_{12} > _{21}$.

$$A + \xrightarrow{1} 2 , \quad + \xrightarrow{2} B, \quad A + \xrightarrow{3} 2 , \qquad (6.56)$$
$$+ \xrightarrow{4} B, \quad + \xrightarrow{5} B, \quad + \xrightarrow{6} + B,$$

ch, acc d g he LMA,

$$\begin{cases} \frac{d}{d} = (_1) - _2 {}^2 - _5 , \\ \frac{d}{d} = (_3) - _4 {}^2 - (_5 + _6) . \end{cases} \qquad (6.57)$$

If e de f , h N_1, N_2, a d

$$(_1) \leftrightarrow _1, \quad _2 \leftrightarrow _1, \quad _5 \leftrightarrow _{21}, \quad (_3) \leftrightarrow _2, \quad _4 \leftrightarrow _2, \quad (_5 + _6) \leftrightarrow _{12},$$

he (6.57) he a e a (6.55). N e ha he a eac , $+ \rightarrow + B$, d ced e e e $_{12} > _{21}$.

A c e ec f he e f che ca eac (6.56) d ca e ha he e a eac $2A \rightarrow B$. S ce each a d e e eac e e b e, he e ca be che ca e b . Ra he , he e e e a eache a *nonequilibrium steady state* h ch he e a c e a che ca fl c e g $2A$ B.

6.5.3 *Logistic Model and Keizer's Paradox*

We d g e e e e -de h. Le c de a ch e che ca eac e ,

$$A + \xrightarrow{1} 2 , \quad + \xrightarrow{2} B. \qquad (6.58)$$

I ea ee ha he ODE acc d g he LMA,

$$\frac{d}{d} = \left(1 - \frac{}{K}\right) , \quad = _1 , \quad K = \frac{}{_2}, \qquad (6.59)$$

he ce eb a ed *logistic equation* a d a c I he ec g ca c e , a he e ca a g h a e he ab e ce f a- ec e c e ; a d K a *carrying capacity*.

h ch μ de e ed b he a c c e f a ea e, e.g., e a e e g . $_B$ B a c a , a d T e e a e Ke . The he G bb f ee e e g f he h f (6.62) he f he che ca e a

$$G = \sum_{=1} \nu \big(\mu + {}_B T \big). \tag{6.65}$$

Whe he eac eache e b , he ha he a che ca e a be g e a b h de:

$$\sum_{=1} (\nu - \kappa)\big(\mu + {}_B T \big) = 0. \tag{6.66}$$

Th e

$$\prod_{=1} ( )^{\nu - \kappa} = {}^{-\frac{(\nu - \kappa)\mu}{{}_B T}} = \frac{-}{+}, \tag{6.67}$$

$$\Delta G = \Big(\sum_{=1} \kappa\mu\Big) - \Big(\sum_{=1} \nu\mu\Big) = {}_B T \Big(\frac{-}{+}\Big). \tag{6.68}$$

Th a e e - f a ha ca be f d e e c ege che e b .

6.6.2 Mass-Action Kinetics

F g E (6.34) a d (6.35) e ha e

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}} &= \sum_{=1} (\kappa - \nu)\big(\hat\varphi^{+} - \hat\varphi^{-}\big) \\
&= \sum_{=1} (\kappa - \nu)\hat\varphi^{-} \Big\{ \mathrm{e} \Big[\sum_{\ell=1} (\kappa_{\ell} - \nu_{\ell}) \Big(\frac{\ell}{\ell}\Big)\Big] - 1 \Big\} \\
&= \sum_{=1} (\kappa - \nu)\hat\varphi^{+} \Big\{ 1 - \mathrm{e} \Big[\sum_{\ell=1} (\nu - \kappa) \Big(\frac{\ell}{\ell}\Big)\Big]\Big\}.
\end{aligned} \tag{6.69}$$

E a o (6.69) h wh he $\ell =$ $_\ell$, he e [· · ·] = 0 a d he e {· · · } = 0 a e , f o e e . The ef o e, he e e a o (6.69) c o e h he che ca e b acc o d g o he od a c e.g., E . (6.66) a d (6.67). I e e g , ece o ha h a b o h ac o c o c e c a (6.69) a d e b he od a c Sec . 6.6.1 a e c o e e ce f a ocha c e c de c o f a eac o e [10].

6.6.3 Stochastic Chemical Kinetics

We o a he ab o e f a o a o ea che ca eac o a a a o e V h a be f o eo e $_A$, $_B$, a d $_C$ be of A, B, a d C:

$$A + B \underset{-}{\overset{+}{\rightleftharpoons}} C. \tag{6.70}$$

We o e ha he $_A +$ $_C$ a d $_B +$ $_C$ d o o cha ge he eac o . He ce e ca de o e $_A +$ $_C =$ $_A$ a d $_B +$ $_C =$ $_B$ a he o a a o f A a d B, c d g ho e C, a he a e. N e e $_C$ a he o -ega e ege - a ed a d o , a ab e o de c be he ocha c che ca e c , h e o ea che ca eac o , acc o d g o DGP, a o e-d e o a b h-a d-dea h o ce h a e-de e de b h a d dea h a e $=$ $^+$ $_A$ $_B$ a d $=$ $_-$ $_C$. The , acc o d g o E . (6.45) e ha e a e b d b o $) = \mathrm{P}\{$ $_C =$ $\}$:

$$\frac{(\;+1)}{(\;)} = \frac{{}^{+}(\;_A - \;)(\;_B - \;)}{{}^{-}(\;+1)V}, \tag{6.71}$$

h ch $_A =$ $_A(0) +$ $_C(0)$ a d $_B =$ $_B(0) +$ $_C(0)$. The ef o e,

$$(\;) = \frac{\Xi^{-1}\;_A!\;_B!}{!(\;_A - \;)!(\;_B - \;)!}\left(\frac{+}{-V}\right) , \tag{6.72}$$

he e Ξ a o a a o fac o

$$\Xi(\lambda) = \sum_{=0}^{(\;_A,\;_B)} \frac{_A!\;_B!\;\lambda}{!(\;_A - \;)!(\;_B - \;)!}, \quad \lambda = \left(\frac{+}{-V}\right). \tag{6.73}$$

Mo e o a , b o g $_A +$ $_B +$ $_C =$ ${}^0_A +$ ${}^0_B -$ $_C$,

$$- \quad (\;_C)$$

$$= - \left[\frac{\lambda^{\;_C}}{_C!(\;_A - \;_C)!(\;_B - \;_C)!}\right] + \mathrm{co} .$$

$$
\begin{aligned}
&= \quad _A \left(\frac{A}{V}\right) - \quad _A + \quad _B \left(\frac{B}{V}\right) - \quad _B + \quad _C \left(\frac{C}{V}\right) - \quad _C - \quad _C \left(\frac{+}{-}\right) \\
&= \quad _A \quad _A + \quad _B \quad _B + \quad _C \quad _C + \quad _C\left(\frac{\mu_C - \mu_A - \mu^0_B}{_B T}\right) - (\quad _A + \quad _B + \quad _C) \\
&= \sum_{\sigma = A,B,C} \quad _\sigma \left(\frac{\mu_\sigma}{_B T} + \quad _\sigma - 1\right).
\end{aligned} \tag{6.74}
$$

Th ag ee h E . (6.65).

I c a ca che ca e c f a g e $\mathbf{x}($ $)$, he Idea fi c f he che ca eac e

$$
G \quad [\mathbf{x}(\ )] = \sum_{\sigma=1} \quad _\sigma \left(\mu \quad _\sigma + \quad _B T \quad _\sigma - \quad _B T\right). \tag{6.75}
$$

The , f g E . (6.34), a g each a d e e eac e e b h a e c a $^+$ a d $^-$,

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}} G \quad [\mathbf{x}(\ )] &= \sum_{=1} \frac{\mathrm{d}}{\mathrm{d}} \left(\mu \quad + \quad _B T \quad \right) \\
&= \quad _B T \sum_{=1} \sum_{=1}
\end{aligned}
$$

are strong conditions on the dynamics. When a chemical reaction system that is attached to source and sink with different chemical potentials, it cannot reach a chemical equilibrium. Rather, it reaches a *nonequilibrium steady state* (NESS).

Let us consider the following two examples: the Schlögl model for bistability [34] and Schnakenberg model for nonlinear oscillations [17, 25, 35].

6.6.4.1 Schlögl Model

$$A + 2X \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} 3X, \qquad X \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} B, \tag{6.78}$$

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

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k_1^+ a x^2 - k_1^- x^3 - k_2^+ x + k_2^- b \equiv f(x), \tag{6.79}$$

which is a third-order polynomial. It can exhibit bistability and saddle-node bifurcation phenomenon. A necessary condition for it is when $\mu_A \neq \mu_B$. Note at the chemical equilibrium $\mu_A = \mu_A^o + k_BT \ln a = \mu_B^o + k_BT \ln b$, and

$$\left(\frac{b}{a}\right)^{eq} = \frac{k_1^+ k_2^+}{k_1^- k_2^-}. \tag{6.80}$$

Differential equation (6.79), with this parameter $k_1^+ k_2^+ a = k_1^- k_2^- b$, has the right-hand-side

$$\begin{aligned} f(x) &= k_1^+ a x^2 - k_1^- x^3 - k_2^+ x + k_2^- b \\ &= k_1^+ a x^2 - k_1^- x^3 - k_2^+ x + \frac{k_1^+ k_2^+ a}{k_1^-} \\ &= \left(x^2 + \frac{k_2^+}{k_1^-}\right)\left(k_1^+ a - k_1^- x\right). \end{aligned} \tag{6.81}$$

Therefore, the $f(x)$ has a unique fixed point at $x = \frac{k_1^+ a}{k_1^-}$, the chemical equilibrium. In general, (6.78) can exhibit chemical bistability; but this is only possible when A and B have a sufficiently large chemical potential difference, e.g., *a chemostat*.

More interesting when a and b are far from satisfying (6.80), the DGP of the number of X, $n(t)$, is again a one-dimensional birth-and-death process with

$$= \frac{{}^{+}_{1} \quad (\quad - 1)}{V} + {}^{-}_{2} \quad V = \frac{{}^{+}_{1}}{V} \left(\quad (\quad - 1) + \frac{{}^{+}_{2} V^2}{{}^{-}_{1}} \right), \tag{6.82}$$

$$_{+1} = \frac{{}^{-}_{1}(\quad + 1) \quad (\quad - 1)}{V^2} + {}^{+}_{2}(\quad + 1)$$

$$= \frac{{}^{-}_{1}(\quad + 1)}{V^2} \left(\quad (\quad - 1) + \frac{{}^{+}_{2} V^2}{{}^{-}_{1}} \right).$$

The ef e, e a a d b , acc d g E . (6.45),

$$= C \prod_{\ell=0}^{-1} \frac{{}^{+}_{1} \quad / V}{{}^{-}_{1}(\ell + 1)/V^2} = \frac{\lambda}{!} \quad ^{-\lambda}, \quad \lambda = \left(\frac{{}^{+}_{1} \quad V}{{}^{-}_{1}} \right). \tag{6.83}$$

Th a P d b e ec ed a e be g $\mathbb{E}[\quad] = \lambda$. The ef e, e e ec ed c ce a (${}^{+}_{1}$ / ${}^{-}_{1}$).

6.6.4.2 Schnakenberg Model

S a ,

$$A \underset{{}^{-}_{1}}{\overset{{}^{+}_{1}}{\rightleftharpoons}} \quad , \quad B \xrightarrow{2} \quad , \quad 2 \quad + \quad \xrightarrow{3} 3 \quad , \tag{6.84}$$

a *Schnakenberg model* e d a c f

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}} = {}^{+}_{1} \quad - {}^{-}_{1} \quad - {}_{3} \quad ^{2} \quad = \quad (\; , \;), \\ \dfrac{\mathrm{d}}{\mathrm{d}} = {}_{2} \quad - {}_{3} \quad ^{2} \quad = \quad (\; , \;). \end{cases} \tag{6.85}$$

Th e ca e b c c e c a a d H f b ca . I e f e DGP, e b a a a d ffi . We efe e eade [25, 35] f a -de a a f e de .

6.7 The Law of Large Numbers—Kurtz's Theorem

6.7.1 *Diffusion Approximation and Kramers–Moyal Expansion*

S a g he a e e a (6.43), e c de a a a d ffe e a e a (PDE) f a c de fi c (,)d = $_V$ ( ) he e = $\frac{}{V}$, d = $\frac{1}{V}$, he

$$\frac{\partial (\ ,\ )}{\partial} = V \frac{\mathrm{d}\ \ _V(\ )}{\mathrm{d}}$$
$$= \frac{1}{\mathrm{d}}\Big((\ -\mathrm{d}\ ,\ )\hat{}(\ -\mathrm{d}\ ) - (\ ,\ )\big(\hat{}(\ ) + \hat{}(\ )\big)$$
$$+ (\ +\mathrm{d}\ ,\ )\hat{}(\ +\mathrm{d}\ )\Big)$$
$$= \frac{\partial}{\partial}\Big((\ +\mathrm{d}\ /2,\ )\hat{}(\ +\mathrm{d}\ /2) - (\ -\mathrm{d}\ /2,\ )\hat{}(\ -\mathrm{d}\ /2)\Big)$$
$$\approx \frac{\partial}{\partial}\left\{\frac{\partial}{\partial}\left(\frac{\hat{}(\ ) + \hat{}(\ )}{2V}\right) (\ ,\ ) - \big(\hat{}(\ ) - \hat{}(\ )\big) (\ ,\ )\right\} + \cdots \tag{6.86}$$

h ch

$$V^{-1}\ \ _V = \hat{}(\ ),\quad V^{-1}\ \ _V = \hat{}(\ ), \tag{6.87}$$

a $V \to \infty$.

6.7.2 *Nonlinear Differential Equation, Law of Mass Action*

The ef e, he f $V \to \infty$,

$$\frac{\partial (\ ,\ )}{\partial} = -\frac{\partial}{\partial}\big(\hat{}(\ ) - \hat{}(\ )\big) (\ ,\ ), \tag{6.88}$$

h ch c e d he d a d ffe e a e a

$$\frac{\mathrm{d}}{\mathrm{d}} = \hat{}(\ ) - \hat{}(\ ), \tag{6.89}$$

ha defi e he cha ac e c e f (6.88).

6.7.3 Central Limit Theorem, a Time-Inhomogeneous Gaussian Process

N c de he ce

$$(\ ) = \frac{(\ ) - V \ (\ )}{\sqrt{V}}, \tag{6.90}$$

h ch cha ac e e he de a f $\frac{(\ )}{V}$ f ( ). I he f $V \to \infty$, df (,) a fie a ea PDE h e- a g c effic e

$$\frac{\partial \ (\ , \ )}{\partial} = \frac{\partial}{\partial}\left\{\frac{\partial}{\partial}\left(\frac{\hat{\ }(\ (\ )) + \hat{\ }(\ (\ ))}{2}\right) \ (\ , \ ) \right.$$

$$\left. - \left(\hat{\ }'(\ (\ )) - \hat{\ }'(\ (\ ))\right) \ (\ , \ )\right\}. \tag{6.91}$$

The ef e, ( ) a c e, ea - a ed, e- h ge e Ma ce N e he PDE (6.91) e d ffe e f PDE (6.86). The a e h k c e a ea he K a e M a e a a d a Ka e Ω-e a , e ec e [32]. The f e e a ed he ce a he e .

6.7.4 Diffusion's Dilemma

T ca g he E . (6.86) af e he ec d de , ha a a a d

$$- \ \hat{\ } \ (\ ) = 2V \int \left(\frac{\hat{\ }(\ ) - \hat{\ }(\ )}{\hat{\ }(\ ) + \hat{\ }(\ )}\right) \mathrm{d} \ . \tag{6.92}$$

O he he ha d, he a a g e (6.45),

$$= \ _0 \prod_{=1} \left(\frac{\ _{-1}}{\ }\right),$$

he f $V \to \infty$ h $V^{-1} \ _V = \hat{\ }(\ )$, $V^{-1} \ _V = \hat{\ }(\ )$, a d $V^{-1} = \mathrm{d}$, e d

$$- \ \ _V = - \sum_{=1} \left(\frac{\ _{-1}}{\ }\right) + C \leftrightarrow - \ \ (\ ) = V \int \left(\frac{\hat{\ }(\ )}{\hat{\ }(\ )}\right) \mathrm{d} \ . \tag{6.93}$$

I be E (6.92) a d (6.93) a e ac a e a e? We ce a b a e de ca ca e e a:

$$\frac{d}{d}\left(- \quad ( )\right) = 2V \left(\frac{\hat{}( ) - \hat{}( )}{\hat{}( ) + \hat{}( )} \right) = 0 \implies \hat{}( ) = \hat{}( ). \tag{6.94}$$

I fac , e a ea a ca e e de ca :

$$\left[\frac{d^2}{d^{\ 2}}\left(- \quad ( )\right) \right]_{\hat{} = \hat{}} = 2V \left(\frac{\hat{}'( ) - \hat{}'( )}{\hat{}( ) + \hat{}( )} \right) = V \left(\frac{\hat{}'( ) - \hat{}'( )}{\hat{}( )} \right)$$

$$= \left[\frac{d^2}{d^{\ 2}}\left(- \quad ( )\right) \right]_{\hat{} = \hat{}} . \tag{6.95}$$

H e e , ca be , a e a e, a e g ba ca be d ffe e [20, 37]! T e a K a e M a e a a a d a a f cha c e c ab . C e, ea - a ed Ma ce e a e a ca ed *diffusion processes*. The ab e e a e a e e g ba a d d ffi a a f cha c a e c ge e a .

6.8 The Logic of the Mechanical Theory of Heat and Nonequilibrium Thermodynamics

I de e e a e ece e Sec . 6.9

The e a g be eel B a he a d he he be he d a c I add he c e a he de G -Ma a ach a e e he *entropy balance equation* [5],

$$\frac{\mathrm{d}S}{\mathrm{d}} = \quad + J_S, \tag{6.96}$$

a e f fi da e a e e he e he e d c a e a d J_S he a e f e ed a e b d g The ec d a f he d a c e.g., C a e a , d c a e ha ≥ 0. U f a e , B a echa ca he f hea ab e de e a e a e (6.96) f a Ha a d a c e g add a a ba ed a *stosszahlansatz.*[1] A ee f Sec . 6.9, e e , Ma d a c ab e de ce a e a e (6.96). A cha c d a c a ach e b he d a c ab e fi g c ga , a a fi de a ed b Be g a a d Leb 1955 [2].

6.8.1 Boltzmann's Mechanical Theory of Heat

The e d, a g a e e e ed he e a ha a e a a ca e (e.g., a) a d c e he eed f gh (e.g., e a), f he N a echa c h ch ca be e e ed a he a ca e f a Ha a e

$$\frac{\mathrm{d}}{\mathrm{d}} = \frac{\partial H(\ ,\ )}{\partial}, \quad \frac{\mathrm{d}}{\mathrm{d}} = -\frac{\partial H(\ ,\ )}{\partial}. \tag{6.97}$$

O e f he a e c ce g he E . (6.97) he d a c a a ce f $H(\ (\ ),\ (\ ))$:

$$\frac{\mathrm{d}}{\mathrm{d}} H(\ (\ ),\ (\ )) = \frac{\partial H}{\partial} \Big(\quad \mathrm{H}$$

Now, we assume that the Hamiltonian function contains additional parameters $H(x, v, V, N)$ where V is the boundary of a mechanical system and N is the number of particles inside the boundary, then there is [illegible], but interesting, which has not been extensively studied, is this: What is the long-time behavior of the phase area as function of V, N, and other parameters?

A Hamiltonian system, however, is fundamentally different from the reasonable system we have discussed, which has a unique fixed point ([illegible]). In fact, it is clear that the long-time behavior is a function of the initial condition $H\big(x(0), v(0)\big) = E$. Helmholtz and Boltzmann (1884) realized that a thermodynamic state, [illegible], of a mechanical system is *not a single point in the phase space, but rather, it is an entire invariant manifold* defined by the level set $H(x, v, V, N) = E$. It was Boltzmann's ingenious idea that one can define

$$
\begin{aligned}
S\big(E, V, N\big) &= k_B \ln\big\{ \text{phase volume enclosed by the surface } H(x, v) = E \big\} \\
&= k_B \ln \int_{H(x,v) \le E} \mathrm{d}x\, \mathrm{d}v. \qquad (6.99)
\end{aligned}
$$

Since $S(E)$ is monotonic, one has its inverse function $E = E(S, V)$. Then

$$
\begin{aligned}
\mathrm{d}E &= \left(\frac{\partial E}{\partial S}\right)_{V,N} \mathrm{d}S + \left(\frac{\partial E}{\partial V}\right)_{S,N} \mathrm{d}V + \left(\frac{\partial E}{\partial N}\right)_{S,V} \mathrm{d}N \\
&= T\mathrm{d}S - p\,\mathrm{d}V + \mu\, \mathrm{d}N. \qquad (6.100)
\end{aligned}
$$

What is the significance of Eq. (6.100)? First, it is a result based on the fact that a Hamiltonian system has a *conservation of mechanical energy* H. For the first time, however, it [illegible] of energy [illegible] for a large Hamiltonian system [illegible] the Hamiltonian system [illegible] and [illegible] Hamiltonian systems with varying V and N, and other parameters. It becomes [illegible], *the First Law of Thermodynamics*. Note, according to this theory, the thermodynamic potentials T, p, μ are all mechanical quantities defined via Eq. (6.100). They are emergent phenomena.

T and p have mechanical interpretations through their effects, as mean kinetic energy and mean [illegible] and [illegible] μ, however, has not been given a mechanical interpretation; rather, it has an interpretation of Brownian motion:

$$
\frac{\partial \rho(x, t)}{\partial t} = D \frac{\partial^2 \rho(x, t)}{\partial x^2} = -\frac{1}{\eta} \frac{\partial (\hat{F} \rho)}{\partial x}, \qquad (6.101)
$$

where

$$
\hat{F} = -\frac{\partial \mu}{\partial x}, \text{ and } \mu = D\eta \ln \rho(x, t) = k_B T \ln \rho(x, t). \qquad (6.102)
$$

$\hat{F}$ is known as *entropic force* in chemistry, and μ is known as chemical potential.

6.8.2 Classical Macroscopic Nonequilibrium Thermodynamics

E a (6.100) a d he he e e $H(\ , \ ) = E$ ed he g e ; h a *ergodicity*. I he d h e d, he e a a d he he dS a d dV a e e cha g g. Wha ha e f he cha ge a e ? The , he *Second Law of Thermodynamics* a e ha

$$T\mathrm{d}S \geq \mathrm{d}Q = \mathrm{d}E - \mathrm{d} \quad , \tag{6.103}$$

h ch dQ he a f hea ha fl he e , a d d he a d e he e . B h a e a h de e de , a d ca ed b he d. E . (6.103) a he C a e a . The f *entropy production* d ced acc f he e a :

$$\frac{\mathrm{d}S}{\mathrm{d}} = \quad - \frac{}{T}, \qquad \geq 0, \tag{6.104}$$

h ch ca ed e d c h ch e e ega e. $= -\mathrm{d}Q/\mathrm{d}$ ca ed hea d a . I ge e a , he a e de a e. E . (6.104) a a *entropy balance equation.*

6.8.2.1 Local Equilibrium Assumption and Classical Derivation of Entropy Production

If e a e ha E . (6.100) a d ca ace a d e, he e ha

$$\frac{\partial \ (\ , \ )}{\partial} = \frac{1}{T}\frac{\partial \ (\ , \ )}{\partial} - \sum_{=1} \mu \frac{\partial \ (\ , \ )}{\partial}, \tag{6.105}$$

h ch e ha e a ed c e b d$V = 0$. (,), (,), a d (,) a e e de , e e g de , a d c ce a f he h ec e .

Rea g ha b h e e g a d a c e f c e a ace- e, e ha

$$\frac{\partial \ (\ , \ )}{\partial} = -\frac{\partial J \ (\ , \ )}{\partial}, \quad \frac{\partial \ (\ , \ )}{\partial} = -\frac{\partial J \ (\ , \ )}{\partial}. \tag{6.106}$$

The , b g he e E . (6.105), a d e a ce a a f h ca , e a e a

$$\frac{\partial \ (\ , \ )}{\partial} = \quad (\ , \ ) + J_S(\ , \ ) \tag{6.107a}$$

he e e d c a e e

$$(\, , \,) = J \frac{\partial}{\partial} \left(\frac{1}{T} \right) - \sum_{=1} J \frac{\partial}{\partial} \left(\frac{\mu}{T} \right) - \sum_{=1} \frac{\Delta\mu \quad \hat{\varphi}}{T}, \tag{6.107b}$$

a d e fl

$$J_S(\, , \,) = \frac{\partial}{\partial} \left(\frac{J}{T} - \sum_{=1} \frac{\mu \quad J}{T} \right). \tag{6.107c}$$

Acc d g O age he [18], each e he e d c a

$$a \quad \text{fl} \quad \times \text{ d } g \text{ f ce} \tag{6.108}$$

h ch h d be -ega e. The he f e b he d a c c ce a ce e f a d d ffi , hea , cha ge, che - ca , e c. M e f a he a a fl e ca be b a ed, he e ca , f e g ee g.

6.9 Mathematicothermodynamics of Markov Dynamics

We c de d c e e- a e Ma e cha c d a c e f c e a f bab a e ace , e.g., Cha a K g e a , a e e a

$$\frac{\mathrm{d} \, ( )}{\mathrm{d}} = \sum_{=1}^{N} \left(\quad - \quad \right), \tag{6.109}$$

h ch a e he fi e a a bab a e g e (6.27).

We ha f he a e g c e f B a , a ed Sec . 6.8.1, de e a he d a c he ba ed he ge e a d a c b d c g he f e . E . (6.109) e ace he Ha a e (6.97), a d he ace f B a ce eb a ed $S = \;_B \ln \Omega(E)$ be he G bb -Sha e :

$$S( ) = - \sum_{=1}^{N} \, ( ) \ln \, ( ). \tag{6.110}$$

The , e ha

$$\frac{\mathrm{d}S}{\mathrm{d}} = \quad + J_S, \tag{6.111a}$$

he e

$$( ) = \frac{1}{2} \sum_{, =1}^{N} \left(( ) - ( ) \right) \left(\frac{( )}{( )} \right), \quad (6.111b)$$

$$J_S( ) = \frac{1}{2} \sum_{, =1}^{N} \left(( ) - ( ) \right) \left(\frac{}{} \right). \quad (6.111c)$$

I ed a e b ha ≥ 0 ce f e e a f , E . (6.111b), he e ha he f f (−) (/) ≥ 0. We a e he e e b a ce f (6.111b) E . (6.76).

The ef e, e ha e de ed a e ba a ce e a ba ed Ma d a c he a f ca e b . E a (6.111b) a d (6.111c) fi he g e e c e e e f he { ( )}, f he e fl J_S he -ega e e d c . A e ha be , he e a c e e e b he d a c he e c c ca e, a e ace. Th he effec e a he a he h he e e a e be g 1.

6.9.1 Non-Decreasing Entropy in Systems with Uniform Stationary Distribution

If he a e E . (6.109) ha a a a d b $= 1 \ \forall$, he

$$\sum_{=1}^{N} (-) = \sum_{=1}^{N} = 0, \quad \forall .$$

I h ca e,

$$\frac{\mathrm{d}S}{\mathrm{d}} = -\sum_{=1}^{N} \left(\frac{\mathrm{d} ( )}{\mathrm{d}} \right) = -\sum_{, =1}^{N} (-) $$
$$= \sum_{, =1}^{N} \left(\frac{}{} \right) \geq \sum_{, =1}^{N} \left(\frac{}{} - 1 \right)$$
$$= \sum_{=1}^{N} \left(\sum_{=1}^{N} \right) = 0. \quad (6.112)$$

We he ef e ha e a he e a g ha f he a a bab d b f , he he e S -dec ea g f c f e.

6.9.2 Q-Processes with Detailed Balance

If a Q ce ha a a a d b , = , a *detailed balance*, he

$$
\begin{aligned}
J_S( ) &= \frac{1}{2}\sum_{ , =1}^{N} \Big(( ) - ( ) \Big) \Big(\Big) \\
&= \frac{1}{2}\sum_{ , =1}^{N} \Big(( ) - ( ) \Big) \Big(\Big) \\
&= \sum_{ , =1}^{N} \Big(( ) - ( ) \Big) = -\sum_{=1}^{N} \frac{\mathrm{d} \ ( )}{\mathrm{d}} \\
&= \frac{\mathrm{d}}{\mathrm{d}} \left(\sum_{=1}^{N} ( ) \big(- \big) \right) = \frac{1}{T}\frac{\mathrm{d}\overline{E}}{\mathrm{d}},
\end{aligned}
\tag{6.113}
$$

h ch

$$
\overline{E} = \sum_{=1}^{N} ( ) E , \tag{6.114}
$$

h d be de fied a he ea e e g h $E = -T$ a he e e g f he a e acc d g B a . The , E . (6.111a) bec e

$$
\frac{\mathrm{d}}{\mathrm{d}} \left(\frac{\overline{E}}{T} - S \right) = - \le 0. \tag{6.115}
$$

$F = \overline{E} - TS$ a he f ee e e g f a he d a c e . I e ec ed d ca dec ea e h e a e a ach g e b . I a e b ead a e, he f ee e e g each .

6.9.3 Monotonicity of F Change in General Q-Processes

E[illegible]c[illegible] aged b[illegible] [illegible]e ab[illegible]e e[illegible] [illegible] e[illegible] [illegible]c[illegible]de [illegible]e K[illegible] bac[illegible] Le[illegible]b[illegible]e d[illegible]e ge[illegible]ce, a[illegible] [illegible] [illegible] a[illegible] e a[illegible] e e[illegible] [illegible]:

$$F(\ ) = \sum^{N}_{=1} (\ )\big(- \ \ + \ (\ )\big) = \sum^{N}_{=1} (\ ) \left(\frac{(\ )}{}\right) \geq 0. \tag{6.116}$$

O[illegible]e ca[illegible] ac[illegible] a[illegible] [illegible] [illegible]a dF/d ≤ 0 f[illegible] ge[illegible]e a[illegible] Q-[illegible]ce[illegible] [illegible] [illegible]e de a[illegible]ed ba a[illegible]ce:

$$\begin{aligned}\frac{\mathrm{d}F(\ )}{\mathrm{d}} &= \sum^{N}_{=1}\left(\frac{\mathrm{d}\ (\ )}{\mathrm{d}}\right) \left(\frac{(\ )}{}\right) = \sum^{N}_{,\ =1}\big(\quad - \quad \big) \left(\frac{(\ )}{}\right) \\ &= \sum^{N}_{,\ =1} \left(\frac{(\ )}{(\ )}\right) \leq \sum^{N}_{,\ =1} \left(\frac{(\ )}{(\ )} - 1\right) \\ &= \sum^{N}_{=1} \left(\sum^{N}_{=1}\big(\quad - \quad \big)\right) = 0. \end{aligned} \tag{6.117}$$

6.9.4 F Balance Equation of Markov Dynamics

M[illegible]e [illegible] e e[illegible]g [illegible] e [illegible]a e a[illegible], ba a[illegible]ce e[illegible] a[illegible] f[illegible] [illegible]e $F(\ )$:

$$\frac{\mathrm{d}F(\ )}{\mathrm{d}} = E(\ ) - \quad (\ ), \tag{6.118a}$$

[illegible] [illegible]e e $(\ ) \geq 0$ [illegible]g[illegible] e[illegible] [illegible] (6.111b), a[illegible]d

$$E(\ ) = \frac{1}{2}\sum^{N}_{,\ =1}\big((\ ) \quad - \quad (\ ) \big) \left(\frac{}{}\right) \geq 0. \tag{6.118b}$$

See [9] f[illegible] [illegible]e [illegible]f [illegible]e[illegible] a[illegible]. B[illegible] $E(\ )$ a[illegible]d $(\ )$ a e [illegible]-[illegible]ega[illegible] [illegible]c[illegible] ea[illegible] [illegible]a E[illegible]. (6.118a) ca[illegible] be [illegible] e e ed a[illegible] [illegible]e $F(\ )$ [illegible]a a[illegible] ce a[illegible]d a[illegible], [illegible] c[illegible]a[illegible]ge e[illegible] a[illegible] a[illegible] $E(\ )$, a[illegible] ce e[illegible], a[illegible]d d[illegible] a[illegible] $(\ )$, a[illegible] e[illegible]. T[illegible]e e[illegible]a e[illegible]c[illegible] c[illegible]e a[illegible] [illegible]f [illegible]e [illegible]a[illegible] F. E[illegible] a[illegible] (6.118a) [illegible]e ea[illegible]gf[illegible] [illegible]a[illegible] [illegible]e E[illegible]. (6.111a), [illegible] [illegible]c[illegible] J_S d[illegible]e[illegible] [illegible]a e a defi[illegible] e [illegible]g[illegible].

T[illegible]e ba a[illegible]ce E[illegible]. (6.118a) a[illegible]d [illegible]e [illegible] [illegible]f dF/d ≤ 0 [illegible]a e e a ab e e[illegible]e b a[illegible]ce [illegible] [illegible]e fi[illegible] a[illegible]d [illegible]e [illegible]ec[illegible]d [illegible] [illegible]f [illegible]e [illegible]d [illegible]a [illegible]c[illegible] B[illegible] [illegible]e a e ea[illegible] a a [illegible]f a[illegible] a [illegible]e a[illegible]ca [illegible]c[illegible] e [illegible]f a[illegible] [illegible]c[illegible]a[illegible]c Ma[illegible] [illegible]d [illegible]a [illegible]c[illegible]

[illegible], *mathematicothermodynamics* [9, 10, 21, 24].

6.9.5 Driven System and Cycle Decomposition

The [illegible] (6.111b) can be [illegible]

$$= \sum_{\text{a} \ \text{edge}}^{N} \left(\varphi - \varphi\right) \ln\left(\frac{\varphi}{\varphi}\right), \tag{6.119}$$

[illegible] Q- [illegible] [14]

$$= \sum_{\text{a} \ \text{c c e}\ \Gamma}^{N} \left(\varphi_\Gamma^+ - \varphi_\Gamma^-\right) \ln\left(\frac{\varphi_\Gamma^+}{\varphi_\Gamma^-}\right), \tag{6.120}$$

[illegible] $\varphi_\Gamma^{\pm}$ [illegible] Γ [illegible] back[illegible]. M[illegible] $\Gamma = (\ldots, \ldots)$

$$\frac{\varphi_\Gamma^+}{\varphi_\Gamma^-} = \frac{\cdots}{\cdots}, \tag{6.121}$$

[illegible] The[illegible], $\ln\left(\varphi_\Gamma^+/\varphi_\Gamma^-\right)$ can and [illegible] be [illegible] $\left(\varphi_\Gamma^+ - \varphi_\Gamma^-\right)$ [illegible]. A [illegible] (6.121); [illegible] [27]. If a Ma[illegible] balanced, [illegible] each and [illegible].

I[illegible] A. N. K[illegible] (6.121) [illegible] each and [illegible] Ma[illegible] balanced. The[illegible] *detailed balance* [illegible] fi[illegible] . F[illegible] Γ [illegible] balanced [illegible]: $\varphi_\Gamma^+ \neq \varphi_\Gamma^-$.

6.9.6 Macroscopic Thermodynamics in the Kurtz Limit

F[illegible] a DGP [illegible] N [illegible] ec[illegible] a[illegible]d M eac[illegible] he F fi [illegible]c [illegible] [illegible]ced [illegible] Sec. 6.9.4 [illegible] a fi [illegible]c [illegible] a [illegible]f he [illegible]bab[illegible] d[illegible] [illegible] $_V(\mathbf{n},\ )$ [illegible] h[illegible]ch [illegible]e f a fi [illegible]c [illegible] [illegible]f he eac[illegible] [illegible]e [illegible] e V. The[illegible] he [illegible]a a a[illegible] ha ac[illegible] [illegible]a $V \to \infty$ a[illegible] he K[illegible]? I ca[illegible] be [illegible] ha [10]

$$\frac{F[\ _V(\mathbf{n},\ )]}{V} = \frac{1}{V}\sum_{\mathbf{n}} \ _V(\mathbf{n},\ ) \left[\frac{\ _V(\mathbf{n},\ )}{\ _V(\mathbf{n})}\right]$$

$$= -\frac{1}{V}\sum_{\mathbf{n}} \ _V(\mathbf{n},\ ) \ \ _V(\mathbf{n})$$

$$= G\ [\mathbf{x}(\ )], \tag{6.122}$$

[illegible] h[illegible]ch $\mathbf{n} = (\ _1,\ _2, \cdots,\ _N)$, [illegible] he [illegible] be [illegible]f [illegible]e[illegible] e[illegible] [illegible]f he h[illegible] ec[illegible]e[illegible] $\mathbf{x} = (\ _1, \cdots,\ _N)$ [illegible] he c[illegible] e[illegible] [illegible]d[illegible]g [illegible] be de[illegible] $\mathbf{x} = \frac{\mathbf{n}}{V}$. The K[illegible] he[illegible]e [illegible] Sec. 6.7 [illegible]a e[illegible] ha he [illegible]cha[illegible]c a ec[illegible] [illegible]f a DGP, $\mathbf{n}_V(\ )$,

$$\frac{\mathbf{n}_V(\ )}{V} = \mathbf{x}(\ ), \tag{6.123}$$

[illegible] he e $\mathbf{x}(\ )$ [illegible] he [illegible] he de e[illegible]c, [illegible] [illegible]ea a e e[illegible] a[illegible] (e.g., E[illegible]. (6.89)). M[illegible] [illegible] e e[illegible]g , acc[illegible]d[illegible]g he a ge de[illegible] a[illegible] [illegible]c[illegible] e f[illegible] he he[illegible] [illegible]f [illegible]bab[illegible] he[illegible] he [illegible]ead [illegible]a e [illegible]bab[illegible] $_V(\mathbf{n})$ c[illegible] e ge[illegible] a D[illegible] ac-δ fi [illegible]c[illegible], [illegible] a[illegible] [illegible]bab[illegible] ha[illegible]a[illegible] a[illegible] [illegible]c e e[illegible]

$$-\frac{\ \ _V(\mathbf{n})}{V} = -\frac{\ \ _V(V\mathbf{x})}{V} = G\ (\mathbf{x}). \tag{6.124}$$

Th[illegible] [illegible]ead [illegible]a e a ge de[illegible] a[illegible] a e fi [illegible]c[illegible] $G\ (\mathbf{x})$ ca[illegible] be [illegible]de[illegible]fied a[illegible] a ge[illegible]e a[illegible]ed G[illegible]bb[illegible] fi [illegible]c[illegible] f[illegible] [illegible]e[illegible] [illegible]b[illegible] che [illegible]ca eac[illegible] [illegible]e I ca[illegible] be [illegible] ha

$$\frac{\mathrm{d}}{\mathrm{d}\ }G\ [\mathbf{x}(\ )] = \left(\frac{\mathrm{d}\mathbf{x}(\ )}{\mathrm{d}\ }\right) \cdot \nabla_{\mathbf{x}} G\ (\mathbf{x}) \le 0. \tag{6.125}$$

Th[illegible]a ge[illegible]e a[illegible] a[illegible] [illegible]f he [illegible]e[illegible] a[illegible] [illegible] E[illegible]. (6.77). See [10] f[illegible] he [illegible]f.

6.10 Summary and Conclusion

Th[illegible] cha e e[illegible]e[illegible] a [illegible] [illegible]de[illegible]g a ad[illegible]g f[illegible] b[illegible]g[illegible]ca [illegible]e a[illegible]d [illegible] ce[illegible]e[illegible] ha c[illegible] [illegible]f [illegible]e [illegible] a[illegible] [illegible]f [illegible]d[illegible] a[illegible] each[illegible] a[illegible] [illegible]fi[illegible]e a[illegible] [illegible] e [illegible]a deg ee[illegible]f f eed[illegible]. The [illegible]d[illegible] a[illegible]a e g[illegible] ed [illegible] b[illegible] a[illegible] a d a e a ca e e e ed b e a ca be a e f b , dea , g a , a d a e ch g. We a e a e c e f ea d a d ffe e a e a (ODE) de e ed a e a ca b g fi da e a a cha c e c e . T cha c a e c e e e a f b g ca ea ca be ced e g , c de e c fide ce e c c d f a e a ca a a We ca ed f a *Delbrück-Gillespie process*. I e a ge a , T. G. K e e , a f a ge be e d a e f ea a e e a a ca e a ODE I Sec. 6.9, e ece e e c e b e d a c a d c e d g ac c c e b e d a c a e e ed. T ge e e ee a (1) cha c e c e f DGP, (2) de e c ea d a c e f ODE a d (3) e a e a c e d a c de a c e e e a e a ca e f a de a ge f b g ca e a d ce e f b c e ec g .

6.11 Exercises: Simple and Challenging

6.11.1 Simple Exercises

1. C e e e ec ed a e a d e a a ce f a e e a d b ed a d a ab e a e λ.

2. Le $_1, \cdots,$ be d. e e a a d a ab e a e λ. Le $^* =$ $\{ _1, _2, \cdots, \}$. S a $_{T^*}( ) = \lambda \; ^{-\lambda}$.

3. If a e f d. a d e a d b $_T( )$, $_T(0) = 0$ b $'_T(0) \neq$ 0, a e d b f $T^* =$ $\{T_1, T_2, \cdots, T\}$ e f $\to \infty$?

6.11.2 More Challenging Exercises

4. C de a a c g f de ca a d de e de d d a ga- each a e e a d b ed e f g g b a e λ, a d g g dea a e μ.

() N e e a a e ac d d a a e bab d b f e e g e e e b ? W a e bab d b f e g e e e dea ? W a e bab d b f e g e e e b dea e e ?

( ) Le ( ) be he bab f ha g e ac d d a he a a e :

$$\sum_{=0}^{\infty} \quad ( ) = 1.$$

Wha e f d ffe e a e a d ( ) a f ?

( ) The ea a a e defi ed a

$$\langle \ \rangle( ) = \sum_{=0}^{\infty} \quad ( ).$$

Ba ed he e f d ffe e a e a b a ed ( ), ha

$$\frac{\mathrm{d}}{\mathrm{d}}\langle \ \rangle = \left(\lambda - \mu \ \right)\langle \ \rangle.$$

5. The 3- a e Ma e ,

$$A \underset{-1}{\overset{1}{\rightleftharpoons}} B \underset{-2}{\overset{2}{\rightleftharpoons}} C \underset{-3}{\overset{3}{\rightleftharpoons}} A, \tag{6.126}$$

ha bee de ed b che de he c f a a cha ge f a g e e ea e de g g h gh h ee d ffe e a e A, B, a d C. F e a e, A -ac e, B a a ac e, a d C fi ac e.

( ) The bab e f he a e $\mathbf{p} = (\ _A, \ _B, \ _C)$, a fie a d ffe e a e a

$$\frac{\mathrm{d}}{\mathrm{d}}\mathbf{p}( ) = \mathbf{p}( )\mathbf{Q},$$

he e $\mathbf{Q}$ a 3×3 a . W e he $\mathbf{Q}$ e f he . Sh ha he f each a d e e e . D bab e ha he ea g f h e ?

( ) C e he ead a e bab e $_A$, $_B$, a d $_C$, a d ha , he ead a e, he e (bab) fl f a e A B,

$$J_{A \to B} = \ _1 \ _A - \ _{-1} \ _B,$$

he a e a he e fl f a e $B \to$ a e C, a d a he e fl f $C \to A$. S ce he a e a he a e, ca ed he ead a e fl J f he b che ca eac c c e (6.126).

( ) Wha he c d , e f a he f $J = 0$?

6. C de a g e e e E he ea f b a e ea e S. The M chae Me e e c

$$E + S \underset{-1}{\overset{1}{\rightleftharpoons}} ES \xrightarrow{2} E^* + P. \tag{6.127}$$

Beca e he e a g e e e ea e g, he c ce a f S ca be a ed a a a c a , a he a e $_S$.

W e he d ffe e a e a f he ab f he e e be g a e E, ES, a d E^*: $_E(\ )$, $_{ES}(\ )$, a d $_{E^*}(\ )$.

G e a c d $_E(0) = 1$, $_{ES}(0) = 0$, a d $_{E^*}(0) = 0$, e $_{E^*}(\ )$.

I c ea ha he e f he e e e f a e E E^* cha c. Le T be he a d e. Wha he ab d b f T, $_T(\ )$? H e a ed $_{E^*}(\ )$?

C e e ec ed a e $\mathbb{E}[T]$. C a e e h he M chae Me e f a.

References

1. D.A. Bea d, H. Q a , *Chemical Biophysics: Quantitative Analysis of Cellular Systems*, Te B ed ca E g ee g (Ca b dge U e P e , L d , 2008)
2. P.G. Be g a , J.L. Leb , N a ach e b ce e Ph Re . **99**, 578 587 (1955)
3. R.D. C , *Renewal Theory* (Me h e & C a , N Y , 1970)
4. P.G. de Ge e , M ea a d d a . Sc e ce

16. A.J. Lotka, Analytical note on certain rhythmic relations in organic systems. Proc. Natl. Acad. Sci. USA **6**, 410–415 (1920)
17. J.D. Murray, *Mathematical Biology I: An Introduction*, 3rd ed. (Springer, New York, 2002)
18. L. Onsager, Reciprocal relations in irreversible processes. I. Phys. Rev. **37**, 405–426 (1931)
19. H. Qian, Cellular biology in terms of stochastic nonlinear biochemical dynamics: emergent properties, isogenetic variations and chemical system inheritability. J. Stat. Phys. **141**, 990–1013 (2010)
20. H. Qian, Nonlinear stochastic dynamics of mesoscopic homogeneous biochemical reaction systems—an analytical theory (invited article). Nonlinearity **24**, R19–R49 (2011)
21. H. Qian, A decomposition of irreversible diffusion processes without detailed balance. J. Math. Phys. **54**, 053302 (2013)
22. H. Qian, *Nonlinear Stochastic Dynamics of Complex Systems, I: A Chemical Reaction Kinetic Perspective with Mesoscopic Nonequilibrium Thermodynamics* (2016). ArXiv:1605.08070
23. H. Qian, L.M. Bishop, The chemical master equation approach to nonequilibrium steady-state of open biochemical systems: linear single-molecule enzyme kinetics and nonlinear biochemical reaction networks (Review). Int. J. Mol. Sci. **11**, 3472–3500 (2010)
24. H. Qian, M. Qian, X. Tang, Thermodynamics of the general diffusion process: time-reversibility and entropy production. J. Stat. Phys. **107**, 1129–1141 (2002)
25. H. Qian, S. Saffarian, E.L. Elson, Concentration fluctuations in a mesoscopic oscillating chemical reaction system. Proc. Natl. Acad. Sci. USA **99**, 10376–10381 (2002)
26. H. Qian, P. Ao, Y. Tu, J. Wang, A framework towards understanding mesoscopic phenomena: Emergent unpredictability, symmetry breaking and dynamics across scales. Chem. Phys. Lett. **665**, 153–161 (2016)
27. H. Qian, S. Kjelstrup, A.B. Kolomeisky, D. Bedeaux, Entropy production in mesoscopic stochastic thermodynamics: nonequilibrium kinetic cycles driven by chemical potentials, temperatures, and mechanical forces (Topical review). J. Phys. Condens. Matter **28**, 153004 (2016)
28. D.B. Saakian, H. Qian, *Nonlinear Stochastic Dynamics of Complex Systems, III: Nonequilib-*