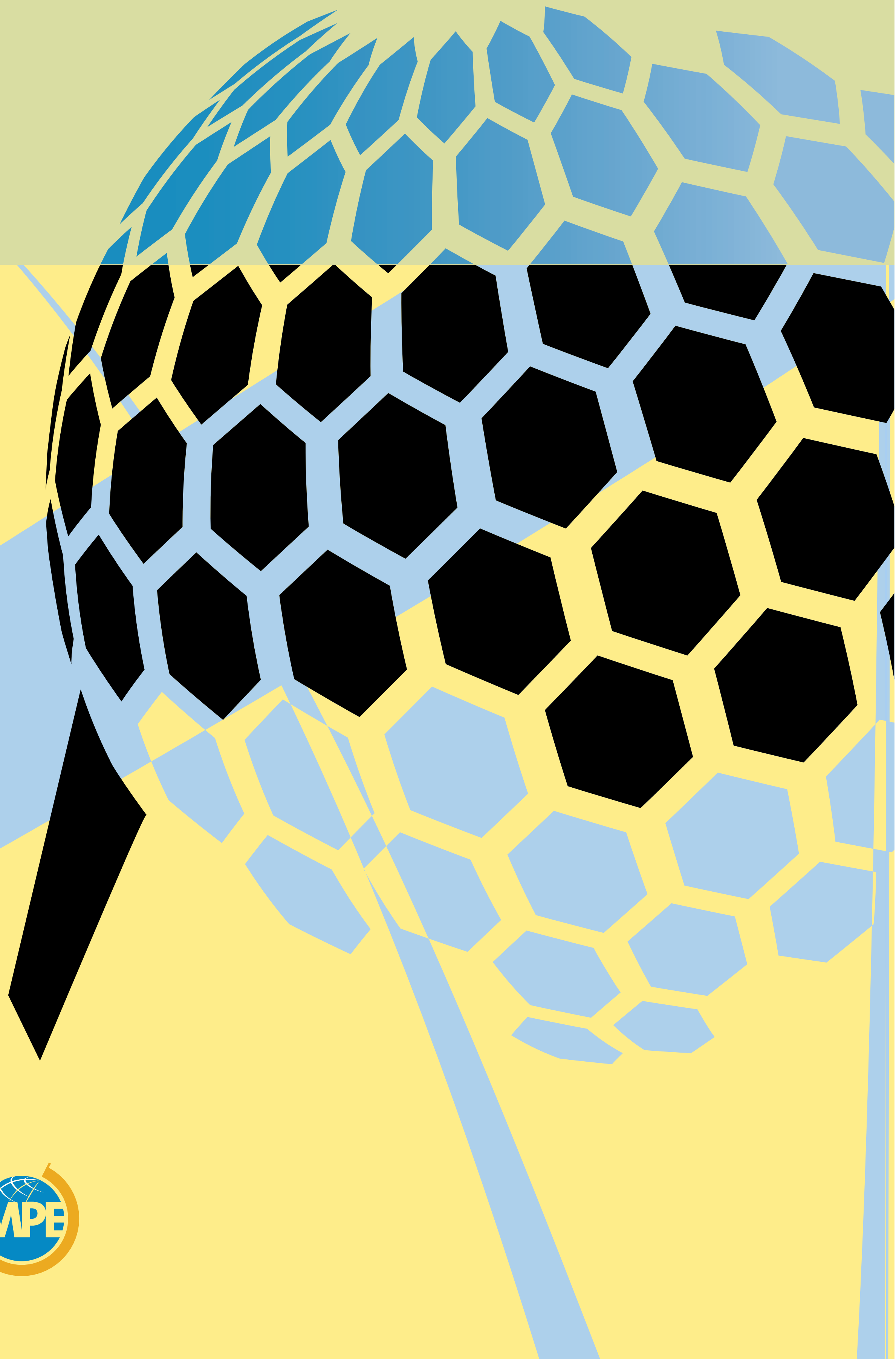

MPE

Chapter 6
Stochastic Population Kinetics and Its Underlying Mathematicothermodynamics

Hong Qian

Abstract [illegible]

6.1 Introduction

[illegible] Jac[illegible] (1920 [illegible] 2013), [illegible] [13] [illegible]

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H. Q[illegible] (✉)
[illegible], WA, USA
[illegible]

[illegible] AG 2019
A. B[illegible] (ed[illegible]), *The Dynamics of Biological Systems*, [illegible]
[illegible] 4, [illegible]://d[illegible]/10.1007/978-3-030-22583-4_6

[illegible] [4] [illegible] *V*, [illegible] Ma[illegible]

[illegible] [17]. [illegible]

Af[illegible] Sec. 6.9 [illegible] *mathematicothermodynamics* [illegible]

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

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

T[illegible] (a) [illegible] (b) [illegible] c ca , ec ca , c a , ...) ba ed e g, e ab ed f a d e a . F ac f be e g e a ca e f e ***data-driven modeling*** d e a e ***mechanistically derived modeling***. N e, acc d g Ka P e (1902 1994) d f c ce, e eg a e c fic ac fa f g a e : a e e fi f a e a e , c e e g f a e e da a (e.g., e ca e) d e e g a ec (e.g., de g); d (b) de e g ed c f a e c a f f g ca , a a ca , ded c .

Le e e f e e a ead d c ed, de ed, f e e c a e _ b e be c ca . C a .1 H d L d ced e g a e g a g ce : f a a g e e e 100 da , "e a e e e e 50 da , d a f a e e e 25 da . fac , e g a e

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

a e a e (fl) e f e c ce f Ne ca c ! B d e a e e f a g ? A a f f a e , e f a e ? C ea e ca be e e Δ a : *population change* ca a e - ege be .

Sec d, a e e e e c a eg a a g e ac e e fi 100 da , d e e 100 da ? I e e f a " a a e age .

deed, *discreteness* d *probability* a e f da a e a - d c . B a e be ed e d ffe a e a -ba ed de c f a d c . We a a d c g a e c be . M f a e a a e a f [1, 19, 20, 22, 23, 28, 31].

6.2.1 Brief Review of Elementary Probabilities

A ***random variable*** a g a c ea a e a a bab d f c (df) ( ):

$$\int_{-\infty}^{\infty} ( )d = 1, \quad ( ) \geq 0. \tag{6.1}$$

T e e g f e ( ) : f fl e a d , e bab f be g $\in (, +d]$ ( )d :

$$\Pr\{ < \leq +d \} = ( )d . \tag{6.2}$$

T , e c a e bab d b f def ed a

$$F\ (\ ) = \Pr\{\ \le\ \} = \int_{-\infty}\ (\ )\mathrm{d}\ ,\quad \mathrm{d}\ (\ ) = \frac{\mathrm{d}F\ (\ )}{\mathrm{d}}. \tag{6.3}$$

T e ea (e ec ed a e) d a ce f e d a ab e a e

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

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

c e a e d ed $\mathbb{E}[\ ]$ b . T e e f d a ab e a g ea a e a e "e a d a , a ca ed Ga . T e f e a e da d f

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

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

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

ea d a ce σ^2.

Ga a d b de d c ed; c d g a e [11]. I de d a a c e ce f e *central limit theorem*. I a a ca e g g f a age c ec f d ca , de d a . e f g ec e a a f d ca ce e g a , e e a c e , b e a f e a ca : e d a d b ed e be ea "a e e . c a de g f a d c , e a f c e d be f d d a a a a c a e; a e e d e f e e e a c ge e be f d d a b e.

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

6.2.2 Radioactive Decay and Exponential Time

Le e e e d ffe a e a

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

w e e $\lambda > 0$. T e a a be d ced a a a a ca de f e a g f ac f a ad ac a e a a e

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

If a e a c c e a e *identical and independent*,

$$\Pr\{a c e a g ad ac e a e \} = \ ^{-\lambda} . \tag{6.10}$$

H e e , f T e d e a c e e f ad ac e deca cc ,

$$\Pr\{a c e a g ad ac e a e \} = \Pr\{T \geq \ \}. \tag{6.11}$$

T a ega e ea - a ed d a ab e c a e bab d b $F_T(\ ) = \Pr\{T \leq \ \} = 1 - \ ^{-\lambda}$ d bab d f c $f_T(\ ) = \mathrm{d}F(\ )/\mathrm{d} \ = \lambda \ ^{-\lambda}$.

W a e f b , e ec e " c a d " ec g e e e a d b ed a g e? W e a ? A g d de d g f e e e de e eade a dee e de- d g f e a a ca f da f a d c , a e g a ca a , e f e g d be a f a ge a f d d a [15].

6.2.2.1 Rare Event

Le T be e d e a c a ce a e cc . If e cc ce f c e de d e e a $[\ _1, \ _2]$ d $[\ _2, \ _3]$, d f cc ce f e (e.g., e d a e a a),

$$\Pr \ b. \ f \ e \ cc \ g \ [0, \ + \Delta \ ] = \tag{6.12}$$

$$\Pr \ b. \ f \ e \ cc \ g \ [0, \ ] \times \Pr \ b. \ f \ e \ cc \ g \ [\ , \ + \Delta \ ].$$

T a ,

$$\Pr\{T > \ + \Delta \ \} = \Pr\{T > \ \} \times \Pr \ b. \ f \ e \ cc \ g \ [\ , \ + \Delta \ ].$$

N f e bab f e c e cc g e e e a $[\ , \ + \Delta \ ]$ a Δ , d e bab f e e e $\propto (\Delta \ )$,

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

T ,

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

E e: T e a g e f e fi e c g a e e g a eg a da .

6.2.2.2 Memoryless

O e f e , fac def g, e e f e a d b ed a g e

$$\frac{\Pr\{T \geq \ + \tau\}}{\Pr\{T \geq \ \}} = \frac{\ ^{-\lambda(\ +\tau)}}{\ ^{-\lambda}} = \ ^{-\lambda\tau}. \tag{6.15}$$

E e: Y d a b e d g e e b e e e f e a d b ed e . E g b e a c g e a e a e , e g a c be e ac e e a !

M e e e g , e e d d a a a , e fa e e e e cc a a ca e : f a $T \sim \lambda\ ^{-\lambda}$ d e a e de dd d b ed, $T^* =$ $(T_1, T_2, \cdots, T\ )$ a a e a d b

$$\begin{aligned}\Pr\{T^* > \ \} &= \Pr\{T_1 > \ , \cdots, T\ > \ \}\\ &= \Pr\{T_1 > \ \} \times \Pr\{T_2 > \ \} \times \cdots \times \Pr\{T\ > \ \} = \ ^{-}\ ,\end{aligned} \tag{6.16}$$

e e $= \lambda_1 + \lambda_2 + \cdots + \lambda$. T , $f_{T^*}(\ ) = \ ^{-}$.

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

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

$$\Pr\{T^* > \ \} = \Big(1 - F_T(\ )\Big)\ . \tag{6.17}$$

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

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

T e ef e, f $F'_T(0) = f_T(0)$ e, e ba e a d b ed e.
We e e a a ca c d $f_T(0) > 0$: a ca , e a e e ca e ed e ec f e cc ce f e e e a de f ag de fa e e e ca e e .

6.2.3 Known Mechanisms That Yield an Exponential Distribution

e e ec e a e de ed e e a d b ed a g e ba ed e e e a a c ce g (1) e g e d (2) de d . F e e, Sec . 6.2.2.3 e a e a f e a T, a g a $f_T(0) \neq 0$, f a a ge c ec f d. T bee a . T a g a g f e c e, a a e e ca e, e e a e (6.8) de a d c .

6.2.3.1 Khinchin's Theorem

Le c de a e a e g b b . O e b g a a ge b e g b b , d e a e a e b b a g d ca , de d d b ed fe e df f ( ). F eac g -b b c e, e a b b e d e b . T e e e ce 0, T_1, T_2, $\cdots$, T , $\cdots$ ca ed a *renewal process*, c $T = \sum_{\ell=1}$ $^{(\ell)}$ e e e $^{(\ell)}$ d ffe ℓ a e . .d. d a ab e d f e d b f ( ). N f e e, e e a e d ca , de d e a ce e . T e e e ce f b b c g g f a *superposition* f e e a ce e [3], a a ed F g. 6.1.
F a g e a ce e a e d b f ( ), e c e d g c g ce , e.g., e be f a cc ed bef e e , N , a e d b

$$\Pr\{N \geq \ \} = \Pr\{T \leq \ \} = F_T(\ ) = \int_0 f_T(\ )d \quad (6.19)$$

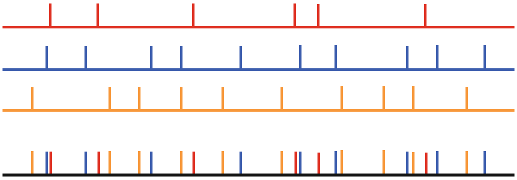

Fig. 6.1 If e ed, ge, d b e ce e e e a e f g b b f 3 d ffe c e , e f e c b ed ce f a e b b c ge . I e e f e ee d d a ce e . W e d c e , a a ca e ge

T e ef e,

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

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

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

T e ef e, e bab d f c f e a a T^*

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

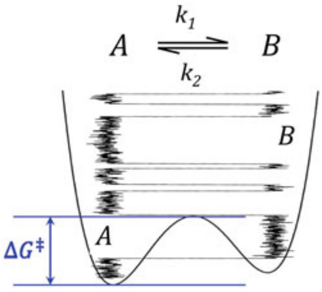

Fig. 6.2 T e a a ca de c f a c ca -eac f a g e ec e. I e-g a ca a f a a-ge be- f d c-e e, c a c-eac $_1 \propto$ $^{-\Delta G\ /\ _BT}$

6.2.4 Population Growth

We a e d c ed $\frac{d}{d} = -\lambda$ w e λ: ad ac e deca . A d d e e a a a d c ca be a ed $\frac{d}{d} =$ w a e , e e a f f a a d a c .

T e w e be e b f d: e d ea e b a e ! T e w a g e f e e b e ec ed be e a . F e e, e a e e ec ed be a e be f d d a c (E e c e 1.2), a ( ). T e ef e, *on average the growth is 1 additional person in* $(\ \mathbb{E}[\ \ ])^{-1}$ *time*:

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

Dea e , b a e e , a e e . M b g ca d c ab c g e a , d ab b g ca e a ead c g g a . S c a c e g f e a e . T w J. D. M a a ed [17] a c g w de f a ec e a e a e e e a c e a e a :

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

w e e ( ) e a d .

6.2.5 Discrete State Continuous Time Markov (Q) Processes

D c e e a e c e Ma ce e a e e e ca ed a Ma - , Q- ce e , a e g fi d ced A e J 1954 b *A Distribution Model, Applicable to Economics* d b Da d F eed 1971 b *Markov Chains.* e f e bab f a e a e , ( ), e a

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

w e e $_\ell$ d e bab f a e ℓ w e fi e a e e a d . E . (6.27) ca ed a *master equation*. I f d a a **P**( ) = $^{\mathbf{Q}}$ w e e e **Q** a a ff-d ag a e e ≥ 0 d

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

T e ef e, **Q** a eac d e e . I f efe ed a
fl e a a e a . I ea a ca e, e

$$\sum_{=1}^{N} \quad ( )$$

de d f e . T e a bab c e ed e e. N e e e a
d ffe ce be e E . (6.26) d (6.27): T e f e e a
f a *density* ( ) e e a e e a f e bab f
a *size* $( ) \equiv \mathrm{P}\{N( ) = \ \}$; e g - d de f f e a a
ea f c f e e a e ece a ea . T e d f e
a e ODE , e e , c g e e f e .

6.2.5.1 Kolmogorov Forward and Backward Equations

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

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

T a d ffe d ffe a e a :

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

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

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

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

$$\sum_{=1}^{N} \ ( )\pi$$

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

T e e K g f a d d bac a d e a a a e e . Le ( ) d ( ) be a f a d e a d ffe a d b (0) d (0). T

$$\frac{d}{d} \sum^{N}_{=1} ( ) \left(\frac{( )}{( )} \right) \leq 0. \tag{6.31}$$

e ec a ca e f c de , e c ce f ( ) = π , f π > 0 ∀ .

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

$$\frac{d}{d} \sum^{N}_{=1} \left(\pi \quad ( ) \right) \left(\frac{( )}{( )} \right) \leq 0. \tag{6.32}$$

e ec a ca e f c g ( ) ≡ 1. T e E . (6.32) ca ed *H*-f c ; e E . (6.31) ca ed e a e , K bac Le b e d e ce f a e , ee e g ca c - . T e e e a e a dee ca f e ec d f d c .

6.3 Theory of Chemical and Biochemical Reaction Systems

A g e a e e a f c e c ca eac

$$\nu_{1} \quad {}_{1} + \nu_{2} \quad {}_{2} + \cdots \nu \quad \longrightarrow \kappa_{1} \quad {}_{1} + \kappa_{2} \quad {}_{2} + \cdots \kappa \quad . \tag{6.33}$$

1 ≤ ≤ . T e a e ec e d eac . (ν − κ) a e ca ed *stoichiometric coefficients*, e e a e a ec e e eac . a b ade e, a "eac a e f "e .

6.3.1 *Differential Equation and Nonlinear Dynamics*

Beca e f e c e a f a e,

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

w e e e c c a f c ca ec e , 1 ≤ ≤ , a d

$$\hat{\varphi}(\mathbf{x}) = {}^{\nu\ 1}_{1}\ {}^{\nu\ 2}_{2} \cdots {}^{\nu} \tag{6.35}$$

ca ed e a e fl f e eac . $\mathbf{x} = (\ _1,\ _2, \cdots, \ )$. E . (6.34) ca ed a e e a , a d E . (6.35) ca ed *the law of mass action* (LMA).

6.3.2 Delbrück-Gillespie Process (DGP)

Le w c de bab ca e d c e e, d d a e f e b e eac E . (6.33), e a a e. T e DGP a e a e eac cc f w g e a d b ed w a g e, w a e a a e e

$$\varphi(\mathbf{X}) = \ V\prod_{\ell=1}\left(\frac{\ \ell!}{(\ \ell-\nu\ \ell)!V^{\nu\ \ell}}\right), \tag{6.36}$$

w e ec a be f c ca ec e be g . N e $\varphi(\mathbf{X})$ a e d f [e]$^{-1}$. C ea 7061(C).2(ea 52.369MKd)65.49.9625997.90002441()-43

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

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

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

6.3.3 Integral Representations with Random Time Change

6.3.3.1 Poisson Process

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

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

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

6.3.3.2 Random Time Changed Poisson Representation

f P ce e , e c a c a ec f a DGP e e g e ege be f ec e a e ,

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

c φ ($\mathbf{X}$) g (6.36). We a e ab ed e a a b e b f a e f ec e, a E . (6.33), d be e eac .

We ee a e f $\mathbf{X} \to \infty$ d $V \to \infty$,

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

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

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

6.3.4.1 One-Dimensional System

C de e c a c a e c f a g e ec e . Le ( ) be e bab f a g d d a e a a e . T ( ) a fie a e e a

$$\frac{\mathrm{d}\ (\ )}{\mathrm{d}} = \quad {}_{-1} \quad {}_{-1} - \quad (\quad + \quad) + \quad {}_{+1} \quad {}_{+1}, \tag{6.43}$$

c a d a e e b a e a d dea a e f e a e ac d d a . T e a a d b E . (6.43) ca be b a ed:

$$\frac{}{{}_{-1}} = \frac{{}_{-1}}{}. \tag{6.44}$$

T e ef e,

$$= \ {}_{0} \prod_{=1} \left(\frac{{}_{-1}}{} \right), \tag{6.45}$$

c $_{0}$ be de ed b a a .

E . (6.43) e DGP c e d g e ea a d a c f a g e ec e b a d dea a e ˆ( ) a d ˆ( ) ( ) ≡ $\frac{(\ )}{V}$,

$$\frac{\mathrm{d}}{\mathrm{d}} = \hat{}(\ ) - \hat{}(\ ), \tag{6.46}$$

e e,

$$\hat{}(\ ) = \lim_{V\to\infty} \frac{V}{V}, \quad \hat{}(\ ) = \lim_{V\to\infty} \qquad E\ .\ ($$

C de a a b a x = (1, 2, ⋯ ,), a ≥ 0. e ab ce g a , e d e e ca a g a e = − ,

$$\frac{d}{d} = \,. \tag{6.48}$$

F c e a a e a b e ca a b a e d dea a e a e c . T e e ca a g a e f e e a c a e ea e ca a g a e,

$$^{-} = \frac{\sum_{=1} \frac{d}{d}}{\sum_{=1}} = \frac{\sum_{=1}}{\sum_{=1}}, \quad \geq 0. \tag{6.49}$$

T ,

$$\frac{d^{-}(\mathbf{x})}{d} = \left[\frac{\sum_{=1} {}^{2}}{\sum_{=1}} - \left(\frac{\sum_{=1}}{\sum_{=1}} \right)^{2} \right]. \tag{6.50}$$

We e a e de [⋯] e g - d de e e ega e:

$$\frac{\sum_{=1} {}^{2}}{\sum_{=1}} - \left(\frac{\sum_{=1}}{\sum_{=1}} \right)^{2} = \frac{\sum_{=1} \left(- ^{-} \right)^{2}}{\sum_{=1}} \geq 0. \tag{6.51}$$

fac , e ac e a ce f g e d ffe b a . T e ef e, a e f e e a e a a g . T a a ca e a a f e dea f b Ad , ec c , d C a e D , e a a e ec . fac , e [⋯] E . (6.50) a be fied b R. A. F e, e B a c d e a b g , a e "g f fi e d e a a e ec [6]. He e a e f *magnum opus* " e Na e d Ca e f e Wea f Na (1776):

> A e e d d a , e ef e, dea a c a e c b ca a e f d e c d , d d ec a d a d ce a be f e g ea e a e; e e d d a ece a ab de e a e e f e c e a g ea a e c . He g e a , deed, e e d e e b c e e , c e g . B efe g e f d e c a f f e g d , e d ec ; d b d ec g a d c a e a d ce a be f e g ea e a e, e d ga , d e , a e ea e , ed b be d e d c a a f . N a e e f e c e a a a f . B g e e f e e a f e c e effec a e ea d e . I a e e e c g d d e b e affec ed ade f e b c g d. I affec a , deed, e c g e c , d e f d eed be ed d ad g f .

6.5 Ecological Dynamics and Nonlinear Chemical Reactions: Two Examples

6.5.1 Predator and Prey System

Le ( ) be e a d f a eda a e d ( ) be e a d f a e a e e. T e e eda e d a c [17]

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

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

Le w c de e f w g c ca eac :

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

T acc d g e LMA, e c c a f d w fi ed c c a- f A d B be g d :

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

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

6.5.2 A Competition Model

Le w c de e w de d ed ec g ca d a c w c e- [17]:

$$\begin{cases} \dfrac{\mathrm{d}N_1}{\mathrm{d}} = {}_1 N_1 - {}_1 N_1^2 - {}_{21} N_1 N_2, \\ \dfrac{\mathrm{d}N_2}{\mathrm{d}} = {}_2 N_2 - {}_2 N_2^2 - {}_{12} N_2 N_1. \end{cases} \tag{6.55}$$

C e "de a f c ca eac a e d d ca f d ffe a e a ? W f g e a , e a e a $_{12} >\ _{21}$.

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

c , acc d g e LMA,

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

If e d f , $N_1, N_2,$ d

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

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

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

6.5.3 Logistic Model and Keizer's Paradox

We d g e e e -de . Le c de c e c ca eac ,

$$A + \xrightarrow{1} 2\ ,\quad + \xrightarrow{2} B. \tag{6.58}$$

I ea ee a e ODE acc d g e LMA,

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

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

w c de ed b e a c c e f a ec e, e.g., e a e g . $_B$ B c , d T e a e Ke . T e G bb f ee e g f e f (6.62) e f e c ca a

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

W e eac eac e e b , e a e a c ca a be g e a b de :

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

T e

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

$$\Delta G \; = \left(\sum_{=1} \kappa \quad \right) - \left(\sum_{=1} \nu \quad \right) = \;_B T \; \left(\frac{-}{+}\right). \tag{6.68}$$

T a e w e - w f a a ca be f d e e c ege c e b .

6.6.2 Mass-Action Kinetics

F w g E . (6.34) d (6.35) w e a e

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

E a (6.69) a d $\ell =$ $_\ell$, e e [$\cdots$] = 0 d e e {$\cdots$} = 0 a e , f e e . T e ef e, e e c e a (6.69) c e c a e b acc d g e d a c , e.g., E . (6.66) d (6.67). e e g , ec a a b ac c c e c a (6.69) d e b e d a c Sec . 6.6.1 a e c e ce f a c a c e c de c f a eac [10].

6.6.3 Stochastic Chemical Kinetics

We a e ab e f a a ea c ca eac a a e V a be f ec e , $_A$, $_B$, d $_C$ be f A, B, d C:

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

We e a e $_A +$ $_C$ d $_B +$ $_C$ d c ge e eac . He ce e c d e $_A +$ $_C =$ $_A$ d $_B +$ $_C =$ $_B$ a e a f A d B, c d g e C, a e a e. N f e e $_C$ a e ega e ege a ed d a ab e de c be e c a c c ca e c , e ea c ca eac , acc d g DGP, a e-d a b - d-dea ce a e-de d b d dea a e $=$ $^+$ $_A$ $_B$ d $=$ $_-$ $_C$. T , acc d g E . (6.45), e a e e b d b ( ) = Pr{ $_C$ = }:

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

c $_A =$ $_A(0) +$ $_C(0)$ d $_B =$ $_B(0) +$ $_C(0)$. T e ef e,

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

e e Ξ a a a fac

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

M e , b g $_A +$ $_B +$ $_C =$ $^0_A +$ $^0_B -$ $_C$,

$$- \ (\ _C)$$

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

$$= {}_A \left(\frac{A}{V}\right) - {}_A + {}_B \left(\frac{B}{V}\right) - {}_B + {}_C \left(\frac{C}{V}\right) - {}_C - {}_C \left(\frac{+}{-}\right)$$

$$= {}_A \; {}_A + {}_B \; {}_B + {}_C \; {}_C + {}_C\left(\frac{{}_C - {}_A - {}^0_B}{{}_B T}\right) - ({}_A + {}_B + {}_C)$$

$$= \sum_{\sigma=A,B,C} {}_\sigma\left(\frac{\sigma}{{}_B T} + {}_\sigma - 1\right). \quad (6.74)$$

T ag ee E . (6.65).

c a ca c ca e c , f a g x( ), e Idea f c f e c ca eac

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

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

$$\frac{\mathrm{d}}{\mathrm{d}} G \; [\mathbf{x}( )] = \sum_{=1} \frac{\mathrm{d}}{\mathrm{d}}\left(\; + {}_B T \; \right)$$

$$= {}_B T \sum_{=1} \sum_{=1}$$

7.7.57159990 0 7.57159996 149.72999572 3 a e g c d e d c . W a c ca eac a a a ed ce d d ffe c ca a , c eac a c ca e b . Ra e , eac e a *nonequilibrium steady state* (NESS).

Le c de e f g e e , e Sc ég de f b ab [34] d Sc a be g de f ea c a [17, 25, 35].

6.6.4.1 Schlögl Model

$$A + 2 \underset{1}{\overset{1}{\rightleftharpoons}} 3 , \quad \underset{2}{\overset{2}{\rightleftharpoons}} B, \tag{6.78}$$

c e c c a (c ca a) f A d B a e a ed b e e a ag . T eac a *Schlögl model* e d c c be de c bed b e d ffe a e a

$$\frac{d}{d} = {}_1^{+}\ {}^2 - {}_1^{-}\ {}^3 - {}_2^{+} + {}_2^{-} = ( ), \tag{6.79}$$

c a d de a . I c e b b ab d add e de b f ca . A f cc de d c d $_A \neq {}_B$. N e e c ca e b : $_A = {}_A + {}_B T = {}_B + {}_B T$, d

$$\left(-\right) = \frac{{}_1^{+}\ {}_2^{+}}{{}_1^{-}\ {}_2^{-}}. \tag{6.80}$$

D ffe a e a (6.79) a e e $_1^{+}\ {}_2^{+} = {}_1^{-}\ {}_2^{-}$, a e g d de

$$\begin{aligned} ( ) &= {}_1^{+}\ {}^2 - {}_1^{-}\ {}^3 - {}_2^{+} + {}_2^{-} \\ &= {}_1^{+}\ {}^2 - {}_1^{-}\ {}^3 - {}_2^{+} + \frac{{}_1^{+}\ {}_2^{+}}{{}_1^{-}} \\ &= \left({}^2 + \frac{{}_2^{+}}{{}_1^{-}} \right) \left({}_1^{+} - {}_1^{-} \right). \end{aligned} \tag{6.81}$$

T e ef e, e ( ) a a e fi ed a $= \frac{{}_1^{+}}{{}_1^{-}}$, e c ca e b . g e a , (6.78) c e b c ca b ab ; b b e A d B a e a ffic a ge c ca a d ffe ce, e.g., *a chemostat*.

M e e e g d a f g (6.80), e DGP f e be f , ( ), aga a e-d a b d-dea ce

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

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

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

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

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

T a P d b e ec ed a e be g $\mathbb{E}[\quad] = \lambda$. T e ef e, e e ec ed c c 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

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

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

6.7 The Law of Large Numbers—Kurtz's Theorem

6.7.1 Diffusion Approximation and Kramers–Moyal Expansion

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

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

c

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

a $V\to\infty$.

6.7.2 Nonlinear Differential Equation, Law of Mass Action

T e ef e, e f $V\to\infty$,

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

c c e d e d a d ffe a e a

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

a def e e c a ac e c e f (6.88).

6.7.3 Central Limit Theorem, a Time-Inhomogeneous Gaussian Process

Nw c de e ce

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

w c c a ac e e e "de a f $\frac{( )}{V}$ f ( ). e f $V \to \infty$, df (,) a fie a ea PDE w e a g c effic

$$\frac{\partial (,)}{\partial} = \frac{\partial}{\partial}\left\{\frac{\partial}{\partial}\left(\frac{\hat{}(( )) + \hat{}(( ))}{2}\right) (,) - \left(\hat{}'(( )) - \hat{}'(( ))\right) (,)\right\}. \tag{6.91}$$

T e ef e, ( ) a c , e, ea a ed, e g e Ma ce . N e e PDE (6.91) e d ffe f PDE (6.86). T e a e w c e a e a e K a e M a e d Ka Ω-e , e ec e [32]. T e f e e a ed e c a e .

6.7.4 Diffusion's Dilemma

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

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

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

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

e f $V \to \infty$ w $V^{-1}\ _V = \hat{}( )$, $V^{-1}\ _V = \hat{}( )$, d $V^{-1} = d$, e d

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

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

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

fac , e c a e a a ca e d ca :

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

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

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

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

de e e a e ecc e Sec . 6.9 a e c e , e fi e e ce eh a ed f L. B e *mechanical theory of heat* [8 e b e d c e ed e c a c ea e f de G d Ma [5 Sec . 6.9, a e a e f d g f a g be e e ab e e e .

a defi f f c $S = -\quad _B\ \Omega(E)$ 6.9 e g e a Ma d c d a a defi f f c acc d g S [29]. N e a B a a c , e Sec . 6.9, E . (6 × c d ffe ce .

T e e a g be e B e d e e b e d a c . add e c e a , e de G -Ma a ac a e e e *entropy balance equation* [5],

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

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

6.8.1 Boltzmann's Mechanical Theory of Heat

T e e d, a g a e e ed a a a e a a a ca e (e.g.,) d c e e eed f g (e.g., e a), f e Ne ec c c be e e ed a a ca e f a Ha

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

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

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

N , e a e a e Ha f c c a a e e a a e e , $H(, , V, N)$, e e V e b e f a ec ca d N e be f a c e e b , e e e c a ed a a c g a , b e e g c a bee e e d ed, : "W a e g e be a f e a a f c f $V, N,$ d e a e e ?

A Ha , e e , f da a d ffe f e ea e e a e d ed c a e a ac e fi ed ( ). fac , c ea a e g e be a a f c f e a c d $H\big((0), (0)\big) = E$. He d B (1884) ea ed a a " e d ce b a e f a ec ca *not a single point in the phase space, but rather, it is an entire invariant manifold* defi ed b e e e e $H(, , V, N) = E$. I a B g ea e a e c defi e

$$S\big(E, V, N\big) = {}_B \big\{ \text{ a e e c a ed b e face } H(,) = E \big\}$$
$$= {}_B \int_{H(,)\leq E} \mathrm{d} \ \mathrm{d} \ . \tag{6.99}$$

S ce $S(E)$ c, e a c f c $E = E(S, V)$. T

$$\mathrm{d}E = \left(\frac{\partial E}{\partial S}\right)_{V,N} \mathrm{d}S + \left(\frac{\partial E}{\partial V}\right)_{S,N} \mathrm{d}V + \left(\frac{\partial E}{\partial N}\right)_{S,V} \mathrm{d}N$$
$$= T\mathrm{d}S - \ \mathrm{d}V + \ \mathrm{d}N. \tag{6.100}$$

W a e fica ce f E . (6.100)? F , c e e ba ed e fac a a Ha a a *conservation of mechanical energy H*. F e e, e e , c e a f e g a d f a g e Ha a ge a , b a e Ha e e e , de a g e c a f Ha a g V d N, d e a e e . I bec e a e a a de a , a *the First Law of Thermodynamics*. N e, acc d g e , e d a c e T, , a e a a ca defi ed a E . (6.100). T e a e e g a.

T d a e ec ca e e a , g e fec , a ea e c e g d ea fe a a . , e e , a e e a e f c a ca ; a e , a e e a e f B a :

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

e e

$$\hat{F} = -\frac{\partial}{\partial}, \text{ d } = D\eta \ \rho(,) = {}_B T \ \rho(,). \tag{6.102}$$

$\hat{F}$ a *entropic force* c , d a c ca a .

6.8.2 Classical Macroscopic Nonequilibrium Thermodynamics

E a (6.100) a d e e $H(,) = E$ ed e g e ; a *ergodicity.* e d e d, e e a a d e dS dV a e e c g g. W a a f e c ge a e ? T , e *Second Law of Thermodynamics* a e a

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

c dQ e f ea a fl e , d d e f d e e . B a e a de d , a d ca ed b e d. E . (6.103) a e C a e a . T e f *entropy production* d ced acc f e e a :

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

c ca ed d c c e e ega e. $= -\mathrm{d}Q/\mathrm{d}$ ca ed ea d a . g e a e e a e de a e. E . (6.104) a *entropy balance equation.*

6.8.2.1 Local Equilibrium Assumption and Classical Derivation of Entropy Production

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

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

c e a e a ed c e b d$V = 0$. (,), (,), d (,) a e d , e g d , d c c a f e ec e .

Rea g a b e g d a c e f c e a ace e, e a

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

T , b g e e E . (6.105), d e a ce a f ca , e a e a

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

w e e d c a e e e

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

d fl

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

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

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

w c d be ega e. T e e f e b e d c c ce w ce e f a d : d ff , ea , c a ge, c - ca , e c. M e f a e a fl e c be b a ed, g ca , f g ee g.

6.9 Mathematicothermodynamics of Markov Dynamics

We w c de d c e e- a e Ma w c a c d c e f "c e a f bab ae ace , e.g., C a K g e a , a e e a

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

w c a e e fl e a bab a e g (6.27).

We a w f w e e g c e f B , a ed Sec . 6.8.1, de e a" e d c e ba ed e g e a d c b d c g e f . E . (6.109) e ace e H (6.97), d e ace f B ce eb a ed $S = {}_B \quad \Omega(E)$ w be e G bb -S :

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

T , e a

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

w e e

$$( ) = \frac{1}{2}\sum_{, =1}^{N}\Big(( ) - ( ) \Big)\Big(\frac{( )}{( )}\Big), \tag{6.111b}$$

$$J_S( ) = \frac{1}{2}\sum_{, =1}^{N}\Big(( ) - ( ) \Big)\Big(\text{—}\Big). \tag{6.111c}$$

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

T e ef e, e a e de ed ba ce e a ba ed Ma d c , e a f ca e b . E a (6.111b) d (6.111c) f e g e e c e e , f e { ( )}, f e fl J_S e ega e d c . A e a be , e e a c e e e b d c e c c ca e, a e ace. T e effec e a e e " e a e be g 1.

6.9.1 Non-Decreasing Entropy in Systems with Uniform Stationary Distribution

If a e E . (6.109) a a a a d b = 1 ∀ ,

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

ca e,

$$\begin{aligned} \frac{dS}{d} &= -\sum_{=1}^{N}\Big(\frac{d ( )}{d}\Big) = -\sum_{, =1}^{N}\Big(- \Big) \\ &= \sum_{, =1}^{N} \Big(\text{—}\Big) \geq \sum_{, =1}^{N} \Big(\text{—} - 1\Big) \\ &= \sum_{=1}^{N} \Big(\sum_{=1}^{N} \Big) = 0. \end{aligned} \tag{6.112}$$

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

6.9.2 Q-Processes with Detailed Balance

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

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

c

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

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

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

$F = \overline{E} - TS$ a e "f ee e g f a e d a c . I e ec ed ca dec ea e e e a a ac g e b . e b ead a e, e f ee e g eac e .

6.9.3 Monotonicity of Change in General Q-Processes

E c aged b e ab e e , e c de e K bac Le b e d e g ce, a a e a e :

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

O e c ac a a dF/d ≤ 0 f g e a Q- ce e de a ed ba ce:

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

$$= \sum_{,\ =1}^{N} \left(\frac{(\ )}{(\ )}\right) \leq \sum_{,\ =1}^{N} \left(\frac{(\ )}{(\ )} - 1\right)$$

$$= \sum_{=1}^{N} - \left(\sum_{=1}^{N} \big(\quad - \quad \big)\right) = 0. \tag{6.117}$$

6.9.4 Balance Equation of Markov Dynamics

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

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

e e $(\ ) \geq 0$ g (6.111b), d

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

See [9] f e f f e a . B E ( ) d ( ) a ega e c e a E . (6.118a) c be e ed a " e F( ) a a ce d a , c ge e a E ( ), a ce e , d d a ( ), a e . T e a e c c c e a f e F. E a (6.118a) e e g e E . (6.111a), c J_S d e a e a def e .

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

T a e a a ca a e e ca a e e ec , c ec e , ***mathematicothermodynamics*** [9, 10, 21, 24].

6.9.5 Driven System and Cycle Decomposition

T e d c g (6.111b) ca be a

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

e e φ = ( ) e e a bab fl f a e . I ca be a , a a a Q ce , e ab e e e ca be e e ed a a [14]

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

c $\varphi_\Gamma^{\pm}$ e be f Γ c c e c e ed a e, e f a d d bac a d d ec . M , f c c e $\Gamma = (_0, _1, \cdots, , _0)$

$$\frac{\varphi_\Gamma^{+}}{\varphi_\Gamma^{-}} = \frac{_{01}\ _{12} \cdots \ _{-1}\ _{0}}{_{10}\ _{21} \cdots \ _{-1}\ _{0}}, \tag{6.121}$$

c de d f e bab e ! T e ef e, $\left(\varphi_\Gamma^{+}/\varphi_\Gamma^{-}\right)$ ca d d be de d a e d c e c c e, d e $\left(\varphi_\Gamma^{+} - \varphi_\Gamma^{-}\right)$ a a c e a c e be f c c e c e ed a g a a ec . A e e b d c c a ed e (6.121); ab e c c c e [27]. If a Ma ce de a ba ced, d c e eac d e e e c c c e.

I e ce f A. N. K g a e (6.121) e a f eac d e e c c e f d f e Ma ce de a ed ba ced. T e ef e, a a ca f *detailed balance* de a fi g de c f a -d e c e ead a e e b . F a d e c , a ea e f e c c e e a e ace Γ a ba ced c c a : $\varphi_\Gamma^{+} \neq \varphi_\Gamma^{-}$.

6.9.6 Macroscopic Thermodynamics in the Kurtz Limit

F a DGP N ec e d M eac , e F f c d ced Sec . 6.9.4 a f c a f e bab d b $_V(\mathbf{n},)$ c e f a f c f e eac e V. T e a a a a ac c c a $V \to \infty$ a e K ? I c be a [10]

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

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

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

c $\mathbf{n} = (\ _1, \ _2, \cdots, \ _N)$, e be f ec e f e ec e , $\mathbf{x} = (\ _1, \cdots, \ _N)$ e c e d g be d $\mathbf{x} = \frac{\mathbf{n}}{V}$. T e K e Sec . 6.7 a e a e c a c a ec f a DGP, $\mathbf{n}_V(\ )$,

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

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

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

T ead a e a ge de a a e f c $G \ (\mathbf{x})$ c be d fied a a g e a ed G bb f c f e b c ca eac . I c be a

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

T a g e a a f e e a E . (6.77). See [10] f e f.

6.10 Summary and Conclusion

T c a e e a e de g a ad f b g ca d - ce e a c f e a f d d a , eac e e a deg ee f f eed . T e d d a a e g ed b a [illegible] *Delbrück-Gillespie process*. [illegible] T. G. K[illegible] [illegible] ODE[illegible] Sec. 6.9, [illegible] (1) [illegible] DGP, (2) [illegible] ODE, and (3) [illegible]

6.11 Exercises: Simple and Challenging

6.11.1 Simple Exercises

1. [illegible] λ.
2. [illegible] λ. [illegible] $^{*} =$ [illegible] $\{\ _1, \ _2, \cdots, \ \}$. [illegible] $J_{T^*}(\ ) = \ \lambda \ ^{-\ \lambda \ }$.
3. [illegible] $J_T(\ ), J_T(0) = 0$ [illegible] $J_T'(0) \neq 0$ [illegible] $T^* =$ [illegible] $\{T_1, T_2, \cdots, T\ \}$ [illegible] $\to \infty$?

6.11.2 More Challenging Exercises

4. [illegible] λ, [illegible]

   (a) [illegible] ? [illegible] ? [illegible] ?

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

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

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

( ) T e ea a a e defi ed a

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

Ba ed e f d ffe a e a b a ed ( ), w a

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

5. T e 3- a e Ma ,

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

a be w de ed b c de e c f a a c ge f a g e e ec e de g g ee d ffe a e A, B, d C. F e e, A -ac e, B a a ac e, d C f ac e.

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

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

w e $\mathbf{Q}$ a 3×3 a . W e $\mathbf{Q}$ f e . S w a e f eac d e e w e . D bab c w a e ea g f e ?

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

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

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

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

6. C de a g e e E e ea f b a e ec e S. T e M c ae Mn n e c

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

Beca e e e a g e e ec e g, e c c a f S c be a ed a a c , a e a e $_S$.

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

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

I c ea a e e f e e e f a e E E^* c a c. Le T be e d e. W a e bab d b f T, $_{J T}(\ )$? H e a ed $_{E^*}(\ )$?

C e e ec ed a e $\mathbb{E}[T]$. C a e e e M c ae M f a.

References

1. D.A. Bea d, H. Q , *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 , J.L. Leb , Ne a ac e b ce e . P . Re . **99**, 578 587 (1955)
3. R.D. C , *Renewal Theory* (Me & C , Ne Y , 1970)
4. P.G. de G e , M ec a d d a . Sc ceE

16. A.J. L a, A a ca e ce a c e a ga c . P c. Na . Acad. Sc . USA **6**, 410 415 (1920)
17. J.D. M a , *Mathematical Biology I: An Introduction*, 3 d ed. (S ge , Ne Y , 2002)
18. L. O age , Rec ca e a e e be ce e , I. P . Re . **37**, 405 426 (1931)
19. H. Q a , Ce a b g e f c a c ea b c ca d c : e g e e , g e c a a d c ca e ab . J. S a . P . **141**, 990 1013 (2010)
20. H. Q a , N ea c a c d c f e c c g e b c ca eac a a ca e (edac e). N ea . **24**, R19 R49 (2011)
21. H. Q a , A dec f e e b e d ff ce e de a ed ba ce. J. Ma . P . **54**, 053302 (2013)
22. H. Q a , *Nonlinear Stochastic Dynamics of Complex Systems, I: A Chemical Reaction Kinetic Perspective with Mesoscopic Nonequilibrium Thermodynamics* (2016). A X :1605.08070
23. H. Q a , L.M. B , T e c ca a e e a a ac e b ead a e f b c ca : ea g e ec e e e c d ea b c ca eac e (Re). J. M . Sc . **11**, 3472 3500 (2010)
24. H. Q a , M. Q a , X. Ta g, T e d c f e g e a d ff ce : e e e b d d c . J. S a . P . **107**, 1129 1141 (2002)
25. H. Q a , S. Saffa a , E.L. E , C c a fl c a a e c c c a g c ca eac . P c. Na . Acad. Sc . USA **99**, 10376 10381 (2002)
26. H. Q a , P. A , Y. T , J. Wa g, A f e a d de d g e c c a a: E e g ed c ab e b ea g d d c ac ca e . C . P . Le . **665**, 153 161 (2016)
27. H. Q a , S. K e , A.B. K e , D. Bedea , E d c e c c c a c e d c N e b e c c c e d b c ca a , e a e , d ec ca f ce (T ca e). J. P . C d . Ma e **28**, 153004 (2016)
28. D.B. Saa , H. Q a , *Nonlinear Stochastic Dynamics of Complex Systems, III: Nonequilib-*