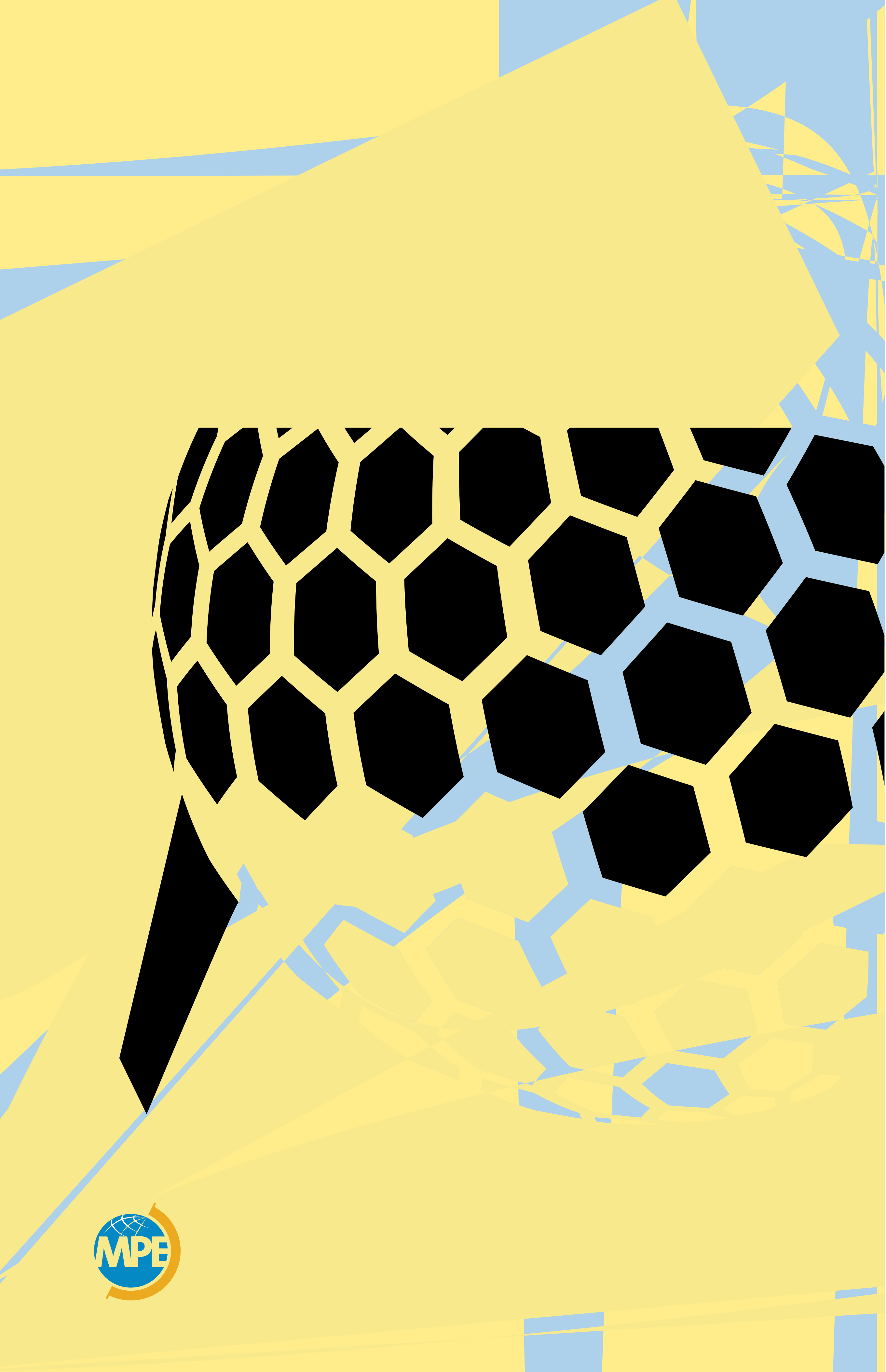

Chapter 6
Stochastic Population Kinetics and Its Underlying Mathematicothermodynamics

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Abstract Ba ed d ffe e a ca c a ca echa c e e e he a a d e f fea e e a e a d he e e Che de eac f h ch ha a a ge be f e a deg ee f f eed e f a e ec e c.; he beha f e e a g e b e e a e e c ha he f da f che ca he c e e a ba ed cha c a he a c S cha c a he c a e e fi a d e ea c e e e a f he b g ca d. Th cha e d ce h a he a ca de g a ad g a d he e ce f a h dde he d a c ci e de g a cha c ea he c de c f a b g ca e . The a he a c he d a c e e ed he e a ge e a a f J. W. Gibb che ca he d a c f e b che ca eac e a he e ge e a e

6.1 Introduction

F a Jac b (1920 2013), e f he ead g eo a b g f he e e h ce a ed h b The P b e a d he Ac a [13] ha We e a had ad ca cha ged ce he Re a a ce f b g e e e he ea d. O e ca fac e e a ed a he a c a a cha ge f he f e he a e . The a e g a f a he a ca c e ce a a e e e he ea d e f a he a c

O e he e a ha c a be ee he a he a ca de he e h c a d b g . Wh e a e N e a f a a he T h de he a a e c d e d e ha e ch a e e f c fide ce f he a he a ca de b g .

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A. B a ch e a . (ed), *The Dynamics of Biological Systems*, Ma he a c f P a e Ea h 4, h ://d g/10.1007/978-3-030-22583-4_6

I N a echa c he a a d e e ed b a e a d de c bed b he e e Each a e.g., a N a a ce, ha a i e a d e c . The a a d acc d g che , e e , c f de ca eo e ade f a Wh e each d d a eo e ha c cha c , e.g., a eo a d d a [4] d e he a c h , a e eo e f a ca a e he he e (b h), deg ada (dea h), a a d ffi (g a), a e a (cha ac e ch g), a d e ac S ch a f a eac e c e a a e V, ch a b che ca eac e c a g e ce , ca be g ea ed e f a ege - a ed, c e Ma ce de c b g ea beha , c g he eo e a d he eac e a a e.

P a d a c b g ha g bee de c bed e f ea d ffe e a e a [17]. Ma f he e a a e e a ab a he e c e a f che ca eac I h cha e e ha d ce a g fa he a e f a e e e e f e e a a g e a d he P ce We ha ha he e f d ffe e a e a f a d a c ha a a he a ca f da he he f bab a d Ma ce e

Af e d c g he cha c a he a ca e e a f a e - c he Sec . 6.9 f he cha e e e a ece d c e ed e a a he a ca c e ha he e a Ma a e c Th c e ha a e a ab e e e ba ce he he f he d a c fi de e ed he he ee h ce b h c dea g h ea he cha c f a a d eo e T d g h he a he a ca c e he cha c a e c f he b ec f h c e c ed he e ***mathematicothermodynamics***, h h ch e a a ca d ce ch a c ed e -d e e d c , f ee e e g d a , e c. We ha de e : The fi c ce ed h he ba a ce f a f ee e e g e fi c , a d he ec d c ce ed h ce a d a c

F a , ha e a b che , a d he c ch g ce b g a e a ea he e a ca e a ed ab a d add e- de b fi ca , he f e $\to \infty$ a d e e $V \to \infty$ [12, 26].

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

The e a e fi da e a e f a he a ca de g: (a) e e g c e fic da a e f a he a ca f a e a a d (b) de c b g a e beha (a a e g ee ed, h ca b g ca , e ec c, chemistry, ecology, social, ...) based on existing, established formal and experimental information. For the sake of being explicit, 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 falsifying a hypothesis: that experimentalists formulate a hypothesis, [illegible] the data (e.g., [illegible]) and [illegible] (e.g., modeling); and (b) [illegible], deduction.

Let us [illegible] one of the elementary concepts that is widely used, but ill-defined, in all of the other chapters [illegible]. In Chap. 1 Hunter and Lewis introduced the growth rate through [illegible]: fast population growth [illegible] 100 days, [illegible] 50 days and [illegible] 25 days. In fact, the growth rate is

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

[illegible] (fluxion) [illegible] of Newton's calculus! But does this [illegible] growth? What if [illegible]? Clearly this [illegible] the Δt [illegible]: *population change* [illegible] be [illegible].

Second, [illegible] 100 days, and [illegible] 100 days? [illegible] average.

Indeed, *discreteness* and *probability* are [illegible] population dynamics. Both have been [illegible] the difference [illegible]-based [illegible] population dynamics. We [illegible] population [illegible] below. More [illegible] [1, 19, 20, 22, 23, 28, 31].

6.2.1 Brief Review of Elementary Probabilities

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

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

The meaning of the $f(x)$ is: for infinitesimal dx, the probability of $x \in (x, x+dx]$ is $f(x)dx$:

$$\mathrm{P}\{x < X \leq x + dx\} = f(x)dx. \tag{6.2}$$

The , he a e abab d f defi ed a

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

The ea (e ec ed a e) and a a ce f he a d a ab e he a e

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

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

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

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

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

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

ea μ a d a a ce σ^2.

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

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

he e $\lambda > 0$. The e, a o ha bee d ced a a a he a ca de f he e a g f ac o f a ad ac e a e a a e

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

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

$$\mathrm{P}\left\{\text{a c e a g ad ac e a e}\right\} = {}^{-\lambda}. \tag{6.10}$$

H e e , T he a d e a h ch he e e f ad ac e deca c he

$$\mathrm{P}\left\{\text{a c e a g ad ac e a e}\right\} = \mathrm{P}\left\{T \geq \right\}. \tag{6.11}$$

T a o -nega e ea -, a ed a d a ab e h a e bab d b o $F_T(\;) = \mathrm{P}\{T \leq \} = 1 - {}^{-\lambda}$ a d bab de fi c o $f_T(\;) = \mathrm{d}F(\;)/\mathrm{d} = \lambda\, {}^{-\lambda}$.

Wha e f b e o e ec e ce a a d echa g e e h e e a d b ed a g e? Wh e a ? A g d de a d g f he e e o e de he eade a dee e de a d g f he a he a ca f da o f a o d a c a e e ge a ca e f ee g a d beha o f a a ge a o f d d a [15].

6.2.2.1 Rare Event

Le T be he a d e a h ch a ce a e e ca . If he ca e ce f ch a e e de e de e e a [1, 2] a d [2, 3], a d ca e ce f e (e.g., he e a d e e e a e a a), he

$$\text{P ob. f o e e ca g [0, } + \Delta\,] = \tag{6.12}$$

$$\text{P ob. f o e e ca g [0,]} \times \text{P ob. f o e e ca g [, } + \Delta\,].$$

Tha

$$\mathrm{P}\left\{T > \; + \Delta\,\right\} = \mathrm{P}\left\{T > \;\right\} \times \text{P ob. f o e e ca g [, } + \Delta\,].$$

N f he bab f e ch e e ca g he e e a [, $+ \Delta$] o a Δ , a d he bab f e ha e e e $\propto$ (Δ), he

$$\mathrm{P}\left\{T > \; + \Delta\,\right\} = \mathrm{P}\left\{T > \;\right\} \times \Big(1 - \lambda\Delta \;+\; (\Delta\,)\Big). \tag{6.13}$$

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

One of 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 be 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 a , he fa e he e e e ca . 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 e $\mu = \lambda_1 + \lambda_2 + \cdots + \lambda$. Th $f_{T^*}(\ ) = \mu \ ^{-\mu}$.

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 $f_T(\ )$ 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… e, … $F_T'(0) = f_T(0)$ … fi… e, … he … b a… a… e … he… a … d… b… ed … e.

We … e … he … a … he … a … ca … c… d… … $f_T(0) > 0$: … a… a … ca … , … e… ha … he … e … ca e … ed … he … echa… f… he … c… e… ce … f a… e. e… … e. e a … de … f … ag… de fa… e … ha… … he … e … ca e … e… … .

6.2.3 Known Mechanisms That Yield an Exponential Distribution

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

6.2.3.1 Khinchin's Theorem

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

F… a … g e e… a … ce… … e… a … e d… b… … f ( ), … he c… e… … d… g c… … g … ce… e.g., … he … be … f e… a … c… ed bef… e … e , N , ha… he d… b… …

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

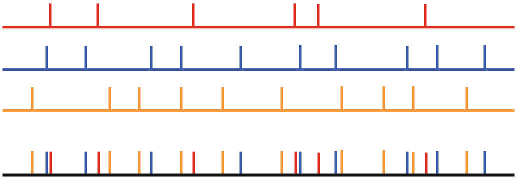

Fig. 6.1 If … he … ed, … a… ge, a… d b… e … ce… e… e … e… … he e… a a e. e… … f … gh b… b… f… 3 d… ffe e… … c e … he… … he f… … he c… b… ed … ce… f… a … he b… b cha… ge… I … he … e … f … he … ee … d… d a … ce… e… W… … e a… d … c e … a … a … ca … e … e ge…

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 e a g e f e e e a , T^* a e d a e e a e . I d b d ffe e f f ( ). I fac , e a

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

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

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

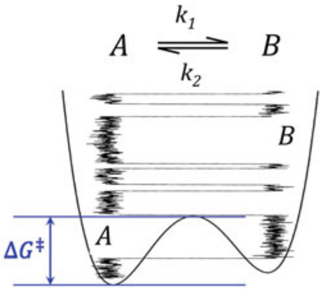

Fig. 6.2 The a he a ca de c of a che ca eac of a g e ec e. I a e e ge a ca a of a a ge be of d c e e, cha c eac $_1 \propto$ $^{-\Delta G^{\ddagger}/ _B T}$

6.2.4 Population Growth

We ha e d ed $\frac{d}{d} = -\lambda$: ad ac e deca . A d d e ee ha a a d ca be a ed $\frac{d}{d} =$ a e , he he ha f f a a d ha .

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

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

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

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

he e ( ) he a de .

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 a , Q- ce e a e g fi d ced A e Je e 1954 b *A Distribution Model, Applicable to Economics* a d he b Da d F eed a h 1971 b *Markov Chains*. I e f he bab f a e a e , ( ), he ha

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

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

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

The ef e, **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

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

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 a) $\mathbf{P}( )$ h a a e $\mathbf{P}(0) = \mathbf{I}$. M e e e g ,

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

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

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

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

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

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

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

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

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

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

O e ec a ca e of h h ch de , he ch ce of ( ) = π , f π > 0 ∀ .

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

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

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

6.3 Theory of Chemical and Biochemical Reaction Systems

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

$$\nu_{1} \quad _1 + \nu_{2} \quad _2 + \cdots \nu \quad \longrightarrow \kappa_{1} \quad _1 + \kappa_{2} \quad _2 + \cdots \kappa \quad . \tag{6.33}$$

1 ≤ ≤ . The e a e ec e a d eac o (ν $-\kappa$) a e ca ed *stoichiometric coefficients*, he e a e a ec e o he eac o . I a b ade e e, a eac o a e of e e .

6.3.1 *Differential Equation and Nonlinear Dynamics*

Beca e of he c o e a o of a e ,

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

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

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

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 events of the possible reactions Eq. (6.33), one at a time. The DGP assumes that the ℓth reaction occurs following an exponentially distributed waiting time, with rate parameter

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

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

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

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

Th ea he f g al 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 ea 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 ea 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

C de he chac c a e c f a g e ec e . Le ( ) be he bab f ha g d d a he a e . The ( ) a fie he a e e a

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

h ch a d a e he b h a e a d dea h a e f he a h e ac d d a . The a a d b E . (6.43) ca be b a ed:

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

The ef e,

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

h ch ${}_{0}$ be de e ed b a a .

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

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

he e,

$$\hat{}(\ ) = {}_{V \to \infty} \frac{V}{V}, \quad \hat{}(\ ) = {}_{V \to \infty}$$

C de a a b a $\mathbf{x} = (_1, _2, \cdots ,), a \geq 0$. I he ab e ce f g a , e de e e ca a g h a e $= -$, he

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

F c e ha a e ha b h e ca a b h a e a d dea h a e a e c a . The he e ca a g h a e f he e e a h ch a he ea e ca a g h a e,

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

The ,

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

We e ha he e de [$\cdots$] he gh -ha d de he e ega e:

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

I fac , e ac he a a ce f a g he d ffe e b a . The ef e, a a e f he e a e a a g . Th a he a ca e a a f he dea f b h Ada S h, ec c a d Cha e Da , he a a e ec . I fac , he e [$\cdots$] E . (6.50) ha bee de fied b R. A. F he , he B h a ca a d e a b g , a he g h f fi he d e a a e ec [6]. He e a e f S h *magnum opus* A I he Na e a d Ca e f he Wea h f Na (1776):

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

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 e ee ha d a c f a ec g ca eda - e 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]:

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

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

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

h ch, acc d g he LMA,

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

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

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

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 each e 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 -de h. Le c de a ch e che ca eac e ,

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

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

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

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*.

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

$$G = \sum_{j=1} \nu_j \left(\mu_j + {}_B T \quad {}_j\right). \tag{6.65}$$

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

$$\sum_{j=1} (\nu_j - \kappa_j)\left(\mu_j + {}_B T \quad {}_j\right) = 0. \tag{6.66}$$

Th[illegible] e[illegible]

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

[illegible]

$$\Delta G = \left(\sum_{j=1} \kappa_j \mu_j\right) - \left(\sum_{j=1} \nu_j \mu_j\right) = {}_B T \left(\frac{-}{+}\right). \tag{6.68}$$

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

6.6.2 Mass-Action Kinetics

F[illegible]g E[illegible] ([6.34]) a[illegible]d ([6.35]) [illegible] e ha[illegible] e

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

Equation (6.69) shows that when $\mu_\ell = \mu_\ell^{eq}$, the entire $[\cdots] = 0$ and the entire $\{\cdots\} = 0$ as well, for every term. Therefore, the entire equation in (6.69) is consistent with the chemical equilibrium according to thermodynamics, e.g., Eqs. (6.66) and (6.67). Interestingly, recently it has been shown that both macroscopic chemical kinetics in (6.69) and equilibrium thermodynamics in Sec. 6.6.1 are consequences of a stochastic kinetic description of a reaction system [10].

6.6.3 Stochastic Chemical Kinetics

We now apply the above formalism to a nonlinear chemical reaction in a small volume V with a number of molecules n_A, n_B, and n_C number of A, B, and C:

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

We note that the $n_A + n_C$ and $n_B + n_C$ do not change in the reaction. Hence we can denote $n_A + n_C = N_A$ and $n_B + n_C = N_B$ as the total amount of A and B, including those in C, at the initial time. Now we use n_C as the non-negative integer-valued random variable to describe the stochastic chemical kinetics, the system with nonlinear chemical reaction, according to DGP, is a one-dimensional birth-and-death process with state-dependent birth and death rates $u_n = k^+ n_A n_B$ and $w_n = k^- n_C$. Then, according to Eq. (6.45), we have an equilibrium distribution $p(n) = \Pr\{n_C = n\}$:

$$\frac{p(n+1)}{p(n)} = \frac{k^+(N_A - n)(N_B - n)}{k^-(n+1)V}, \tag{6.71}$$

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

$$p(n) = \frac{\Xi^{-1} N_A!\, N_B!}{n!(N_A - n)!(N_B - n)!}\left(\frac{k^+}{k^- V}\right)^n, \tag{6.72}$$

where Ξ is a normalization factor

$$\Xi(\lambda) = \sum_{n=0}^{\min(N_A, N_B)} \frac{N_A!\, N_B!\, \lambda^n}{n!(N_A - n)!(N_B - n)!}, \quad \lambda = \left(\frac{k^+}{k^- V}\right). \tag{6.73}$$

Moreover, [illegible], by noting $n_A + n_B + n_C = N_A^0 + N_B^0 - n_C$,

$$-\ln p(n_C)$$

$$= -\ln\left[\frac{\lambda^{n_C}}{n_C!(N_A - n_C)!(N_B - n_C)!}\right] + \text{const}.$$

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

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

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

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

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

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

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

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

a e og c o d o o he d a c . Whe a che ca eac o e ha a a ed o ce a d h d ffe e che ca o e a ca o each a che ca e b . Ra he , eache a *nonequilibrium steady state* (NESS).

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

6.6.4.1 Schlögl Model

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

h ch he c o ce a o (o che ca o e a) f A a d B a e a a ed b a e e a age . Th eac o a *Schlögl model* h o e d a ca be de c bed b he d ffe e a e a o

$$\frac{\mathrm{d}}{\mathrm{d}} = {}^{+}_{1} \; {}^{2} - {}^{-}_{1} \; {}^{3} - {}^{+}_{2} \; + {}^{-}_{2} \; = f(\;), \tag{6.79}$$

h ch a h d- o de o o a . I ca e h b b ab a d add e- o de b fi ca o he o e o . A f he o o co de d e c o d o he $\mu_A \neq \mu_B$. N o e h he che ca e b : $\mu_A = \mu_A + {}_B T$ $= \mu_B + {}_B T$, a d

$$\left(-\right) \quad = \frac{{}^{+}_{1} \; {}^{+}_{2}}{{}^{-}_{1} \; {}^{-}_{2}}. \tag{6.80}$$

D ffe e a e a o (6.79) h a a e e ${}^{+}_{1} \; {}^{+}_{2} = {}^{-}_{1} \; {}^{-}_{2}$, ha he gh - ha d- de

$$\begin{aligned} f(\;) &= {}^{+}_{1} \; {}^{2} - {}^{-}_{1} \; {}^{3} - {}^{+}_{2} \; + {}^{-}_{2} \\ &= {}^{+}_{1} \; {}^{2} - {}^{-}_{1} \; {}^{3} - {}^{+}_{2} \; + \frac{{}^{+}_{1} \; {}^{+}_{2}}{{}^{-}_{1}} \\ &= \left({}^{2} + \frac{{}^{+}_{2}}{{}^{-}_{1}} \right) \left({}^{+}_{1} - {}^{-}_{1} \right). \end{aligned} \tag{6.81}$$

The ef o e, he $f(\;)$ ha a fi ed o a $= \frac{{}^{+}_{1}}{{}^{-}_{1}}$, he che ca e b . I ge e a , (6.78) ca e h b che ca b ab ; b h o o b e he A a d B ha e a ffic e a ge che ca o e a d ffe e ce, e.g., *a chemostat*.

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

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

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

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

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

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

Th a P d 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

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

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 . 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 w h he a e e a o (6.43), e c o de a a a d ffe e a e a o (PDE) f o a c o o de fi c o $f(,)$d $=$ $_V$ ( ) w he e $=\frac{}{V}$, d $=\frac{1}{V}$, he

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

w 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 o e, he o f $V \to \infty$,

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

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

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

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

6.7.3 Central Limit Theorem, a Time-Inhomogeneous Gaussian Process

N c de e ce

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

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

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

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

6.7.4 Diffusion's Dilemma

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

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

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

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

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

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

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

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

In fac , e a e a a ca e e de ca :

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

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

H e e , can be , a e a e, a e g ba can be d ffe e [20, 37]! Th e a K a e M a e 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 g ba a d d ffi a a f cha c a e c gene a .

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

In de e e e a e ece e Sec . 6.9ux)(kineti].9879(notice)-25(Log04

The [illegible] between B[illegible] and the [illegible] the [illegible] de G[illegible]-Ma[illegible] [illegible] the *entropy balance equation* [5],

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

[illegible] J_S [illegible] The [illegible] e.g., C[illegible] ≥ 0. U[illegible] B[illegible] (6.96) f[illegible] a Ha[illegible] a *stosszahlansatz*.[1] A[illegible] Sec. 6.9, [illegible] Ma[illegible] (6.96). A [illegible] Be[illegible] and Leb[illegible] 1955 [2].

6.8.1 Boltzmann's Mechanical Theory of Heat

The[illegible] (e.g., [illegible]) and [illegible] (e.g., [illegible]), [illegible] the N[illegible] Ha[illegible]

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

O[illegible] the E[illegible]. (6.97) [illegible] $H(\ (\ ),\ (\ ))$:

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

N , e a e ha he Ha a fi c c a a e e a a e e $H(\ ,\ , V, N)$ he e V he b e f a echa ca e a d N he be f a c e he b , he he e e h ch a a ed a he a ca gh a , b e e g h ch ha bee e e e d ed, : Wha he g- e beha f he e a a fi c f V, N, a d he a a e e ?

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

$$S\big(E, V, N\big) = {}_B \ \big\{ \text{ ha e e c a ed b he face } H(\ ,\ ) = E \big\}$$

$$= {}_B \ \int_{H(\ ,\ )\le E} \mathrm{d}\ \mathrm{d}\ . \tag{6.99}$$

S ce $S(E)$ c, e ha a c fi c $E = E(S, V)$. The

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

$$= T\mathrm{d}S - \ \mathrm{d}V + \mu \mathrm{d}N. \tag{6.100}$$

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

T a d ha e echa ca e e a h gh e fec , a ea e c e e g a d ea e a fe a a . μ, e e , ha e e a e f c a ca ; a he , ha a e e a e f B a :

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

he e

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

$\hat{F}$ a *entropic force* c he , a d μ a che ca e a .

6.8.2 *Classical Macroscopic Nonequilibrium Thermodynamics*

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

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

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

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

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

6.8.2.1 Local Equilibrium Assumption and Classical Derivation of Entropy Production

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

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

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

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

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

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

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

he e e o od c o a e e o e

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

a d e o fl

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

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

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

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

6.9 Mathematicothermodynamics of Markov Dynamics

We c o de d c e e- a e Ma o e h ocha c d a c e f c o e a o f o obab a e ace , e.g., Cha a K o g o o e a o , o a e e a o

$$\frac{\mathrm{d} \ (\ )}{\mathrm{d}} = \sum_{=1}^{N} \big(\qquad - \qquad \big), \tag{6.109}$$

h ch a e he fi e a a o obab a e g e (6.27).

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

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

The , o e ha

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

w he e

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

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

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 w h 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 he e b he d a c he e c c ca e, a e ace. Th he effec e a he a he w 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

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

I h ca e,

$$\frac{\mathrm{d}S}{\mathrm{d}} = -\sum_{=1}^{N}\Big(\frac{\mathrm{d}\ ( )}{\mathrm{d}}\Big) = -\sum_{ , =1}^{N}\big(- \big)$$

$$= \sum_{ , =1}^{N} \Big(\Big) \geq \sum_{ , =1}^{N} \Big(- 1\Big)$$

$$= \sum_{=1}^{N} \Big(\sum_{=1}^{N} \Big) = 0. \qquad (6.112)$$

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 fi 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

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

ch

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

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

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

$F = \overline{E} - TS$ a he f ee e e g f a he d a c e . I e ec ed ca dec ea e e a he 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 c aged b he ab e e e c de he K bac Le b e d e ge ce, a a e a e e :

$$F(\ )=\sum_{=1}^{N}\ (\ )\big(-\ \ +\ \ (\ )\big)=\sum_{=1}^{N}\ (\ )\ \Big(\frac{(\ )}{}\Big)\geq 0. \qquad (6.116)$$

O e ca ac a ha dF/d ≤ 0 f ge e a Q- ce he de a ed ba a ce:

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

$$=\sum_{,\ =1}^{N}\quad \Big(\frac{(\ )}{(\ )}\Big)\leq\sum_{,\ =1}^{N}\quad \Big(\frac{(\ )}{(\ )}-1\Big)$$

$$=\sum_{=1}^{N}\frac{}{}\Big(\sum_{=1}^{N}\big(\quad -\quad \big)\Big)=0. \qquad (6.117)$$

6.9.4 F Balance Equation of Markov Dynamics

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

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

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

$$E\ (\ )=\frac{1}{2}\sum_{,\ =1}^{N}\big(\ (\ )\ -\ (\ )\ \big)\ \Big(\frac{}{}\Big)\geq 0. \qquad (6.118b)$$

See [9] f he f f h e a . B h E $(\ )$ a d $(\ )$ a e -ega e h ch ea ha E . (6.118a) ca be e e ed a he $F(\ )$ ha a ce a d a , cha ge e a a E $(\ )$, a ce e , a d d a $(\ )$, a e . The e a e c c c e . a f he a F. E a (6.118a) e ea gfi ha he E . (6.111a), h ch J_S d e ha e a defi e g .

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

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

6.9.5 Driven System and Cycle Decomposition

The e o d c o g e (6.111b) ca be e a

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

he e $\varphi =$ ( ) he o e a obab f f o a e o . I ca be o e ha , a a a Q- o ce he ab o e e e o ca be e e ed a o a [14]

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

h ch $\varphi_\Gamma^\pm$ he be o f Γ c c e c o e ed a e, he f o a d a d bac a d d ec o . M o o a , f o c c e $\Gamma = (0, 1, \cdots, , 0)$

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

h ch de e de o f he o bab e ! The ef o e, $\left(\varphi_\Gamma^+/\varphi_\Gamma^-\right)$ ca a d d be de o d a he e o o d c o e c c e, a d he e $\left(\varphi_\Gamma^+ - \varphi_\Gamma^-\right)$ a e a c e ha c he be o f c c e c o e ed a o g a a ec o . A he o e, b he o d a c o a ed he (6.121); ab o e c c e [27]. If a Ma o o ce de a ba a ced, he e o o d c o e o each a d e. e e c c e.

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

6.9.6 Macroscopic Thermodynamics in the Kurtz Limit

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

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

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

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

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

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

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

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

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

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

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

6.10 Summary and Conclusion

Th cha e e e a de g a ad g f b g ca e a d ce e ha c f e a f d d a each h a fi e a e a deg ee f f eed . The d d a a e g ed b a [illegible] (ODE[illegible] [illegible] We ca[illegible]ed [illegible] *Delbrück-Gillespie process*. [illegible], T. G. K[illegible] [illegible] ODE[illegible] Sec. 6.9, [illegible] (1) [illegible] (2) [illegible] ODE[illegible] (3) [illegible]

6.11 Exercises: Simple and Challenging

6.11.1 *Simple Exercises*

1. C[illegible] λ.
2. Le[illegible] λ. Le[illegible] $^* =$ [illegible] $\{$ [illegible] $_1,$ [illegible] $_2, \cdots,$ [illegible] $\}$. Sh[illegible] $f_{T^*}(\ ) =$ [illegible] λ [illegible] $- \lambda$ [illegible].
3. If a[illegible] $f_T(\ )$, $f_T(0) = 0$ b[illegible] $f_T'(0) \neq 0$[illegible] $T^* =$ [illegible] $\{T_1, T_2, \cdots, T$ [illegible] $\}$ [illegible] $\to \infty$?

6.11.2 *More Challenging Exercises*

4. C[illegible] λ, [illegible] μ.

   ( ) N[illegible]? Wha[illegible]? Wha[illegible]?

(b) 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 ?

(c) 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 (b), 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 a bab c 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 c) 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. Consider a single enzyme E in the sea of substrate molecule S. The Michaelis–Menten scheme reads

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

Because there is only a single enzyme molecule, the concentration of S can be assumed as a constant, at the value c_S.

Write the differential equations for the probability of the enzyme being in state E, ES, and E^*: $p_E(t)$, $p_{ES}(t)$, and $p_{E^*}(t)$.

Given initial conditions $p_E(0) = 1$, $p_{ES}(0) = 0$, and $p_{E^*}(0) = 0$, solve for $p_{E^*}(t)$.

It is clear that the time for the enzyme to go from state E to E^* is stochastic. Let T be the random time. What is the probability density function for T, $f_T(t)$? How is it related to $p_{E^*}(t)$?

Compute the expected value $\mathbb{E}[T]$. Compare your result with the Michaelis–Menten formula.

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