

Chapter 6 Stochastic Population Kinetics and Its Underlying Mathematicothermodynamics

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Abstract Baed on differential calculus, classical mechanics represents the natural mecha \blacksquare world in terms of featureless point masses and their movements. The studies of \blacksquare when \blacksquare m_{ϕ} each of the state of a large number of ϕ internal degrees of freedom internal degrees of ϕ $\mathbf{e}_r = \mathbf{e}_r \mathbf{a}_r$, e.g., the behavior of e.g. \mathbf{a} , \mathbf{e}_s of \mathbf{e}_r , \mathbf{e}_s is e n is often so complex that the foundation of chemical solution of e based on stochastic mathematics. Stochastic population α and population α or ψ efful and be ealing the biological world. This chapter is chapter introduces and α $h \cup h$, a he a ca, delle a della modeling and h , and existence of a hidden thermodynamic structure underlying any stochastic nonlinear kinetic under any of a multi-population biological system. The mathematicothermodynamics presented \vec{h} e \vec{e} a general \vec{e} a \vec{e} \vec{b} . W. \vec{G} bbs \vec{c} che \vec{c} a \vec{d} thermodynamics \vec{d} che ca eac $\sqrt{2}$ - $\frac{1}{2}$ - a heterogeneous matters.

6.1 Introduction

Fah. Jacob (1920–2013), she of the eading molecular biology of the two ends of the two states of the two states of the two states of the twentieth contract of the two states of the twentieth contract of the twentieth cont century, stated in his book "The Possible and the Actual" [\[13\]](#page-39-0) that Western art had ad can changed since the Renamic from \log_{10} to \log_{10} represent the real world. One can in fact view pure versus applied mathematics and a change from the set of \mathbb{R} f_{\bullet} e $_{\bullet}$ be a e. The ultimate goal of mathematical science is to $_{\bullet}$ at $_{\bullet}$ e e^r e.g. he easy of d $\log a$ and a he a e^r . $C \cdot e$ between the contrast between the mathematical models, or theories, or theories, or theories, or theories, $C \cdot e$ in physical in biology. Which we are Newton's equation of motion as almost motion as almost \mathbb{R}

the Truth θ inder the appropriate appropriate approximate θ of θ of θ of θ and θ of θ of confidence for the mathematical models in biology.

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H. Qa \setminus (\boxtimes)

De a_n en of A ed Mate a c University of Warthematics, Seattle, WA, USA $e_{\overline{M}}$ a \overline{M} and \overline{M} and

In New \mathbf{a}_1 \mathbf{a}_2 and \mathbf{a}_3 are point mechanics, the natural \mathbf{a}_1 are point mass set of \mathbf{a}_2 are point mass set of \mathbf{a}_3 are point mass set of \mathbf{a}_4 are point mass set of \mathbf{a}_5 are point and described by the secret movements. Each point mass, a New only in sec. has a unique **position** and velocities and according to chemistry, $\mathbf{a} \cdot \mathbf{b} = \mathbf{c}$ however, consists of \det_a at ca of ca and ca at a is a . While each \det_a is a molecule has intrinsic stochastic a tomic motions with motions with more follow statistical rate laws in the laws in the statistical rate laws i their syntheses (birth), degradations (death), spatial diffusion (migration), state ah \Box el character switching), and interactions. Such a formal reaction \Box is c $s-g$, a small volume V, \downarrow chas biochemical reaction k in a single cell, can be rigorously treated in terms of an integer-valued, continuous-times-Ma \bullet certer blg log let behave, colling the moleculative e eac \Box one at a time.

Por a on dynamics in bonagy has only been described \mathbb{R} expected in the nonlinear differential equations $[17]$. Many of the equations are remarkable similar to the remarkable similar to the equations are remarkable similar to the equations are remarkable similar to the equations are remarkable similar iffe en a control. If \int is chemical reaction for chemical reactions. In this chapter, we shall intervent a control of \int chapter in a control intervent intervent and control of \int chapter in a control of \int chapt rigorous fashion the are $e_n = \frac{1}{n}$ of exponential e_n of exponential e_n of exponential e_n of exponential e_n and the Poisson of the shall show that the type of different a constructions of the type of differential equations for the type of differential equations for the type of differential equations for the type of differential $p \cdot a$ and $\lim_{n \to \infty} a$ a mathematical foundation in the tensor $a \cdot b$ $Ma \cdot \cdot \cdot e^{\cdot \cdot} e$

Afericing the stochastic mathematic mathematical representation of \mathbf{a} of \mathbf{a} of \mathbf{b} and \mathbf{b} \mathcal{L} , in the Sec. 6.9 of the cha^{rt}e _s with each a recently discovered universal discove m_A a m_B a m_B is the independent in any Markov population in any Markov population in any Markov population m_B structure has a remarkable regular balloc of the theory of the theo developed in the nineteenth century by physicial intervalsed in the stochastic dealing with heat—the stochastic motions of a same models of a to distinguish the molecules in the mathematical structure in the mathe schastic population of \mathbf{A}^T be \mathbf{A} be the coing the subject from physics, we consider the term physics of \mathbf{A} *mathematicothermodynamics*, with we know a second left of a seconduce notions in the seconduce \mathbb{R} . \downarrow chas closed systems of energy systems production, free energy production, free energy dissipation of the first is c. We shall derived the first is concerned with the balance of the same concerned with the balance of a free energy left of c_0 , and the second is concerned with c_1 and c_2 \Box hed \Box \Box F_a nally, phase a and b in physics, conformation in physics, a is a in a in b in c in c

and ben_otypic suit ching in cell biology are all nonlinear phenomena in the ca related \mathbf{r} is \mathbf{r} -ability and saddle-node bifurcation, in the limit \mathbf{r} of \mathbf{r} is $\mathbf{r} \to \infty$ $a_{\mathbb{N}}^{\mathbb{N}} d_{\mathscr{L}} \mathfrak{g}^{\mathbb{N}} \mathfrak{g}^{\mathbb{N}} \mathfrak{g} \mathfrak{g}$

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

There are find and the model of mathematical model in the contract of mathematical model in the contract of \log \mathfrak{so} fic data in terms of mathematical formula or equations and (b) describing a ζ system behavior (natural or engineered, physical or biological or economic,

che ca, economica, social, ...) based on e \log , established for a and $e_n^{\dagger}a_{n\ell}$. For $\int_a^b e^{i\ell} e^{$ *modeling* and the atter *mechanistically derived modeling*. Note, $\frac{1}{2}$ acc_od $\frac{1}{2}$ $\frac{1}{2}$ Ka Po e (1902–1994) and h_{is} h_{is philosophy} of science, the only leg_{itimat}e scientific activity is falsifying a hypothesis of the requires first to formulate a hypothesis, a hypothesis, a hypothesis $H \circ \text{Lap}$ e \downarrow e \downarrow , oo Lg for a e Lg , he data (e.g., Mg e ca hypothesis) and sometime is not a mechanism (e.g., when not and (b) of deperture and \mathbf{e} of depth \mathbf{e} and \mathbf{e} rigorous predictions a hypothesis from a form of experiment is a form of logical, ϵ and ϵ and ϵ $ded \ c \ o$.

Let $e \rightarrow e$ of the key notions already discussed, or $de + ed$, in many a of the other cha^{rt}e is but let us to be clear. If Chart I Hillen and Lewis and Lewis to be clear. If Chart I Hillen and Lewis and in the growth rate through a limiting process: if a population growth g of α propulation growth g person events in the state of e_{\bullet} is e_{\bullet} and e_{\bullet} every \bullet on e_{\bullet} every \bullet such and half a e_{ve}le. e $25 da$ Il fac, he g_v h a e

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

In a most vector rate (fluxion) is one of the most important concepts of Newton's ca culus **But does these** a clear to puantify puantify population growth? A half of a e. \bullet , she eh h of a \circ \bullet \bullet 2. These cannot be true when the Δ - \bullet a : *population change* call \bullet have \bullet be \bullet

 $\int \sec \phi \, d\phi$, has any one even such a regular population growth with exactly to e_{rs} in the first 100 days, and another two in the next 100 days? I amplies the next 100 days? I am sure some \mathbf{d} \mathbf{d} \mathbf{v} will say that is just an average.

Indeed, *discreteness* and *probability* a e_v of Id en any e_x and Id is any population degrees been in the differential equation-based description-based description-based descriptionof population dynamics. We shall start discussion of \mathbb{R} below. The start discussion \mathbb{R} M_{or} of the a e^{t} a e a et f_{rom} [\[1,](#page-39-3) [19,](#page-40-2) [20,](#page-40-3) [22,](#page-40-4) [23,](#page-40-5) [28,](#page-40-6) [31\]](#page-40-7).

6.2.1 Brief Review of Elementary Probabilities

A **random variable** $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ a continuous real value has a probab_{ility} density and a probability density density density density densi fi lc \Box (df) f ():

$$
\int_{-\infty}^{\infty} f(\cdot) d = 1, f(\cdot) \ge 0.
$$
 (6.1)

The ealing of $\text{Re } f$ () is this if $\text{Im } f \text{Re } g$ and , the probability of observing $\ddot{\in}$ (, +d] $-f$ ()d :

$$
P\{\leq s \leq +d\} = f\ ()d\ . \tag{6.2}
$$

Then, heq_{α} as e obability distribution of is defined as

$$
F(\) = \mathbf{P}\left\{ \ \leq \ \right\} = \int_{-\infty}^{\infty} f(\)\mathbf{d} \ , \ \mathbf{a}^{\mathbf{r}}_{\mathbf{p}}\mathbf{d} f(\) = \frac{\mathbf{d}F(\)}{\mathbf{d}}. \tag{6.3}
$$

The eah (\bullet expection and and \bullet and \bullet of the and \bullet variable then are

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

Va [] =
$$
\mathbb{E}[(-\mu)^2] = \int_{-\infty}^{\infty} (-\mu)^2 f(.) d(0.5)
$$

 \mathcal{N} h che e have denoted E[] by μ . Two most important examples of $\mathbf{a}_{\mathbf{a}}^{\mathbf{b}}$ a ables a \lg ea aues ae eiles a^r ald " \lg a , also ea ed Gaussial". The f_{ore} e has he standard for

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

w $\frac{1}{\sqrt{n}}$ can and a and being λ^{-1} and λ^{-2} ; the a c has a summarized d form

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

$$
\mathbf{w} \perp \mathbf{h} \quad \text{e} \mathbf{a} \mathbf{h} \mu \mathbf{a} \mathbf{h} \mathbf{d} \cdot \mathbf{a} \quad \mathbf{a} \mathbf{h} \text{ce } \sigma^2.
$$

 Ga ussian normal distribution is distributed; including in popular press Ga [\[11\]](#page-39-4). I \Box is understand as a consequence of the *central limit theorem*. I \Box a $-a$ and c emerging from a large collection of del ca. Independent parts. In the following \mathbb{R} sections, we show that for dynamical processes involving \mathbb{R} populations, there is a much exactly into the integration of \mathbb{R} is a more important statistical \mathcal{A} : exponentially distributed to be the education of \mathbb{R} . In stochastic modeling of population density dynamics of the random number of \mathbb{N} be \mathbb{R} of \mathbb{N} density of \mathbb{N} a a $a \circ a \circ a$ e; a he $a \circ b$ he and $a \circ b$ and $c \circ b$ he next event that changes the $\n **b**$ be of \mathbf{M} due a by one.

The best known discrete, hege-valued $\lim_{n \to \infty} a_n$ are Bernoulli, bino $m \neq a$, Poisson, and geometric $\in [30]$ $\in [30]$.

6.2.2 Radioactive Decay and Exponential Time

Let
$$
\mathbf{e} = \mathbf{e} \cdot \mathbf{e}
$$
 be defined as $\mathbf{e} \cdot \mathbf{e}$ of the equation $\mathbf{e} \cdot \mathbf{e}$ and $\mathbf{e} \cdot \mathbf{e}$ is a point of the equation $\frac{d}{d} = -\lambda$, (6.8)

6 S
$$
\bullet
$$
 Cha \bullet P \bullet a \bullet N. Me c \bullet aldI \bullet U \bullet de \bullet Mg h a \bullet he \bullet d \bullet g \bullet

where $\lambda > 0$. The e_luation has been interested as a mathematical model for the remaining fraction of a radioactive material at time

$$
\frac{1}{(0)} = -\lambda \tag{6.9}
$$

If a **heap** \mathcal{L} is c e_a e identical and independent, hes

Pr a nucleus remaining radioactive at time ⁼ [−]λt . (6.10)

However, if $T = \text{Re}$ and $\theta = \pi$ is a random time at a random time at $\theta = \pi$ hel

$$
P\left\{a \mod \mathbb{Z}^e \text{ and } a \mod a \text{ and } a \mod e \text{ and } a \mod P\right\} = P\left\{T \geq \mathbb{Z}^e\right\}.
$$
 (6.11)

 $T = a \cdot a + b$ -hega $\leq e$ ea-ared $a \cdot b$ a ab e \sqrt{a} $a \cdot a \cdot e$ ab distribution $F_T() = P\{T \leq \} = T - \lambda$ and probability density function $f_T(\cdot) = dF(\cdot)/d = \lambda^{-\lambda}.$ What e_{τ} of ϕ by e_{τ} or e_{τ} expared ϕ and ϕ ϕ echanisms $-\psi$ is give is the conentially distributed was \mathbf{g}_\perp of $\mathbf{W}\mathbf{h}$ it so universal? A good under canding of these precisions will provide the reader a deeper nide-

 sublog of the mathematical foundation of population dynamics, as exergently statistical laws, in the contraction of α of a large population \mathbf{d}_r **d** \mathbf{d}_r a \mathbf{d}_r [\[15\]](#page-39-5).

6.2.2.1 Rare Event

Le T be the a_1d_2 , easy hich a certain event of such a certain event of s an e.e. \Box de endent \Box e \Box e a \Box 1, 2] and [2, 3], and $f \Box$ cq ence \Box $\iota \mathbf{f}_{\mathbf{g}}$ in time (e.g., he system and its environment and its environment are stationary), then

$$
\mathbf{P} \cdot \mathbf{b} \cdot \mathbf{f} \cdot \mathbf{e} \cdot \mathbf{e} \cdot \mathbf{e} \cdot \mathbf{c} \quad \mathbf{f} \cdot \mathbf{g} \cdot \mathbf{f} \cdot [0, +\Delta] = \tag{6.12}
$$

P ob. of θ or event of θ of θ or event of θ or θ and θ and θ in θ . In θ

Tha \Box

$$
P\left\{T > +\Delta\right\} = P\left\{T > \right\} \times P\text{ ab. of }\text{be.} \text{ e.g. } \text{g.c. } \text{ Mg } \text{J. } +\Delta\text{.}
$$

Not if the \bullet bab_{il} of \bullet e ticke el \bullet corring in the time interval [the time interval]. **the proportional to the proportional one of the set of** $\mathbf{z} = \mathbf{x}$ (Δ), then

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

The_h.

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

 E a \sim e: The waiting \log_{\bullet} of the first shopper coming in the morning in the m \bullet a regular day.

6.2.2.2 Memoryless

One of he most important in fact defining, we can also be only a distributed of exponential distribution of he $a_n g_n e_n$ $P\left\{T\geq +\tau\right\}$ $\frac{1}{P\{T\geq 0\}}$ = $\frac{-\lambda(+\tau)}{-\lambda} = \frac{-\lambda\tau}{\lambda}.$ (6.15)

Eqame: You and our and brother doing experiments to observe the mean f experiments to observe the mean f an'e den a du bredeen. Een hough o bote a coon by gu whole hour later than you, his resulting statistics we say that if \mathcal{L} M_{\bullet} e interestingly, the more individuals in a population, the faster the next event e **to** occur. In a he a called terms: if a $T \sim \lambda$ $^{-\lambda}$ and the alled endently distributed, then $T^* = \mathcal{N}(T_1, T_2, \cdots, T)$ also has an exponential distribution of $\mathcal{N} = \mathcal{N}$ $P\{T^* > \} = P\{T_1 > \dots, T > \}$ $= P \{ T_1 > \} \times P \{ T_2 > \} \times \cdots \times P \{ T > \} = \{-\mu \},$ (6.16) where $\mu = \lambda_1 + \lambda_2 + \cdots + \lambda$. The $f_{T^*}(\cdot) = \mu^{-\mu}$.

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

 N **d** consider a set $\mathbf{a}^{\mathbf{b}}$ of $\mathbf{a}^{\mathbf{b}}$ or \mathbf{e} (T). The are *identical, independently distributed* (*j*,d.) and $\int e \psi \cdot h \, df \, f_T(\psi) \, a \cdot b \, d\phi \quad \text{and} \quad b \cdot \phi$ $F_T(\cdot)$. Then $T^* = \pi^T \mathbb{I}(T_1, T_2, \cdots, T)$ has it distribution

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

Now, in the class scale $\hat{T}^* = T^*$ and considering to be very age, its d_{min} d_{ive} b

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

The ef \mathbf{e} , $\mathbf{f} F'_T(0) = f_T(0)$ is finite, one obtains and obtain distributed time. We hoe he are a called $f_T(0) > 0$: han a called f_T implies that the time scale involved in the mechanism for the occurrence of an event is \mathbf{r} . \mathcal{L} e a orde \mathcal{L} agnitude fa \mathcal{L} eral the time scale in question.

6.2.3 Known Mechanisms That Yield an Exponential Distribution

In the previous section, we have derived the exponentially distributed waiting time based **o**n some very element assumptions of the concerning concerning concerning concerning concerni and (2) independent. Furthermore, in Sect. 6.2.2.3, we have shown that for nonexploit a T , as $\log a$, $f_T(0) \neq 0$, $\log \lim_{\substack{m \to \infty}} t$ of a a geopection of i.i.d. T . \blacksquare bee one a. This is a strong argument for which one can use, on an approximation a ϵ cae, heela ϵ is ϵ [\(6.8\)](#page-4-0) to model population dynamics.

6.2.3.1 Khinchin's Theorem

Let Lc_0 de a house has uses light bulbs. One bought a large box of \mathcal{M} is gh bulbs, and entity each bulbs having dentical, independently distributed for the bulbs of the bulbs of the bulbs having independent of the bulbs π e with df f^{π} (). For each light-bulb socket, one puts on a new bulb when the **od** one is but if the time sequence $0, T_1, T_2, \cdots, T$, \cdots called a *renewall process*, \oint **h** \oint **h** \oint \int \int \int \int **b** \int **c** \int **b** \int **c** \int **b** \int **d** \int **c** \int **c** a abe different details details developed the distribution for the entire f (). Not for the entire house, there are del ca. Ide eldent changing a cerewal process renewal experiment renewal processes. a *superposition* of he elod a ce. $\epsilon = [3]$ $\epsilon = [3]$, a_{-1} and R_{-1} Fig. [6.1.](#page-7-0)

 F_{\bullet} a single end a single equal process with renewal time distribution f (x), the corre- \bullet old $sgc\bullet$ here sgn , e.g., the number of \mathcal{C} also \bullet contributed before the \bullet subsets of \mathcal{C} , N , ha , he d $_b$ $_b$

$$
P\{N \geq \} = P\{T \leq \} = F_T \ (\) = \int_0^{\infty} f_T \ (\)dt \ . \tag{6.19}
$$

- 1 || || || || || || || || || || || ||

Fig. 6.1 If he ed, orange, and bule point processes represent the engine events of gh bulbs f_{\bullet} 3 different sockets, then the fourth row is the combined point process for all the bulb changes. $I = \text{he } \downarrow$ e \bullet is the three individual processes. With \bullet ealed \bullet e \bullet a superposition of the three individual law e ege

The $ef_{\bullet}e$,

$$
P\{N = \} = F_T \ (\) - F_{T+1} \ (\). \tag{6.20}
$$

Not if one and ρ is $a = e$, and e T * be the $a = \log_e e$ if the next time for $r = r \cdot \frac{1}{2}$ is $r = r \cdot \frac{1}{2}$ is distribution in renewal theory. It is distribution is different in renewal theory. It is distribution is different in renewal theory. It is distribution is different in renewal to $r = r$ $f \in f$ (). If fac, ole has

$$
P\{T^* \leq \} = \sum_{\ell=0}^{\infty} P\{N = \ell\} P\{T_{\ell+1} \leq +\}
$$

$$
= \sum_{\ell=0}^{\infty} \Big(F_{T_{\ell}}() - F_{T_{\ell+1}}() \Big) F_{T_{\ell+1}}(+). \qquad (6.21)
$$

obab₋ de \mathbf{I}_{∞} fi \mathbf{I}_{∞} be \mathbf{I}_{∞} be \mathbf{I}_{∞} be \mathbf{I}_{∞} (6.22)

The efore, he shability density function for the station T^*

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

Fig. 6.2 The a chemical description of a chemical eaction of a single molecule. I say e e gel statistical la a gel bet discrete, stochastic reactions. 1 ∞ $-4G/kB$

6.2.4 Population Growth

We have discussed $\frac{d}{d} = -\lambda \psi \psi$ is not all added it does not does not decay. $\frac{\partial e}{\partial x}$ ha a similar discussion can be a similar discussion of $\frac{d}{dx}$ = $\frac{d}{dx}$ with a similar discussion can be a similar disc half of a population dynamics.

The answer turns of the simple but to be simpled to be but profound: \int on a , a event ! The a \lg \lrcorner event birth is expected to be exponential. \mathtt{F} be expected to be proportional to the number of \mathtt{M} and \mathtt{m} c $\vec{e}_1^{\mathbb{F}}$ **b** be **a a b** (E e c **c** 1.2), **a** (). The $\vec{e}_2^{\mathbb{F}}$ e, *on average the* growth is 1 additional person in $\left(\begin{array}{cc} \mathbb{E} \left[& \right] \end{array} \right)^{-1}$ time:

$$
\frac{\mathrm{d}}{\mathrm{d}}\mathbb{E}[\quad (0\quad = \mathbb{E}[\quad (0)]\tag{6.25}
$$

Dea h is an event, birth is an event, state the angle of \mathbb{R} and event. Most biological d ha $c \cdot \cdot$ about $c \cdot \cdot$ has been about about biological events that ead to changing populations. Stochasticity is in the timings of the various events. This is \blacksquare b J. D. Murray stated in [\[17\]](#page-40-0) hands in \blacksquare in \blacksquare stated \blacksquare is odels for a species at species at time have here $\mathbf{L} = \mathbf{A} \cdot \mathbf{C} \cdot \mathbf{A} \cdot \mathbf{A} \cdot \mathbf{A} \cdot \mathbf{A}$:

$$
\frac{d}{d} = b_{\bullet} h_{\bullet} - \text{dea } h_{\bullet} + \underset{\neg \text{f}}{\perp} g a_{\bullet}.
$$
\n(6.26)

where \bigcirc is the potation density.

6.2.5 Discrete State Continuous Time Markov (Q) Processes

Discrete state continuous time Markov processes are sometime called quasi Marko- \mathcal{A}_s , or Q-processes, a $e^{\mathcal{A}}_s$ find $e^{\mathcal{A}}_s$ and \mathcal{A}_s introduced in Arne Jensen's 1954 book *A Distribution Model, Applicable to Economics* and hen by David Freed and his 1971 boo *Markov Chains*. In the probability of state at the state of $(1, 0)$, \bullet e has

$$
(+\mathbf{d}) - (-\epsilon) = \left(\sum_{\ell=1}^{N} \ell(\epsilon) \ell\right) \mathbf{d},\qquad(6.27)
$$

where ℓ d is the answer obability from state ℓ or ℓ in the infinitesimal \Box e \Box e \Box a d \Box E_q. [\(6.27\)](#page-10-0) \Box ca ed a *master equation*. I \Box fi \Box da e \Box a \Box e \Box $\mathbf{P}(t) = \mathbf{Q} \cdot \mathbf{A}$ here the **Q** is a matrix has off-diagonal elements if $\mathbf{P}(t) = \mathbf{Q} \cdot \mathbf{A}$

$$
H_{\text{H}} = -\sum_{\mu \neq 0} \frac{1}{\mu} \tag{6.28}
$$

The ef_{ore}, **Q** has each and e.e. $\psi \rightarrow \psi$ is equal to ψ as ψ is often referred to as If \int is equal to show that is interesting to show that is equal to show that is equal

$$
\sum_{i=1}^{N} (x_i - x_i)
$$

Ide endent of the total probability is conserved over the ender \mathcal{L} e. Note that \mathcal{L} e. e. a **important differences between Eqs. [\(6.26\)](#page-10-1) and [\(6.27\)](#page-10-0): The former is an equation is an equation** for \bullet and density ($\downarrow \downarrow$ by the latter is an equation for the probability of \bullet **p** a **b** size (θ) \equiv P {N(θ) = }; he gh -hand de of former usually is a hon linear function of while the are line exaction of the dimension of the linear. The dimension of the linear a e ODE s_{max} , $\frac{1}{2}$ e e, $\frac{1}{2}$ is chingher hand the former.

6.2.5.1 Kolmogorov Forward and Backward Equations

 $\prod_{\alpha} a$ for f_{α} , E_{α} [\(6.27\)](#page-10-0) can be e e_{α} ed $a_{\alpha} \frac{d}{d}$ = **Q**, where = (p. ···, n) \mathbb{Z}^n a \mathcal{F} . \mathbb{R}^n **c** \mathbb{R}^n is a \mathbb{Z}^n called *Kolmogorov forward equation*. Note \mathbb{Z}^n speaking the formation is not about the probability distribution is not about the probability distribution of α . b about the $a_n = b_n$ $ab_n = a_n$ (fundamental solution) **P**($\forall t \in \mathbb{R}$ in initial solution) $u \circ \mathbf{P}(0) = \mathbf{I}$. More $\mathbf{I} \circ \mathbf{e}$, $\mathbf{I} \circ \mathbf{g}$,

$$
\frac{\mathrm{d}}{\mathrm{d}}\mathbf{P} = \mathbf{P}\mathbf{Q} = \left(\begin{array}{c} \mathbf{Q} \end{array}\right)\mathbf{Q} = \mathbf{Q}\mathbf{P}.\tag{6.29}
$$

Th_{om} a different different different and:

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

which is called *Kolmogorov backward equation*. If $\{\pi\}$ is a stationary probability probability probability probability probability of π d_{max} distribution, e.g., the solution to d_{max}

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

then the solution to the backward equation, (i) has the important property of e in e

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

belig lide endent of e.g., \Box a conserved \Box and

The solutions to the Kolmogorov for and and backward equations also have another important property. Let α and α is a formulate to a formulate to a formulate to a formulate α equation with different initial distribution \mathbf{b} on \mathbf{c} (0) and (0). Then

$$
\frac{d}{d} \sum_{i=1}^{N} (1) \sqrt[n]{\left(\frac{1}{d}\right)} \leq 0. \tag{6.31}
$$

Ohe special case of this, which is dely known, is the choice of ($t = \pi$, if $\pi > 0$ \forall .

 \mathcal{S}_\bullet , and the positive solutions to a \mathcal{K}_\bullet back and \mathcal{S}_\bullet and \mathcal{S}_\bullet and \mathcal{S}_\bullet . (t) and (\mathcal{H} which different initial conditions (0) and (0), exectively, have

$$
\frac{d}{d} \sum_{i=1}^{N} \left(\pi - \left(\cdot \right) \right) \oint \left(\frac{\left(\cdot \right)}{\left(\cdot \right)} \right) \le 0. \tag{6.32}
$$

Ohe special case of this is $\cos \theta$ is $\sinh \theta$ is $\sinh \theta$ in Eq. [\(6.32\)](#page-12-0) ca ed an H-function; the quantity in Eq. [\(6.31\)](#page-12-1) is called relative entropy, or Kulback–Leibler divergence in information theory, or free help in the scale chem- \Box is The conducted inplication for the second \mathcal{A} of the seconducted law \Box

6.3 Theory of Chemical and Biochemical Reaction Systems

A general representation for complex calculations is $\frac{1}{2}$ and $\frac{1}{2}$ reaction systems is $\frac{1}{2}$ for complex is $\frac{1}{2}$ reaction systems in $\frac{1}{2}$ reaction systems is $\frac{1}{2}$ reaction systems in $\frac{1}{2}$ v_1 1 + v_2 2 + \cdots $v \longrightarrow \kappa$ 1 1 + κ 2 2 + \cdots κ . (6.33)

1 ≤ \leq The e a e cececal d eac $\bigcup_{n=0}^{\infty}$ ($v_1 - \kappa_1$) a e called *stoichiometric coefficients*, he e a e a \neq ec e_{\leftarrow} be eac \downarrow . In a b ader \downarrow e. a "eac \downarrow $\qquad \qquad \blacksquare$ i = a e e f e e e .

6.3.1 Differential Equation and Nonlinear Dynamics

Because of $\text{Re }c_0$, e and θ and f matter,

$$
\frac{\mathrm{d}}{\mathrm{d}} + \frac{1}{2} \sum_{j=1}^{d} \left(\kappa_j - \nu_j \right) \hat{\varphi} \tag{6.34}
$$

6 S
$$
\bullet
$$
 Chalgebra \bullet N. \bullet L. \bullet R. \bullet C. \bullet R. \bullet C. \bullet R. \bullet C. \bullet R. \bullet

$$
\mathbf{w} \quad \text{he } \mathbf{e} \quad \text{the } \mathbf{e}
$$

ca ed he $\lceil x \rceil$ also $\lceil x \rceil$ of he heaction. **x** = (1, 2, ···,). E_n. [\(6.34\)](#page-12-2) called α equation \Box and E ₁. [\(6.35\)](#page-13-0) 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 eac_t on E_q. [\(6.33\)](#page-12-3), one a a time. The DGP assumes that the the the th reaction of \mathbf{r} on the \mathbf{v} distribution of \mathbf{r} and \mathbf{r} are defined waiting time, with rate $\lim_{n \to \infty}$ e e

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

 H hen the mode mode mode is H be H of it has chemical species being i. Note φ (**X**) has he d_{imension} of $\left[\begin{array}{cc}e^{-at}\\-e\end{array}\right]^{-1}$. Cea⁷ he

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

$$
= \left(\frac{\lambda}{\lambda_{1} + \dots + \lambda} \right)^{-(\lambda_{1} + \dots + \lambda)}.
$$
(6.39)

This easy he following important fact: the minimal time and set of T is easy to and a $r^* \equiv \mathbb{I} \{T\}$ and $r^* \equiv a \cdot g \cdot \mathbb{I} \{T'\}$; the minimal time T^* and $te \, de \, \cdot \cdot \cdot$ * a e = a $\cdot \cdot$ ca $\cdot \cdot$ de endent.

6.3.3 Integral Representations with Random Time Change

6.3.3.1 Poisson Process

A standard Poisson process () is an integer-valued, contribution of A is an integer-valued, contribution A pe d h d h d

$$
P\left\{ (0,0) = \frac{1}{2} \right\} = \frac{1}{2} \tag{6.40}
$$

A Poisson process e e e d a \Box , T_1, T_2, \cdots, T , and a *counting process* e e.e. a. **d.** (). The former is a positive real-valued, discrete- τ e Markov ce ψ is hele endent in $\log e$ en and $T_{j+1} - T_j = e$ onen a d_r bed the act.

6.3.3.2 Random Time Changed Poisson Representation

In e_r of Poisson processes, the stochastic travels of a DGP representing the $\frac{1}{2}$ ege $\frac{1}{2}$ be of the occurrence,

$$
\mathbf{y}(\cdot) = \mathbf{y}(0) + \sum_{i=1}^n \left(\kappa_i - \nu_i \right) \left(\int_0^{\cdot} \varphi \left(\mathbf{X}(\cdot) \right) \mathbf{d} \right) \tag{6.41}
$$

in kich φ (**X**) is given in [\(6.36\)](#page-13-1). We have abused the notation is as both the symbol of a transition of molecules, as in Eq. [\(6.33\)](#page-12-3), and \Box in the reaction system. We see that $\lim_{M \to \infty} \lim_{n \to \infty} f(X \to \infty)$ and $V \to \infty$,

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

 φ (**X**) also called the *propensity* of the the eac \Box .

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

6.3.4.1 One-Dimensional System

 C_0 , de the stochastic population kinetics of a single section let (t) be the phab_{il} of ha \lg Id_r dividuals in the population at the population of he a e e_{l} a e

$$
\frac{d}{d} \left(\begin{array}{ccc} 0 \end{array} \right) = -1 -1 - (-1) + 1 + 1 + 1, \tag{6.43}
$$

in high and are the birth rate and death are of the population with rate and the act the population with exactly id _rd a \sim The \sim a \sim h a d \sim d \sim d \sim d \sim E_q. [\(6.43\)](#page-15-0) call be obtained:

$$
\frac{1}{-1} = \frac{-1}{-1}.
$$
\n(6.44)

The $ef_{\bullet}e$,

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

 \mathbf{M} hch $_0$ = \bullet be deed hed by normalization. E_{\bullet} . [\(6.43\)](#page-15-0) is the DGP corresponding to the nonlinear population depending to the non- $\log e = e c e \psi$, k b, h and death a e^2 (c) and $\log \psi$, where $\psi(x) \equiv \frac{C}{V}$,

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

 w he e,

$$
\hat{p}(x) = \frac{V}{\sqrt{2\pi}\pi} \sum_{k=0}^{\infty} \frac{V}{k}
$$

C_1.2,...,), a
0.11 he ab.
$$
\cos \theta
$$
 = 0.11 he ab. $\sin \theta$ = 0.11 he ab. $\sin \theta$

$$
\frac{\mathrm{d}}{\mathrm{d}}t = \frac{1}{4}t.\tag{6.48}
$$

For simplicity, we shall assume that both per capita birth rate ⁱ and death rate ⁱ are constants. Then the e-call a growth a e-for the entire population, which is also $\frac{\partial}{\partial x}$ eal e ca ag \sqrt{h} ae,

$$
-\frac{\sum_{j=1}^{d} \frac{d}{d} \cdot \sum_{j=1}^{d}}{\sum_{j=1}^{d} \frac{1}{d} \cdot \sum_{j=1}^{d}} \cdot \frac{1}{d} \ge 0.
$$
 (6.49)

The_n,

$$
\frac{d^{-}(x)}{d} = \left[\frac{\sum_{j=1}^{n} 2}{\sum_{j=1}^{n} 4} - \left(\frac{\sum_{j=1}^{n} 4}{\sum_{j=1}^{n} 4} \right)^{2} \right].
$$
\n(6.50)

We held the term instand the right-hand side is negative:

$$
\frac{\sum_{j=1}^{n} 2}{\sum_{j=1}^{n} 4} - \left(\frac{\sum_{j=1}^{n} 4}{\sum_{j=1}^{n} 4}\right)^2 = \frac{\sum_{j=1}^{n} \binom{n}{j} - 2}{\sum_{j=1}^{n} 4} \ge 0.
$$
 (6.51)

In fact, it is exactly the variance of integrations of $\lim_{n \to \infty} \log \text{h}$ and $\lim_{n \to \infty} \log \text{h}$ and $\lim_{n \to \infty} \log \text{h}$ \Box it is always positive if the each and \Box i. This mathematical results and \Box is a \Box is a a of the deas of both Adam Smith, on economics, and Charles Day I, on the $\text{Max } a \neq \text{ec } A$. Is fac, $\text{Re} \in \mathbb{C}^T$ [\cdots] $\text{Re} \in \{6.50\}$ has been designed by R. A. Fike, $heB = \lambda - \rho A$ and $e \cdot \lambda$ and $e \cdot \lambda$ and $e \cdot \rho A$ and $e \cdot \rho B$ are $g \cdot \lambda$ that file de \bullet ^hat a \neq ec \bullet [\[6\]](#page-39-7). Here a just \bullet **S** \bullet *magnum opus* An In_{gu} into the Nature and Causes of the Wealth of Nations" (1776):

A e e Id dia, he efore, endeavours as much as he can both og so he capital as I he support of domestic industry, and so direct hand induce \mathbf{a} to direct a be of the greatest at every labours to render the annual necessarily labours to render the annual revenue of \det the \sec as a as he can. He generally, indeed, neither intends to promote the public to promote the public to promote the public state of public states the public states of public states of public states of public states interest, nor knows how much he is promoting it. By preferring the support of domestic to that of foreign industry, the intended \mathbf{A} intended by and by deciding that industry in \mathbf{A} in \mathbf{A} in $\mathbf{$ \downarrow ch a manner as \downarrow channer as its produce may be only here intends on \downarrow channer \downarrow be \downarrow and \downarrow gain, and he \Box h \Box as in this in the eases, ed by an invisible hand to promote an end which was in n_0 and n_1 intention. Norginally the society of α is n_1 intention. By α is α intention. $p \downarrow \text{log } h$ intervelse on the society of the society of the society more effectually than h when he called by out. I have never he had done by he called the problems of he called by the much good done by those who had he affeced of ade for the uping good. I has affected, in the common and an angle \mathbb{R} and \mathbb{R} e chants, and extra θ of θ and θ and θ in discussions of θ in the from it.

6.5 Ecological Dynamics and Nonlinear Chemical Reactions: Two Examples

6.5.1 Predator and Prey System

Let (be the population density of a predator at time and α predator and α density of a c a height present predator-predator-prediction of \log_{ϕ} containing $\epsilon = [17]$ $\epsilon = [17]$ $\sqrt{ }$ $\sqrt{ }$ $\overline{\mathsf{I}}$ $\frac{d}{d} = \alpha - \beta$, $\frac{d}{d} = -\gamma + \delta$. (6.52)

The detaged analysis of the nonlinear dynamics \mathbb{R} and \mathbb{R} and \mathbb{R} books on \mathbb{R} a he a ca b \bullet \bullet \bullet differential equations $[17]$. $L \ddot{e}$ us $\mathbf{I}_{\mathbf{w}}$ and $\mathbf{v}_{\mathbf{w}}$ and $\mathbf{v}_{\mathbf{w}}$ be for $\mathbf{v}_{\mathbf{w}}$ be $\mathbf{v}_{\mathbf{w}}$ and $\mathbf{v}_{\mathbf{w}}$ and $\mathbf{v}_{\mathbf{w}}$ is $\mathbf{v}_{\mathbf{w}}$.

 $A + \longrightarrow 2$, $+ \longrightarrow 2$, $\longrightarrow B$. (6.53)

Then $acc_{\bullet} d_{\bullet}g_{\bullet}$ be LMA, he concentrations of and \mathbf{w} the deconcentrations of a- $\bigcup_{n=0}^{\infty}$ of A and B being and :

$$
\frac{d}{d} = 1 - 2 , \frac{d}{d} = -3 + 2 .
$$
 (6.54)

The efortherefore that dynamics of an econogical predator-pressure p and p able similar to that of a chemical caction system with a second reaction system with a second $\frac{1}{\sqrt{16}}$: the first reaction in [\(6.53\)](#page-17-0) requires and existing serving as a catalogue of the reaction in $\log a$ $A \rightarrow A + \text{ec.}e + \text{ha}$ a ea $\rightarrow \text{he}$ he both $\rightarrow \text{de}$ a che called a chemical reaction is called a *catalyst*.

6.5.2 A Competition Model

Let us now consider another widely studied ecological dynamics with competi- \blacksquare

$$
\begin{cases}\n\frac{dN_1}{d} = 1N_1 - 1N_1^2 - 21N_1N_2, \\
\frac{dN_2}{d} = 2N_2 - 2N_2^2 - 12N_2N_1.\n\end{cases} (6.55)
$$

Can one design $a = g$ of chemical call reactions that g denotes an identical system of d fferential equation. The second generality of $\det A = \det A$ of generality, $\det B = \det B$

$$
A + \xrightarrow{1} 2 , + \xrightarrow{2} B, A + \xrightarrow{3} 2 ,
$$

+ \xrightarrow{4} B, + \xrightarrow{5} B, + \xrightarrow{6} + B, (6.56)

 \mathbf{w} kch, according the LMA,

$$
\begin{cases}\n\frac{d}{d} = (1) - 2^2 - 5, \\
\frac{d}{d} = (3) - 4^2 - (5 + 6).\n\end{cases}
$$
\n(6.57)

If $\mathbf{y} \in \mathbf{d}\mathbf{e}$ if $\mathbf{y} \in \mathbf{M}_1$, N_2 , and

$$
(1)
$$
 \leftrightarrow 1 , $2 \leftrightarrow$ 1 , $5 \leftrightarrow$ 21 , (3) \leftrightarrow 2 , $4 \leftrightarrow$ 2 , $(5 + 6) \leftrightarrow$ 12 ,

 $teh (6.57)$ $teh (6.57)$ is the same as [\(6.55\)](#page-17-1). Note that the assume as $et h$, $+ \rightarrow + B$, \therefore d ced \bullet e e e \downarrow $_{12}$ > $_{21}$.

A c **a** close inspective inspection of the system of chemical reactions in [\(6.56\)](#page-18-1) indicates that the overall reaction is $2A \rightarrow B$. Since each and every reaction is every reaction is in every reaction in the eventual every reaction is in every reaction in the eventual eventual eventual eventual eventual eventual eventual e be $\log \cosh \cosh 2\pi$ chemical equilibrium. Rather, the system eventual each example a *nonequilibrium steady state* in which there is a continuous, overall chemical flux converting 2A $\bullet B$.

6.5.3 Logistic Model and Keizer's Paradox

We wat to study some in-depth. Let us now consider a much ϵ e che ca eac ϵ , ϵ ϵ ,

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

I easy see has the ODE according to the LMA,

$$
\frac{d}{d} = \left(1 - \frac{1}{K}\right) , \quad = 1, K = -\frac{1}{2}, \tag{6.59}
$$

is the celebrated *logistic equation* $\mathbf{I}_{\mathbf{A}} \bullet \mathbf{I}$ and $\mathbf{I}_{\mathbf{B}} \circ \mathbf{I}_{\mathbf{A}} \bullet \mathbf{I}$ the ecological context, equation during $\mathbf{I}_{\mathbf{B}}$ and $\mathbf{I}_{\mathbf{B}}$ be equation during the set of $\mathbf{I}_{\mathbf{B}}$ \mathcal{L} is known as the performance in the absence of interactions competition; and $K = \mathbb{N}$ is a carrying capacity.

In h ch μ deep hed b he as c internal mode e, e.g., he has energy. B $\mathcal{L}B_{\bullet}$ and $\mathcal{L}_{\bullet}A_{\bullet}$ and \mathcal{L}_{\bullet} in \mathcal{L}_{\bullet} are in the \mathcal{L}_{\bullet} in Then the Gibbs fee energy of he lhs of (6.62) is the sum of the chemical potential p

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

When the eac_t of eaches is equilibrium, one has the one chemical potentials $be_{g}e_{g}$ a $\phi_{g}b_{g}h_{g}de_{g}$:

$$
\sum_{j=1} (\nu_j - \kappa_j) (\mu_j + B T)^{-1} = 0.
$$
 (6.66)

The graph shows
$$
f(x) = \frac{e^{x}}{\sqrt{1 - e^{x}}} = \frac{e^{x}}{\sqrt{1 - e^{x}}} = \frac{1}{e^{x}}
$$
 (6.67)

$$
\Delta G = \left(\sum_{j=1}^N \kappa_j \mu_j\right) - \left(\sum_{j=1}^N \nu_j \mu_j\right) = \, B \, T \, \mathbb{I}\left(\frac{-}{+}\right). \tag{6.68}
$$

This is a very well-known formula that can be found in every college chemistry of \mathbb{R} in every college chemistry college chemistry college chemistry college chemistry college chemistry college chemistry college chemi e $b_{\bullet \bullet}$.

6.6.2 Mass-Action Kinetics

 F_{\bullet} \downarrow gE_{\bullet} = [\(6.34\)](#page-12-2) and [\(6.35\)](#page-13-0), e have

$$
\frac{d}{d}t = \sum_{i=1}^{d} (\kappa_{i} - \nu_{i})(\hat{\varphi}^{+} - \hat{\varphi}^{-})
$$
\n
$$
= \sum_{i=1}^{d} (\kappa_{i} - \nu_{i})\hat{\varphi}^{-} \left\{ e \left[\sum_{\ell=1}^{d} (\kappa_{\ell} - \nu_{\ell}) \sum_{j} \left(\frac{\ell}{\ell} \right) - 1 \right\}
$$
\n
$$
= \sum_{i=1}^{d} (\kappa_{i} - \nu_{i})\hat{\varphi}^{+} \left\{ 1 - e \left[\sum_{\ell=1}^{d} (\nu_{i} - \kappa_{i}) \sum_{j} \left(\frac{\ell}{\ell} \right) \right] \right\}. \quad (6.69)
$$

Equation [\(6.69\)](#page-20-0) shows that when ⁼ eq , the term [· · ·] = 0 and the term {· · · } = 0 as every dividend therefore, the second in (6.69) is consistent with the consistent α is consistent with the consistent α che cal e_{quilibrium according to the reading c_{rea} e.g., E_{qs}. [\(6.66\)](#page-20-1) and [\(6.67\)](#page-20-2).} Interestingly, recent work has shown that both macroscopic line \mathcal{L} as in [\(6.69\)](#page-20-0) and e_{\bullet} by the radial section of a stochastic consequences of a stochastic line of description of a reaction subsets \det [\[10\]](#page-39-8).

6.6.3 Stochastic Chemical Kinetics

We \mathbb{N} a he above $f \circ \mathbb{R}$ as nonlinear chemical calculation in a small $\omega_{\rm m}$ e $V_{\rm M}$ where $\omega_{\rm m}$ is small numbers of A , B , and C : $A + B \rightleftharpoons$ − (6.70)

We held the $A + c$ and $B + c$ do not change in the reaction. Hence we can expect the reaction can denote $A + c = A$ and $B + c = B$ as the order of A and B, including those in C, at the initial time. Not if \mathbf{f}_i is the non-negative. Non-negative in C , at the non-negative independent of C , at the non-negative independent of C , at the non-negative independent of C , \Box eger-ared a \Box de and able odescribe to stochastic chemical \Box entropy in the stochastic chemical kinetics, this simple nonlinear chemical reaction, according of DGP, is a one-dimensional birthand-death coe_{rrib} \Box h \Box a e-dependent birth and death a e \Box = \Box A B and $=$ $-c$. Then, $acc \cdot d \cdot dg \cdot e$, (6.45) , we have an $e_1 \cdot b \cdot d$ distribution equilibrium distribution equilibrium equilibrium distribution equilibrium equilibrium equilibrium equilibrium equilibrium equilibrium equilibrium $_{C}$ = $\;$:

$$
\frac{(+1)}{(-)} = \frac{+(-4)(-1)(-8)}{(-(-1))}
$$
\n(6.71)

 \bigcup_{A} h ch $\bigcap_{A} = A(0) + C(0)$ and $\bigcap_{B} = B(0) + C(0)$. The ef.

$$
(\) = \frac{\Xi^{-1} A! B!}{\frac{1}{2} (A-1)! (B-1)!} \left(\frac{+}{-V} \right) , \qquad (6.72)
$$

where $\Xi = a \log_a a = a \log_a$ factor

$$
\Xi(\lambda) = \sum_{k=0}^{\mathcal{M}} \frac{\lambda(\Delta + B)}{k} \frac{A^k}{\lambda(\Delta - \lambda)(B^k - \lambda)}, \quad \lambda = \left(\frac{A^k}{\lambda - \lambda}\right). \tag{6.73}
$$

$$
M \bullet \underbrace{e}_{\neg \uparrow} \bullet a \quad , b \quad b \quad g \quad A + B + C = \begin{cases} 0 & 0 \\ A + B - C, \end{cases}
$$
\n
$$
- \int (C) = - \int \left[\frac{\lambda^C}{C!(A - C)!(B - C)!} \right] + c \delta.
$$

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

$$
= A \left(A + B \left(A \right) + C \left(\frac{\mu_C - \mu_A - \mu_B^0}{B} \right) - (A + B + C) \right)
$$

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

Th_{rangees} \mathbb{E}_{\bullet} . [\(6.65\)](#page-20-3).

In ca_{rrie}cal chemical kinetics, for a given **x**(t), the Ideal function of the chemical grad **in** the chemical state of the chemical e eac \blacksquare eaction system is

$$
G \quad [\mathbf{x}(\)] = \sum_{\sigma=1} \sigma \Big(\mu_{\sigma} + B T \cdot \mathbf{y} \quad \sigma = B T \Big). \tag{6.75}
$$

 $\text{The} \S, f_\bullet, \emptyset, \text{ and } \text{Bg} \to 0.34$, assuming the action is reaction is reaction is reaction in f_\bullet and f_\bullet is reaction is reaction is reaction. c_{\bullet} , and $-$,

$$
\frac{d}{d}G \quad [\mathbf{x}(\cdot)] = \sum_{j=1}^{\infty} \frac{d}{d} \left(\mu_j + B T \parallel j \right)
$$
\n
$$
= B T \sum_{j=1}^{\infty} \sum_{j=1}^{\infty} \mathbf{x}^{-1} \mathbf{x}^{-1} \mathbf{x}^{-1}
$$

a e \rightarrow ong condition on the dynamics. When a chemical eaction single reaction system has a \downarrow a led \downarrow ce and \downarrow \downarrow \downarrow chemical potentials, it can not reach a che ca e_st b_y Rathe, eache a *nonequilibrium steady state* (NESS). Let Le is consider the following text of Le model in Le model is the schelog model for bistability of Le $[34]$ and Schna enberg odel for nonlinear oscillation [\[17,](#page-40-0) [25,](#page-40-11) [35\]](#page-40-12).

6.6.4.1 Schlögl Model

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

In hich the concentrations (or chemical potentials) of A and B are \downarrow and by an external agent. This eaction is a *Schlögl model*, whose dynamics can be divided to a *schlogl model*, whose can described by the differential equation

$$
\frac{d}{d} = \frac{1}{1} \quad 2 - \frac{3}{1} \quad 3 - \frac{1}{2} \quad + \frac{1}{2} \quad = f(\cdot), \tag{6.79}
$$

which is a third-order polynomial. It can exhibit bistability and saddle-node bifurcation phenomenon. All of the mondition of the driven condition, when \mathbf{b} $\mu_A \neq \mu_B$. Note in the chemical equilibrium: $\mu_A = \mu_A + B T$ in $\mu_B + B T$ in , a_{nd}

$$
\left(-\right) = \frac{\frac{1}{1} + \frac{1}{2}}{\frac{1}{1} - \frac{1}{2}}.
$$
\n(6.80)

Dffeel a e_l a $\sqrt{(6.79)}$ $\sqrt{(6.79)}$ $\sqrt{(6.79)}$, k_r a_n ee $\sqrt{\frac{1}{1}}$ $\frac{1}{2}$ = $\frac{1}{1}$ $\frac{1}{2}$, ha, he gh $ha\ddagger d$ - de

$$
f() = \frac{+}{1} \quad 2 - \frac{-}{1} \quad 3 - \frac{+}{2} \quad + \frac{-}{2}
$$
\n
$$
= \frac{+}{1} \quad 2 - \frac{-}{1} \quad 3 - \frac{+}{2} \quad + \frac{-}{1} \quad + \frac{+}{2}
$$
\n
$$
= \left(\frac{2 + \frac{+}{2}}{1} \right) \left(\frac{+}{1} - \frac{-}{1} \right). \tag{6.81}
$$

The ef e, he f (x) has a unique fixed point at $=$ $\frac{1}{1}$, he che ca e up $\frac{1}{2}$. In gene $a_1 - e$ [\(6.78\)](#page-23-1) can exhibit chemical bistability; but the subwhen A and B have a \downarrow fficent a set α and α and difference, e.g., *a chemostat*.

 M_{\bullet} e $_{\bullet}$ e $_{\bullet}$ is $_{\bullet}$ the number of $_{\bullet}$ interesting [\(6.80\)](#page-23-2), the DGP of the number of $_{\bullet}$, (), agaha ole-dimensional birth-and-death process, a birth-and-death process, with \mathbf{r}

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

$$
+1 = \frac{1}{V^2} \left(\frac{1}{V^2} + \frac{1}{2} (1) + \frac{1}{2} V^2 \right)
$$

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

The efore, he a \Box and distribution distribution of Eq. [\(6.45\)](#page-15-1),

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

This is a Poisson distribution of \mathbf{b} is a complete value being $\mathbb{E}[\Box] = \lambda$. The efter he e ec ed coleel a **o**l $\left(\begin{array}{cc} + & - \\ 1 & 1 \end{array} \right)$.

6.6.4.2 Schnakenberg Model

$$
\frac{S}{A} = \frac{1}{A} \quad , \quad B \stackrel{?}{\longrightarrow} \quad , \quad C \quad + \quad \stackrel{3}{\longrightarrow} \quad 3 \quad , \tag{6.84}
$$

is known as *Schnakenberg model*, where dynamics for the set of \mathbb{R}^n

$$
\begin{cases}\n\frac{d}{d} = \frac{1}{1} - \frac{1}{1} - 3^2 = f(\cdot, 0), \\
\frac{d}{d} = 2 - 3^2 = (\cdot, 0).\n\end{cases}
$$
\n(6.85)

This system can exhibit limit can exhibit can exhibit can exhibit cation. In the system of \mathbb{R}^n the DGP, it exhibits a rotational diffusion. We refer the reade \bullet $(25, 35]$ $(25, 35]$ for any \Box -depthalysis of the model.

6.7 The Law of Large Numbers—Kurtz's Theorem

6.7.1 Diffusion Approximation and Kramers–Moyal Expansion

Sa \log is the master equation in [\(6.43\)](#page-15-0), e use of solution a particle in a e_s a \bullet (PDE) for a continuous density function function for $f(x, y)$ and $f(x, y)$ are exponentially function for $f(x, y)$ $=\overline{V}$, d $=\frac{1}{V}$, hel

$$
\frac{\partial f(\cdot, \cdot)}{\partial} = V \frac{d \ V(\cdot)}{d}
$$
\n
$$
= \frac{1}{d} \Big(f(-d, \cdot)^{\hat{}}(-d) - f(\cdot, \cdot) \Big(\hat{}}(\cdot) + \hat{}}(\cdot) \Big)
$$
\n
$$
+ f(+d, \cdot)^{\hat{}}(-d) \Big)
$$
\n
$$
= \frac{\partial}{\partial} \Big(f(+d/2, \cdot)^{\hat{}}(-d/2) - f(-d/2, \cdot)^{\hat{}}(-d/2) \Big)
$$
\n
$$
\approx \frac{\partial}{\partial} \Big\{ \frac{\partial}{\partial} \Big(\frac{\hat{}}{-2V} \Big) f(\cdot, \cdot) - \Big(\hat{}}(-\cdot) - \hat{}}(\cdot) \Big) f(\cdot, \cdot) \Big\} + \cdots
$$
\n(6.86)

in which

$$
V^{-1} V = \hat{ } () , V^{-1} V = \hat{ } () , \qquad (6.87)
$$

 $a = V \rightarrow \infty$.

6.7.2 Nonlinear Differential Equation, Law of Mass Action

The ef e, \perp he e of $V \to \infty$, $rac{\partial f(\theta, \cdot)}{\partial} = -\frac{\partial}{\partial \theta}$ $(\hat{C}) - \hat{C}(\hat{C}) f(\hat{C}),$ (6.88)

which corresponds to the ordinary differential equation

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

ha defile, he cha ac e I_c le, of [\(6.88\)](#page-25-0).

6.7.3 Central Limit Theorem, a Time-Inhomogeneous Gaussian Process

 N_d consider the second

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

 \blacksquare h ch cha acterizes the deviation of $\frac{()}{V}$ from \blacksquare (). If the limit \blacksquare of $V \to \infty$, df f (,) a fie a lea PDE time-value of a linear fields.

$$
\frac{\partial f(\cdot, \cdot)}{\partial} = \frac{\partial}{\partial} \left\{ \frac{\partial}{\partial} \left(\frac{\hat{\alpha}(\cdot(\cdot)) + \hat{\alpha}(\cdot(\cdot))}{2} \right) f(\cdot, \cdot) - \left(\hat{\alpha}(\cdot(\cdot)) - \hat{\alpha}(\cdot(\cdot)) \right) f(\cdot, \cdot) \right\}.
$$
\n(6.91)

The efore, () is a continuous time-index in each ear-and ed, the effect is Markovalued, the effect is $a \cdot a$ **processe.** Note the PDE (6.91) is very different from PDE (6.86) . The are known in Index section in a section of \mathbb{R} . **b** \mathcal{L} e and as the K g e Mo a e and and and Kg expansion and van K e_{τ} ec_{τ}e [\[32\]](#page-40-13). The f_{orem} is not related to the central limit theorem.

6.7.4 Diffusion's Dilemma

Truncating the E_q. [\(6.86\)](#page-25-1) after the second order, stationary distribution of the station of the stationary distribution of the stationary distribution of the stationary distribution of the stationary distribution of the

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

On the other hand, the stationary solution given in (g, e) , $(h(6.45),$ $(h(6.45),$ $(h(6.45),$

$$
= 0 \prod_{i=1}^{n} \left(\frac{-1}{i} \right),
$$

 \therefore he limit of $V \to \infty$ th V^{-1} $V = \hat{ } ()$, V^{-1} $V = \hat{ } ()$, and $V^{-1} = d$, e_d

$$
- \mathbf{1}_{V} = -\sum_{i=1}^{N} \mathbf{1}_{V} \left(\frac{-1}{\cdot} \right) + C \leftrightarrow - \mathbf{1}_{V} f \quad () = V \int \mathbf{1}_{V} \left(\frac{\hat{\lambda}(t)}{\hat{\lambda}(t)} \right) \mathrm{d} \quad . \tag{6.93}
$$

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I_{s and} $e E_{\bullet}$ [\(6.92\)](#page-26-1) and [\(6.93\)](#page-26-2) are actually the same? We note that both have del ca ca e e a:

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

If fac, he curvature a local extremum is $\lim_{n \to \infty} \frac{1}{n}$ at $\lim_{n \to \infty} \frac{1}{n}$

$$
\left[\frac{d^2}{d^2}\left(-\mathbf{1}f\left(\cdot\right)\right)\right]_{\hat{f}=\hat{f}} = 2V\left(\frac{\hat{f}'\left(\cdot\right)-\hat{f}'\left(\cdot\right)}{\hat{f}\left(\cdot\right)+\hat{f}\left(\cdot\right)}\right) = V\left(\frac{\hat{f}'\left(\cdot\right)-\hat{f}'\left(\cdot\right)}{\hat{f}\left(\cdot\right)}\right)
$$
\n
$$
= \left[\frac{d^2}{d^2}\left(-\mathbf{1}f\left(\cdot\right)\right)\right]_{\hat{f}=\hat{f}}.\tag{6.95}
$$

However, can be \downarrow in an equipment of the global minimum can be different $[20, 37]!$ $[20, 37]!$ $[20, 37]!$ $[20, 37]!$ This implicit that King expansion is not also in the input $[20, 37]!$ This note as \mathbb{R} f_{\bullet} schastic the stop intervals f_{\bullet} in equation of \mathbb{R} intervalued Markov times, real-valued Markov f_{\bullet} \bullet ce. e , a e a \bullet called *diffusion processes*. The above $e \cdot e$ illustrates that there ℓ is globally valid diffusion approximation for stocking approximation for stocking ℓ ge he a.

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

In order to present some recent results in Sec. 6.9ux)(kineti].9879(notice)-25(Log04

The e a_n and b_n between b_n and the nonequilibrium a_n and the nonequilibrium b_n t hermodynamics. In added to the continuity equation to de Groot-Mature a^t ach also e_st extraproach equation [\[5\]](#page-39-9),

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

as one of still damental premises in the entropy premises \mathbf{a} are and J_S is the rate of entropy supplied to a system by its subplied to a system by its surface of d and J_S . of the odynamics, causing intervalses that ≥ 0 . Unfortunately B_{\bullet} and \bullet if \bullet able of heat is not a set of \bullet and \bullet and \bullet and \bullet is not an equation like \bullet is not an equation like \bullet is not an equation like \bullet is not an equation is not an equation is not an f ra Hamiltonian dynamics without resorting to additional assumptions f \int_a^b a *stosszahlansatz*.^{[1](#page-28-1)} A^H , \int_a^b ex f exect. 6.9, \int_a^b e. e., Markov d \int_a^b e. able **o** del ce alle to provide it [\(6.96\)](#page-28-0). A schastic dynamic ach stochastic dynamic approach **to none** $\begin{bmatrix} 1 & b \\ c \end{bmatrix}$ thermodynamics is a subset of the sectors is as we as first demonstrated by Bergmann and Lebow \Box 1955 [\[2\]](#page-39-10).

6.8.1 Boltzmann's Mechanical Theory of Heat

The entire world, as $\deg a$ s interested in temple in the small and $\deg a$ and $\mathcal{L}a$ e (e.g., $\mathbf{a}_{\mathbf{a}}$ too close to the speed of light (e.g., relativity), follows the Newtonian mechanics which can be represented a be a can be represented mathematically in terms of a $H_4 = \Delta_4 \Delta_5 = 0$

$$
\frac{d}{d} = \frac{\partial H(\cdot, \cdot)}{\partial}, \frac{d}{d} = -\frac{\partial H(\cdot, \cdot)}{\partial}.
$$
 (6.97)

o also the colce like here. (6.97) is the dynamics Ole of he_{π} or eh_{π} and he_{π} and he_{π} (π), π):

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

Now, e \log_{α} e hanke $\lim_{n \to \infty}$ of $n \log_{\alpha}$ also see an agree. $H(x, y, N)$ where $V = \text{heb}_{\bullet} = e_{\bullet}f$ a mechanical size and $N = \text{heb}_{\bullet}$ be e_{\bullet} is the number of a set of heb_{\bullet} is the number of a set of heb_{\bullet} . of a cell $\begin{bmatrix} \text{keb} \\ \text{keb} \end{bmatrix}$, then the next $\begin{bmatrix} 0 \\ -\frac{1}{2} \end{bmatrix}$ which and a $\begin{bmatrix} 0 \\ -\frac{1}{2} \end{bmatrix}$ are a call a_{τ} , but extends which has not been extended, if \vec{k} is $Wh\vec{a}^{\dagger}$ is the \log_{2} ebehave of the system as function of V, N, and other parameters? A Hamiltonian system, however, in hold and different from the earlier of Hamiltonian different from the earlier $\frac{1}{2}$ s $\frac{1}{2}$ e have $\frac{1}{2}$ d₃ h ch have a $\frac{1}{2}$ e fi ed **p**. ($\frac{1}{2}$). In fac_t, $\frac{1}{2}$ c ea ha^{ri}he $\log_{\frac{1}{2}}$ e behavior is a function of the initial condition $H((0), (0)) = E$. He holand Bo_r and (1884) ea ed halaihe od na realized that a state thermodynamic equipped that a state $\frac{1}{2}$ are of a mechanical system is *not a single point in the phase space, but rather, it is an entire invariant manifold* defiled by the e.e. \neq H (x, y, N) = E. I_v a B_{\bullet} all - lgel - or ea - e hat ole cal defile

$$
S(E, V, N) = B \setminus \{ \text{ ha.e. } \underset{\mathfrak{M}}{\bullet} \text{ e c} \underset{\mathfrak{M}}{\bullet} \text{ a} \text{ Med } b \text{ he } \downarrow \text{ face } H(\ , \) = E \}
$$

= $B \setminus \int_{H(\ , \) \le E} d \ d \ .$ (6.99)

Shee $S(E)$ is ϕ on ϕ is monotonic function $E = E(S, V)$. Then

$$
dE = \left(\frac{\partial E}{\partial S}\right)_{V,N} dS + \left(\frac{\partial E}{\partial V}\right)_{S,N} dV + \left(\frac{\partial E}{\partial N}\right)_{S,V} dN
$$

= $TdS - dV + \mu dN.$ (6.100)

What is the significance of E_p. [\(6.100\)](#page-29-0)? F_{igher} equipped on the fact that the fact that a Hamiltonian system has a *conservation of mechanical energy H*. Furthermore, **a** *e*, however, however, is conserved by the conservation of energy is valid not only for a single Hamiltonian \mathbb{R} system on a single invariant top on a section of \mathbb{R}^n and \mathbb{R}^n and \mathbb{R}^n and \mathbb{R}^n multiple \mathbb{R}^n multiple \mathbb{R}^n multiple \mathbb{R}^n multiple \mathbb{R}^n multiple \mathbb{R}^n multiple \mathbb{R} level sets, and even and entire class of Hamiltonian systems with varying V and N, and other algrees. It becomes a universally value of N , and N as *the First Law of Thermodynamics*. \overline{N} **e**, according to the teq theory, the ding c q_1 and q_2 if T , , μ are are are mathematically defined via E_q. [\(6.100\)](#page-29-0). The are e e geh heho eha.

 T and have echanical interpretations, though not perfect, as ean interpretations, T and \mathbb{R} is enegand can entum ante ead a μ , however, has no interpretation \mathbb{I} e, J \mathbb{I} ca \mathbb{I} ca \mathbb{I} , ake, Itaal \mathbb{I} e ea \mathbb{I} in terms of B \mathbb{I} $m \cdot$

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

 w ke e

$$
\hat{F} = -\frac{\partial \mu}{\partial}, \text{ and } \mu = D\eta \cdot \rho(\ , \) = gT \cdot \rho(\ , \). \tag{6.102}
$$

$$
\hat{F} = \mathbb{N} \bullet \mathbb{I} \text{ a-entropic force } \mathbb{I} \text{ che } \quad , \text{ a} \mathbb{I} \text{ d} \mu = \mathbb{N} \bullet \mathbb{I} \text{ a-che } \text{ ca } \bullet \text{ e} \mathbb{I} \text{ a}.
$$

6.8.2 Classical Macroscopic Nonequilibrium Thermodynamics

E and [\(6.100\)](#page-29-0) is a d only when the entire torus H (x, $y = E$ is reading the $\log_e e$ time limits is a *ergodicity*. In other other with the end of the intervals of the intervals of $\log_e e$ and $\log_e e$ e_n a \Box a \Box a \Box d \Box when the dS and dV are exponentially changing. What harpens if the change are θ_{\bullet} and ? Then, the *Second Law of Thermodynamics* are that

$$
TdS \ge dQ = dE - d \quad , \tag{6.103}
$$

In the choicle is the amount of heat that flows into the system, and d is the system, $dQ = \log d$ is the system of the system, $dQ = \log d$ is the system of the system of $dQ = \log d$ is the system of $dQ = \log d$ is the system of dQ $a \bullet b$ of $a \bullet d$ done to the system. Both are path dependent, as indicated by the d. E_{\bullet} . [\(6.103\)](#page-30-0) is known as the Clausius inequality. The notion of *entropy production* is \Box do ced account for the Λ e_s a

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

in which is called entropy of class production, which is negative. $= -dQ/d$ is ca ed head dissipation. In general, neither normal edge a telephone derivative derivative. Eq. [\(6.104\)](#page-30-1) \Box **kd h** a_r_a**h** *entropy balance equation.*

6.8.2.1 Local Equilibrium Assumption and Classical Derivation of Entropy Production

If ∂e assumes that E_q. [\(6.100\)](#page-29-0) is a d called ∂e and time and time, then ∂e has $rac{\partial}{\partial}(\theta, \theta) = \frac{1}{T}$ $\frac{\partial}{\partial} \left(\cdot, \cdot \right) - \sum_{j=1}$ $\mu_j^{\partial} \overrightarrow{\partial} (\cdot, \cdot)$ (6.105) **in which we have assumed in the compressibility dV** = 0. (,), (,), and \int_1^1 (,)

are entropy density, energy density, and concentration of the ith species. $\text{Re}a$, $\text{Im}b$ hat both energy and particles follow continuity equation in space-time, $\text{Re}a$ ∂e has

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

Then, \downarrow b_r \downarrow g here \downarrow \bullet E_p. [\(6.105\)](#page-30-2), and use a certain amount of physical $\mathbf{I} \cup \mathbf{I}$, ore arrives at e , a

$$
\frac{\partial}{\partial t} \left(\begin{array}{cc} 0, & 0 \end{array} \right) = (0, 0) + J_S(0, 0)
$$
 (6.107a)

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where e_n and e_n are e_n being e_n

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

 $a \cdot b \cdot d$ fluxe

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

$$
\text{Acc}_{\bullet} d_{\bullet} g \bullet O_{\bullet} \text{age} \downarrow \text{hee} \quad [18], \text{each} \underset{\text{def}}{e} \quad \text{A} \text{hee} \quad \bullet \quad \text{def} \quad \bullet \quad \text{cd} \quad \bullet \quad \text{da}
$$
\n
$$
a_{\bullet} \bullet f \bullet \times d \downarrow \text{fg} f \bullet \text{ce} \quad (6.108)
$$

I h chich should be non-negative. The theory of nonequilibrium theory of nonegular contains \mathcal{L} conce i.g. transport processes of various kinds: diffusion, charge, chem ca , e.c. More M_{\odot} and $\ddot{\bullet}$ transport fluxes on the various transport fluxes can only be obtained, beho eho engine \mathbb{R} gically, engineering.

6.9 Mathematicothermodynamics of Markov Dynamics

We not consider discrees a e-state of \bullet such as \bullet such as \bullet in terms of $\text{Coh}_{\mathcal{A}}$ is equation for position $\text{Coh}_{\mathcal{A}}$ in state space , e.g., Chapman–Kolmogorov e_{\bullet} uation, or master e $_{\bullet}$ uation

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

In hich is are the $\text{inf}_{z \in \mathcal{Z}}$ and dist_{z} are dist_{z} are dist_{z} [\(6.27\)](#page-10-0). We shall now follow the same logic steps a, b, c, d and $b, c, d, 8.1$, ode e o a hermodynamic theory based of hegeneral dynamics by interval dynamics by interval dynamics by interval dynamics by intervalse on the general dynamics by intervalse on the general dynamics by intervalse on the con the notion of entropy. Eq. [\(6.109\)](#page-31-0) replaces the Hamiltonian system [\(6.97\)](#page-28-2), and in he ace of B_{oltzm}ann ce eb a ed $S = B \setminus \mathfrak{A}(E)$ be the G_{ibb}-Shannon $e_{\mathbb{R}}$.

$$
S() = -\sum_{j=1}^{N} \binom{j}{j} \binom{n}{j} \tag{6.110}
$$

Then, ∂e has

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

 we

$$
(\tau) = \frac{1}{2} \sum_{j=1}^{N} \left(\frac{1}{j} (\tau)^{-1} - \frac{1}{j} \tau \right) \sqrt{1 + \left(\frac{1}{j} \tau \right)^{-1} \tau}
$$
\n(6.111b)

$$
J_S() = \frac{1}{2} \sum_{j'}^{N} \left(\begin{array}{cc} 1 & 0 \\ 0 & j \end{array} \right) \begin{array}{c} -1 & 0 \\ 0 & j \end{array} \begin{array}{c} \text{if } j \text{ (6.111c)} \end{array}
$$

It is immediately obvious that ≥ 0 since for every pair in Eq. [\(6.111b\)](#page-32-0), the t_{eff} is hadden of $\left(\begin{array}{c} - \\ - \end{array}\right)$ (bigger) and respect the respective to the respective of $(6.111b)$ E_{\bullet} . [\(6.76\)](#page-22-0).

The efore, et have derived and entropy balance equation balance on Markov on Markov entropy balance equation balance eq dyamics, with the assumption of ocal equilibrium. Equations [\(6.111b\)](#page-32-0) and $(6.111c)$ further give explored explicit expressions, in the $\frac{1}{4}$ of the $\frac{1}{4}$ (1), for the entropy flux J_S the non-negative entropy production \mathbf{r} . As we shall show below, there is a complete nonequilibrium the mesoscopic on the mesoscopic scale, in the mesoscopic sca vac. Theory is the space. Theory is the space of the vec and vec be $\lg 1$.

6.9.1 Non-Decreasing Entropy in Systems with Uniform Stationary Distribution

If he a e E_q. [\(6.109\)](#page-31-0) has a stationary distribution space station subsets he \sum N $=1$ $\begin{pmatrix} 1 & -1 \\ 0 & 1 \end{pmatrix} = \sum$ N $=1$ $\mathbf{y} = 0, \mathbf{y}$.

In h _{case},

$$
\frac{dS}{d} = -\sum_{j=1}^{N} \left(\frac{d}{d} \left(\frac{1}{d} \right) \right) \mathbf{1}_{j} = -\sum_{j'=1}^{N} \left(\frac{1}{d} - \frac{1}{d} \right) \mathbf{1}_{j}
$$
\n
$$
= \sum_{j'=1}^{N} \mathbf{1}_{j} \mathbf{1}_{j} \left(\frac{1}{d} \right) \ge \sum_{j'=1}^{N} \frac{1}{d} \left(\frac{1}{d} - 1 \right)
$$
\n
$$
= \sum_{j=1}^{N} \left(\sum_{j=1}^{N} \frac{1}{d} \right) = 0. \tag{6.112}
$$

6 S
$$
\mathbf{c}
$$
h a \mathbf{c} P \mathbf{e} i a \mathbf{d} K \mathbf{e} \mathbf{c} \mathbf{a} M I \mathbf{c} U \mathbf{d}

We helefore have a heorem is a statistic theorem in the stationary probability distribution \mathbf{b} is uniform, then the entropy of $S = \int_0^T S$ is non-decreasing function of the set

6.9.2 Q-Processes with Detailed Balance

If a Q **process has a same distribution such as** $\mathbf{a} = \mathbf{b}$ if $\mathbf{a} = \mathbf{c}$ is \mathbf{b} if \mathbf{a} as *detailed balance*, hel

$$
J_S() = \frac{1}{2} \sum_{j'=1}^{N} \left(\frac{1}{4} \left(\frac{1}{4} - \frac{1}{4} \right) \right) \left(\frac{1}{4} \right)
$$

\n
$$
= \frac{1}{2} \sum_{j'=1}^{N} \left(\frac{1}{4} \left(\frac{1}{4} - \frac{1}{4} \right) \right) \left(\frac{1}{4} \right)
$$

\n
$$
= \sum_{j'=1}^{N} \left(\frac{1}{4} \left(\frac{1}{4} - \frac{1}{4} \right) \right) \left(\frac{1}{4} - \frac{1}{4} \right)
$$

\n
$$
= \sum_{j'=1}^{N} \left(\frac{1}{4} - \frac{1}{4} \right) \left(\frac{1}{4} \right) \left(\frac{1}{4} - \frac{1}{4} \right) \left(\frac{1}{4} \right) \left(\frac{1}{4} - \frac{1}{4} \right) \left(\frac{1}{4} \right)
$$

\n
$$
= \frac{1}{4} \left(\sum_{j=1}^{N} \left(\frac{1}{4} \right) \left(\frac{1}{4} - \frac{1}{4} \right) \right) = \frac{1}{4} \frac{1}{4} \frac{1}{4} \frac{1}{4} \tag{6.113}
$$

in which

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

 \mathcal{L} id be identified as the mean energy, with $E = -T$ least as the energy of λ he \Box a e \Box accord \Box g \Box Boltzmann and \Box and \Box and \Box Then, E_n. [\(6.111a\)](#page-31-1) becomes

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

 $F = E - TS$ is \mathbb{N} is a the fee energy of a the \mathbb{N} of \mathbb{N} is $S - g$. It is e $\text{eced } \bullet$ on only decreases to monotonically define in an in an in an in an in an isothermal system approaching \bullet \bullet e_r \downarrow \downarrow \downarrow \downarrow and \downarrow \downarrow \downarrow and \downarrow area its minimum steady reaches in a state in \downarrow \downarrow \downarrow .

6.9.3 Monotonicity of F Change in General Q-Processes

Encouraged by the above $e \downarrow e \downarrow e$ above the Kullback–Leibler divergence, $a \rightarrow M$ $a \rightarrow ca \rightarrow ee$ $a \rightarrow ee$

$$
F() = \sum_{j=1}^{N} \binom{j}{j} \left(-\frac{1}{N} \binom{j}{j} + \frac{1}{N} \binom{j}{j} \right) = \sum_{j=1}^{N} \binom{j}{j} \left(\frac{j}{j} \binom{j}{j} \right) \ge 0. \tag{6.116}
$$

One can act a Δ by the dF/d \leq 0 for general Q-process with the detailed ba alce:

$$
\frac{dF(1)}{d} = \sum_{j=1}^{N} \left(\frac{d}{d} \frac{1}{d} \right) \mathbb{I}\left(\frac{1}{d}\right) = \sum_{j'=1}^{N} \left(\frac{1}{d} - \frac{1}{d}\right) \mathbb{I}\left(\frac{1}{d}\right)
$$

$$
= \sum_{j'=1}^{N} \frac{1}{d} \left(\frac{1}{d} \frac{1}{d} \right) \le \sum_{j'=1}^{N} \frac{1}{d} \left(\frac{1}{d} \frac{1}{d} \right) = \sum_{j'=1}^{N} \frac{1}{d} \left(\frac{1}{d} \frac{1}{d} \right) = \sum_{j'=1}^{N} \frac{1}{d} \left(\frac{1}{d} \frac{1}{d} \right) = 0.
$$
(6.117)

6.9.4 F Balance Equation of Markov Dynamics

 M_{\bullet} e \searrow e e \searrow M_{\bullet} we have a M_{\bullet} , balance equation for the F ():

$$
\frac{dF(\)}{d} = E_{\ j} \ (\) - \ (\), \tag{6.118a}
$$

where ($0 \ge 0$ gen in [\(6.111b\)](#page-32-0), and

$$
E_j^{-}(x) = \frac{1}{2} \sum_{j'}^{N} \left(\frac{1}{j} (x)_{j'} - x^{(j)}_{j'} \right) \sqrt{1 + \frac{1}{j}} \ge 0. \tag{6.118b}
$$

See [\[9\]](#page-39-11) for the reset of h_{\bullet} independent Both E_i (b) and (b) are h_{\bullet} integative which eans that E_q. [\(6.118a\)](#page-34-0) can be interpreted as "the F(t) has a source and a single single change e_1 a \Box and \Box in E_i (), a source term, and dissipation (t), a \Box by e_i . The e is a mesoscopic conservation of the $\lceil a \rceil$ and $\lceil F. E_1 a_1 \rceil$ [\(6.118a\)](#page-34-0) is $\lceil e \rceil$ ean near than the E_q. [\(6.111a\)](#page-31-1), in which J_S does not have a definition e_{max} .

The balance Eq. [\(6.118a\)](#page-34-0) and the monotonicity of dF/d ≤ 0 have remarkable resemblance to the first and the second laws of thermodynamics. But they are really a part of a mathematical structure of any stochastic Markov dynamics.

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To g has eller this all the algorithment of the results in the results c_{\bullet} ¹ec_{-c}e, *mathematicothermodynamics* [\[9,](#page-39-11) [10,](#page-39-8) [21,](#page-40-16) [24\]](#page-40-17).

6.9.5 Driven System and Cycle Decomposition

The entropy production given \mathbb{R} entropy in \mathbb{R} entropy in \mathbb{R} as assumed be written as assumed be written as assumed be written as assumed be assumed by a set of \mathbb{R} as assumed by a set of \mathbb{R} as

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

where ϕij = i(t)qij is the one-way probability flux from state i to . It can be proven that, in a stationary Q -process, the above expression can be expressed also $a_{-}[14]$ $a_{-}[14]$

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

In h ch φ_{Γ}^{\pm} be in the number of Γ c cec of Γ e ed Γ a unit Γ e, Γ be for a d and bac_w a d d_ec **s**. Most a algebra in the cycle $\Gamma = (i_0, i_1^T, \dots, i_j, i_0^0)$

$$
\frac{\varphi_{\Gamma}^{+}}{\varphi_{\Gamma}^{-}} = \frac{\varphi_{1}^{0} + \varphi_{1}^{1} + \varphi_{2}^{2} + \cdots + \varphi_{1}^{0}}{\varphi_{1}^{1} + \varphi_{1}^{1} + \cdots + \varphi_{1}^{0} + \varphi_{1}^{0}},
$$
\n(6.121)

I h_ch ____de endent of he should be shown the efore, $\frac{1}{2}$ $(\varphi_{\Gamma}^{+}/\varphi_{\Gamma}^{-})$ can and \Box d be $\frac{1}{2}$ Me – od a – he entropy per cycle, and the term $(\varphi_{\Gamma}^+ - \varphi_{\Gamma}^-)$ – $\frac{1}{2}$ a he a counts that counts the number of complete along a trajectory. All the $\int_0^L e^{-\int_0^L}$ is identically the $\int_0^L e^{-\int_0^L}$ is integrated in the $\int_0^L e^{-\int_0^L}$ is integrated in the $\int_0^L e^{-\int_0^L}$ c c e_r [\[27\]](#page-40-18). If a Markov **process is determined balanced, then its entropy production is determined in the set** e...each and e.e hecce.

It is well known since the work of A. N. Kolmogorov that the quantity in \mathbb{I} [\(6.121\)](#page-35-0) e_{\bullet} uals \Box for each and every cycle if and only if the Markov process is detailed ba alced. The ef_{ore}, he a he a callo of *detailed balance* of detail notion of \log description of a non-driven \mathbb{R} e strategy whose state is an equipped state is F_{\bullet} a d \Box elged \Box e \Box elged \Box at least one of the cycles in the state space \Box by \Box by a lead c_ a _ $\phi_{\Gamma}^+ \neq \phi_{\Gamma}^+$.

6.9.6 Macroscopic Thermodynamics in the Kurtz Limit

For a DGRI when $N =$ edges and M reactions, the F function integral integration in Sect. 6.9.4 **La functional of the probability distribution v (n,) which is it is it is clear of of** the eaction system's volume V. Then one natural limit is matter what is made it is matter what it may be not its matter what it is $a = V \rightarrow \infty$ as in the Kurtz limit of the shown that $[10]$

$$
\tau \mathbf{I}_{\infty} \propto \frac{F[\nu(\mathbf{n}, \cdot)]}{V} = \tau \mathbf{I}_{\infty} \frac{1}{V} \sum_{\mathbf{n}} \nu(\mathbf{n}, \cdot) \mathbf{I} \left[\frac{\nu(\mathbf{n}, \cdot)}{\nu(\mathbf{n})} \right]
$$

$$
= -\frac{1}{\tau \mathbf{I}_{\infty}} \frac{1}{V} \sum_{\mathbf{n}} \nu(\mathbf{n}, \cdot) \mathbf{I}_{\infty} \nu(\mathbf{n})
$$

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

In heh $n = (n_1, 2, \dots, n)$, is the $\lim_{n \to \infty}$ be $\lim_{n \to \infty}$ of he h sees. $\mathbf{x} = (x_1, \dots, x_N)$ is the corresponding $\mathbf{k} = \mathbf{y}$ is the corresponding $\mathbf{x} = \frac{\mathbf{n}}{V}$. The Kurtz theorem **i** Sec. $6.7 - a e$, ha he scharch $\frac{1}{2}$ of a DGP, $\mathbf{n}_V()$,

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

where $x()$ is the solution to the deterministic, had hear a contracted (e.g., E_{\bullet} . [\(6.89\)](#page-25-2)). Most interestingly, according to the large deviation principle from the large deviation principle $\begin{bmatrix} \n\text{he}_0 & \text{of} \n\end{bmatrix}$ $\begin{bmatrix} \text{beh}_1 & \text{beh}_2 & \text{hend} \n\end{bmatrix}$ a $\begin{bmatrix} \text{tab} \text{em} \end{bmatrix}$ a $\begin{bmatrix} \text{tab} \text{em} \end{bmatrix}$ a $\begin{bmatrix} \text{tab} \text{em} \end{bmatrix}$ a $\begin{bmatrix} \text{sub} \text{em} \end{bmatrix}$ a $\begin{bmatrix} \text{sub} \text{em} \end{bmatrix}$ a $\begin{bmatrix} \text{sub} \text{em$ δ file \bullet , \bullet and \bullet bability has an asymptotic expression

$$
-\frac{1}{\sqrt{2\pi}\omega} \frac{V(\mathbf{n})}{V} = -\frac{1}{\sqrt{2\pi}\omega} \frac{V(V\mathbf{x})}{V} = G \quad (\mathbf{x}).
$$
 (6.124)

The steady state a gende as $\{x \in \mathbb{R} \mid x \in G \mid x \in G \}$ can be dentified as a gehe a ed Gbbs function for $\log_1 z$ on $\log_2 z$ can eaction superior I can be \downarrow that \downarrow has

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

The a generalization of the neutrality in Eq. [\(6.77\)](#page-22-0). See [\[10\]](#page-39-8) for the position

6.10 Summary and Conclusion

This chapter presents a new modeling paradigm for biological systems and procettes that consist of multiple populations of individuals, each with an infinite many internal degrees of freedom. The individuals are grouped into subport a \blacksquare

and a he a can be e c birth represents behaviors in terms of b h, death, igation, and take suitching. We that the population \mathbb{R}^n is \mathbb{R}^n . $e_x = f \circ f$ nonlinear ordinary differential equations (ODE) widely employed in hat he a sa b \bullet \bullet \bullet if Id a stochastic kinetic keory. This stochastic kinetic theory. This stochastic kinetic k population and the contraction of biological reality can be introduced \mathbf{r} of \mathbf{r} and \mathbf{r} rigorously, thus in the confidence in the conclusions of f is f in the conclusions drawn from f is f a he a ca aha — We ca ed h f_{ore} a *Delbrück-Gillespie process*. In the alget population limits. T. G. Kurtz's theorem, a split of a get \mathbb{N} , be specified theorem. $a = g \cdot f \cdot h \cdot h$ lear $a \cdot e, a = h \cdot h$ ath is consistent with the traditional ODEs. In Sect. 6.9, ${\rm e\, \cdot}$ eccht ${\rm e\, \cdot}$ ${\rm e\, \cdot}$, ${\rm e\, \cdot}$ and ${\rm e\, \cdot}$ and ${\rm e\, \cdot}$ and ${\rm e\, \cdot}$ and ${\rm e\, \cdot}$ and corresponding acroscopic nonequipties of the corresponding corresponding c Together the three $a' = (1)$ stochastic in the strong of DGP, (2) deterministics in the stochastic stochastic stochastics in the stochastic stochastics in the stochastic stochastics in the stochastic stochastics in the sto nonlinear dynamics in the mathematics in the mathematics in the mathematics in the mathematical mathematics in provide a c_omprehensive a key a key a camp of a wide a get of biological theory for a wide range of biological contract of a wide range of biological extension of a wide range of a wide a second contract of a wide a sec \mathcal{L} sesses from biochemistry occology.

6.11 Exercises: Simple and Challenging

6.11.1 Simple Exercises

1. C_p i e he e eced at e and he a ance of an e one and the variance of an exponential distributed \overrightarrow{a} d_o a abe \sqrt{a} k a e λ . **2.** Le^{t 1}₁, \cdots , be **j**, d. e **o**le is a ald **j** a ab exponential rate $* =$ \mathbb{N} 1, 2, ···, }. Show that $f_{T^*}(\cdot) = \mathbb{N} - \lambda$. **3.** If a c of \Box d. and \Box e a_N c hd but distribution ft (), $f_T(0) = 0$ but $f'_T(0) \neq$ 0, ha is the distribution for $T^* = \mathbb{N}\{T_1, T_2, \cdots, T\}$ in the limit of $\rightarrow \infty$?

6.11.2 More Challenging Exercises

- 4. Consider a population consisting of densities and independent individual organization or α or α is each with an exponential distribution of exponential head, is birth and head, $a \cdot d$ goggedeath ψ . hae μ .
	- $($ Now when the population has exactly individuals, when \mathbb{R} is the probability individuals, when \mathbb{R} is the probability individuals, when \mathbb{R} is the probability individuals, when \mathbb{R} is the probabili distribution for the \lg is the next birth? What is the probability of the \lg is the probability of \lg is th d_r b **o** for the a \lg is the next death? What is the post distribution for the waiting time to the next birth or death event ?

\n- \n
$$
\begin{array}{c}\n \text{Let } & \text{else, } \\
 a_{\text{max}} & \text{else, } \\
 a_{\text{max}} & \text{else.}\n \end{array}
$$
\n
\n- \n $\sum_{i=0}^{\infty} & \text{else, } \\
 \text{What } \sum_{i=0}^{\infty} & \text{else, } \\
 \text{What } \sum$

5. The 3-_ca e Ma_c \bullet \neq $\frac{e}{\sqrt{n}}$,

$$
A \xrightarrow[{-1}]{1} B \xrightarrow[{-2}]{2} C \xrightarrow[{-3}]{3} A,
$$
 (6.126)

has been yield in sed in biochemistry of \mathbf{e}_i and \mathbf{e}_i and \mathbf{e}_i are conformational changes of a $\log e$ or $e \log \log e$ is the good undergoing through its three different states A, B, and $C. F_{\bullet}$ e g is non-active, $B = \{a, a\}$ active, and $C = \{f : a \in A\}$ active.

() The **c**bab_{ilities} for the states, **p** = (\overline{A} , \overline{B} , \overline{C}), \overline{A} is a differential e_{\bullet} a \bullet

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

I hee Q _a 3×3 a _ W _e he Q out in the 's. Show that he sum of each and every row is zero. Discuss in probabilistic terms, what is the $\text{real}\$ is of h_{max} et ? $(\overline{\ }^{\eta}C_{\bullet})$ i e he ead a e obab_{ilities} show that, if \overline{B} , and \overline{C} , and \overline{C} has \overline{B} \mathbb{R}^d ead are, he net (possibilities) fluid from state A \bullet B,

$$
J_{A\rightarrow B} = 1_A - 1_B,
$$

is the same as the net flux from state B → state C, and also the net flux from $C \to A$. Since the are all the same, it is called the steady state fluid $C \to A$. the b_r chemical reaction cycle in $\binom{126}{6}$.

() What is the condition, in the set all the \sqrt{s} state $J = 0$?

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- **6.** Consider a single entity below a simple of \Box in the sea of \Box below a give beam of S. The Michaelis– $Me\$ en de c -

$$
E + S \xrightarrow[{}]{\longrightarrow} ES \xrightarrow{2} E^* + P. \tag{6.127}
$$

Because the entry a single entry e_i and e_i on e_i on e_i of S can be a μ ed a μ a μ constant, at the value s. W ϵ he differential equations for the probability of the en_{zy} e being in $\text{a.e } E, ES, \text{a} \text{d } E^*$: $E(\cdot), E(S(\cdot), \text{a} \text{d } E^*).$ G_e en \Box a cond d_{\Box} en $E(0) = 1$, $ES(0) = 0$, and $E^*(0) = 0$, to solve E^* (). I is cear that the time of the chapter of e is e is e is e is state E^* is stated E to E∗ is stochastic. Le T be the and \bullet is the \bullet T is the probability distribution for T , f_T ()? However, i.e. \longrightarrow e a ed \bullet E^* ()? Compute expected and E[T]. Compare your result with the Michaelis– Me^{$\int_{\mathbb{R}}^{\mathbb{N}}$ e_n f_o i a.}

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