Emerging of Stochastic Dynamical Equalities and Steady State Thermodynamics from Darwinian Dynamics∗

P. Ao
Department of Mechanical Engineering and Department of Physics, University of Washington, Seattle, WA 98195, USA

(Received November 30, 2007)

Abstract The evolutionary dynamics first conceived by Darwin and Wallace, referring to as Darwinian dynamics in the present paper, has been found to be universally valid in biology. The statistical mechanics and thermodynamics, while enormous successful in physics, have been in an awkward situation of wanting a consistent dynamical understanding. Here we present from a formal point of view an exploration of the connection between thermodynamics and Darwinian dynamics and a few related topics. We first show that the stochasticity in Darwinian dynamics implies the existence of a unified stochastic dynamical framework both near and far from equilibrium.

PACS numbers: 05.70.Ln, 05.10.Gg, 72.70.+m, 87.15.Ya

Key words: non-equilibrium processes, Darwinian dynamics, generalized Einstein relation, absence of detailed balance, stochastic dynamical equalities

One of the principle objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity.

Josiah Willard Gibbs (1839–1903)

1 Introduction

1.1 What Is Darwinian Dynamics?

The dynamical theory proposed by Darwin and Wallace on evolution in biology has formed the fundamental theoretical structure for understanding biological phenomena for one and half centuries. We refer to it in the present paper as “Darwinian dynamics”. It has been confirmed by thousands and thousands of field observations and laboratory experiments, and extended to virtually all levels of biology. There is no known valid evidence against it in biology, as in the same status of relativity and quantum mechanics in physics. There exists a concise and accessible discourse of this dynamics by a renowned researcher in physical sciences that we recommend to the reader. Its essence may be summarized by a single word equation most familiar to biological scientists:

\[ \ln q = \ln q^0 - TS \]

Evolution by Variation and Selection.

In its initial formulation the theory was completely narrative. Not a single mathematical equation was used. There have been constant efforts by biologists and by others to clarify its meaning and to make it more quantitative and hence more predictive. Tremendous progress has been made during the past 100 years. Two of the most important concepts emerged in Darwinian dynamics are Fisher’s fundamental theorem of natural selection, which connects the variation to the speed to reach an optimal value in evolution, and Wright’s adaptive landscape, which describes the ultimate selection as a potential function of a landscape in a gigantic genetic space. Nowadays the use of mathematics in this area is comparable to that of any mathematically sophisticated field of natural science. Darwinian dynamics is a bona fide nonequilibrium stochastic dynamical theory, which governs the processes leading to complex creatures such as Methanobacterium and Homo sapiens on Earth.

What would be a possible mathematical structure for Darwinian dynamics? Though the scope of Darwinian dynamics is very broad and its quantification appears formidable, we will present here a precise and nevertheless general enough formulation. Intuitively evolution is about successive processes: Quantities at a later stage are related to their values at its earlier stage under both predictable (deterministic) and unpredictable (stochastic) constraints. For example, the world population of humans in next 20 years will be surely related to its current one. Hence, the genetic frequency, the probability in the population, of a given form of gene (allele) in the next generation is related to its present value. Here sexual conducts and other reproduction behaviors are treated as means to realize the variation and selection for evolution. We may denote those genetic frequencies as \( q \) with \( n \) components denoting all possible alleles. Thus \( \mathbf{q} = (q_1, q_2, \ldots, q_n) \) is a vector (Here \( \mathsf{T} \) denotes the transpose). There are huge amount of human traits related to genetics (or genes):

∗The project supported in part by USA NIH Grant under HG002894
height, skin color, size of eye ball, faster runner, gene for liver cancer, gene for smartness, etc. The number \( n \) is then large: it could be as large, and likely larger, as the number of genes in human genome, which is about 20 000, if one simply assigns one allele to a trait to one gene without any combinatorial consideration. (This is certainly very crude. In addition, we do not know the exact way to specify such relationship yet). This number is far larger than the number of chemical elements, which is about 100, and than the number of elementary particles, about 30. With a suitable choice of time scale equivalent to an averaging over many generations, the incremental rate in such an evolutionary process may be represented by a deterministic force \( \dot{\vec{q}} = \mathbf{f}(\vec{q}, t) \). The deterministic constraint at a given time may be represented by a deterministic force \( \mathbf{f}(\vec{q}, t) \). For example, there is a high confidence to predict the eye color of a child based on the information from his/her parents, but the smartness of an offspring is not so strongly correlated to that of the parents. The random constraint, the unknown and/or irrelevant force, is approximated by a Gaussian-white noise term \( \zeta(q, t) \), with zero mean, \( \langle \zeta \rangle = 0 \) and the \( n \times n \) variance matrix \( D: \langle \zeta(q, t')\zeta(q, t) \rangle = 2D(q, t)\delta(t - t') \). Here the factor 2 is a convention and \( \delta \) is a positive numerical constant reserved for the role of temperature in physical sciences. \( \delta(t) \) is the Dirac delta function. With these notations we are ready to transform the word equation into a precise mathematical equation, which now reads

\[
\dot{\vec{q}} = \mathbf{f}(\vec{q}, t) + \zeta(q, t)
\]

To physicists and chemists, this equation looks similar to an equation already known for 100 years,[21,22] proposed by Langevin 50 years after Darwin and Wallace. There are some difficult issues in connection to the Langevin equation, such as the absence of detailed balance condition, to be discussed below. To mathematicians as well as biologists, it is in the form of standard formulation of stochastic differential equations.[23,24] We will return to above equation as Eq. (1) in next section. However, an immediate question arises: while we may represent the variation in evolution by the variance matrix \( D \), where is Wright’s adaptive landscape and the corresponding potential function?

It is known that the deterministic force \( \mathbf{f}(\vec{q}, t) \) in general cannot be related to a potential function in a straightforward way, that is, \( \mathbf{f}(\vec{q}, t) \neq -D(\vec{q}, t)\nabla \phi(\vec{q}, t) \). Here \( \nabla = (\partial/\partial q_1, \partial/\partial q_2, \ldots, \partial/\partial q_n)^T \) is the gradient operation in the phase space formed by \( \vec{q} \), and \( \phi(\vec{q}, t) \) is a scalar function. In fact, the existence of such an inequality is ubiquitous in nonequilibrium processes. It is the breakdown of detailed balance. A nonequilibrium process typically has the following five qualitative characteristics:

i) dissipative, \( \nabla \cdot \mathbf{f}(\vec{q}, t) \neq 0 \);

ii) asymmetric, \( \partial f_j(\vec{q}, t)/\partial q_i \neq \partial f_i(\vec{q}, t)/\partial q_j \) for at least one pair of indices of \( i, j \);

iii) nonlinear, \( \phi(\vec{q}, t) \neq \theta f(\vec{q}, t) \);

iv) stochastic with multiplicative noise, \( D(\vec{q}, t) \) depending on the state variable \( \vec{q} \); and

v) possibly singular, that is, \( \det(D(q, t)) = 0 \).

The asymmetry is the reason that \( \mathbf{f}(\vec{q}, t) \) cannot be equal to \( -D(\vec{q}, t)\nabla \phi(\vec{q}, t) \), which will become explicit below. These are the main reasons that a consistent formulation of nonequilibrium processes has been difficult.[25–29] Progress in recent biological studies has shown that a quantitative Wright adaptive landscape is indeed embedded in the above stochastic differential equation. It emerges in a manner completely consistent with its use in the physical sciences,[19,30–33] which will be explored further in the present paper.

### 1.2 Outstanding Questions on Statistical Mechanics and Thermodynamics

In the physical sciences there has been a sustained interest during past several decades in nonequilibrium processes, see, for example, references [21], [25] ~ [29], and [34] ~ [36]. Important goals are to bridge its connection to equilibrium processes and to clarify the roles of entropy and the Second Law of thermodynamics within deterministic and conserved dynamics and to balance the descriptions between the single particle trajectory and the ensemble distribution. In this content we should also mention the enormous effort since Boltzmann to understand the associated direction of time from reversible dynamics, e.g. in Ref. [37].

There is also an active interest from the philosophical point of view on the foundations of statistical mechanics and thermodynamics.[38,39] Relevant to the present paper, the following three fundamental questions have been explicitly formulated:[40]

How can one derive equations that are not time-reversal invariant from a time-reversal invariant dynamics?

How to provide a theoretical basis for the “approach to equilibrium” or irreversible processes?

In the view of the absence of logical consistent answers to above questions from conservative dynamics, Newtonian dynamics or quantum mechanics,[41,42] it should be desirable to look into these problems from a completely different perspective.

### 1.3 What Can We Learn from Darwinian Dynamics?

Thanks to recent progress in experimental technologies, particularly in nanotechnology, many previously inaccessible regimes in time and space have now been actively exploring. There have renewed interests in stochastic phenomena, ranging from physics,[41,43–51] chemistry,[52–55] material science,[56–58] biology,[19,59–61] and to other fields.[24] These works demonstrate the strong on-going exchange of ideas between physical and biological sciences. In particular, quantitative experimental and theoretical physical methodologies have been finding their way into the study of cellular and molecular processes of life, which has been very useful. On the other hand, we think it is of at least equal value to consider the opposite direction of the flow of ideas. Darwinian dynamics may generate new insights in the physical sciences.
For example, Darwinian dynamics can address all three fundamental questions in previous subsection in its own way. For the first question, as long as statistical mechanics is formulated according to the Boltzmann–Gibbs distribution, it will be shown below that Darwinian dynamics indeed implies this distribution, and that the main structures of statistical mechanics and thermodynamics are equivalent. For the second question, it is found that thermodynamics is based on the energy conservation (the First Law) and on the Carnot cycle. It deals with quantities at equilibrium or steady state. There is no role for dynamics. Thus, there is no requirement for the direction of time: Both conservative and nonconservative dynamics can be consistent with it. The explicit independence of the Carnot cycle and the First Law on dynamical properties in Darwinian dynamics will become clear below. Hence, there is no conflict between thermodynamics and the time-reversal dynamics dominated in physics. For the third and last question, Darwinian dynamics comes with an adaptive behavior\cite{1,2,5,7,9,11,14,16–20} and with an intrinsically built-in direction of time. This is due to the explicitly stochastic or probabilistic nature of Darwinian dynamics. Such a behavior was summarized as the fundamental theorem of natural selection\cite{5} and extended further as the F-theorem\cite{19}. Thus, Darwinian dynamics provides a general framework to address the question of “approaching to equilibrium”.

1.4 Organization of the Paper

The rest of the paper is organized as follows. In Sec. 2 Darwinian dynamics will be summarized. In Sec. 3 it will be shown that statistical mechanics and the canonical ensemble follow naturally from Darwinian dynamics. In Sec. 4 the connection to thermodynamics is explored. There it will be shown that the Zeroth Law, the First Law, and the Second Law follow directly and naturally from Darwinian dynamics, but not the Third Law. In Sec. 5 two types of simple, but seemingly profound, dynamical equalities discovered recently are discussed. One is based on the Feynman–Kac formula and one is a generalization of Einstein relation. In Sec. 6 the range of present ideas is put into perspective.

Two disclaimers should be made at the beginning of our discussion. First, we will mainly be concerned with the theoretical structures, not with specific details. Specifically, we will focus on which structural elements should be presented in various equations, where consensus can be reached, not so much as what would be details forms of each elements. In fact, many of detailed forms are still unknown and are active research topics. Second, rigorous mathematical proofs will not be provided, though care has been taken to make presentations as clear and consistent as possible.

2 Darwinian Dynamics, Adaptive Landscape, and F-Theorem

This section summarizes recent results on Darwinian dynamics, in more detail than provided in the Introduction.
Darwinian dynamics was conceived graphically by Wright\[^6\] as the motion of the system in an adaptive landscape in genetic space. Since then such a landscape has been known as the fitness landscape in some part of literature.\[^{14,18,62}\] However, there exists a considerable amount of confusion about the definition of fitness.\[^{11,14,19}\]

In the present paper a more neutral term, the (Wright evolutionary) potential function, will be used to denote this landscape. The adaptive landscape connecting both the individual dynamics and its final destination is intuitively appealing. Nevertheless, it has been difficult to prove its existence in a general setting. The major difficulty lies in the fact that typically the detailed balance condition does not hold in Darwinian dynamics, that is, $D^{-1}(q)f(q)$ cannot be written as a gradient of scalar function.\[^{21,25,28,34,35}\]

During our study of the robustness of the genetic switch in a living organism\[^{63,64}\] a constructive method was discovered to overcome those difficulties: equation (1) can be transformed into the following stochastic differential equation,

$$\begin{align*}
[R(q) + T(q)] & \dot{q} = -\nabla \phi(q; \lambda) + N_{II}(q)\xi(t),
\end{align*}$$

(4)

where the noise $\xi$ is from the same source as that in Eq. (1). The parameter $\lambda$ denotes the influence of non-dynamical and external quantities. It should be pointed out that the potential function $\phi$ may also implicitly depend on $\theta$. The friction matrix $R(q)$ is defined through the following matrix equation

$$N_{II}(q)N_{II}^T(q) = R(q),$$

(5)

which guarantees that $R$ is both symmetric and nonnegative. This is the second type of the F-theorem.\[^{19}\] The F-theorem emphasizes the connection between adaption and variation and is essentially a reformulation of fluctuation-dissipation theorem in physics\[^{65–67}\] and of Fisher’s fundamental theorem of natural selection. The connection between Fisher’s fundamental theorem of natural selection and the fluctuation-dissipation theorem was also noticed recently by others.\[^{68}\] It should be emphasized here that the F-theorem is not confined to the neighborhood of an equilibrium or steady state. It is valid in nonlinear cases without detailed balance: There is no reference to the existence in a general setting. The major difficulty lies in the fact that typically the detailed balance condition does not hold in Darwinian dynamics, that is, $D^{-1}(q)f(q)$ cannot be written as a gradient of scalar function.\[^{21,25,28,34,35}\]

The $n \times n$ symmetric, non-negative “friction matrix” $R$ and the “transverse matrix” $T$ are directly related to the diffusion matrix $D$:

$$R(q) + T(q) = \frac{1}{D(q) + Q(q)}.$$

Here $Q$ is an antisymmetric matrix determined by both the diffusion matrix $D(q)$ and the deterministic force $f(q)$.\[^{30,70}\] One of more suggestive forms of above equation is

$$[R(q) + T(q)]D(q)[R(q) - T(q)] = R(q).$$

(6)

This symmetric matrix equation implies $n(n + 1)/2$ single equations from each of its elements. We need another $n(n - 1)/2$ equations in order to completely determine the matrices $R$ and $T$, which will come from the conditions for the potential function.

The Wright evolutionary potential function $\phi(q)$ is connected to the deterministic force $f(q)$ by

$$-\nabla \phi(q; \lambda) = [R(q) + T(q)]f(q).$$

Or its equivalent form,

$$\nabla \times [R(q) + T(q)]f(q) = 0.$$  

(7)

Here the operation $\nabla \times$ on an arbitrary $n$-dimensional vector $\mathbf{v}$ is a matrix generalization of the curl operation for lower dimensions ($n = 2, 3$): $(\nabla \times \mathbf{v})_{i,j} = \partial v_j/\partial q_i - \partial v_i/\partial q_j$. Above matrix equation is hence antisymmetric and gives the needed $n(n - 1)/2$ single equations from each of its elements. From Eqs. (6) and (7) the friction matrix, $R$, the transverse matrix, $T$, and the potential function, $\phi$, can be constructed from the diffusion matrix $D$ and the deterministic force $f$. The boundary condition in solving Eq. (7) is implied by the requirement that the fixed points of $f$ should coincide with the extremals of the potential function $\phi$. The local construction, the construction near any fixed point, was demonstrated in detail in Ref. [30], where the connection to the fluctuation-dissipation theorem in physical sciences was explicitly demonstrated. For
the global construction valid in the whole phase space an
iterative method was outlined in Ref. [70]. Some of its
mathematical and properties, such as the speed of conver-
gence, are not generally known at this moment.

For the case where the stochastic drive may be ignored,
that is, \( \theta = 0 \), the relationship between Eqs. (3) and (4)
remains unchanged, but equation (4) becomes determin-
istic,

\[
[R(q) + T(q)] \dot{q} = -\nabla \phi(q; \lambda). \tag{8}
\]

The nonlinear dynamics typical in evolutionary processes
is usual explored in the framework of game theory,[9,71]
The typical mathematical equation is of the form in
Eq. (1) without noise: \( \dot{q} = f(q; \lambda) \). The universal con-
struction of Lyapunov function in the game theory had
been an unsolved problem before the present formulation.
On the other hand, above equation indicates, with the
non-negativeness of the friction matrix,

\[
\frac{d}{dt} \phi(q; \lambda) = q \cdot \nabla \phi(q; \lambda) = -q^T [R(q) + T(q)] \dot{q}
= -q^T R(q) \dot{q} \leq 0. \tag{9}
\]

It is clear then that the Wright evolutionary potential
function \( \phi(q; \lambda) \) is a Lyapunov function. The determin-
istic dynamics makes it non-increasing, and it approaches
the nearby potential minimum to achieve the maximum
probability. This is precisely what was conceived by
Wright. Adaptive dynamics has been actively exploring
in biology.\[18,20\]

The idea of potential function landscape has a long
history in biological sciences. Such an idea was first
proposed in population genetics.\[6\] It was proposed again in
developmental biology as a developmental landscape,\[72\]
and again in the description of a genetic switch in mole-
cular biology.\[73\] Similar landscape idea was proposed in
the ecological evolution embedded in the concept of ascendancy.\[74\] The landscape has been used not only to
model neural computation,\[75,76\] but also to understand
the protein folding dynamics.\[77\] The problem of absence
of detailed balance, however, had been previously regar-
ded as an obstacle. For example, it was noted that
genuine nonequilibrium and asymmetric dynamics such
as limit cycle might make the construction of the Hopfield
potential function in neural computation impossible.
Recently, it was shown this can be overcome by the present
formulation.\[32\]

Conservative Newtonian dynamics may be regarded as
another limit of the above formulation: zero friction limit,
where \( R = 0 \) in addition to \( \theta = 0 \). Hence, from Eq. (8),
Newtonian dynamics may be expressed as

\[
T(q) \dot{q} = -\nabla \phi(q; \lambda). \tag{10}
\]

Here the value of potential function is evidently conserved
during the dynamics since \( \dot{q} \cdot \nabla \phi(q; \lambda) = 0 \). The system
moves along equal potential contours in the adaptive land-
scape. This conservative behavior suggests that the rate of
approaching to equilibrium is associated with the friction
matrix \( R \), not with the diffusion matrix \( D \). There are sit-
uations where the diffusion matrix is finite but the friction
matrix is zero, and thus the dynamics is conservative.\[32\]

2.2 Fokker–Planck Equation: the Ensemble and
Distribution View

It was reasoned heuristically\[70\] that the steady state
distribution \( \rho(q) \) in the state space, if exists, is

\[
\rho(q, t = \infty) \propto e^{-\beta \phi(q; \lambda)}. \tag{11}
\]

Here \( \beta = 1/\theta \). It takes the form of Boltzmann–Gibbs
distribution function. Therefore, the potential function \( \phi \)
acquires both the dynamical meaning through Eq. (4) and
the steady state meaning through Eq. (11).

It was further demonstrated that such a heuristic ar-
ument can be translated into an explicit algebraic proce-
dure such that there is an explicit Fokker–Planck equation
whose steady state solution is indeed given by Eq. (11).\[31\]
Starting with the generalized Klein–Kramers equation,
taking the limiting procedure of the zero mass limit, the
desired Fokker–Planck equation corresponding to Eq. (4) is

\[
\frac{\partial \rho(q, t)}{\partial t} = \nabla^T [D(q) + Q(q)] [\theta \nabla + \nabla \phi(q; \lambda)] \rho(q, t). \tag{12}
\]

This equation is equivalent to a statement of conserva-
tion of probability. It can be rewritten as the probability
continuity equation:

\[
\frac{\partial \rho(q, t)}{\partial t} + \nabla \cdot j(q, t) = 0, \tag{13}
\]

with the probability current density \( j \) defined as

\[
j(q, t) \equiv -[D(q) + Q(q)] [\theta \nabla + \nabla \phi(q; \lambda)] \rho(q, t). \tag{14}
\]

The reduction of dynamical variables has often been done
in the well-known Smoluchowski limit. In the above deri-
vation we take the mass to be zero, keeping other param-
ters finite. Those two limits are in general not ex-
changeable.

The steady state configuration solution of Eq. (12) is
indeed given by Eq. (11). It is interesting to point out that
the steady state distribution function, equation (11), is
independent of both the friction matrix \( R \) and the transverse
matrix \( T \). Furthermore, we emphasize that no detailed
balance condition is assumed in reaching this result. In
addition, both the additive and multiplicative noises are
treated here on an equal footing.

Finally, it can be verified that above construction lead-
ing to Eq. (12) is valid, and remains unchanged, when
there is an explicit time dependence in \( R, T \), and/or \( \phi \).
There may not exist a steady state distribution, for ex-
ample, if the Wright evolutionary potential function \( \phi \)
depends on time.
3 Nonequilibrium Statistical Mechanics

3.1 Central Relation in Statistical Mechanics

If we treat the parameter \( \theta = 1/\beta \) as temperature, the steady state distribution function in phase space is indeed the familiar Boltzmann–Gibbs distribution, Eq. (11). The partition function, or the normalization constant, is then

\[
Z_\theta(\lambda) \equiv \int d^n q e^{-\beta \phi(q; \lambda)}.
\]  

The integral \( \int d^n q \) denotes the summation over whole phase space. The normalized steady state distribution is

\[
\rho_\theta(q) \equiv \frac{1}{Z_\theta} e^{-\beta \phi(q; \lambda)}.
\]  

For a given observable quantity \( O(q) \), its average or expectation value is

\[
\langle O \rangle_q \equiv \int d^n q O(q) \rho_\theta(q) \equiv \frac{1}{Z_\theta} \int d^n q O(q) e^{-\beta \phi(q; \lambda)}.
\]  

The subscript \( \theta \) denotes that the average is over phase space, not over the noise in Eq. (1) or (4). Equation (17) is the main fortress of statistical mechanics. Working in statistical mechanics then may be classified into two types: conquering the fortress from outside, that is, formulating as instance of Eq. (17); and conquering more territory from the fortress, that is, applying Eq. (17).

There has been tremendous amount of efforts to derive the canonical distribution of Eq. (16) from conservative dynamics. One of the best results is the typicality of such distribution for large systems already attempted by Boltzmann.[78] On the other hand, all experiments have shown a universal validity of Eq. (16) for both large and small systems, hence more than typicality. We note that Darwinian dynamics is consistent with such empirical observations.

There is a difference in the use of potential function \( \phi \) in Eq. (12) and Eq. (15): One is in the form of “force” — gradient with respect to the coordinate \( q \), and another is its integration which may carry an arbitrary function of the parameter \( \lambda \) : \( \phi(q; \lambda) = \phi_0(q; \lambda) + \phi_1(\lambda) \). For a static parameter, this would not be of any problem: It simply reflects the fact that only the difference of the potential function with respect to a given reference is meaningful. Nevertheless, if we are going to compare the potential function at two different parameter values, \( \phi(q; \lambda_1) \) and \( \phi(q; \lambda_2) \), connected by a dynamical processes controlled by \( \lambda(t) \), such an arbitrary function \( \phi_1(\lambda) \) has to be fixed up to a constant. Otherwise, the free energy to be discussed in Secs. 4 and 5 would be arbitrary. For a conservative dynamics described by Eq. (10), this function may be determined by a procedure named the minimum gauge condition: Assume an adiabatic (slow) process connecting two states specified by \( \lambda_1 \) and \( \lambda_2 \), and let \( \delta f(q; \lambda(t)) = -\nabla [\phi(q; \lambda(t)) - \phi(q; \lambda = 0)] \), the force directly controlled by the parameter \( \lambda \), the minimum gauge condition to determine \( \phi_1(\lambda) \) may be expressed as

\[
\phi_1(\lambda_2) - \phi_1(\lambda_1) = W|_{\lambda_2 - \lambda_1 \rightarrow -\infty},
\]

and \( W = \int_{\lambda(t_1) = \lambda_1, \lambda(t_2) = \lambda_2} dq \delta f(q; \lambda(t)) \), that is, the work done in the adiabatic process by the external force related to the parameter is equal to the change in potential function, a known relation in classical mechanics.

3.2 Stochastic Processes and the Canonical Ensemble

A fundamental question raised by our formulation is: for a given Fokker–Planck equation, can the corresponding stochastic differential equation in the form of Eq. (4) be recovered (the inverse problem)? That is, is there a one-one correspondence between the local and global dynamics connected by a potential function? The answer is yes, and the procedure for carrying it out is implicitly contained in Eq. (12), which will be demonstrated below.

A generic form for the Fokker–Planck equation is expressed as follows:

\[
\frac{\partial \rho(q, t)}{\partial t} = \nabla^\top [\theta D(q) \nabla - f(q)] \rho(q, t). \tag{18}
\]

Here \( D(q) \) is the diffusion matrix and \( f(q) \) the drift force. The main motivation for such a form is simple: In the case detailed balance condition is satisfied, i.e., \( Q(q) = 0 \) and \( T(q) = 0 \), the potential function \( \phi \) can be directly inferred from above equation: \( \nabla \phi = D^{-1} f \). This makes the diffusion effect very prominent. Any other form of the Fokker–Planck equations can be easily transformed into the above form. This generic form of the Fokker–Planck equation is less amenable to additional complications such as the noise induced phase transitions caused by the \( q \)-dependent diffusion constant.

A potential function \( \phi(q) \) can always be defined from the steady state distribution. There is an extensive mathematical literature addressing this problem.[23] After this is done, though it can be a difficult problem, the procedure to relate the Fokker–Planck equation to Eq. (12) is straightforward. Equation (12) can be rewritten as

\[
\frac{\partial \rho(q, t)}{\partial t} = \nabla^\top [\theta D(q) \nabla - \theta \nabla^\top Q(q)]
- [D(q) + Q(q)] \nabla \phi(q) \rho(q, t). \tag{19}
\]

The antisymmetric property of the matrix \( Q(q) \) has been used in reaching Eq. (19). Thus, comparing Eqs. (18) and (19), we have

\[
D(q) = \hat{D}(q),
\]

\[
\phi(q) = -\phi(q),
\]

\[
f(q) = \hat{f}(q) + \theta \nabla^\top Q(q),
\]

where we have used the relation

\[
-[D(q) + Q(q)] \nabla \phi(q) = f(q).
\]

The explicit equation for the anti-symmetric matrix \( Q \) is

\[
\theta \nabla^\top Q(q) + [D(q) + Q(q)] \nabla \phi(q; \lambda) = \hat{f}(q),
\]

which is a first order, linear, inhomogeneous, partial differential equation. The solution for \( Q \) can be formally written as

\[
\phi(q) = \hat{\phi}(q),
\]

\[
f(q) = \hat{f}(q),
\]

\[
Q(q) = \hat{Q}(q),
\]

\[
D(q) = \hat{D}(q),
\]

\[
\rho(q, t) = \hat{\rho}(q, t),
\]

\[
\langle O(q, t) \rangle = \hat{\langle O(q, t) \rangle},
\]

\[
Z_\theta(q, t) = \hat{Z}_\theta(q, t),
\]

\[
\hat{\phi}(q; \lambda) = \phi(q; \lambda),
\]

\[
\hat{f}(q) = f(q),
\]

\[
\hat{Q}(q) = Q(q),
\]

\[
\hat{D}(q) = D(q),
\]

\[
\hat{\rho}(q, t) = \rho(q, t),
\]

\[
\langle O(q, t) \rangle = \langle \hat{O}(q, t) \rangle,
\]

\[
Z_\theta(q, t) = Z_\theta(q, t),
\]

\[
\hat{\phi}(q; \lambda) = \phi(q; \lambda),
\]

\[
\hat{f}(q) = f(q),
\]

\[
\hat{Q}(q) = Q(q),
\]

\[
\hat{D}(q) = D(q),
\]

\[
\hat{\rho}(q, t) = \rho(q, t),
\]

\[
\langle O(q, t) \rangle = \langle \hat{O}(q, t) \rangle,
\]

\[
Z_\theta(q, t) = Z_\theta(q, t),
\]
The extremals of the steady state distribution are not necessarily determined by the zero’s of drift. This shift can occur even when \( D = \text{constant} \). The indication for such a shift appeared extensive in numerical studies. It was also noted analytically.

Thus, the zero-mass limit approach to the stochastic differential equation is consistent in itself. The meaning of the potential, \( \phi \), is explicitly manifested in both the local trajectory, according to Eq. (4), and the ensemble distribution, according to Eq. (12). In particular, no detailed balance condition is assumed. There is no need to differentiate between the additive and multiplicative noises. This zero mass limit procedure which leads to Eq. (4) from Eq. (12) may be regarded as another prescription for stochastic integration, in addition to those of Itô, of Stratonovich–Fisk and of Hanggi–Klimontovich and of others. They have been discussed from a unified mathematical perspective in terms of an initial-point, middle-point, and end-point discretization rules. All those previous methods of treating the stochastic differential equation are mathematically consistent in themselves and are related to each other. The connection of the present method to those previous methods is suggested by Eqs. (18) and (12) (or Eq. (19)). For example, equation (18) is just what can be obtained from the Hanggi–Klimontovich type treatment, which has been noticed by others as well. It is interesting to note that Itô’s method puts an emphasis on the martingale property of stochastic processes, which may be viewed as a prescription from mathematics. The Stratonovich–Fisk method stresses the differentiability such that the usual differential chain-rule can be formally applied, which may be viewed as the prescription from engineering. The Hanggi–Klimontovich type stresses the generalized detailed balance, important in physics. The present approach emphasizes the role played by the potential function in both trajectory and ensemble descriptions, as well as the existence of a generalized Einstein relation (see below) when the detailed balance is absent. It may be regarded as the prescription from natural sciences. All those stochastic integration methods point to the need for an explicit partition between the stochastic and deterministic forces, the hallmark of hierarchical structure in dynamics. This feature corresponds precisely to the hierarchical law in the evolutionary dynamics of biology.

Two more remarks are in order here. First, by construction the present method preserves the fixed points:

\[
Q(q) = \frac{1}{\theta} \int_{q}^{\theta} dq' [f(q') - D(q') \nabla \phi(q'; \lambda)] e^{\beta(\phi(q'; \lambda) - \phi(q'; \lambda))} + Q_0(q) e^{\beta \phi(q'; \lambda)}. \tag{24}
\]

Here \( Q_0(q) \) is a solution of the homogenous equation \( \theta \nabla T \phi(q) = 0 \), and the two parallel vectors in the integrand, \( dq' f(q') \), defines a matrix. This completes our answer to the inversion problem. It is interesting to note that the shift between the zero’s of the potential gradient and the drift is given from Eq. (22) as,

\[
\Delta f = \theta \nabla T Q(q). \tag{25}
\]

The fixed points of \( f \) are also those of \( \nabla \phi \). The introducing of the stochastic force would not shift the fixed points. This is very useful in that, the results of powerful bifurcation analysis of deterministic dynamics can be carried over to the stochastic situation. Second, there is a one to one correspondence between Eq. (4) and the dynamical equation in dissipative quantum phenomena. The latter has been discussed in context beyond white noise, this connection suggests an immediate generalization of Eq. (4) to colored noise situations.

We may conclude that a stochastic process leads to the canonical ensemble with a temperature and a Boltzmann–Gibbs type distribution function, independent of how it is treated. Other related stochastic ensembles, such as the grand canonical ensemble, may be introduced in the same way by including additional constraints.

### 3.3 Discrete Stochastic Dynamics

There is another kind of modelling predominant in population genetics and other fields which is discrete in phase space and/or time. The existence of potential function in such stochastic dynamical systems has been convincingly argued. We will not discuss it in any detail, and simply quote a few relevant results. The reasons to do so are:

(i) It is known mathematically that any discrete model can be represented by a continuous one exactly according to the embedding theorem, though sometimes such a process may turn a finite dimension problem into an infinite dimension one;

(ii) By a coarse graining, averaging process, the discrete dynamics in population genetics can often be simplified to continuous ones such as diffusion equations or Fokker–Planck equations. It is generally acknowledged in population genetics and in other fields that the diffusion approximation is often a good approximation.

For the steady state distribution, all one needs to know is the potential function \( \phi \). The temperature can be set to be unity: \( \theta = 1 \). Hence, despite possible additional mathematical issues, the discrete or continuous representation does not seem to be a physically or biologically important factor.

### 4 Steady State Thermodynamics

Given the Boltzmann–Gibbs distribution, the partition function can be evaluated according to Eq. (15). Hence, in steady state, all observable quantities are known in principle according to Eq. (17). One may wonder then what can we learn about a system from thermodynamics. First, there is a practical value. In many cases the calculation of the partition function is hard, if possible. It would be desirable if there are alternatives. Thermodynamics gives us a set of useful relations between observable quantities based on general properties of the system, such as...
symmetries. Precise information on one observable can be inferred from the information on other observables. Second, there is a theoretical value. Thermodynamics has a scope far more general than many other fields in physics. It is the only field in classical physics whose foundation and structure not only have survived quantum mechanics and relativity, but also become stronger. Furthermore, thermodynamics exhibits a sense of formal beauty, elegance, and simplicity, which is exceedingly satisfying aesthetically. Its influence is far beyond physical sciences, because it is also based on probability and statistics.

There are numerous excellent books deriving thermodynamics from statistical mechanics. A thorough treatment can be found, for example, in Ref. [96]. A more reader-friendly treatment can be found in Ref. [97] or [98]. Concise and elementary treatments from thermodynamics point of view have been presented in Refs. [99] and [100]. A modern discussion of the approaching to the steady state was presented in Ref. [101]. Reference [102] gave a comprehensive review from the point of view of thermodynamics, even though at a first glance it seems to the extreme end of nonequilibrium processes. In the light of thermodynamics, even though it is also based on probability and statistics.

The principal objective in this section is to show that Darwinian dynamics indeed implies the main structures of thermodynamics, even though at a first glance it seems to have no connection, because Darwinian dynamics is at the extreme end of nonequilibrium processes. In the light of those superb expositions mentioned above, the present discussion may appear incomplete as well as arbitrary. For a systematic discussion on thermodynamics the reader is sincerely encouraged to consult those books and/or any of her/his favorites. Nevertheless, we wish to show that a logically consistent dynamical understanding of thermodynamics can be obtained. Specifically, it is explicitly demonstrated that absence of detailed balance condition does not prevent us to obtain thermodynamics.

4.1 Zeroth Law: Existence of Absolute “Temperature”

From Darwinian dynamics, the steady state distribution is given by a Boltzmann–Gibbs type distribution, Eq. (11), determined by the Wright evolutionary potential function $\phi$ of the system and a positive parameter $\theta$ of the noise strength. Hence, the analogy of the Zeroth Law of thermodynamics is implied by Darwinian dynamics: There exists a temperature-like quantity, represented by the positive parameter $\theta$. This “temperature” $\theta$ is “absolute” in that it does not depend on the system’s material details. It is evident that the existence of the “temperature” is a direct consequence of stochasticity in Darwinian dynamics, as exemplified in Eqs. (1) ~ (6).

4.2 First Law: Conservation of “Energy”

(i) Fundamental relation and the differential forms

From the partition function $Z_\theta$, we may define a quantity

$$F_\theta \equiv -\theta \ln Z_\theta .$$

We may also define the average Wright evolutionary potential function,

$$U_\theta \equiv \int d^n q \phi(q; \lambda) \rho_0(q) .$$

From the distribution function we may further define a positive quantity

$$S_\theta \equiv -\int d^n q \rho_0(q) \ln \rho_0(q) .$$

It is then straightforward to verify that

$$F_\theta = U_\theta - \theta S_\theta ,$$

precisely the fundamental relation in thermodynamics satisfied by free energy, $F_\theta$, internal energy, $U_\theta$, and entropy, $S_\theta$. The subscript $\theta$ denotes the steady state nature of those quantities. Due to the finite strength of stochasticity, that is, $\theta > 0$, not all the $U_\theta$ is readily usable: $F_\theta$ is always smaller than $U_\theta$. A part of $\theta S_\theta$ called “heat” cannot be utilized.

It can also be verified from these definitions that if the system consists of several non-interacting parts, $F_\theta$, $U_\theta$, and $S_\theta$ are sum of those corresponding parts. Hence, they are extensive quantities. The “temperature” $\theta$ is an intensive quantity: it must be the same for all those parts because they are contacting the same noise source. Therefore, we conclude that the First Law of thermodynamics is implied by Darwinian dynamics.

The fundamental relation for the free energy, Eq. (29), as well as the internal energy, Eq. (27), may be expressed in their differential forms as well. Considering an infinitesimal process which causes changes in both the Wright evolutionary potential function via parameter $\lambda$ and in the steady state distribution function, the change in the internal energy according to Eq. (29) is

$$dU_\theta = \int d^n q \frac{\partial \phi(q; \lambda)}{\partial \lambda} d\rho_0(q) + \int d^n q \phi(q; \lambda) d\rho_0(q)$$

$$= \mu d\lambda + \theta dS_\theta .$$

This is the differential form for the internal energy. Here the steady state entropy definition of Eq. (28) has been used, along with $\int d^n q d\rho_0(q) = 0$, and

$$\mu \equiv \frac{\partial U_\theta}{\partial \lambda} \bigg|_{\theta = 0} .$$

Equation (30) can be written in the usual form in thermodynamics:

$$dU_\theta = dW + dQ .$$

The part corresponding to the change in entropy is the “heat” exchange: $dQ = \theta dS$ and the part corresponding to the change in the Wright evolutionary potential function is the “work” $dW = \mu d\lambda$. The conservation of “energy” is most clearly represented by Eq. (30). For the free energy, following Eqs. (30) and (29) the differential form is

$$dF_\theta = dU_\theta - d\theta S_\theta - \theta dS_\theta.$$
\[ \mu d\lambda - S_0 d\theta. \]  
\[ \text{(32)} \]

(ii) Steady state thermodynamic definition of temperature
Equations (30) and (32) may be useful in some applications. For example, the “temperature” can be found from Eq. (30):
\[ \theta = \frac{\partial U_\theta}{\partial S_\theta} \bigg|_\lambda. \]  
\[ \text{(33)} \]

There are situations in which an effective temperature may be needed. Equation (33) may be then used to find the “temperature” in a nonequilibrium process if it cannot be identified \textit{a priori}.  

The convexity of a thermodynamic quantity is naturally incorporated by the Boltzmann–Gibbs distribution. There is no restriction on the size of the system. Even for a finite system, however, phase transitions can occur, because singular behaviors can be built into the potential function, and controlled by external quantities.

4.3 Second Law: Maximum Entropy
(i) Second law and Carnot cycle
First, we remind the reader of a few important definitions.

A \textit{reversible process} is such a process that all the relations between quantities and parameters are defined through the Boltzmann–Gibbs distribution, Eq. (11). From Darwinian dynamics point of view, a reversible process in reality is necessarily a slow or quasi-static process in order to ensure the relevancy of steady state distribution for its realization.

An \textit{isothermal process} is a reversible process in which “temperature” \( \theta \) remains unchanged, \( \theta = \text{constant} \). Do not confuse this with thermostated processes, which are, in general, nonequilibrium dynamical processes.

A \textit{reversible adiabatic process} is a reversible process in which the coupling between the system and the noise source is switched off and the system varies in such a way that the distribution function remains unchanged along the dynamic trajectory at each point in phase space. The corresponding “temperature” can be restored at any position during such a process. This implies that the entropy remains unchanged, \( S_\theta = \text{constant} \). Then an irreversible adiabatic process is one that there is no coupling between the system and the noise environment and the system dynamics is deterministic and conserved.

The Carnot cycle, on which the Carnot heat engine is based, is a fundamental construction in classical thermodynamics. The Carnot cycle consists of four reversible processes: two isothermal processes and two reversible adiabatic processes [Figs. 2(a) and 2(b)]. The efficiency \( \nu \) of the Carnot heat engine is defined as the ratio of the total net work performed over the heat absorbed at high temperature:
\[ \nu \equiv \frac{\Delta W_{\text{total}}}{\Delta Q_{12}}. \]  
\[ \text{(34)} \]

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{carnot_cycle.png}
\caption{Carnot cycle. (a) The \( \mu-\lambda \) representation. (b) The \( \theta-S \) representation. In this temperature-entropy representation, the Carnot cycle is a rectangular.}
\end{figure}

The total net work done by the system is represented by the shaded area enclosed by the cycle. For the heat absorbed at the high isothermal process \( 1 \rightarrow 2 \),
\[ \Delta Q_{12} = \theta_{\text{high}} \Delta S_{\theta,12}. \]  
\[ \text{(35)} \]

For the adiabatic process \( 2 \rightarrow 3 \), an external constraint represented by \( \lambda \) is released (or applied),
\[ \Delta S_{\theta,23} = 0, \quad \Delta Q_{23} = 0. \]  
\[ \text{(36)} \]

For the heat absorbed (rather, released) at the low isothermal process \( 3 \rightarrow 4 \),
\[ \Delta Q_{34} = \theta_{\text{low}} \Delta S_{\theta,34} = -\Delta Q_{43}. \]  
\[ \text{(37)} \]

For the adiabatic process \( 4 \rightarrow 1 \), an external constraint is applied (released),
\[ \Delta S_{\theta,41} = 0, \quad \Delta Q_{41} = 0. \]  
\[ \text{(38)} \]

Using the First Law, equation (29) and the fact that the free energy is a state function,
\[ \Delta F_{\text{total}} = \Delta Q_{\text{total}} - \Delta W_{\text{total}} = 0. \]  
\[ \text{(39)} \]

The minus sign in front of the total work represents that it is the work done by the system, not to the system. The total heat absorbed by the system is
\[ \Delta Q_{\text{total}} = \Delta Q_{12} + \Delta Q_{34} = \Delta Q_{12} - \Delta Q_{43} = \Delta W_{\text{total}}. \]
We further have
\[ \Delta S_{\theta,12} = \Delta S_{\theta,43}. \]  
\[ \text{(40)} \]

From Eqs. (34), (39), and (40) the Carnot heat engine efficiency is then
\[ \nu = 1 - \frac{\Delta Q_{43}}{\Delta Q_{12}} = 1 - \frac{\theta_{\text{low}}}{\theta_{\text{high}}}. \]  
\[ \text{(41)} \]
precisely the form in thermodynamics. The Second Law of thermodynamics may be stated as that for all heat engines operating between two temperatures, Carnot heat engine is the most efficient. The Second Law is thus implied by Darwinian dynamics.

The beauty of Carnot heat engine is that its efficiency is completely independent of any material details. It brings out the most fundamental property of thermodynamics and is a direct consequence of the Boltzmann–Gibbs distribution function and the First Law. It reveals a property of Nature which may not be contained in a Gibbs distribution function and the First Law. It reveals a property of Nature which may not be contained in a conservative dynamics, at least it is still not obviously to many people from Newtonian dynamics point of view after more than 150 years of intensive studies.[41] On the other hand, it appears naturally implied in Darwinian dynamics.

Having discussed various thermodynamics processes, let us return to the issue of fixing the arbitrary function in potential function discussed in Subsec. 3.1, which is now directly connected to free energy. The minimum gauge condition to determine \( \phi_1(\lambda) \) may be extended as

\[
F_\phi(\lambda_2) - F_\phi(\lambda_1) = \langle W \rangle_{\text{reversible}},
\]

with \( W = \int_{x_1}^{x_2} dq \cdot \delta f(q; \lambda(t)) \), that is, the work done in the reversible process by the external force related to the parameter is equal to the change in free energy. Again, it is an accepted relation in statistical thermodynamics. It is possible that that \( \phi_1(\lambda) \) determined thermodynamically may depend on temperature.

(ii) Maximum entropy principle
There are many versions of the Second Law. Here we refer to two equivalent versions from the stability point of view, which frame the discussion in this subsection.

Minimum free energy statement Given the potential function and the temperature, the free energy achieves its lowest possible value if the distribution is the Boltzmann–Gibbs distribution.

Maximum entropy statement Given the potential function and its average, the entropy attains its maximum value when the distribution is the Boltzmann–Gibbs distribution.

The latter version of the Second Law is the most influential. Its inverse statement, the so-called maximum entropy principle, has been extensively employed in probability inference[106] both within and beyond the physical and biological sciences.\[107,108]\n
We generalize here the definitions of the entropy to include the arbitrary time-dependent distribution in analogy to Eq. (28):

\[
S(t) \equiv -\int d^n q \rho(q, t) \ln \rho(q, t).
\] (42)

There are two apparent drawbacks to such a definition, however. First, even if the evolution of the distribution function \( \rho(q, t) \) is governed by the Fokker–Planck equation, Eq. (12), in general the sign of the time derivative, \( dS(t)/dt = \dot{S}(t) \), cannot be determined, whether or not it is close to the steady state distribution. Though \( \dot{S}(t) \) might indeed be divided into an always positive part and the rest, such a partition usually appears arbitrary. Even more problematically, in general \( S(t) \) can be either larger or smaller than \( S_0 \), which makes such a definition lose its appeal in view of the maximum entropy statement of the Second Law. We will return to \( S(t) \) later.

Nevertheless, if we take the lesson from the potential function that only the relative value is important, we may introduce a reference point in functional space into a general entropy definition. One previous definition for the referenced entropy is\[65\]

\[
S_r(t) \equiv -\int d^n q \rho(q, t) \ln \frac{\rho(q, t)}{\rho_0(q)} + S_0.
\] (43)

With the aid of the inequality \( \ln(1 + x) \leq x \) and the normalization condition \( \int d^n q \rho(q, t) = \int d^n q \rho_0(q) = 1 \), it can be verified that

\[
S_r(t) = \int d^n q \rho(q, t) \ln \left(1 + \frac{\rho(q, t) - \rho(q, t)}{\rho_0(q)}\right) + S_0
\]

\[
\leq \int d^n q \rho(q, t) - \rho(q, t) + S_0 = S_0.
\] (44)

The equality holds when \( \rho(q, t) = \rho_0(q) \). This inequality is independent of the details of the dynamics and is evidently a maximum entropy statement. Furthermore, with the aid of the Fokker–Planck equation, Eq. (12), the time derivative of this referenced entropy, \( dS_r(t)/dt = \dot{S}_r(t) \) is always non-negative:

\[
\dot{S}_r(t) = -\int d^n q \frac{\partial \rho(q, t)}{\partial t} \ln \frac{\rho(q, t)}{\rho_0(q)}
\]

\[
= -\int d^n q \frac{\partial \rho(q, t)}{\partial t} \ln \frac{\rho(q, t)}{\rho_0(q)} + \int \frac{1}{\theta \rho_0(q, t)} \left(\ln \frac{\rho(q, t)}{\rho_0(q)} + D(q)\right) \text{d}q = 0.
\] (45)
Hence, this referenced entropy $S_r(t)$ has all the desired properties for the maximum entropy statement of the Second Law.

Two important remarks are in order. First, in the derivation reaching Eq. (45), the dynamics responsible for breaking the detailed balance condition, the antisymmetric matrix $Q$, does not contribute to the change of relative entropy. Only the dissipative part of dynamics represented by $D$ leads to the monotonic change of relative entropy. Given the present interpretation from both trajectory and ensemble points of view, it is clear that $Q$ is what needed for the Poisson bracket in conservative dynamics explored elsewhere $^{[109]}$. The present demonstration suggests a unified treatment for both near and far from equilibrium dynamical processes.

Second, by the probability current density definition of Eq. (14) $j$ is zero at the steady state. This is in accordance with the understanding that at equilibrium there is no change in (relative) entropy, that is, the entropy production should be zero at equilibrium. Now, we have generalized this conclusion to steady state. We note that the present probability current density may differ from the usual probability current density definition which may be based on Eq. (18) and takes the form $j(q, t) \equiv -[\theta D \nabla - f(q)]\rho(q, t)$, which is not zero at the steady state. Instead, $\nabla \cdot j = 0$ at the steady state. Even with the usual definition, the zero relative entropy production at steady state always remains valid.

Though the definition of entropy of Eq. (42) may not be appealing, a related definition of free energy is consistent with the Second Law. We demonstrate it here. First, a general definition for the internal energy may be:

$$U(t) = \int d^n q \rho(q; \lambda) \ln \rho(q, t). \quad (46)$$

Given the distribution and the potential function, quantities defined in Eqs. (42) and (46) can be evaluated. Following the form of Eq. (26) a general definition of free energy would be, with the “temperature” $\theta$,

$$F(t) \equiv U(t) - \theta S(t) \quad (47)$$

It can be verified that $F(t) \geq F_0$ and its time derivative is always non-positive, $\dot{F}(t) \leq 0$. So defined time-dependent free energy indeed satisfies the minimum free energy statement of the Second Law. It differs from the referenced entropy $S_r(t)$ by a minus sign and by a constant:

$$\dot{F}(t) = -\theta S_r(t) + U_\theta.$$

The generalized entropy $S(t)$ has one desired property regarding to the adiabatic processes (either reversible or irreversible) in that $D = 0$ during the adiabatic process. Hence,

$$\dot{S}(t) = -\int d^n q \frac{\partial \rho(q, t)}{\partial t} \ln \rho(q, t)$$

$$= -\int d^n q [\nabla^T Q(q) \nabla \phi(q; \lambda) \rho(q, t)] \ln \rho(q, t)$$

$$= -\int d^n q [(Q(q) \nabla \phi(q; \lambda)) \cdot \nabla] \int^{\rho(q,t)} d\rho' \ln \rho'$$

$$= 0. \quad \text{(adiabatic)} \quad (48)$$

This is the known result in conservative Newtonian dynamics that the entropy remains unchanged. In deriving the above equation we have used two properties:

(a) The no-coupling to the noise environment has been translated into the fact that the terms associated with the diffusion matrix $D$ and “temperature” $\theta$ are set to be zero in Eq. (12), because they are related to the noise source which is decoupled during an adiabatic process;

(b) The incompressible condition of $\nabla \cdot [Q(q) \nabla \phi(q; \lambda)] = 0$, the Liouville theorem, which is typically satisfied in Newtonian dynamics.

In this conservative case, it can be verified that $\dot{S}_r(t) = 0$, too, for any adiabatic process. Nevertheless, it is possible that while the dynamics is conservative, $R = 0$, and even satisfying the Jacob identity in classical mechanics, the Liouville theorem can be violated. Hence, in this case the general entropy $S(t)$ is not a constant during the dynamical process, and the general free energy $F(t)$ and the referenced entropy $S_r(t)$ are not well defined either, because there is no “temperature” to define a steady state distribution. But the “energy” can be conserved during such a process.$^{[109]}$

(iii) Connection to information theories

It may be worthwhile to define another referenced entropy $S_{-2}(t)$ which approaches the steady state entropy $S_0$ from above. Its form is simple:

$$S_{-2}(t) \equiv -\int d^n q \rho(q) \ln \rho(q, t). \quad (49)$$

It can be verified that $S_{-2}(t) \geq S_0$ and $\dot{S}_{-2}(t) \leq 0$.

The relation defined by Eq. (43) is in the same form as the relative information in information theories. The reference $^{[110]}$ contains discussions of many other useful inequalities. A rather complete coverage of information theory can be found in Ref. $^{[108]}$, and some current discussions of its connection to thermodynamics can be found in Refs. $^{[111]}$ and $^{[112]}$.

4.4 Third Law: Unattainability of Zero “Temperature”

Now we consider the behavior near zero “temperature”, $\theta \rightarrow 0$. To be specific, we assume the system is dominated by a stable fixed point, taking as $q = 0$. As suggested by the Boltzmann–Gibbs distribution, Eq. (11), only the regime of phase space near this stable fixed point will be important. Hence the Wright evolutionary potential function can be expanded around this point:

$$\phi(q; \lambda) = \phi(0; \lambda) + \frac{1}{2} \sum_{j=1}^{n} k_j(\lambda)q_j^2. \quad (50)$$

Here we have also assumed that the number of independent modes is the same as the dimension of the phase space, though it may not necessary be so. This assumption will not affect our conclusion below. Those independent modes are represented by $q_j$ without loss of generality. The “spring coefficients” $\{k_j\}$ are functions of external parameters represented by $\lambda$.

The partition function according to Eq. (15) can be
readily evaluated in this situation:
\[ Z_\theta = e^{-\beta \phi(0, \lambda)} \prod_{j=1}^{n} \frac{2\pi \theta}{k_j}. \]  
(51)

So, the entropy according to Eq. (28), is:
\[ S_\theta = n \left( \theta - \frac{1}{2} \ln \theta \right) + \frac{1}{2} \sum_{j=1}^{n} \frac{k_j}{2\pi}. \]  
(52)

The first term does not depend on external parameters, but the second term does. This suggests that the entropy depends on the specific control process to achieve low temperature: different processes would lead to different sets of \( \{k_j\} \), hence a difference between entropies at low temperatures. The Third Law states that in the limit of zero temperature the difference in entropy between different processes is zero. Thus, Darwinian dynamics as formulated in the present paper does not imply the Third Law.

One should not be surprised by the above conclusion, because Darwinian dynamics here is essentially “classical”. The same conclusion could also be reached from classical Newtonian dynamics. This means that within Darwinian dynamics one could easily conceive the zero “temperature” limit without any logic inconsistency. With quantum mechanics, the agreement to the Third Law is found and a stronger conclusion is reached: Not only the difference in entropy should be zero, the entropy itself is zero at zero temperature. We may conclude that, in general, completely neglecting the noise is not a viable choice: The temperature cannot be zero. When the noise is small enough, new phenomena may occur. Phrasing differently, there appears to exist a bottom near which there is something. It should be pointed out that in the present formulation of Darwinian dynamics, particularly the Eq. (4), the existence of an anti-symmetric matrix \( \phi \) suggests a natural route to define a Poisson bracket. Therefore, it is possible to extend Darwinian dynamics into the quantum regime by following the usual canonical quantization procedure, possibly following the suggestions from dissipative quantum dynamics. Studies show that the Third Law can be regained in this way.

### 5 Stochastic Dynamical Equalities

We have explored the steady state consequences of Darwinian dynamics in statistical mechanics and in thermodynamics. In this section we explore its general dynamical consequences. Two types of recently discovered dynamical equalities will be discussed: one based on the Feynman–Kac formula and other a generalization of Einstein relation. For a background on path integral formulation, Feynman’s lucid exposition is highly recommended.

#### 5.1 Feynman–Kac Formula

Previous discussions demonstrate that the Boltzmann–Gibbs distribution plays a dominant role. It is natural to work in a representation in which Boltzmann–Gibbs distribution appears in a most straightforward manner, or, as close as possible. The standard approach in this spirit is as follows. First, choose the dominant part of the evolution operator \( L \). The remaining part is denoted as \( \delta L \). In this subsection a general methodology to carry out this procedure is summarized.

The Fokker–Planck equation, Eq. (12), can be rewritten as
\[ \frac{\partial}{\partial t} \rho(q, t) = L(\nabla q; \lambda) \rho(q, t), \]  
(53)

with \( L = \nabla q [D(q) + Q(q)] [\theta \nabla + \nabla \phi(q)] \). Its solution can be expressed in various ways. The most suggestive form in the present context is that given by Feynman’s path integral. If at time \( t' \) the system is at \( q' \), the probability for system at time \( t \) and at \( q \) is given by summation of all trajectories allowed by Eq. (4) connection those two points:
\[ \pi(q, t; q', t') = \sum_{\text{trajectories}} \{ q(t) = q; q(t') = q' \}. \]  
(54)

In terms of the summation over the trajectories, the solution to Eq. (53) (and Eq. (12)) may be expressed as
\[ \rho(q, t) = \int d^n q' \pi(q, t; q', t') \rho(q, t = 0) \equiv \langle \delta(q(t) - q) \rangle_{\text{trajectory}}. \]  
(55)

The delta function \( \delta(q(t) - q) \) is used to specify the end point explicitly. There is a summation over initial
points, \( q', \) weighted by the initial distribution function, \( \rho(q', t = 0) \).

Now, considering that the system is perturbed by \( \delta L(q; \lambda) \), represented, for example, by a change in control parameter \( \lambda \). The new evolution equation is

\[
\frac{\partial}{\partial t} \rho_{\text{new}}(q, t) = [L(\nabla, q; \lambda) + \delta L(q; \lambda)]\rho_{\text{new}}(q, t). \tag{56}
\]

The perturbation may act as a source or sink for the probability distribution. The probability is no longer conserved: in general \( \int dq \rho_{\text{new}}(q, t) \neq \int dq \rho_{\text{new}}(q, t = 0) \). According to the Feynman–Kac formula,\(^{124}\) the solution to this new equation can be expressed as

\[
\rho_{\text{new}}(q, t) = \left\langle \delta(q(t) - q) \exp\left[ \int_0^t dt' \delta L(q(t')) \right] \right\rangle_{\text{trajectory}}, \tag{57}
\]

with \( \rho_{\text{new}}(q', t = 0) = \rho(q', t = 0) \) and the trajectories following the dynamics of Eq. (4), the same as that in Eq. (55). Thus, the evolution of the distribution function under new dynamics can be expressed by the evolution in the original dynamics. The corresponding procedure in quantum mechanics is that in the “interaction picture”\(^{119}\). Equation (57) is a powerful equality. Various dynamical equalities can be obtained starting from Eq. (57). Indeed, its direct and indirect consequences have been extensively explored.\(^{120,121}\)

5.2 Free Energy Difference in Dynamical Processes

(i) Jarzynski equality

We have noticed the special role played by the Boltzmann–Gibbs distribution, Eq. (11). In particular, it is independent of the friction and transverse matrices \( R, T \). Evidently the instantaneous Boltzmann–Gibbs distribution with \( \lambda = \lambda(t) \) is

\[
\rho_0(q; \lambda(t)) = \frac{e^{-\beta \phi(q; \lambda(t))}}{Z_\rho(\lambda(0))}. \tag{58}
\]

Here we have explicitly indicated that the parameter \( \lambda \) is time-dependent. This distribution function is no longer

\[
\frac{e^{-\beta \phi(q; \lambda(t))}}{\int dq e^{-\beta \phi(q; \lambda(0))}} = \left\langle \delta(q - q(t)) \exp\left[ -\beta \int_0^t dt' \lambda'(t') \frac{\partial \phi(q(t'); \lambda(t'))}{\partial \lambda} \right] \right\rangle_{\text{trajectory}}. \tag{59}
\]

Following Ref. [124] we define the dynamical work as

\[
W_t = \int_0^t dt' \lambda'(t') \frac{\partial \phi(q(t'); \lambda(t'))}{\partial \lambda}. \tag{60}
\]

The equality between the free energy difference \( \Delta F_\rho = F_\rho(t) - F_\rho(0) \) and the dynamical work \( W_t \) is, then, after summation over all final points of the trajectories in Eq. (60),

\[
e^{-\beta \Delta F_\rho} = (e^{-\beta W_t})_{\text{trajectory}}. \tag{61}
\]

This elegant equality connects the steady state quantities \( \Delta F_\rho \) to the work done in a dynamical process. Such parametrized form was first discovered by Jarzynski\(^{124}\). It should be emphasized that there is no assumption of steady state at time \( t \) for the system governed by Eq. (12).

In fact, it is known, for example, in the case of the Landau–Zener transition that it is not steady state.\(^{114,123}\) the solution of the Fokker–Planck equation of Eq. (12), however. There will be transitions out of this instantaneous Boltzmann–Gibbs distribution function due to the time-dependence of the parameter \( \lambda \). While such transitions may be hard to conceive of in classical mechanics, they can be easily rationalized in quantum mechanics, because of the discreteness of states. One such well-studied model is the dissipative Landau–Zener transition.\(^{114,122,123}\)

An interesting question is that whether the transitions can be “reversed” such that the instantaneous distribution is indeed an explicit solution for another but closely related evolution equation. This means that the original Fokker–Planck equation has to be modified in a special way to become a new equation. Indeed, this modified evolution equation can be solved for any function \( \bar{\rho}(q, t) \), which reads,

\[
\frac{\partial}{\partial t} \rho_{\text{new}}(q, t) = \left[ L(\nabla, q, t) - \frac{1}{\bar{\rho}(q, t)} (L(\nabla, q, t) \bar{\rho}(q, t)) \right] \rho_{\text{new}}(q, t). \tag{59}
\]

It can be verified \( \rho_{\text{new}}(q, t) = \bar{\rho}(q, t) \) is a solution of above equation. Treating

\[
\delta L = -\frac{1}{\bar{\rho}(q, t)} L(\nabla, q, t) \bar{\rho}(q, t) + \frac{\partial \ln |\bar{\rho}(q, t)|}{\partial t},
\]

and the Feynman–Kac formula Eq. (57) may be applied. The analoguous procedure has been well studied for transitions during adiabatic processes in interaction picture of quantum mechanics\(^{114,119,123}\) and of statistical mechanics.\(^{118}\)

Now, let \( \bar{\rho} \) be the instantaneous Boltzmann–Gibbs distribution of Eq. (58): \( \bar{\rho} = \rho_0(q; \lambda(t)) \). We have \( \delta L = -\beta \lambda \partial \phi(q; \lambda)/\partial \lambda \). Equation (59) can be solved by summing over all trajectories using the Feynman–Kac formula, Eq. (57). At the same time, we know the instantaneous Boltzmann–Gibbs distribution of Eq. (58) is its solution. Since these two are solutions to the same equation, we have the following equality

\[
\frac{e^{-\beta \phi(q; \lambda(t))}}{\int dq e^{-\beta \phi(q; \lambda(0))}} = \left\langle \delta(q - q(t)) \exp\left[ -\beta \int_0^t dt' \lambda'(t') \frac{\partial \phi(q(t'); \lambda(t'))}{\partial \lambda} \right] \right\rangle_{\text{trajectory}}. \tag{60}
\]

This equality has been discussed and extended by various authors from various perspectives.\(^{125–132}\) The connection of this equality to the Feynman–Kac formula was first explicitly pointed out in Ref. [126]. There have also been experimental verifications of this equality.\(^{133}\) This type of equalities was reviewed recently.\(^{134}\)

Three points may be made here. First, the derivation of Jarzynski equality presented here is valid both with and without detailed balance condition, with both additive and multiplicative noises. It has only one result. Second, for Jarzynski equality, neither \( D \) nor \( Q \) enter into the equality, while the dynamics are obviously determined by those matrices. Third, Feynman–Kac formula may be used to generate more dynamical equalities, as already noted.

In the light of those observations, we may infer two im-
mediate but somewhat surprising physical results. First, the “temperature” can be time-dependent, too. Thus, a work equality for “temperature” can be established by explicitly going through the procedure, hence extends the work relation to a different dynamical domain. Second, the validity of the demonstration of Jarzynski equality does not depend on the details of the operator $L$ in Eq. (53), as long as the steady state exists. This would suggest that colored noises can be entered into Eq. (53). In fact, we already know such examples.\cite{87,114,123} The dynamical equation as expressed by Eq. (4) also allows a straightforward extension to colored noises. Third, given the potential function determined by a reversible process discussed in case (i) in Subsec. 4.3 and that using Feynman-Kac formulae we have\cite{120,135,136}

$$ \langle \exp[-(W - W_0)] \rangle_{\text{trajectory}} = \left\langle \exp\left\{ - \int dq \cdot \delta f(q(t'))/\lambda(t') - \int_0^t dt' \lambda(t') \partial_q \phi(q(t'); \lambda(t')) \right\} \right\rangle_{\text{trajectory}} = 1 ,$$

Jarzynski equality may be used to check consistency in our understanding of related dynamical quantities. For example, a discrepancy may indicate possibly a missing term in the potential function $\phi$.

(ii) **Microcanonical and canonical ensembles**

The Jarzynski equality places the Boltzmann–Gibbs distribution hence the canonical ensemble in the central position. They are simply natural consequences from Darwinian dynamics. However, if we start from conservative, Newtonian dynamics, the appropriate ensemble is the microcanonical ensemble. Any distribution function which is a function of the potential function or Hamiltonian would be the solution of the Liouville equation. From this point of view the Boltzmann–Gibbs distribution and the associated temperature appear arbitrary: It is just one among infinite possibilities. This concern has been raised in the literature\cite{137} regarding to the generality of the equality of Eq. (62). No satisfactory treatment of this concern within Newtonian dynamics has been given. Rather, it has been an “experimental attitude”: If one does this and makes sure the procedure is correct one gets that, and it works. Darwinian dynamics, however, provides an a priori reason to fully justify the use of the Boltzmann–Gibbs distribution in the derivation of the Jarzynski equality.

### 5.3 Generalized Einstein Relation

In deriving the Boltzmann–Gibbs distribution from Darwinian dynamics, Eq. (6):

$$ [R(q) + T(q)]D(q)[R(q) - T(q)] = R(q) , $$

has been used. This general and simple dynamical equality was termed as the generalized Einstein relation.\cite{70} If the detailed balance condition is satisfied, that is, if $T = 0$ or $Q = 0$, the above relation reduces to $RD = 1$, which was discovered a century ago by Einstein,\cite{138} and since then has been known as Einstein relation. Variants of Einstein relation in different settings were obtained earlier and independently by Nernst,\cite{139} by Planck,\cite{140} by Townsend,\cite{141} and by Sutherland.\cite{142} Similar to the dynamical equality exemplified by Jarzynski equality, the generalized Einstein relation is a consequence of the Boltzmann–Gibbs distribution and the canonical ensemble embedded in Darwinian dynamics.

Experimentally, all those quantities in Eq. (6) can be measured independently. Hence, this generalized Einstein relation should be subject to experimental tests in the absence of detailed balance, that is, when the antisymmetric matrix $T$ does not vanish. While in evolutionary processes in biology the data can be organized by the present dynamical structure,\cite{8} the parameters are typically fixed by Nature. We need situations where all these elements, $R$, $T$, $\phi$, and $\theta$, are accessible to experimental control.

For simplicity, we consider a nonequilibrium situation realizable with current technology as an illustration: a charged nanoparticle or macromolecule, an electron or a proton, with charge denoted by $e$, in the presence a strong, uniform magnetic field $B$ and immersed in a viscous liquid with friction coefficient $\eta$. Indeed, similar situation has already been considered experimentally.\cite{143} Here we restrict our attention to the two-dimensional case ($n = 2$). The corresponding Darwinian dynamical equation of Eq. (4) in this case is the Langevin equation with the Lorentz force for a “massless” charged particle:\cite{144}

$$ e \hat{q} = \frac{e}{c} B \times \hat{q} = -\nabla \phi(q(t)) + N_{II} \xi(t) . $$

The friction matrix is

$$ R = \eta \left( \begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array} \right) . $$

The transverse matrix is

$$ T = \frac{e}{c} \left( \begin{array}{cc} 0 & 1 \\ 1 & 0 \end{array} \right) , $$

and the “temperature” is $\theta = k_B T_{BG}$, with the Boltzmann constant $k_B$ and the thermal equilibrium temperature $T_{BG}$. If the system is out of thermal equilibrium, the effective temperature, such as defined by Eq. (33), should be used. This is a physically realizable situation in two-dimensional electrons extensively discussed recently.\cite{145} The corresponding Fokker–Planck equation, following Eq. (12), is

$$ \frac{\partial \rho(q,t)}{\partial t} = \nabla[D \nabla + \{D + Q \nabla \phi(q)\} \rho(q,t)] . $$

This is precisely a diffusion equation with diffusion matrix $D$. Both $D$ and $Q$ can be obtained from the generalized Einstein relation, Eq. (6):

$$ D = \frac{\eta}{\eta^2 + (eB/c)^2} \left( \begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array} \right) , $$

$$ Q = \frac{(eB/c)^2}{\eta^2 + (eB/c)^2} \left( \begin{array}{cc} 0 & 1 \\ 1 & 0 \end{array} \right) . $$

In a typical situation, though all quantities can be measured experimentally, the friction coefficient is likely to be less sensitive to the magnetic field. Then one may need to focus experimentally on the diffusion in the presence of the magnetic field without any potential field. In this
The solution to Eq. (69) with \( \rho(q, t) = 0 = \delta q(t = 0) - q \) is standard (two dimensions, \( n = 2 \)):

\[
\rho(q, t) = \frac{1}{2\pi t} \exp\left\{ -\frac{q^2}{2d_n t} \right\}.
\]

Averaging over trajectories governed by Eq. (69), \( \langle q(t) - q(t = 0) \rangle_{\text{trajectory}} = 0 \) and

\[
\text{An experimental system, for example, may be that of injection of electrons into a semiconductor, wherein one measures their diffusion in the presence of a magnetic field.} \quad \text{Every quantity in the generalized Einstein relation of Eq. (6) can be measured and controlled experimentally. An another experimental system may be on ionized hydrogen or deuterium. For charged macromolecules and nano-particles, the friction coefficient may be too large to allow a measurable magnetic field effect accessible by current magnets. As a numerical example, for the zero magnetic field diffusion constant of \( d_n = k_B T_{BG} \sim 10^{-4} \text{ cm}^2/\text{sec} \), which implies diffusing of about 100 cm in 1 second, the friction coefficient is \( \eta = 1/d_{n,o} \sim 4 \times 10^{-16} \text{ dyne/(cm/sec)} \) at temperature \( T_{BG} = 300 \text{ K} \). Assuming one net electron charge, for magnetic field \( B = 1 \text{ Tesla} \), we have \( eB/c \sim 1.6 \times 10^{-16} \text{ dyne/(cm/sec)} \), comparable to the friction coefficient.

6 Outlook

In the present paper we have presented statistical mechanics and steady state thermodynamics as natural consequences of Darwinian dynamics. Two types of general stochastic dynamical equalities have been explored. Both can be directly tested experimentally. Everything appears fully consistent except for one issue. The point of view in physics has been that we should start from conservative dynamics, not Darwinian dynamics. This view has indeed strong experimental and historical supports during past 150 years. It is still the subject of current research. The troubling issue may be expressed by an attempt to answer the following question. The natural consequence of conservative dynamics is the micro-canonical ensemble, from which the canonical ensemble just appears to be one of its infinite possibilities. How and why does Nature choose the canonical ensemble and the Second Law? There does not seem to be a consensus yet on the answer.

The difficulty in reaching the Second Law from conservative dynamics in nonequilibrium setting may encourage us to consider Darwinian dynamics. There is, however, a more compelling reason: Darwinian dynamics is the most fundamental and successful dynamical theory in biological sciences. Furthermore, as we have demonstrated above, the Second Law and other nonequilibrium properties follow naturally from it. Logically it provides a simple starting point. It must contain a large element of physical truth.

Conservative dynamics and Darwinian dynamics appear to occupy the two opposite ends of the theoretical description of Nature. Both have been extremely successful. In many respects they appear to be complementary to each other. For example, it was noticed that Darwinian dynamics and Newtonian dynamics can be derived from each other under appropriate conditions. What would be the implication of this mutual reduction? Are there hidden reasons for such complementarity? Hints to answers for such questions are perhaps already contained in the discussions of “more is different” and of the immensity of functional space, of the macroscopic quantum effect, and of universe vs multiverse. The formulation and analysis in this paper may provide insights into those fundamental relationships and a stimulus for further studies.

Acknowledgments

I thank M. Dykman, G.L. Eyink, J. Felsenstein, D. Galas, P. Gaspard, P. Hanggi, B.L. Hao, C. Jarzinski, M. Kardar, C. Kwon, P.A. Lee, A.J. Leggett, H. Qian, L.S. Schulman, D.J. Thouless, R.E. Ulanowicz, J. Wang, S.T. Yau, L. Yin, L. Yu, H.D. Zeh, and X.M. Zhu for constructive comments and critical discussions at various stages of this work. I also thank D. Galas for a critical reading of the manuscript.

References

[1] C. Darwin and A. Wallace, J. Proceedings Linnean Society London, Zoology 3 (1858) 45.
[2] C. Darwin, On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life, Penguin, New York (1958).
[3] P. Schuster, Complexity 11 (2005) 12.
[4] E. Mayr, What Makes Biology Unique? Considerations on the Autonomy of a Scientific Discipline, Cambridge University Press, Cambridge (2004).
[5] R.A. Fisher, The Genetical Theory of Natural Selection, Clarendon, Oxford (1930).
[6] S. Wright, The Roles of Mutation, Inbreeding, Cross-breeding and Selection in Evolution, Proceedings of the Sixth International Congress of Genetics, 1 (1932) 356.
[7] C.C. Li, Population Genetics, University of Chicago Press, Chicago (1955).
[8] W.H. Li, ed., Stochastic Modeles in Population Genetics, Dowden, Hutchison and Ross, Stroudsburg (1977).
[9] J. Maynard-Smith, Evolution and the Theory of Games, Cambridge University Press, Cambridge (1982).
[10] M. Kimura, The Neutral Theory of Molecular Evolution, Cambridge University Press, Cambridge (1983).
[11] J.A. Endler, Natural Selection in the Wild, Princeton University Press, Princeton (1986).
[12] Y.M. Svirezhev and V.P. Passekov, Fundamentals of Mathematical Evolutionary Genetics, Kluwer, Dordrecht (1990).

[13] W.D. Hamilton, Narrow Roads of Gene Land, the Collective Papers of W.D. Hamilton, Vol. 1: Evolution of Social Behavior, W.H. Freeman, Oxford (1996).

[14] R.E. Michod, Darwinian Dynamics: Evolutionary Transitions in Fitness and Individuality, Princeton University Press, Princeton (1999).

[15] N.H. Barton and P.D. Keightley, Nat. Rev. Gen. 3 (2002) 11.

[16] W.J. Ewens, Mathematical Population Genetics, Vol. 1: Theoretical Introduction, 2nd ed., Springer-Verlag, New York (2004).

[17] J.H. Gillespie, Population Genetics: a Concise Guide, 2nd ed., Johns Hopkins University Press, Baltimore (2004).

[18] D. Waxman and S. Gavrilets, J. Evol. Biol. 18 (2005) 1139.

[19] P. Ao, Physics of Life Rev. 18 (2005) 1139.

[20] M.W. Blows, J. Evol. Biol. 20 (2007) 1.

[21] N.G. van Kampen, Stochastic Processes in Physics and Chemistry, Enl. ed., Elsevier, Amsterdadam (1992).

[22] W.T. Coffey, Y.P. Kalmykov, and J.T. Waldron, The Langevin Equation, 2nd ed., World Scientific, Singapore (2004).

[23] J.L. Doob, J.L., Classical Potential Theory and Its Probabilistic Counterpart, Springer-Verlag, New York (1984).

[24] P. del Moral, Feynman-Kac Formula: Genealogical and Interacting Particle Systems with Applications, Springer, Berlin (2004).

[25] G. Nicolis and I. Prigogine, Self-Organization in Non-equilibrium Systems, Wiley, New York (1977).

[26] H. Haken, Synergetics, an Introduction: Nonequilibrium Phase Transitions and Self-Organization in Physics, Chemistry and Biology, 2nd ed., Springer, Berlin (1983).

[27] J. Keizer, Statistical Thermodynamics of Nonequilibrium Processes, Springer (1987).

[28] M.C. Cross and P.C. Hohenberg, Rev. Mod. Phys. 65 (1993) 851.

[29] J.S. Langer, in Critical Problems in Physics, eds. V.L. Fitch, D.R. Marlow, and M.A.E. Demeurti, Princeton University Press, Princeton (1997) pp. 11–27.

[30] C. Kwon, P. Ao, and D.J. Thouless, Proc. Natl. Acad. Sci. (USA) 102 (2005) 13029-34.

[31] L. Yin and P. Ao, J. Phys. A 39 (2006) 8593.

[32] X.-M. Zhu, L. Yin, and P. Ao, Int. J. Mod. Phys. B 20 (2006) 817.

[33] P. Ao, C. Kwon, and H. Qian, Complexity 12 (2007) 19.

[34] H. Risken, The Fokker–Planck Equation: Methods of Solution and Applications, 2nd ed., Springer, Berlin (1996).

[35] G.W. Gardiner, Handbook of Stochastic Methods, 3rd ed., Springer, Berlin (2004).

[36] P. Refregier, Noise Theory and Appicataion to Physics: from Fluctuations to Information, Springer, Berlin (2004).

[37] H.D. Zeh, The Physical Basis of the Direction of Time, 5th ed., Springer, Berlin (2007).

[38] L. Sklar, Physics and Chance: Philosophical Issues in the Foundations of Statistical Mechanics, Cambridge University Press, Cambridge (1993).

[39] G.G. Emch and C. Liu, The Logic of Thermostatistical Physics, Springer, Berlin (2002).

[40] J. Uffink, Introduction, Studies in History and Philosophy of Modern Physics 36 (2005) 219.

[41] G. Gallavotti, F. Bonetto, and G. Gentile, Aspects of Ergodic, Qualitative and Statistical Theory of Motion, Springer, Berlin (2004).

[42] E.G.D. Cohen, Boltzmann and Einstein: Statistics and Dynamics—an Unsolved Problem, PRAMANA-Journal of Physics 64 (2005) 635.

[43] C. Bustamante, J. Liphardt, and F. Ritort, Phys. Today 58(7) (2005) 43.

[44] M.W. Deem, Phys. Today 60(1) (2007) 42.

[45] P. Gaspard, Adv. Chem. Phys. 135 (2007) 83.

[46] B. Gaveau and and L.S. Schulman, J. Stat. Phys. 110 (2003) 1317.

[47] P. Hanggi and F. Marchesoni, Chaos 15 (2005) 026101.

[48] D. Karevski, Cond. Matt. Phys. 6 (1999) S46–S357.

[49] D.G. Luchinsky, P.V.E. McClintock, and M.I. Dykman, Rep. Prog. Phys. 61 (1998) 889.

[50] X.S. Xing, Int. J. Mod. Phys. B 12 (1998) 2005.

[51] P. Attard, J. Chem. Phys. 127 (2007) 014503.

[52] H. Qian, J. Phys. Chem. B 109 (2005) 23624.

[53] D. Reguera, J.M. Rubi, and J.M.G. Vilar, J. Phys. Chem. B 109 (2005) 21502.

[54] N.A. Sinitsyn and I. Nemenman, Europhy. Lett. 77 (2005) 58001.

[55] G.P. Beretta, E.P. Gyftopoulos, J.L. Park, and G.N. Hatsopoulos, Nuovo Cimento B 82 (1984) 169.

[56] H.C. Otttinger, Beyond Equilibrium Thermodynamics, Wiley and Sons, New York (2005).

[57] S.I. Sasa and H. Tasaki, J. Stat. Phys. 125 (2006) 125.

[58] M. Kaern, T.C. Elston, W.J. Blake, and J.J. Collins, Stochasticity in Gene Expression: From Theories to Phenotypes, Nature Reviews: Genetics 6 (2005) 451.

[59] E. Kussell and S. Leibler, Sciences 309 (2005) 2075.

[60] J. Wang, B. Huang, X.F. Xia, and Z.R. Sun, Biophys. J. 91 (2006) 154.

[61] S.A. Kauffman, The Origins of Order, Oxford University Press, Oxford (1993).

[62] X.-M. Zhu, L. Yin, L. Hood, and P. Ao, Func. Integr. Genomics 4 (2004) 188.

[63] X.-M. Zhu, L. Yin, L. Hood, D. Galas, and P. Ao, Eficiency, Robustness and Stochasticity of Gene Regulatory Networks in Systems Biology: Lambda Switch as a Working Example, Chapter 18, In Introduction to Systems Biology, ed. S. Choi, Humana Press, New York (2007).

[64] S.R. de Groot and P. Mazur, Nonequilibrium Thermodynamics, Dover, New York (1984).

[65] R. Kubo, M. Toda, and N. Hashitsume, Statistical Physics: Nonequilibrium Statistical Mechanics, Vol. 2, 2nd ed., Springer, Berlin (1992).

[66] R. Zwanzig, Nonequilibrium Statistical Mechanics, Oxford University Press, New York (2001).

[67] K. Sato, Y. Ito, T. Yomo, and K. Kaneko, Proc. Natl. Acad. Sci. (USA) 100 (2003) 14086.
[128] T. Hatano and S.I. Sasa, Phys. Rev. Lett. 86 (2001) 3463.
[129] S. Mukamel, Phys. Rev. Lett. 90 (2003) 170604.
[130] S. Park and K. Schulten, J. Chem. Phys. 120 (2004) 5946.
[131] V. Chernyak, M. Chertkov, and C. Jarzynski, Phys. Rev. E 71 (2005) 025102.
[132] H. Qian, J. Phys. Conden. Matt. 17 (2005) S3783.
[133] D. Collin, F. Ritort, C. Jarzynski, S.B. Smith, I. Tinoco Jr., and C. Bustamante, Nature (London) 437 (2005) 231.
[134] J. Kurchan, J. Stat. Mech. (2007) P07005.
[135] J.M. Schurr and B.S. Fujimoto, J. Phys. Chem. B 107 (2003) 14007.
[136] R.D. Astumian, J. Am. Phys. 74 (2006) 683.
[137] E.G.D. Cohen, and D. Mauzerall, Mol. Phys. 103 (2005) 2923.
[138] A. Einstein, Ann. Physik 17 (1905) 549.
[139] W. Nernst, Z. Phys. Chem. 2 (1888) 613.
[140] M. Planck, Ann. Phys. Chem., Neue Folge 39 (1890) 161.
[141] J.S. Townsend, Philos. Trans. R. Soc. London A 193 (1899) 129.
[142] W. Sutherland, Phil. Mag. 9 (1905) 781.
[143] V. Blickle, T. Speck, C. Lutz, U. Seifert, and C. Bechinger, Phys. Rev. Lett. 98 (2007) 210601.
[144] N.W. Ashcroft and N.D. Mermin, Solid State Physics, Saunders College, Philadelphia (1976).
[145] C.G. Rodrigues, A.R. Vasconcellos, and R. Luzzi, J. Appl. Phys. 99 (2006) 073701.
[146] P.W. Anderson, Science 177 (1972) 393.
[147] R.B. Laughlin, D. Pines, J. Schmalian, B.P. Stojkovic, and P. Wolynes, Proc. Nat. Acad. Sci. (USA) 97 (2000) 32.
[148] W.M. Elsasser, Reflection on a Theory of Organisms: Holism in Biology, Introduced by H. Rubin and by F. Seitz, John Hopkins University Press, Baltimore (1998).
[149] Universe or Multiverse? ed. B. Carr, Cambridge University Press, Cambridge (2007).