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On the Statistical Mechanics of Constrained Biophysical Systems

Charles J. Lumsden[1,2] and L. E. H. Trainor[1]

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A well-known class of biophysical models, first introduced by Kerner, is shown to admit a convenient Hamiltonian formulation in which motion through the phase space of system variables involves explicit constraints. To treat the macroscopic properties of such models, we develop an ensemble theory of systems subjected to phase space constraints. For such systems we obtain a generalized Hamiltonian statistical mechanics which preserves much of the structure and efficacy of the corresponding physical theory. In a first application of the method, we recover Kerner's original "biological ensemble" as a special case involving information optimality and conservative biosystems.

KEY WORDS: Ensemble theory; Hamiltonian dynamics; constraints; macrovariables; generalized Poisson brackets; Liouville equation; biological modeling; dynamical systems; Dirac-Hamilton theory.

1. INTRODUCTION

In physical theory, the Hamiltonian formalism provides a unified description of particle and field dynamics. Its impact on statistical mechanics is well known and has influenced the treatment of both equilibrium[3] and non-equilibrium[4] phenomena. In biology, on the other hand, the significance, or

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[1] Departments of Physics and Medicine, University of Toronto, Toronto, Canada.

[2] Present address: Department of Biology—MCZ Laboratories, Harvard University, Cambridge, Massachusetts.

[3] For example, the axiom of equal a priori probabilities in phase space and the axiom that the energy is the only relevant additive constant of the motion.[1-3]

[4] For example, the geometric properties of ensemble motion, the approach to equilibrium, and the existence of macroscopic properties.[1,3-8]

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even the existence, of unified descriptions is much less clear; in particular, a formalism resembling that achieved in the Hamiltonian theory of physical systems has not been available for analyzing models used in biological explanation at either the dynamical or statistical levels.

In this communication we establish such a generalized Hamiltonian theory for the set of classical biophysical models introduced by Kerner.[9,10] The crux of our development is a demonstration that the standard theory of biological ensembles[9,10] can be structured into a statistical mechanics of appropriately constrained Hamiltonian systems. We then show that powerful tools from both the dynamical and statistical theories of physical systems can be adapted to the biological context, where prediction of variational principles, collective behavior, and macroscopic properties[5] is a central problem.[11–14,17,21,22,36]

The difficulty involved in formulating a satisfactory approach to such calculations arises partly from the diversity of organic phenomena which one is trying to encompass and partly from the highly nonlinear, often dissipative, properties of the underlying dynamics. In many organic processes[15–17] the time development takes the form of a system of first-order differential equations[6]

$$\dot{x}_j = X_j(x_1, x_2, \ldots, x_N, t), \qquad j = 1, \ldots, N \tag{1}$$

where the functions X_j vary from model to model but are usually nonlinear. For complex systems like a metabolic network, N is very large. While it is unrealistic to expect that all models of the type (1) have a simple canonical transcription, we are able to show that such models can be expressed in terms of an exact, constrained, Hamiltonian dynamics. A step of this sort seems crucial in the establishment of a biological statistical mechanics which can build on the concepts and methods so successful in physical theory.

It is well known from the work of Pfaff, Lie, and König, as pointed out by Whittaker[18] and by Kerner,[9,10] that a Hamiltonian structure can be formally achieved for systems of equations of the type (1) by dividing the N variables x_j, suitably transformed, into a set of $N/2$ "space" variables, and a conjugate set of $N/2$ "momentum" variables.[7] For systems with any significant degree of complexity, this construction is usually intractable and algorithms for achieving it have been worked out only in simple cases. It

[5] I.e., properties emerging (observable) at a more macroscopic level of description; e.g., biochemical, cellular, ecologic.

[6] The choice of properties depends on the biological context; e.g., the x_j might be chemical concentrations or animal population densities.

[7] We deal with the standard case of N = even in this paper; the case of N = odd involves additional constraints which can be handled by methods related to those developed here.

has yet to be widely applied to biological modeling. Moreover, this type of construction obscures the fundamental similarity of the x_j variables in their original biophysical or biochemical context.

An alternative possibility is to work with the statistical mechanics in an enlarged phase space of dimension $2N$ where all of the x_j retain their original meanings. In this paper we wish to show that one can adapt to the purpose a new theory of Hamiltonians due to Dirac.[19,20] In this approach one introduces a set of N momentum variables conjugate to the x_j through the device of a Dirac "total" Hamiltonian, along with exactly N constraint equations which ultimately reduce the degrees of freedom in the phase space from $2N$ to N. The time development of the biological ensemble in *both* conservative *and* dissipative biosystems is then governed by a familiar Liouville equation, so the formalism provides a means for formal interpretation as well as practical calculation.

This accomplishes for the first time a general Hamiltonian stage for the program of mapping a biodynamics (1) and its statistical mechanics first to variational and then to Hamiltonian form. This program has been widely discussed[9,10,17,22–25] in recent years, but little progress with the Hamiltonian aspects has previously been documented. For the system of equations (1), a Lagrangian generally exists, at least locally,[10] and the associated variational principle gives an important *optimality rule*[8] for the biosystem's design. The problem of constructing a Lagrangian given the system of equations (1) has been solved in several specific models,[9,10,22–25] and one anticipates that as insight into biological system design sharpens, insight into the construction of Lagrangians will also develop. We recall that even in physical theory no general algorithms exist other than specific ones for specific systems, based on experience.

In Section 2, we carry out the transformation of the bioensemble theory to constrained Hamiltonian form and investigate the consequences for the canonical properties of the system of equations (1). In Section 3 we use the theory of generalized Poisson brackets to relate our work to the point of view of Pfaff, Lie, and König. Although we carry out these developments for Lagrangians which are explicitly independent of time, the theory is readily generalized to cover explicit time dependence. This is briefly discussed in Section 4. As a first application of the formalism, we develop in Section 5 Kerner's biological ensemble theory as a special case involving stationary ensembles in conservative biosystems. The paper concludes with a short discussion of results in Section 6.

[8] It is useful to recall that optimality arguments[17,21,22,36] motivate variational principles, Lagrangians, and Hamiltonians in this subject from the biological side. This adds significantly to the utility of canonical forms for treating the dynamics and statistical mechanics of (1).

2. GENERAL THEORY

In our work, biological ensemble theory emerges from a consideration of reduced descriptions for the dynamics (1) in which the relevant variables are macrovariables (emergent properties) $A_k(\mathbf{x})$, $k = 1,..., M \ll N$. System description at the coarse-grained **A**-level is accompanied by statistical uncertainties in the corresponding description at the "microscopic" **x**-level. If $A(\mathbf{x})$ is one such macrovariable, then its average temporal behavior is given by

$$\langle A \rangle(t) = \int d\mathbf{x}\, A(\mathbf{x})\rho(\mathbf{x}, t) \tag{2}$$

where $\rho(\mathbf{x}, t)$ is the **x**-space ensemble density representing the distribution of **x**-level uncertainties. As in physical theory, in the dynamics of the "biological ensemble" the density $\rho(\mathbf{x}, t)$ follows the conservation law

$$\partial_t \rho = -\mathrm{div}(\rho \mathbf{X}) \tag{3}$$

and the evolution of the ensemble is determined by the properties of the velocity field **X** [see the system of equations (1)]. The variational properties of such fields have been investigated by Kerner and others,[17,22–25] who considered the possibility that Lagrangians $L(\mathbf{x}, \dot{\mathbf{x}}, t)$ exist such that the Euler–Lagrange equations of the variational (optimality) principle

$$\delta \int_{t_1}^{t_2} L\, dt = 0 \tag{4}$$

give the biodynamics (1). The first-order rate structure of (1) suggests[9,10] that model Lagrangians can generally be written and are first order in the $\dot{x}_j$ (summation convention):

$$L = U_j(\mathbf{x}, t)\dot{x}_j - U_0(\mathbf{x}, t) \tag{5}$$

The Euler–Lagrange equations can then be expressed in the form

$$\Gamma_{km}\dot{x}_m = \Lambda_m \tag{6a}$$

where the quantities Γ_{km} are given by

$$\Gamma_{km} = \frac{\partial U_k}{\partial x_m} - \frac{\partial U_m}{\partial x_k} = -\Gamma_{mk} \tag{6b}$$

and the quantity

$$\Lambda_k = -\frac{\partial U_k}{\partial t} - \frac{\partial U_0}{\partial x_k} \tag{6c}$$

can be regarded as a "generalized force." The Γ_{km} satisfy

$$\partial_t \Gamma_{km} = \frac{\partial}{\partial x_k}(\Gamma_{mn} X_n) - \frac{\partial}{\partial x_m}(\Gamma_{kn} X_n) \tag{7}$$

Equations (5)–(7) have been solved in applications of biological ensemble theory to chemical kinetics, biochemical networks, neurobiology, and ecology.[9,10,23–25],[9]

If one follows the usual procedure for constructing a Hamiltonian from the Lagrangian (5),[10]

$$H_0 = p_k \dot{x}_k - L \tag{8}$$

$$p_k \equiv \partial L / \partial \dot{x}_k \tag{9}$$

which leads to the identification $H_0 = U_0(\mathbf{x})$, it becomes apparent that the corresponding canonical equations do not return the appropriate dynamical equations (1). This difficulty is easily traced to the global singularity of the map (9) from the velocities $\dot{x}_k$ to the momenta p_k; the Jacobian of this transformation vanishes everywhere:

$$\det \| \partial^2 L / \partial \dot{x}_j \, \partial \dot{x}_k \| = 0 \tag{10}$$

Regular Hamiltonian theory assumes, on the contrary, that this Jacobian is everywhere *nonvanishing*. The question therefore arises as to whether a Hamiltonian formulation for the ensemble can be constructed at all.

Dirac[20] has succeeded in generalizing Hamiltonian mechanics to include singular Lagrangians of the type (10). We have adapted the Dirac method to statistical mechanics. In the following we use this method to develop exact Hamiltonian equations for the biological ensemble, referring only to those parts of the Dirac theory essential to our formalism; complete descriptions of his work are available elsewhere.[6,19,20]

For the linear Lagrangian (5), all momenta are of the Dirac dependent type,[20] given by velocity-*independent* expressions

$$p_\rho = U_\rho(\mathbf{x}), \qquad \rho = 1, \ldots, N \tag{11}$$

The system dynamics can then be regarded as the motion of a point in $2N$-dimensional phase space, constrained by the N equations

$$\phi_\rho = p_\rho - U_\rho(\mathbf{x}) = 0 \tag{12}$$

[9] Since Eqs. (6) are N equations in $N + 1$ unknown functions, and since both (6) and (7) admit gauge-invariant transformations, neither set alone gives unique solutions for $U_1, \ldots, U_N, U_0$. Auxiliary conditions such as[10] $U_0 = X_k U_k$ are usually specified to complete the system.

[10] Until Section 4 we consider $L(\mathbf{x}, \dot{\mathbf{x}}, t) = L(\mathbf{x}, \dot{\mathbf{x}})$.

The system is thus restricted to an N-dimensional constraint hypersurface $\mathcal{M}$. By incorporating the constraints into the canonical formalism we obtain, following Dirac, the generalized canonical dynamics (GCD)

$$\dot{x}_j = \frac{\partial U_0}{\partial p_j} - \dot{x}_\rho \frac{\partial U_\rho}{\partial p_j} \tag{13a}$$

$$\dot{p}_k = -\frac{\partial U_0}{\partial x_k} + \dot{x}_\rho \frac{\partial U_\rho}{\partial x_k} \tag{13b}$$

where k and ρ both run over 1,..., N and j takes all values on 1,..., N not already covered by ρ. Since ρ covers 1,..., N, there are no applicable values of j; the GCD provides no information on the $\dot{x}_\rho$ directly from (13a). This lack of explicit GCD expressions for the x_ρ is typical of singular Lagrangians and is due to the constraints. In practice, equations for $\dot{x}_\rho$ are constructed from (13b) and the constraint equations. We exemplify this process in the Appendix for the linear Lagrangian model, establishing that for the allowed motion on $\mathcal{M}$, Eqs. (13a) and (13b) return the Euler–Lagrange equations for the biodynamics in the system of equations (1). Equations (13a) and (13b) can be rewritten in algebraic form by using the Dirac "total Hamiltonian," which for the linear Lagrangian (5) turns out to be

$$H = U_0(\mathbf{x}) + [p_\rho - U_\rho(\mathbf{x})]\dot{x}_\rho \tag{14}$$

Using this Hamiltonian, we find that the canonical equations (13a) and (13b) are equivalent to

$$\dot{x}_k \approx [x_k, H] \tag{15a}$$

$$p_k \approx [p_k, H] \tag{15b}$$

($k = 1,..., N$), where $[\cdot, \cdot]$ are the usual Poisson brackets and $\approx$ are the weak equalities of Dirac,[20] by which the Poisson brackets are first fully evaluated and then the limit $p_\rho \to U_\rho$ is taken. When this is done, Eqs. (15b) reduce to our previous equations (13b); (15a) give the consistency relations $\dot{x}_k = \dot{x}_k$, $k = 1,..., N$.

By means of the dynamics (15) we can now relate the time development of the biological ensemble to the Hamiltonian (14):

$$\partial_t \rho(\mathbf{x}, t) \approx -[x_k, H]\, \partial\rho/\partial x_k + \rho D(\mathbf{x}) \tag{16a}$$

where $D(\mathbf{x})$ is the canonical compressibility $-\partial[x_k, H]/\partial x_k$. The term containing the ρ gradient contracts to $-[\rho, H]$, so that Eq. (16a) assumes the form of a canonical Liouville equation which includes the possibility of compressible flow[11]:

$$\partial_t \rho \approx -[\rho, H] + \rho D(\mathbf{x}) \tag{16b}$$

[11] Note that the term "incompressible flow" in physical theory refers to the $2N$-dimensional phase space. Unconstrained flow in the $2N$-dimensional phase space used here is also incompressible and the compressibility of the allowed motion is recovered, when it is nonzero, by applying the constraints.

If the flow in **x** space is everywhere incompressible, one obtains the Dirac–Liouville equation for the ensemble:

$$\partial_t \rho \approx -[\rho, H] \tag{16c}$$

By considering the transformation properties of the Dirac representation one can show that, as in physical theory, the time development of the ensemble corresponds to a *canonical transformation* in the embedding space of phase coordinates (**x**, **p**).

This canonical form for the ensemble dynamics is a direct consequence of the dynamics represented by the system of equations (1) by virtue of the constraint hypersurface $\mathscr{M}$ embedded in the $2N$-dimensional (**x**, **p**) phase space. In the next section we show that this embedding is not fortuitous; on the contrary, it is related to the existence of generalized canonical properties in (1) which emerge clearly in the limit $p_\rho \to U_\rho$.

3. GENERALIZED CANONICAL PROPERTIES

Putting the constraints $\phi_\rho = 0$ on the Hamiltonian dynamics (15), we obtain the limiting form (Appendix)

$$\{\dot{x}_k \approx [x_k, H], \quad \dot{p}_k \approx [p_k, H]\} \xrightarrow{\phi_\rho \to 0} \dot{x}_k = -\Gamma^{-1}_{km} \partial U_0 / \partial x_m \tag{17}$$

The RHS of (17) is the Euler–Lagrange form (6) for the equations of motion; together with the condition $p_\rho = U_\rho$ it determines the system's path on the hypersurface (or equivalently, the path through the **x** space). Let us write this **x**-dynamics in the form

$$\dot{x}_k = \gamma^{km} \frac{\partial U_0}{\partial x_m} = \gamma^{nm} \frac{\partial x^k}{\partial x^n} \frac{\partial U_0}{\partial x_m} \equiv [\![x_k, U_0]\!] \tag{18a}$$

$$\|\gamma^{km}\| = -\|\Gamma_{km}\|^{-1} \tag{18b}$$

It is clear that the operator $[\![\cdot, \cdot]\!]$ shares both the skew-symmetry and bilinearity of the ordinary Poisson bracket. By noting that Γ_{km} is the curl of the field **U**, one can show that $[\![\cdot, \cdot]\!]$ also obeys the Jacobi identity

$$\sum_{\substack{f,g,h \\ \text{cyclic}}} [\![[\![f, g]\!], h]\!] = 0 \tag{19}$$

and is therefore a Lie bracket. The most familiar Lie bracket in classical mechanics is of course the ordinary Poisson bracket (PB), and $[\![\cdot, \cdot]\!]$ is a generalization of the PB, sharing many of its properties.[6,12] It is called a generalized Poisson bracket (GPB) and its properties have in recent times been studied extensively.[6] Hence we find[12] that the motion (17), (18) is a *generalized canonical dynamics*[6] given by

$$\dot{x}_k = [\![x_k, U_0]\!], \qquad k = 1,..., N \tag{20}$$

Applied to an ensemble of system points, this dynamics leads to the generalized canonical Liouville equations

$$\partial_t \rho = -[\![\rho, U_0]\!] \qquad \text{(incompressible flow)} \tag{21a}$$

$$\partial_t \rho = -[\![\rho, U_0]\!] + \rho D(\mathbf{x}) \qquad \text{(compressible flow)} \tag{21b}$$

where

$$D(\mathbf{x}) = -\partial [\![x_k, U_0]\!]/\partial x_k \tag{21c}$$

and where U_0 acts as the conserved GPB Hamiltonian. As a result, constraining the bioensemble dynamics to the N-dimensional form does not destroy its canonical properties, but instead induces a flow which is a *generalized canonical map*[6] of the $\mathbf{x}$ space into itself. Further information on these properties is presented elsewhere.[6,12,26]

It is useful to compare our GPB description of the ensemble with the viewpoint of Pfaff, Lie, and König (PLK).[10,18] Although both are constraint-free and make use of N-dimensional $\mathbf{x}$ space, the goal in PLK is not just a GPB description; one seeks instead a regular Hamiltonian description in which the Poisson bracket replaces the GPB. The difficulties inherent in the PLK program were referred to in Section 1; we note, however, that once a GPB is obtained, the PLK problem can be reduced from the usual analytical procedure[18] to one in linear algebra, mapping GPB $\rightarrow$ PLK.[26,27]

4. EXPLICIT TIME DEPENDENCE

Both the Dirac and the GPB methods can be extended to cover situations involving Lagrangians which depend explicitly on time:

$$L = U_j(\mathbf{x}, t)\dot{x}_j - U_0(x, t) \tag{22}$$

In our applications, time-dependent Lagrangians are encountered both in models subjected to external driving forces and in models with internal dissipation (self-regulation, homeostasis). Here we summarize the essential results; Lumsden[12] discusses the details.

The GPB can be generalized through the time-dependent functions

$$\Gamma_{km}(\mathbf{x}, t) = \frac{\partial U_k}{\partial x_m}(t) - \frac{\partial U_m}{\partial x_k}(t) \tag{23}$$

leading to an "extended" bracket

$$[\![\![f, g]\!]\!] = \gamma^{km}(\mathbf{x}, t)\frac{\partial f}{\partial x_k}\frac{\partial g}{\partial x_m} \tag{24}$$

where f and g can have an explicit time dependence and the Jacobi identity (19) is satisfied at every instant t. Since the Euler–Lagrange equations (6)

now contain terms due to the explicit time dependence, the complexity of the $\dot{x}_k$ equations is somewhat increased:

$$\dot{x}_k = \llbracket x_k, U_0 \rrbracket + \gamma^{km} \partial_t U_m \tag{25}$$

and the generalized Liouville equation contains these new terms as well:

$$\partial_t \rho = -\llbracket \rho, U_0 \rrbracket + \gamma^{ml} \frac{\partial \rho}{\partial x_l} \partial_t U_m + \rho D(\mathbf{x}, t) \tag{26}$$

The Dirac–Poisson bracket is, in contrast, undisturbed by an explicit time dependence, and for a time-dependent Dirac total Hamiltonian the Liouville equation again has the simple canonical structure

$$\partial_t \rho \approx -[\rho, H(t)] + \rho D(\mathbf{x}, t) \tag{27}$$

$D(\mathbf{x}, t)$ vanishes for incompressible flow. The constraints $\phi_\rho(\mathbf{x}, \mathbf{p}, t)$ are now time dependent, so that as the dynamics unfolds on the constraint hypersurface, the constraint hypersurface is itself unfolding within the $(\mathbf{x}, \mathbf{p})$ phase space.

5. STATIONARY ENSEMBLES

In a theory of ensemble dynamics, one of the most interesting questions concerns the asymptotic properties of the ensembles as $t \to \infty$. Attention generally focuses on the existence of stationary (time-independent) ensembles, and to what extent time-dependent ensembles eventually approach these stationary limits.[1–8] Provided that questions regarding the structure of initial ensembles can be settled, such analyses complement arguments from ergodic theory in justifying specific forms for the equilibrium ensembles. As a first application of our formalism, we examine the question of stationary biological ensembles.

In his pioneering papers, Kerner[9,10] suggested a viewpoint based on Gibbsian ensembles. If a biodynamics (1) is conservative and admits an isolating first integral, then the corresponding conserved quantity A is a good macrovariable for the system. Ensembles on the $\mathbf{x}$ space shells corresponding to $A =$ constant give rise to statistical predictions about the system's behavior. Kerner restricted his investigation to time-independent ensembles and thus to stationary expectation values. A Gibbsian $\rho \propto e^{-\gamma A}$ was posited as an intuitively attractive form for this ensemble, but little progress toward justifying the Gibbsian form has since been documented. It is therefore of relevance to consider the possibility that the Gibbsian bioensemble is a stationary solution of the appropriate Dirac–Liouville equation. In this section we show that Kerner's ensemble is in fact the stationary ensemble of maximum information entropy in a conservative system with macrovariable $A = U_0$.

From the Liouville equation (17) it is apparent that for a general biodynamics the stationary ensemble condition is

$$[\rho, H] + \rho D(\mathbf{x}) \approx 0 \tag{28}$$

The compressibility term, when nonzero, can produce a condensation of $\rho(\mathbf{x}, t)$ into selected $\mathbf{x}$ space regions. Here, it is sufficient to note that the Kerner problem corresponds to the case of a conservative, incompressible biodynamics. The condition (28) then specializes to

$$[\rho, H] \approx 0 \tag{29}$$

with $[H, H] \approx 0$. Thus for the Kerner formualtion, the relevant macrovariable is $H \approx U_0$. The U_0 appears to be isolating in the conservative models studied to date.[9,10,23,25]

Equal initial a priori probabilities are motivated in the symplectic geometries of the Dirac and the GPB dynamics.[2] The ensemble of optimal information entropy[2,28] is then proportional to $e^{-\lambda H}$, where λ is a constant analogous to the inverse temperature. From Eq. (29) we see that such an ensemble is stationary, and from the properties of the Dirac weak equalities that (up to normalization factors)

$$\rho \approx e^{-\lambda H} \approx e^{-\lambda U_0} \tag{30}$$

The RHS of (30) is the Gibbsian bioensemble conjectured by Kerner, constructed here on the basis of a canonical nonequilibrium theory.

The Gibbsian bioensemble is thus an information-optimal, stationary solution of the Dirac–Liouville equation (17) in a one-integral, conservative biodynamics. The same conclusion follows from an analysis based on the GPB Liouville equation (21), and similar results hold for more complex systems with two or more isolating integrals. In future work it will therefore be of interest to study the Gibbsian bioensemble as an asymptotic attractor of initial ensembles. Some progress in this direction has been achieved, and is the topic of a separate report.[29]

6. DISCUSSION

A general Hamiltonian representation has not previously been available for the biological ensemble theory; prior work has dealt mainly with hypothesized Gibbslike ensembles at equilibrium in conservative biodynamics. In the present study a complete Hamiltonian representation has been achieved. For N large in (1), this gives for any system macrovariables a Liouville ensemble statistics which covers not only *conservative* but *dissipative* models as well. Nonequilibrium is treated together with equilibrium and the previously hypothesized[9,10,23–25] Gibbs bioensembles are recovered as a subcase. For nonequilibrium ensembles the Hamiltonian form establishes the trans-

formation structure of the ensemble motion through the phase space of biological coordinates. Furthermore, by placing the problems in a common framework it reveals basic points of comparison between handling complex biodynamic and complex physical models via ensemble methods.

In the case of time-independent Lagrangians, the correspondence with physical theory is rather complete, the classical Poisson brackets being replaced by the Dirac–Poisson brackets or by the generalized Poisson brackets. When the time dependence becomes explicit, the formal structure remains unchanged in the Dirac theory, with the ensemble dynamics involving a system of time-dependent constraints. For time-dependent Lagrangians in the GPB representation, the formal similarity to the classical Liouville equations weakens, since the ensemble is then driven by forces dependent upon the time rate of change of the generalized momenta $U_k(\mathbf{x}, t)$.

Although the canonical formalism provides considerable insight into the structure of stationary ensembles (Section 5), it is naturally suited as well to nonequilibrium calculations involving time-dependent ensembles. The canonical Liouville equations (16) and (21) form a starting point equivalent to that which has led to reduced descriptions in physical theory.[5,30] In specific applications, generalized kinetic equations are recovered. For example, in a two-dimensional biodynamics (1), the corresponding GPB equations (Section 3) immediately yield as a special case the generalized Langevin equations constructed by Zwanzig in his recent work on nonlinear Brownian motion.[31] Much less specialized results also follow and we anticipate that the approach developed here will be of utility in treating nonequilibrium biological ensembles.

The linear Lagrangian which we have studied in detail is perhaps the simplest example of the singular Lagrangians which are encountered in a wide variety of purely physical problems as well. Singular Lagrangians figure, for example, in hydrodynamics, electrodynamics, relativistic statistical mechanics, network theory, and geometric mechanics on non-Euclidean manifolds.[6,20,32–35] It is encouraging to note that the Dirac theory opens up the statistical mechanics of these and other constrained Hamiltonian systems for detailed investigation, maintaining a formalism which encompasses as well the whole of physical statistical mechanics concerned with regular Hamiltonian systems.

APPENDIX. APPLICATION OF THE CANONICAL DYNAMICS (13)

The generalized canonical equation (13b) is

$$\dot{p}_k = -\frac{\partial U_0}{\partial x_k} + \dot{x}_\rho \frac{\partial U_\rho}{\partial x_k}, \qquad k = 1,..., N \tag{A1}$$

From (11) it is evident that for the allowed motion on $\mathcal{M}$

$$\dot{p}_k = \frac{\partial U_k}{\partial x_n} \dot{x}_n \tag{A2}$$

which combines with (A1) to give the explicit **x**-dynamics

$$\left(\frac{\partial U_k}{\partial x_n} - \frac{\partial U_n}{\partial x_k}\right)\dot{x}_n = -\frac{\partial U_0}{\partial x_k} \tag{A3}$$

Equations (A3) are exactly the variational dynamics (6) of the original model; hence the full dynamical content of (6) is preserved in the canonical expressions (13).

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