THE STATISTICAL MECHANICS FOR AN EXTENDED NONLINEAR EPIGENETIC DYNAMICS. I

WARREN H. WOOLLEY *and* ANDREW G. DE ROCCO

From the Department of Physics and Astronomy, University of Maryland, College Park, Maryland 20742 and the Physical Sciences Laboratory, Division of Computer Research and Technology, National Institutes of Health, Bethesda, Maryland 20014

ABSTRACT An extension of the control equations discussed by Goodwin is proposed which allows for arbitrary strong coupling and for arbitrary parallel coupling of metabolic pools and genetic loci. It is demonstrated that these generalized control equations can be put into canonical form and further that Liouville's theorem applies. In addition, it is demonstrated that after a suitable canonical transformation the resulting partition function can be solved in closed form, and this result, as well as that for the mean energy, is exhibited. Some remarks appropriate to additional extensions are presented.

INTRODUCTION

The fundamental interest in this problem arises from the important and suggestive advances made by Goodwin concerning the ensemble theory for certain uncoupled or weakly-coupled, nonlinear control loops (1). The motivation is to provide a statistical theory for cellular physiology: that is, events in space and time characteristic of a viable cell (or cell population) from the dynamics of biochemical control loops involving genetic loci, transcription and translation events, metabolic activity and a feedback to the primary locus as well as to others, either directly at the site or indirectly through the coupling of metabolic pools.

In his pioneering investigations Goodwin studied an especially favorable case, the dynamics of which is contained in the equations

$$\frac{dX_i}{dt} = b_i\left[\frac{Q_i}{A_i + k_iY_i} - 1\right] \tag{1.1}$$

$$\frac{dY_i}{dt} = \alpha_i[X_i - p_i]. \qquad (i = 1, 2, \cdots, N) \tag{1.2}$$

These equations represent the case where a genetic locus L_i, a ribosome R_i, and

a cellular locus C_i are connected by an amount X_i of messenger RNA, an amount Y_i of protein, a metabolite M_i, and a feedback upon L_i either through M_i alone or in conjunction with some suitable aporepressor.

The meaning and significance of the symbols appearing in equations 1.1 and 1.2 can easily be described. For example, the time rate of change of protein is determined by its rate of formation from messenger and its subsequent loss to events at an appropriate celllular locus. Thus α_i represents a specific rate constant for protein synthesis and the product $\alpha_i p_i$ describes the degradation, here taken as constant. (The units employed in these and subsequent equations will be molecules per cell—an anology to the conventional number density of traditional statistical mechanics.) It should be noted that the quantity α_i contains implicitly a good deal of information concerning the conditions for template synthesis of protein, none of which are evident in this description.

The equation suitable for messenger RNA (mRNA) is slightly less obvious. The constants now characterize the interaction of both repressor and activated precursor with the template, as well as information pertinent to the feedback signal at the genetic locus. Thus the constants b_i, Q_i, A_i, and k_i represent possibly complicated dynamic events. The study of these events is not the primary purpose of this paper, however, and we defer further comment to later publications.

In Fig. 1 we exhibit the now well-known diagrammatic representation for the system of equations described above.

Goodwin has also considered several other schemes for coupling such elementary loops together, either directly through repression by metabolite or indirectly through the coupling of a sequence of metabolic pools. These cases have been described as "strong" and "parallel" coupling. Typical diagrams are shown in Fig. 2. Calculations, however, were limited to systems of two species, and no general results were obtained.

It is the primary purpose of this paper to define a generalization of the dynamics to arbitrary strong and arbitrary parallel couplings, and to show that the resulting ensemble can be solved in the general case without any restrictions deriving from the integrability conditions.

We shall first define the model, then show that it satisfies Liouville's theorem, and finally evaluate the partition function and one "thermodynamic" function, the mean energy. We conclude with a few remarks pertinent to additional investigations.

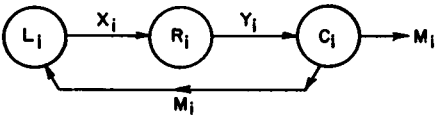

FIGURE 1 Diagrammatic representation of the simplest unit control loop. Quantities X_i of mRNA are formed at locus L_i, determine quantities Y_i of protein at ribosome R_i, which in turn act at a cellular locus C_i to facilitate formation of metabolite M_i a part of which acts to repress the signal at L_i.

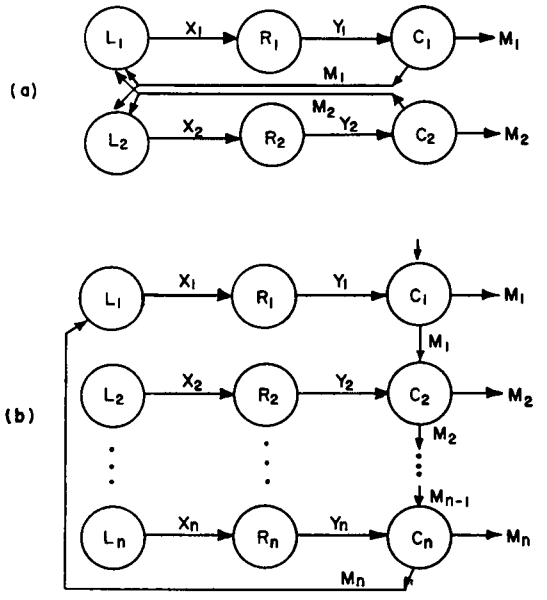

FIGURE 2 Two additional examples of more complex control loops; (*a*) direct repression by adjacent metabolites; (*b*) parallel sequential coupling in which metabolite M_n acts directly at an initial site to which it is coupled through a sequence of metabolic pools.

DEFINITION OF THE MODEL

Each diagram representing a possible control sequence of n loops can be considered as a directed graph of 3n points. Each point in the graph is an articulation or cutting point, in the sense that its removal along with its inputs and outputs renders the remaining figure unconnected.

The enumeration and exhibition of the set of all such graphs for arbitrary general cases is a very complicated process and it is easier for us to go directly to a mathematical generalization of equations 1.1 and 1.2.

Consider the following:

$$\frac{dX_i}{dt} = -b_i + \left(\sum_r \sum_s A_r K_{rs}^{-1} K_{si}/B_s + \sum_t K_{st} Y_t\right) \quad (i = 1, 2, \cdots, N) \quad (2.1)$$

$$\frac{dY_i}{dt} = \sum_j C_{ij} X_j - d_i, \quad (2.2)$$

where K_{rs}^{-1} is the inverse of a matrix element representing all possible couplings through genetic loci and C_{ij} is the corresponding matrix element for parallel coupling. It is clear that if we choose

$$K_{ij} = \delta_{ij} k_i, \qquad C_{ij} = \delta_{ij} \alpha_i, \quad (2.3)$$

then equations 2.1 and 2.2 reduce to the elementary case cited earlier. In these conditions δ_{ij} represents the familiar Kronecker delta.

For the present we shall assume $((C_{ij}))$ to be symmetric, and note that the system of equations 2.1 and 2.2 incorporates the possibility that in parallel coupling a par-

ticular metabolite may influence not only a single locus, but all or some of a sequence, and that the sense of this sequence is not specified.

We will now show that these equations of motion can be derived from a function $G(X_1, X_2, \cdots, X_N; Y_1, Y_2, \cdots, Y_N)$—to be abbreviated as $G(X, Y)$—which plays the role of a generalized hamiltonian, and that equations 2.1 and 2.2 are in fact the canonical equations of motion. The function $G(X, Y)$ is conserved, and so reflects the time translation invariance of the system.

For convenience we introduce the following notation.

A vector will be written in boldface of the same letter as represents its components. Thus $\mathbf{x}^T$ represents the transpose of a vector $\mathbf{x}$, and given that $\mathbf{x}$ and $\mathbf{y}$ are column vectors, then

$$\sum_{i=1}^{N} x_i y_i = \mathbf{x}^T\mathbf{y}.$$

A matrix will be written with a bar above the same letter as represents its components, and given the vectors $\mathbf{x}$ and $\mathbf{y}$ and the matrix $\bar{A}$, then

$$\sum_{i=1}^{N}\sum_{j=1}^{N} x_i A_{ij} y_j = \mathbf{x}^T\bar{A}\mathbf{y}.$$

The function $G(\mathbf{x}, \mathbf{y})$ we construct as follows:

$$G(\mathbf{x},\mathbf{y}) \equiv \sum_{i=1}^{N}\sum_{j=1}^{N} \frac{1}{2} x_i C_{ij} x_j + \sum_{i=1}^{N} b_i y_i - \sum_{i=1}^{N} d_i x_i - \sum_{i=1}^{N}\sum_{j=1}^{N} A_j K_{ji}^{-1} \ln\left(B_i + \sum_{l} K_{il} y_l\right), \quad (2.4)$$

or in more compact notation,

$$G(\mathbf{x},\mathbf{y}) = \tfrac{1}{2}\mathbf{x}^T\bar{C}\mathbf{x} + \mathbf{b}^T\mathbf{y} - \mathbf{A}^T\bar{K}^{-1} \ln(\mathbf{B} + \bar{K}\mathbf{y}) - \mathbf{d}^T\mathbf{x}. \quad (2.5)$$

Differentiation of G yields the equations of motion in a straightforward manner. Observe that

$$\frac{\partial G}{\partial x_l} = \frac{1}{2}\sum_i\sum_j \{\delta_{il} C_{ij} x_j + x_i C_{ij} \delta_{jl}\} - \sum_i d_i \delta_{il}$$

or

$$\frac{\partial G}{\partial x_l} = \frac{1}{2}\left\{\sum_j C_{lj} x_j + \sum_i x_i C_{il}\right\} - d_l. \quad (2.6)$$

But by choice $\bar{C}$ is symmetric and the two sums condense to give

$$\frac{\partial G}{\partial x_l} = \sum_m C_{lm} x_m - d_l, \quad (2.7)$$

and comparison with equation 2.2 reveals that

$$\frac{\partial G}{\partial x_1} = \dot{y}_1 . \tag{2.8}$$

The same procedure can be employed for $\dot{x}_1$ and the steps are given below without further remarks.

$$\frac{\partial G}{\partial y_1} = \sum_i b_i \delta_{i1} - \sum_i \sum_j A_j K_{ji}^{-1} \left(\sum_r K_{ir} \delta_{r1}\right)/(B_i + \sum_r K_{ir} y_r),$$

$$\frac{\partial G}{\partial y_1} = b_1 - \sum_i \sum_j A_j K_{ji}^{-1} K_{i1}/(B_i + \sum_r K_{ir} y_r),$$

therefore,

$$\frac{\partial G}{\partial y_1} = -\dot{x}_1 . \tag{2.9}$$

Equations 2.8 and 2.9 represent the canonical equations of motion for the system whose conservative hamiltonian is given by equation 2.5.

LIOUVILLE'S THEOREM

The use of ensemble theory to discuss the statistical behavior of ecological nets was pioneered by Kerner (2–5). To a large extent this work, and that of Goodwin as well, derives from Kerner's analysis of the statistical mechanics appropriate to the equations suggested by Volterra for population dynamics. A necessary part of this procedure is a demonstration that the volume in phase is conserved, that is, that Liouville's Theorem is satisfied.

We define a 2N dimensional vector

$$\mathbf{v} \quad \begin{matrix} \\ \\ x_N \\ y_N \end{matrix} \tag{3.1}$$

and the matrix

$$\bar{\Gamma} \equiv \begin{bmatrix} 0 & -1 & 0 & \cdots & 0 \\ 1 & 0 & & & \\ 0 & & 0 & -1 & \\ \vdots & & 1 & 0 & \\ & & & & 0 \\ 0 & & \cdots & & 0 \end{bmatrix} . \tag{3.2}$$

In this notation the equations of motion become

$$\dot{v}_r = \Gamma_{rs} \frac{\partial G}{\partial v_s}, \tag{3.3}$$

and since G neither contains time explicitly nor depends on time (as insured by the canonical equations), then to satisfy Liouville's theorem we require that

$$\frac{\partial \dot{v}_r}{\partial v_r} = 0. \tag{3.4}$$

Thus

$$\frac{\partial \dot{v}_r}{\partial v_r} = \frac{\partial}{\partial v_r}\left(\Gamma_{rs} \frac{\partial G}{\partial v_s}\right),$$

$$\frac{\partial \dot{v}_r}{\partial v_r} = \Gamma_{rs} \frac{\partial^2 G}{\partial v_r \partial v_s},$$

and

$$\frac{\partial \dot{v}_r}{\partial v_r} = \sum_{r=1}^{2N} \left(\frac{\partial^2 G}{\partial v_{r+1} \partial v_r} - \frac{\partial^2 G}{\partial v_r \partial v_{r+1}}\right). \tag{3.5}$$

We conclude that the condition expressed in equation 3.4 is satisfied since each term in equation 3.5 is identically zero.

This result insures that the model expressed by equations 2.1 and 2.2 can be treated by the methods of ensemble theory. In order to compute quantities of interest, however, it is necessary first to find the normalization constant for this ensemble, that is, to compute the partition function. For typical cases of interest in physics the hamiltonian function can be written as

$$G(v_1, \cdots, v_{2N}) = \sum_{i=1}^{2N} G_i(v_i), \tag{3.6}$$

but inspection of equation 2.5 reveals a more complicated form for G, and as a result integrations over phase of a quantity such as exp $(-\beta G)$, where β is some constant, cannot be treated by a simple product decomposition. Nevertheless, in the next section it will be shown that the partition function, Z, can be written down explicitly after a suitable canonical transformation has been applied to G.

EVALUATION OF THE PARTITION FUNCTION

First consider a canonical transformation on G which separates the variables **x** and **y**, but retains the equations of motion. This is clearly a desirable step since it greatly facilitates evaluation of the partition function

$$Z = \int \cdots \int dx\, dy \exp\left[-\beta G(x, y)\right]. \tag{4.1}$$

For convenience we adopt a relabeling of the coordinates. Let us define a vector and matrix by analogy to equations 3.1 and 3.2 as follows:

$$\xi \equiv \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_N \\ y_1 \\ \vdots \\ y_N \end{bmatrix}, \qquad \tilde{\gamma} \equiv \left[\begin{array}{c|c} \bar{0} & -\bar{1} \\ \hline \bar{1} & \bar{0} \end{array}\right] \tag{4.2}$$

then the equations of motion can be written as

$$\dot{\xi}_r = \gamma_{rs}\left(\frac{\partial G}{\partial \xi_s}\right). \tag{4.3}$$

Now if we are given a coordinate transformation $\xi \rightarrow \mathfrak{n}$, the condition that this transformation be canonical is for the matrix

$$M_{\alpha\beta} \equiv \frac{\partial \xi_\alpha}{\partial \eta_\beta} \tag{4.4}$$

to satisfy the expression

$$\bar{M}^T \tilde{\gamma} \bar{M} = \tilde{\gamma}. \tag{4.5}$$

Choose the transformation

$$\mathfrak{n} \equiv \begin{bmatrix} H_1 \\ \vdots \\ H_N \\ \hline B_1 \\ \vdots \\ B_N \end{bmatrix} + \left[\begin{array}{c|c} \bar{K}^{T^{-1}} & \bar{0} \\ \hline \bar{0} & \bar{K} \end{array}\right] \xi \tag{4.6}$$

where K_{ij} and B_i are the coefficients contained in dynamical equations, and the vector H is arbitrary.

The inverse transformation is given by

$$\xi = \left[\begin{array}{c|c} \bar{K}^T & \bar{0} \\ \hline \bar{0} & \bar{K}^{-1} \end{array}\right] \left(\mathfrak{n} - \begin{bmatrix} H \\ \hline B \end{bmatrix}\right), \tag{4.7}$$

so that the matrix $\bar{M}$ is given as

$$\bar{M} \equiv \frac{\partial \xi}{\partial \mathfrak{n}} = \begin{bmatrix} \bar{K}^T & \bar{0} \\ \bar{0} & \bar{K}^{-1} \end{bmatrix}.$$

It then follows that

$$\bar{\mathbf{M}}^{\mathrm{T}}\bar{\gamma}\bar{\mathbf{M}} = \begin{bmatrix} \bar{\mathbf{K}} & \bar{0} \\ \bar{0} & \bar{\mathbf{K}}^{\mathrm{T}-1} \end{bmatrix} \begin{bmatrix} \bar{0} & -\bar{1} \\ \bar{1} & \bar{0} \end{bmatrix} \begin{bmatrix} \bar{\mathbf{K}}^{\mathrm{T}} & \bar{0} \\ \bar{0} & \bar{\mathbf{K}}^{-1} \end{bmatrix},$$

$$\bar{\mathbf{M}}^{\mathrm{T}}\bar{\gamma}\bar{\mathbf{M}} = \begin{bmatrix} \bar{\mathbf{K}} & \bar{0} \\ \bar{0} & \bar{\mathbf{K}}^{\mathrm{T}-1} \end{bmatrix} \begin{bmatrix} \bar{0} & -\bar{\mathbf{K}}^{-1} \\ \bar{\mathbf{K}}^{\mathrm{T}} & \bar{0} \end{bmatrix},$$

$$\bar{\mathbf{M}}^{\mathrm{T}}\bar{\gamma}\bar{\mathbf{M}} = \begin{bmatrix} \bar{0} & -\bar{1} \\ \bar{1} & \bar{0} \end{bmatrix} = \bar{\gamma},$$

demonstrating that the chosen transformation is canonical.

The notation can now be made more compact by employing the convenience

$$\mathbf{n} = \begin{bmatrix} \boldsymbol{x} \\ \boldsymbol{y} \end{bmatrix},$$

which permits the transformation to be written as

$$\boldsymbol{x} = \mathbf{H} + \bar{\mathbf{K}}^{\mathrm{T}-1}\mathbf{x} \Leftrightarrow \mathbf{x} = \bar{\mathbf{K}}^{\mathrm{T}}(\boldsymbol{x} - \mathbf{H})$$

$$\boldsymbol{y} = \mathbf{B} + \bar{\mathbf{K}}\mathbf{y} \Leftrightarrow \mathbf{y} = \bar{\mathbf{K}}^{-1}(\boldsymbol{y} - \mathbf{B})$$

and the transformed hamiltonian to take the form

$$\mathbf{G}(\boldsymbol{x},\boldsymbol{y}) = \tfrac{1}{2}(\boldsymbol{x}^{\mathrm{T}} - \mathbf{H}^{\mathrm{T}})\bar{\mathbf{K}}\bar{\mathbf{C}}\bar{\mathbf{K}}^{\mathrm{T}}(\boldsymbol{x} - \mathbf{H}) + \mathbf{b}^{\mathrm{T}}\bar{\mathbf{K}}^{-1}(\boldsymbol{y} - \mathbf{B}) - \mathbf{d}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}}(\boldsymbol{x} - \mathbf{H}) - \mathbf{A}^{\mathrm{T}}\bar{\mathbf{K}}^{-1} \ln \boldsymbol{y}, \quad (4.8)$$

which is to be compared with equation 2.5. Note well the distinction between $\boldsymbol{x}$ and $\mathbf{x}$ and between $\boldsymbol{y}$ and $\mathbf{y}$.

From the form of equation 4.8 it is clear that the partition function can be written as

$$Z = \int \cdots \int d\boldsymbol{x}_1 \cdots d\boldsymbol{x}_N \exp\left[-\beta\{\tfrac{1}{2}(\boldsymbol{x}^{\mathrm{T}} - \mathbf{H}^{\mathrm{T}})\bar{\mathbf{K}}\,\bar{\mathbf{C}}\,\bar{\mathbf{K}}^{\mathrm{T}}(\boldsymbol{x} - \mathbf{H}) - \mathbf{d}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}}(\boldsymbol{x} - \mathbf{H})\}\right] \times \int \cdots \int d\boldsymbol{y}_1 \cdots d\boldsymbol{y}_N \exp\left[-\beta\{\mathbf{b}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}}(\boldsymbol{y} - \mathbf{B}) - \mathbf{A}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}-1} \ln \mathbf{y}\}\right], \quad (4.9)$$

or $Z = Z_x Z_y$.

The choice of limits on these integrals is somewhat arbitrary, but for simplicity we have chosen $(0, \infty)$. Goodwin used a non-zero lower limit and the difference in results will be indicated in the derivation which follows. It is clear, however, that both

$(0, \infty)$ and $(p \neq 0, \infty)$ are oversimplifications of the physical situation, and a method for rectifying this shortcoming will be developed in a subsequent paper.

A final transformation is necessary for the complete separation of Z_x. The phase space is unaffected by a rotation $\bar{\Omega}$, and since $\bar{K}\bar{C}\bar{K}^T$ is symmetric, then it can be diagonalized by a rotation matrix, i.e., since $\bar{C}^T = \bar{C}$, then

$$(\bar{K}\bar{C}\bar{K}^T)^T = (\bar{K}\bar{C}^T\bar{K}^T) = (\bar{K}\bar{C}\bar{K}^T).$$

Consider a diagonal matrix $\bar{\Lambda}$ given by

$$\bar{\Lambda} \equiv \bar{\Omega}\bar{K}\bar{C}\bar{K}^T\bar{\Omega}^T \tag{4.10}$$

and let

$$\omega \equiv \bar{\Omega}x, \tag{4.11}$$

then

$$dx = (\det \bar{\Omega})\, d\omega = d\omega$$

and

$$x^T\bar{\Omega}^T\bar{\Omega}\bar{K}\bar{C}\bar{K}^T\bar{\Omega}^T\bar{\Omega}x = \omega^T\bar{\Lambda}\omega = \sum \omega_i^2\lambda_i .$$

The partition function Z_x can therefore be expressed successively as

$$Z_x = \int \cdots \int dx \exp [- \beta\{\tfrac{1}{2}\, x^T\bar{K}\bar{C}\bar{K}^T x - x^T\bar{K}\bar{C}\bar{K}^T H + \tfrac{1}{2}\, H^T\bar{K}\bar{C}\bar{K}^T H - d^T\bar{K}^T x + d^T\bar{K}^T H\}],$$

$$Z_x = \int \cdots \int d\omega \exp [- \beta\{\tfrac{1}{2}\, \omega^T\Lambda\omega - \omega^T\bar{\Omega}\bar{K}\bar{C}\bar{K}^T H + \tfrac{1}{2}\, H^T\bar{K}\bar{C}\bar{K}^T H - d^T\bar{K}^T\bar{\Omega}\omega + d^T\bar{K}^T H\}],$$

and

$$Z_x = \prod_{i=1}^{N} \int d\omega_i \exp [- \beta\{\tfrac{1}{2}\, x_i\, \omega_i^{\,2} - \omega_i [\Omega_{ij}\, k_{jl}\, C_{lm}\, K_{mn}{}^T H_n + \Omega_{ij}\, K_{jl}\, d_l]\}] \times \exp [- \beta\{\tfrac{1}{2}\, H^T\bar{K}\bar{C}\bar{K}^T H + d^T\bar{K}^T H\}].$$

Next we recall that the vector H was unspecified and can therefore so be chosen that terms linear in ω_i vanish. In particular,

$$\bar{C}\bar{K}^T H + d = 0$$

or

$$\mathbf{H} = -\bar{\mathbf{K}}^{\mathrm{T}^{-1}}\bar{\mathbf{C}}^{-1}\mathbf{d},$$

and upon evaluating the terms in the second exponential we find that

$$\mathbf{H}\bar{\mathbf{K}}\bar{\mathbf{C}}\bar{\mathbf{K}}^{\mathrm{T}}\mathbf{H} = \mathbf{d}^{\mathrm{T}}\bar{\mathbf{C}}^{-1}\bar{\mathbf{K}}^{-1}\bar{\mathbf{K}}\bar{\mathbf{C}}\bar{\mathbf{K}}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}^{-1}}\bar{\mathbf{C}}\mathbf{d} = \mathbf{d}^{\mathrm{T}}\bar{\mathbf{C}}^{-1}\mathbf{d}$$

and

$$\mathbf{d}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}}\mathbf{H} = -\mathbf{d}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}}\bar{\mathbf{K}}^{\mathrm{T}^{-1}}\bar{\mathbf{C}}^{-1}\mathbf{d} = -\mathbf{d}^{\mathrm{T}}\bar{\mathbf{C}}^{-1}\mathbf{d}.$$

Thus Z_x can be written as

$$Z_x = \prod_{i=1}^{N}\left(\frac{\pi}{2\beta\lambda_i}\right)^{1/2}\exp\left[\frac{\beta}{2}\mathbf{d}^{\mathrm{T}}\bar{\mathbf{C}}^{-1}\mathbf{d}\right]$$

or finally

$$Z_x = \exp\left[\frac{\beta}{2}\mathbf{d}^{\mathrm{T}}\bar{\mathbf{C}}^{-1}\mathbf{d}\right]\left(\frac{\pi}{2\beta}\right)^{N/2}(\det\bar{\Lambda})^{-1/2}. \tag{4.12}$$

Readers already familiar with the work of Goodwin will recognize that equation 4.12 is the generalization of the result presented in Goodwin's book (1) as equation 34. Apart from the generalization, the principal difference between the two results is the fact that our choice of a zero lower bound eliminates the need for the error function. Had we picked a nonzero lower bound our result would have contained a corresponding error function.

The evaluation of Z_y proceeds along similar lines, and we will present below the steps involved without additional comment.

$$Z_{y_i} = \int_0^\infty dy_i \exp\left[-\beta\{-\mathbf{b}^{\mathrm{T}}\bar{\mathbf{K}}^{-1}\mathbf{B} + b_j K_{ji}^{-1} y_i - A_j K_{ji}^{-1}\ln y_i\}\right],$$

$$Z_{y_i} = \exp\left[\beta\mathbf{b}^{\mathrm{T}}\mathbf{K}^{-1}\mathbf{B}\right] \times \int_0^\infty dy_i \exp\left[-\beta\{b_j K_{ji}^{-1} y_i\}\right] \times \exp\left[\beta\{A_j K_{ji}^{-1}\ln y_i\}\right]$$

Let

$$\zeta_i = \beta\left(\sum_j b_j K_{ji}^{-1}\right)y_i$$

so that

$$d y_i = d\zeta_i/\beta\left(\sum_j b_j K_{ji}^{-1}\right),$$

then

$$Z_{y_i} = \frac{\exp\,[\beta \mathbf{b}^T \bar{\mathbf{K}}^{-1} \mathbf{B}]}{\beta(\sum_j b_j K_{ji}^{-1})} \times \int_0^\infty d\zeta_i\, e^{-\zeta_i} \zeta_i^{\beta \sum_k (A_k K_{ki}^{-1})} [\beta \sum_j (b_j K_{ji}^{-1})]^{-\beta \sum_k (A_k K_{ki}^{-1})}.$$

Define

$$J_i \equiv 1 + \beta \sum_k (A_k K_{ji}^{-1}),$$

then

$$Z_{y_i} = \frac{\exp\,[\beta \mathbf{b}^T \bar{\mathbf{K}}^{-1} \mathbf{B}]}{(\beta \sum_j b_j K_{ji}^{-1})^{J_i}} \int d\zeta_i\, e^{-\zeta_i} \zeta_i^{J_i - 1}$$

or

$$Z_{y_i} = \frac{\exp\,[\beta \mathbf{b}^T \bar{\mathbf{K}}^{-1} \mathbf{B}]}{(\beta \sum_j b_j K_{ji}^{-1})^{J_i}}\ \Gamma(J_i)$$

so that, finally, the y-component of the partition function becomes

$$Z_y = \exp\,[\beta \mathbf{b}^T \bar{\mathbf{K}}^{-1} \mathbf{B}] \prod_i \Gamma(J_i)\, (\beta \sum_j b_j K_{ji}^{-1})^{-J_i}. \qquad (4.13)$$

Once again we may compare this result to the corresponding one in Goodwin (1), viz. equation 35, and we remark that had we chosen a finite lower bound, then Z_y would contain the incomplete gamma function instead of the ordinary gamma function as above.

To illustrate the use of Z for the calculation of "talandic" properties of the system, we pick the quantity which in this case plays the role of the energy, namely the mean value of G.

It is clear on very general grounds that $\langle G \rangle$ is given by

$$\langle G \rangle = -\frac{\partial}{\partial \beta} \ln Z$$

and the differentiation of ln Z is without complications. The result is

$$\begin{aligned} \langle G \rangle = &- N \{ \tfrac{1}{2}\, \mathbf{d}^T \bar{C}^{-1} \mathbf{d} + \mathbf{b}^T \bar{K} B \} + 3/2 \frac{N}{\beta} \\ &+ \ln \beta \sum_i \sum_k A_k K_{ki}^{-1} + \sum_i \sum_k A_k K_{ki}^{-1} (\ln \sum_j b_j K_{ji}^{-1} + 1) \\ &- \sum_i \sum_k A_k K_{ki}^{-1} \Psi(1 + \beta \sum_k A_k K_{ki}^{-1}) \qquad (4.14) \end{aligned}$$

where Ψ represents the logarithmic derivative of the gamma function, the so-called "digamma function".

The dependence of $\langle G \rangle$ on β, that is, of energy on temperature, is seen to be far richer in this case than the more traditional dynamics of statistical mechanics. In addition to the expected term in β^{-1}, there are terms in β^0, ln β and the implicit dependence in Ψ. The interpretation of this structure is a formidable problem in cellular physiology and has at its roots the appropriateness of the model chosen for the strong interactions.

Additional quantities of thermodynamic interest can be calculated and compared with the more restricted case described by Goodwin, but there does not seem to be any advantage in exhibiting these relations here. Suffice it to say, that in each case the generalization is without complication and reveals in a natural manner the extension accomplished.

ADDITIONAL REMARKS

The implications of this extension seem reasonably clear and our attention has become focused on a class of problems deriving directly from it. We shall report here only briefly on two further and forthcoming developments.

The time scale of interest in this work is that of the epigenetic system. It has seemed reasonable, therefore, to consider the situation where a given set of rate constants (e.g. K_{ij} or A_i) is of comparable value and then to characterize these constants by a distribution with a mean value and some appropriate fluctuation. This leads to a reduction from N numbers to two for any given set, and greatly simplifies attempts to connect the predictions of such a theory with experiment.

A second extension of the theory is concerned with the infinite limits of integration in the evaluation of the partition function. Clearly, arbitrary and unrestricted amounts of chemical species from a fixed minimum to infinity can not be physically justified within the context of a finite cell. We have adopted, therefore, a technique developed in statistical mechanics and employed, for example, in connection with what is there called the "spherical model". We introduce, analytically, the restriction that the sum of all molecules of all species be equal to some large fixed number, N in this case. The resulting partition function then represents a situation which more closely conforms to the biological situation of a finite cell with finite limits to the population of functional biopolymers.

We are indebted to Professor Walter M. Elsasser for some initial support provided through him from an ONR contract.

Dr. De Rocco is thankful to Dr. Martin A. Garstens for calling the work of Goodwin and the general question of temporal organization to his attention.

Mr. Woolley is a Predoctoral Fellow at the Center for Theoretical Physics, University of Maryland.
Dr. De Rocco's permanent address is the Institute for Molecular Physics, University of Maryland, College Park, Maryland 20742.

Received for publication 1 August 1969.

REFERENCES

1. GOODWIN, B. C. 1963. Temporal Organization in Cells. Academic Press, Inc., New York.
2. KERNER, E. H. 1962. *Ann. N. Y. Acad. Sci.* **96**:975.
3. KERNER, E. H. 1959. *Bull. Math. Biophys.* **21**:217.
4. KERNER, E. H. 1961. *Bull. Math. Biophys.* **23**:141.
5. KERNER, E. H. 1964. *Bull. Math. Biophys.* **26**:333.