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Thermodynamic Potentials and Evolution Towards the Stationary State in Open Systems of Far-from-Equilibrium Chemical Reactions: The Affinity Squared Minimum Function.

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ABSTRACT

The "evolutionary" characteristics of several quadratic functions (based both on the affinities and on the reaction velocities), and of the entropy production per unit time, have been studied for a number of 2-variable open systems of far-from-equilibrium chemical reactions. The first and second order systems were chosen to include: straight line, loop (network), autocatalytic and disproportionate kinetic features. All of the functions examined are closely related in form to the entropy production though they differ qualitatively and quantitatively in the non-linear domain. By a combination of analytical and computational methods one function, called $\mathcal{H}$, is seen to have the variational properties of a "thermodynamic potential" for all of the systems, relative to their non-equilibrium stationary states. The "homeostatic-like" stability criterion, $\frac{d\mathcal{H}}{dt} \leq 0$ is also seen to hold for these systems. The function, a composite property of the system, may be interpreted as a "kinetically-weighted system-free-energy" quantity, which would tend to be minimized during the evolution, in configuration and in time space, of a constrained biochemical system.

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I. INTRODUCTION

Evolutionary principles have long excited the physical and biological scientist alike. As noted by Katchalsky and Curran:

"The attempts to discover a universal physical principle underlying the phenomenon of life bring to mind the older attempts of scientists of the 18th Century to show that all mechanical and optical phenomena could be founded in variational principles. Thus the great principle of least action governing the natural mechanical paths and the Fermat principle of least time for optical tracks served scientists and philosophers as an outstanding demonstration of a mathematical structure of the universe."⁶

A physical evolutionary principle much discussed in the past vis a vis the development of life is the second law of thermodynamics. If the modern biophysicist need no longer be concerned about likely contradictions with biogenesis and spontaneous development of complex living systems, nevertheless as a "variational principle" or "potential theory" description of non-equilibrium evolutionary processes in biology, the second law by itself is of no direct use.

One such evolutionary process is the evolution of open systems of chemical reactions towards their particular non-equilibrium stationary states, whose "locations" are determined by the applicable constraints (i.e. by the fixed-out-of-equilibrium concentrations of certain of the reactants and products). A major contribution to such variational and potential theory studies was Prigogine's demonstration that the entropy production per unit time, $\mathcal{P}$, (or alternatively the dissipation function, $T\mathcal{P}$) had a minimum value in the non-equilibrium stationary state, provided the properties of the system were: (a) linear phenomenological laws

between forces and fluxes; (b) constant coefficients in the laws; (c) Onsager relations holding for the off-diagonal coefficients.¹³ Under these conditions, then, the state function $\mathcal{P}$ serves as a thermodynamic potential for the pre-steady state evolution of the system, therefore again in the words of Katchalsky and Curran, "has many characteristics in common with the great principles of the 18th Century." As is well known however, the implications of these conditions, that the entire evolution of the system as well as its stationary state must lie within the near-equilibrium domain, is severely restrictive for chemical reaction systems. An interesting discussion of the domain of validity of the minimum theorem has been given by Klein.⁷

Because of the great interest in working with far-from-equilibrium[†] (i.e. "non linear") systems Glansdorff and Prigogine among others^{4,14} investigated possible extensions of these concepts to the domain of non-linear rate laws, and in so doing were able to demonstrate certain inequalities such as:

$$T d_x \mathcal{P} = \sum_i v_i d \mathcal{R}_i \leq 0, \quad (1)$$

(where the v_i and $\mathcal{R}_i$ are respectively the reaction velocities and affinities, defined precisely in the next section).

Prigogine describes the general expression of this kind as a "universal evolution criterion," though as he points out, since the left side of equation (1) is only half of the total differential of the dissipation function $T\mathcal{P}$ (and itself not a perfect differential), $d_x \mathcal{P}$ can serve in general only as a "local potential" rather than as a general potential in the usual sense.¹⁴ (A recent novel (topological) approach to several aspects of non linear thermodynamics based on use of Tellegen's Theorem, includes a different derivation of inequalities such as equation (1).^{9,10}) Finlayson and Scriven² have presented a detailed theoretical treatment of variational principles applicable to non-linear systems in general. They express a somewhat critical view toward incomplete-differential types of variational principles.

In this paper we analyze the variational and evolutionary properties of several quadratic functions plus the entropy production, $\mathcal{P}$. The analysis is carried out by both analytical and computational methods on a number of sequence-systems of far-from-equilibrium chemical reactions

[†] By this term we imply the usual restrictions that the instantaneous values of concentrations, chemical potentials, etc., are still definable.

all having time-independent stationary states, and chosen to be representative of a wide variety of different chemical kinetics. (That stationary states of this kind, akin to biological homeostatic states, are not necessarily incompatible with oscillations, is pointed out in a later section.) One of these functions, called the Affinity Squared Minimum function, $\mathcal{M}$, is seen to possess the formal properties required for a thermodynamic potential function for the far-from-equilibrium stationary state, to be a state function, and to possess other useful properties as well. It may thus be considered of special interest.

II. FUNCTIONS AND SYSTEMS

The Affinity Squared Minimum function, $\mathcal{M}$, is defined for a system of i chemical reactions as follows:

$$T\mathcal{M} \equiv \sum_i \alpha_i \mathcal{A}_i^2 \quad (2)$$

$\mathcal{A}_i$ is the affinity of reaction i , $= -\sum_r \nu_r \mu_r$ where the ν_r and μ_r are the respective stoichiometric coefficients and chemical potentials for the reactants in each reaction i . For the purposes of this paper, only ideal affinities will be considered. The α_i are constants, to be specified in the next section.

Two quadratic functions of the velocities are also examined, both having the form:

$$T \langle v^2 \rangle = \sum_i \beta_i v_i^2 \quad (3)$$

The choices of the constants β_i are also given in the next section. The reaction velocities, v_i , are defined in the usual way as $\equiv \frac{d\xi_i}{dt} = \frac{1}{\nu_r} \cdot \frac{dn_r}{dt}$ for each individual reaction in the system, with the n_r being the number of moles of each component r involved in that reaction. For simplicity we consider herein only constant temperature systems with the n_r equivalent to the concentrations of the individual components.

Our final comparison function is the well known entropy production per unit time, $\mathcal{P} = \frac{diS}{dt}$, defined by the equation:

$$T\mathcal{P} = \sum_i v_i \mathcal{A}_i \quad (4)$$

To study and compare the properties of these functions, seven two-

variable, multi-reaction-pathway systems were selected to be broadly representative of elementary-reaction-step kinetic sequences. These are summarized in Table 1 (systems I through IVb). For all of these, the concentrations of intermediate species x and y are allowed to evolve from arbitrary initial values to their final non-equilibrium stationary state values, in accordance with the individual kinetics shown for each system. All systems are constrained out of equilibrium by (variously) fixing the concentrations of A and B away from their equilibrium ratios, taken here to be = 1. A single 1-variable system (V) was also included in Table 1 for reasons explained in the next section.

III. COMPARISON OF MINIMUM AND STATIONARY STATE CONDITIONS

In this section we examine the variational properties of $\mathcal{H}$ and the two "velocity squared" functions, complete their definitions, and compare these functions with each other (and with $\mathcal{P}$), to assess their relative qualifications as thermodynamic potentials for far-from-equilibrium chemical reaction systems.

The Affinity Squared function, $\mathcal{H}$.

Having restricted ourselves here to reaction systems involving no more than two concentration variables, the condition for an extremal value of the function $\mathcal{H}$ (or, more conveniently, of $T\mathcal{H}$) is:

$$\frac{\partial(T\mathcal{H})}{\partial x} = 0, \quad \frac{\partial(T\mathcal{H})}{\partial y} = 0. \quad (5)$$

From equation (2):

$$\frac{\partial(T\mathcal{H})}{\partial x} = 2 \sum_i \alpha_i \mathcal{A}_i \frac{\partial \mathcal{A}_i}{\partial x}, \quad (6)$$

$$\frac{\partial(T\mathcal{H})}{\partial y} = 2 \sum_i \alpha_i \mathcal{A}_i \frac{\partial \mathcal{A}_i}{\partial y}. \quad (7)$$

Using the ideal affinities (Table 2) expressions (6) and (7) are evaluated and tabulated in columns 6 and 7 of Table 2, for all of the kinetic systems given in Table 1. These columns can be combined and summarized for all systems by the two expressions:

$$\frac{\partial(T\mathcal{H})}{\partial x} = 2 \frac{\partial \mathcal{A}_1}{\partial x} [\alpha_1 \mathcal{A}_1 - \alpha_2 \mathcal{A}_2 \quad (-\alpha_4 \mathcal{A}_4)] \quad (8)$$

Table 1. Summary of Kinetic Systems.^a

Description		Pathways	Kinetics				
			v_1	v_2	v_3	v_4	v_5
Basic System	I Straight Line, First Order	$A \xrightarrow{1} x \xrightarrow{2} y \xrightarrow{3} B$	$A-x$	$x-y$	$y-B$		
	IIa 1-Loop First Order	$A \xrightarrow{1} x \xrightarrow{2} y \xrightarrow{3} B$ $x \xrightarrow{4} y$	$A-x$	$x-y$	$y-B$	$x-B$	
Networks	IIb 1-Loop First Order	$A \xrightarrow{1} x \xrightarrow{2} y \xrightarrow{3} B$ $x \xrightarrow{5} A$	$A-x$	$x-y$	$y-b$		$A-y$
	IIc 2-Loop First Order	$A \xrightarrow{1} x \xrightarrow{2} y \xrightarrow{3} B$ $x \xrightarrow{4} y$ $x \xrightarrow{5} A$	$A-x$	$x-y$	$y-B$	$x-B$	$A-y$
Autocatalytic	III Straight Line, 1-Step Autocatalytic	$A \xrightarrow{1} x \xrightarrow{2} y \xrightarrow{3} B$	$A-x$	$xy-y^2$	$y-B$		
Disproportionate	IVa Straight Line, Disproportionate (1-Step Second Order)	$2A \xrightarrow{1} 2x \xrightarrow{2} y \xrightarrow{3} B$	$\frac{A-x}{2}$	x^2-y	$y-B$		
	IVb Straight Line, Disproportionate (2-Step Second Order)	$2A \xrightarrow{1} 2x \xrightarrow{2} y \xrightarrow{3} B$	A^2-x^2	x^2-y	$y-B$		
1-Variable Autocatalytic	V Straight Line, 1-Step Autocatalytic	$A \xrightarrow{1} x \xrightarrow{2} B$	$Ax-x^2$	$x-B$			

a) For simplicity all forward and reverse rate constants are taken = 1, $\therefore$ all equilibrium constants = 1; rates are chosen positive from left to right.

Table 2. Affinities and Differential Functions Applicable to
Kinetic Systems of Table 1.^a

	$\frac{A_1}{RT}$	$\frac{A_2}{RT}$	$\frac{A_3}{RT}$	$\frac{A_4}{RT}$	$\frac{A_5}{RT}$	$\left(\frac{1}{2} \frac{\partial A_1}{\partial x}\right) \frac{\partial(TA)}{\partial x}$	$\left(\frac{1}{2} \frac{\partial A_2}{\partial y}\right) \frac{\partial(TA)}{\partial y}$	$\frac{dx}{dt}$	$\frac{dy}{dt}$
I & III	$\ln \frac{A}{x}$	$\ln \frac{x}{y}$	$\ln \frac{y}{B}$			$\alpha_1 A_1 - \alpha_2 A_2$	$\alpha_2 A_2 - \alpha_3 A_3$	$v_1 - v_2$	$v_2 - v_3$
IIa	$\ln \frac{A}{x}$	$\ln \frac{x}{y}$	$\ln \frac{y}{B}$	$\ln \frac{x}{B}$		$\alpha_1 A_1 - \alpha_2 A_2 - \alpha_4 A_4$	$\alpha_2 A_2 - \alpha_3 A_3$	$v_1 - v_2 - v_4$	$v_2 - v_3$
IIb	$\ln \frac{A}{x}$	$\ln \frac{x}{y}$	$\ln \frac{y}{B}$		$\ln \frac{A}{y}$	$\alpha_1 A_1 - \alpha_2 A_2$	$\alpha_2 A_2 - \alpha_3 A_3 + \alpha_5 A_5$	$v_1 - v_2$	$v_2 - v_3 + v_5$
IIc	$\ln \frac{A}{x}$	$\ln \frac{x}{y}$	$\ln \frac{y}{B}$	$\ln \frac{x}{B}$	$\ln \frac{A}{y}$	$\alpha_1 A_1 - \alpha_2 A_2 - \alpha_4 A_4$	$\alpha_2 A_2 - \alpha_3 A_3 + \alpha_5 A_5$	$v_1 - v_2 - v_4$	$v_2 - v_3 + v_5$
IVa & IVb	$\ln \frac{A^2}{x^2}$	$\ln \frac{x^2}{y}$	$\ln \frac{y}{B}$			$\alpha_1 A_1 - \alpha_2 A_2$	$\alpha_2 A_2 - \alpha_3 A_3$	$2(v_1 - v_2)$	$v_2 - v_3$
V	$\ln \frac{A}{x}$	$\ln \frac{x}{B}$				$\alpha_1 A_1 - \alpha_2 A_2$	$\alpha_2 A_2 - \alpha_3 A_3$	$v_1 - v_2$	

a) $\alpha_1 = \frac{v_1^{st}}{A_1^{st}}$

$$\frac{\partial(T\mathcal{H})}{\partial y} = 2 \frac{\partial \mathcal{H}_2}{\partial y} [\alpha_2 \mathcal{H}_2 - \alpha_3 \mathcal{H}_3 (+\alpha_5 \mathcal{H}_5)] \quad (9)$$

The last parenthetical term in each expression applies only when chemical reaction pathways 4 and 5 exist, i.e. for the three systems II (Tables 1 and 2). The essential feature that permits this simple form for (8) and (9) is the validity of the relations:

$$\frac{\partial \mathcal{H}_1}{\partial x} = - \frac{\partial \mathcal{H}_2}{\partial x} \quad \left(= - \frac{\partial \mathcal{H}_4}{\partial x} \right) \quad (10)$$

$$\frac{\partial \mathcal{H}_2}{\partial y} = - \frac{\partial \mathcal{H}_3}{\partial y} \quad \left(= + \frac{\partial \mathcal{H}_5}{\partial y} \right) , \quad (11)$$

Relations such as (10) and (11) are quite general. However, for these (or for similar relations in other networks) to hold it is necessary that the reaction scheme be written with the stoichiometries of the successive steps appearing in a self-consistent form, providing a smooth flow of initial reactant(s) to final product(s) through the various intermediates, as for example in our systems IVa and IVb.

In the final two columns of Table 2 are given the individual forms for $\frac{dx}{dt}$ and $\frac{dy}{dt}$, available from inspection of Table 1. Following the same parenthetical convention these can be summarized, for systems I, IIa,b,c and III:

$$\frac{dx}{dt} = v_1 - v_2 \quad (-v_4) \quad (12)$$

$$\frac{dy}{dt} = v_2 - v_3 \quad (+v_5) , \quad (13)$$

and for systems IVa and IVb:

$$\frac{dx}{dt} = 2(v_1 - v_2) \quad (14)$$

$$\frac{dy}{dt} = v_2 - v_3 \quad (15)$$

If $\mathcal{H}$ is to be a thermodynamic potential and therefore have an extremum at the (far-from-equilibrium) stationary state, it is necessary (though not sufficient) that the vanishing of expressions (8) and (9) exactly coincide with the corresponding kinetic statement of the stationary state - i.e. the vanishing of the appropriate matching expressions (12) through (15). Since $\frac{\partial \mathcal{H}_1}{\partial x}$ and $\frac{\partial \mathcal{H}_2}{\partial y}$ are non-zero for all finite concentrations

of x and y , this requires that in every case:

$$[\alpha_1 \mathcal{A}_1 - \alpha_2 \mathcal{A}_2 (-\alpha_4 \mathcal{A}_4)]^{st} = 0 \iff [v_1 - v_2 (-v_4)]^{st} = 0 \quad (16)$$

$$[\alpha_2 \mathcal{A}_2 - \alpha_3 \mathcal{A}_3 (+\alpha_5 \mathcal{A}_5)]^{st} = 0 \iff [v_2 - v_3 (+v_5)]^{st} = 0 \quad (17)$$

The most obvious and simplest choice of α_i to meet this requirement is the choice:

$$\alpha_i \equiv \frac{v_i^{st}}{\mathcal{A}_i^{st}}, \quad (18)$$

which makes the bracketed left hand expressions in (16) and (17) identically equal to the right hand expressions.

This together with (2) completes our definition of the Affinity Squared Minimum function:

$$T\mathcal{M} \equiv \sum_i \left(\frac{v_i^{st}}{\mathcal{A}_i^{st}} \right) \mathcal{A}_i^2, \quad (19)$$

though some of its properties remain to be demonstrated. To anticipate, the subsequent analysis of the velocity squared functions, however, another possible choice of α_i will be considered briefly:

$$\alpha_i = 1 \quad (20)$$

From inspection of (16) and (17) it is seen that expressions like:

$$\mathcal{A}_1^{st} - \mathcal{A}_2^{st} (-\mathcal{A}_4^{st}) = 0 \text{ and } \mathcal{A}_2^{st} - \mathcal{A}_3^{st} (+\mathcal{A}_5^{st}) = 0 \quad (21)$$

do not generally hold for systems constrained out of equilibrium, so a quadratic form in affinities based on (20) is of no interest for our purposes and will not be further discussed here.

A useful property of $\mathcal{M}$, the identity of $\mathcal{M}^{st}$ with $\mathcal{P}^{st}$, is immediately evident from (19) and (4), whereby:

$$T\mathcal{M}^{st} = \sum_i v_i^{st} \mathcal{A}_i^{st} = T\mathcal{P}^{st}. \quad (22)$$

From (22) and the form of (2), $\mathcal{M}$ and $\mathcal{P}$ are seen to be closely related functions and in fact to have the same units. However, under far-from-equilibrium conditions, they differ both qualitatively and quantitatively. (In near-equilibrium (but non-equilibrium) situations, $\mathcal{M}$ and $\mathcal{P}$ will

again become equal for all reaction sequences with their elementary reaction steps written in phenomenologically uncoupled form.) Because of the positive definite nature of ρ , from (22) we can write:

$$T\mathcal{H}^{st} = \sum_i \alpha_i (\mathcal{A}_i^{st})^2 \geq 0 \quad (23)$$

which permits us to write (by the rules of positive definite quadratic forms):

$$\alpha_i > 0 \quad (24)$$

Therefore the $\mathcal{H}$ function itself must also have the property:

$$T\mathcal{H} = \sum_i \left(\frac{v_i^{st}}{\mathcal{A}_i^{st}} \right) \mathcal{A}_i^2 \geq 0, \quad (25)$$

(where the equality applies to equilibrium).

Thus the extremal of $\mathcal{H}$ in the far-from-equilibrium stationary state given by (16), (17) and (18), is in fact a minimum, hence the name Affinity Squared Minimum function.[‡]

Verification of $\mathcal{H}$'s state function character reveals a point of interest. Calculation of the cross derivative terms from Table 2, columns 6 and 7, gives the result (for all 7 systems):

$$\frac{\partial}{\partial y} \left(\frac{\partial(T\mathcal{H})}{\partial x} \right) = -2\alpha_2 \frac{\partial \mathcal{A}_1}{\partial x} \cdot \frac{\partial \mathcal{A}_2}{\partial y} \quad (26)$$

$$\frac{\partial}{\partial x} \left(\frac{\partial(T\mathcal{H})}{\partial y} \right) = 2\alpha_2 \frac{\partial \mathcal{A}_2}{\partial x} \cdot \frac{\partial \mathcal{A}_2}{\partial y} \quad (27)$$

The identity of (26) and (27) [and hence satisfaction of the Cauchy conditions for a perfect differential] is again seen to reside in (10).

The Velocity Squared functions.

In a search for thermodynamic potentials, the form of (3) most closely corresponding to (19) seems an obvious candidate. Indeed if we write:

$$T\langle v^2 \rangle_{11}^{st} = \sum_i \left(\frac{\mathcal{A}_i^{st}}{v_i^{st}} \right) v_i^2, \quad (28)$$

we note immediately, analogously to (22):

$$T\langle v^2 \rangle_{11}^{st} = \sum_i \mathcal{A}_i^{st} v_i^{st} = T\rho^{st}. \quad (29)$$

[‡] Footnote - see p. 9a.

Footnote - see p. 9a.

* Footnote (for p. 9)

Although the above variational calculation would have been slightly simpler considering the affinities as the independent variable, for convenience, e.g. in comparisons with other functions, it was carried out with respect to the concentrations. At least for all the kinetic systems treated in this paper, the assured minimum in affinity space assures a minimum in concentration space.

However, for none of the systems we are studying does the function $\langle v^2 \rangle_1$, have an extremal in the stationary state. This is readily seen by computing, from Table 1, the x- and y-partial derivatives of this function as we did for $\mathcal{M}$ in (8) and (9). In each case, these partial derivatives are found to be of the form of expression (21) (or slightly more complex expressions involving the stationary affinities) which will not generally vanish in the stationary state.

In attempting to make a more successful choice of β_i for $\langle v^2 \rangle$ in (3), we can carry through the analogous extremal—stationary state correspondence procedure, for this function, that gave us (16), (17) and (18) for the Affinity Squared function. If we do, we find that by choosing all $\beta_i = 1$, we can write for systems I, IIa,b,c and IVb:

$$\begin{aligned} \frac{\partial T \langle v^2 \rangle_2}{\partial x} &= -2[v_1 - v_2 (-v_4)] \\ \frac{\partial T \langle v^2 \rangle_2}{\partial y} &= -2[v_2 - v_3 (+v_5)] , \end{aligned} \quad (30)$$

which clearly do vanish in the respective stationary states. However, for systems III and IVa, the two partial derivatives do not similarly vanish. For example, for III:

$$\begin{aligned} \frac{\partial T \langle v^2 \rangle_2}{\partial x} &= -2[v_1 - yv_2] \\ \frac{\partial T \langle v^2 \rangle_2}{\partial y} &= -2[-(x-2y)v_2 - v_3] , \end{aligned} \quad (31)$$

and these do not have as roots the stationary values of x, y, v_1 , v_2 and v_3 , computed from Tables 1 and 2.

Entropy Production.

Though ρ is known analytically not to be a true thermodynamic potential except in the near-equilibrium configuration, it is interesting to examine quantitatively its "deviation" from such character as the system becomes increasingly constrained away from equilibrium (as done by Klein for his 1-variable photo-induced excitation process⁷). Computer calculations were made of $\rho^{\min}/\rho^{\text{st}}$ for all seven 2-variable systems as a function of out-of-equilibrium constraint. The results plotted in

Fig. 1 indicate that only for system IVa does ρ reasonably well approximate a potential function, as the constraint increases.

For comparison, similarly calculated ratios are included in Fig. 1 for $\langle v^2 \rangle_2$ (all systems) and $\langle v^2 \rangle_1$ (system III). As a check on the program, $\mathcal{N}^{\min}/\mathcal{N}^{\text{st}}$ was also computed for all systems and found to be equal to $1.0000 \pm < 0.0001$. As must be the case, for $B/A \rightarrow 1$ (equilibrium), any of the functions may serve satisfactorily as a thermodynamic potential. The "failures" for $\langle v^2 \rangle_2$ and $\langle v^2 \rangle_1$ in the autocatalytic and disproportionate systems are seen to be greater than those for ρ over the entire range of constraints plotted. (The associated failures for the concentration coordinates are much less.)

A geometrical representation of the variational qualities of $\mathcal{N}$ and ρ in 3-space is given in Fig. 2. As noted in Fig. 1, the relationship between the minima of the two functions, $\rho^{\min} < \mathcal{N}^{\min}$, was also found for all the other systems studied.

IV. TIME DEPENDENT PROPERTIES

Sign of $\frac{d\mathcal{N}}{dt}$.

Closely associated in interest with the variational properties of a thermodynamic potential in concentration space are its time-dependent properties; knowledge of the time derivative of any such function is useful in considering the time-evolution of a system as well as the stability of its stationary state. Ideally one would like a simple analytical expression for the time derivative with a readily determinable sign such as is often available for $\frac{d\rho}{dt}$ near equilibrium. For the 2-variable kinetic systems of Tables 1 and 2, no such simple form is available. For this reason we have included the single 1-variable system in the tables — system V. (For this autocatalytic 2-reaction system it is readily verified by the methods of the previous sections that the same qualitative conclusions hold, as were valid for the autocatalytic 3-step system III: $\mathcal{N}$ has a minimum in the stationary state, but both "velocity potential" functions $\langle v^2 \rangle$ fail in this regard.) We will now demonstrate "analytically" that for system V, for all values of x :

$$\frac{d\mathcal{N}}{dt} \leq 0, \quad (32)$$

(with the equality being valid only for the stationary state). Expanding the left side of (32):

$$\frac{d\mathcal{H}}{dt} = \frac{d\mathcal{H}}{dx} \cdot \frac{dx}{dt} \quad (33)$$

Following Table 2 and rearranging slightly, (33) becomes:

$$\frac{d\mathcal{H}}{dt} = \frac{2}{T} \frac{\partial \mathcal{H}_1}{\partial x} (v^{st}) \left(\frac{\mathcal{H}_1}{\mathcal{H}_1^{st}} - \frac{\mathcal{H}_2}{\mathcal{H}_2^{st}} \right) (v_1 - v_2), \text{ or,} \quad (34)$$

$$\frac{d\mathcal{H}}{dt} = \frac{-2R}{x} (x^{st} - B) \left(\frac{\ln \frac{A}{x}}{\ln \frac{A}{x^{st}}} - \frac{\ln \frac{x}{B}}{\ln \frac{x^{st}}{B}} \right) (v_1 - v_2). \quad (35)$$

To evaluate the sign of $\frac{d\mathcal{H}}{dt}$ in (35) under all possible conditions, we first summarize some useful interrelationships between x , x^{st} , A and B .

(a) The stationary value of the intermediate species x must lie within the range of B to A , (except for equilibrium where $A = B = x^{st}$). That is:

$$B > x^{st} > A, \text{ or} \quad (36)$$

$$A > x^{st} > B \quad (37)$$

These relations can be verified by forming the two differences ($x^{st} - A$) and ($x^{st} - B$), using the value for x^{st} (calculated from Tables 2 and 1):

$$x^{st} = \frac{(A-1) + \sqrt{(A-1)^2 + 4B}}{2}, \quad (38)$$

and noting that for these differences to be positive, $B-A > 0$ or $A-B > 0$, respectively, and vice versa.

$$\begin{aligned} \text{(b) If } x > x^{st}, \text{ then } v_1 - v_2 < 0, \\ \text{If } x < x^{st}, \text{ then } v_1 - v_2 > 0, \end{aligned} \quad (39)$$

where (from Table 1):

$$v_1 - v_2 = -x^2 + (A - 1)x + B. \quad (40)$$

Relations (39) are proved by forming the difference $(x - x^{st})$ using (38), and noting that for it to be positive (or negative) requires (40) to be respectively negative (or positive).

We are now in a position to examine the signs of (35) for the 12

possible relative configurations of x , (six for condition (36) and six for (37)). Without loss of generality this analysis will be carried out only for the cases corresponding to (36). These six cases are (we exclude the trivial case of $x = x^{st}$ where $\frac{d\mathcal{H}}{dt} = 0$):

$$x > B > x^{st} > A \quad (41)$$

$$x = B > x^{st} > A \quad (42)$$

$$B > x > x^{st} > A \quad (43)$$

$$B > x^{st} > x > A \quad (44)$$

$$B > x^{st} > A = x \quad (45)$$

$$B > x^{st} > A > x \quad (46)$$

The signs of the terms $(B - x^{st})$ and $(v_1 - v_2)$ are immediately obvious from (41) through (46) and from (39), respectively, and are entered accordingly in columns i) and j) of Table 3. For cases (41), (42), (45) and (46) the signs of the individual logarithms in (35) combine to give a unique sign for the total logarithmic term, as indicated in columns a) through f) and h) of Table 3. For cases (43) and (44) it is useful to recast the logarithmic term of (35) into the form:

$$\frac{\ln \frac{A}{x} \cdot \ln \frac{x^{st}}{B} - \ln \frac{x}{B} \cdot \ln \frac{A}{x^{st}}}{\ln \frac{A}{x^{st}} \cdot \ln \frac{x^{st}}{B}} \quad (47)$$

For both (43) and (44) the denominator of (47) is positive so the sign of (47) is determined by the relative magnitudes of the two products in the numerator. For (43), each term in the first product is larger in magnitude than the corresponding term in the second product, while for (44) the reverse is true, permitting us uniquely to complete columns g) and h) for (43) and (44). The product of the 3 signs in columns h), i) and j) with the intrinsic negative sign of the coefficient in eq. (35), $(-\frac{2R}{x})$, gives us the final result (Column k) that eq. (32) holds for all cases. This same result can easily be verified for the remaining 6 cases, analogous to (41) through (46), but subject to inequality (37) rather than (36).

Lacking similar simple analytical expressions for $\frac{d\mathcal{H}}{dt}$ analogous to (35) and (47) for the seven more complex 2-variable reaction sequences of

Table 3. The sign of $\frac{d\mathcal{H}}{dt}$ for system V. The signs indicated
refer to the specified sections of (35) & (47).

Case	a $\ln \frac{A}{x}$	b $\ln \frac{A}{x^{st}}$	c a/b	d $\ln \frac{x}{b}$	e $\ln \frac{x^{st}}{B}$	f d/e	g ae-bd	h* ln terms	i $B-x^{st}$	j v_1-v_2	k $\frac{d\mathcal{H}}{dt}$
eq. (41)	-	-	+	+	-	-		+	-	-	-
(42)	-	-	+	0	-	0		+	-	-	-
(43)	-	-	+	-	-	+	+	+	-	-	-
(44)	-	-	+	-	-	+	-	-	-	+	-
(45)	0	-	0	-	-	+		-	-	+	-
(46)	+	-	-	-	-	+		-	-	+	-

* Column h = columns c-f or g/be

Tables 1 and 2, a computer scan was made. For each system, $\frac{d\mathcal{H}}{dt}$ was calculated and tested for negative definiteness over a 10×10 matrix of concentration coordinates, again restricting the analysis to the domain of (36) but including x values in all of the ranges covered by (41) through (46). (For network system IIc where $x^{st} = y^{st}$, a zero divided by zero value made two of the six terms incalculable. In this case, x^{st} was perturbed slightly to $y^{st} - 0.00001$.) The calculations were carried out for the non-equilibrium constraint of $B/A = 10$. In every case, the result was $\frac{d\mathcal{H}}{dt} < 0$, verifying (32).

Kinetic Analysis of System I.

We complete this kinetic section with an analysis for system I of $x(t)$, $y(t)$ and $\mathcal{H}(t)$, and for comparison, $\mathcal{P}(t)$. The equations of motion (from the last two columns of Table 2 plus the rate laws of Table 1) can be written in the form:

$$\begin{aligned} \frac{d^2x}{dt^2} + 4 \frac{dx}{dt} + 3x &= 2A + B \\ \frac{d^2y}{dt^2} + 4 \frac{dy}{dt} + 3y &= A + 2B \end{aligned} \quad (48)$$

Pairs of x and y to satisfy (48) were calculated numerically, the corresponding $\mathcal{H}$ and $\mathcal{P}$ values computed from eqs. (19) and (4) and Tables 1 and 2, and the results plotted in Fig. 3. (From Tables 1 and 2 the applicable stationary values are: $x^{st} = \frac{2A+B}{3}$ and $y^{st} = \frac{A+2B}{3}$.)

The smooth course of $\mathcal{H}(t)$, indicative of a thermodynamic-potential-description of the time-evolution of a system moving towards a single stable stationary state is seen to hold, despite the overshoot of y . Associated with this latter, however, is an overshoot in $\mathcal{P}$, displaying in time-space for this far-from-equilibrium system the failure of $\mathcal{P}(t)$ to properly match the evolving system. It may be noted in passing however that sufficiently far from the stationary state, $\mathcal{P}$ does retain the proper time behavior of an "evolutionary indicator," ($d\mathcal{P}/dt < 0$). This is reminiscent of the result previously noted by Mel also for certain restricted kinetics.⁸ (Overshoots in $\mathcal{P}$, yet a surprisingly small deviation of $\mathcal{P}^{min}$ from $\mathcal{P}^{st}$ were also noted by Klein for his photo-excitation process.⁷)

V. DISCUSSION

Comparative Qualities of $\mathcal{M}$

It is always possible to construct a positive definite quadratic form having the formal properties of a minimum at any given point in multi-dimensional space. From (16) and (17) alone it is also clear that the choice of function for assuring an extremal, (even a minimum) in the stationary state is not a unique one (though neither is entropy, as usually defined, the only function for which we can write a "second law"). Significant about our "variationally successful" $\mathcal{M}$, however, is its particular form (2), (18), with the additional properties that followed: $\mathcal{M}^{\text{st}} = \mathcal{P}^{\text{st}}$, positive definite, extremal — minimum, state function, $\frac{d\mathcal{M}_T}{dt} \leq 0$, (plus below). This is in contrast with the behavior of the three other (formally and conceptually) closely related quadratic forms (20), (28), (30) which were seen to fail as thermodynamic potentials for some or all of the systems summarized in Table 1.

The close link of $\mathcal{M}$ to $\mathcal{P}$ provided more than aesthetic satisfaction: it directly "converted" the less stringent requirement of an extremal into the more restrictive (and more desirable) extremum-minimum condition. Interestingly, the "velocity potential" candidate that likewise interfaced with $\mathcal{P}$ in the stationary state ((28), (29)) was seen to fail variationally for all kinetic systems.

The Form of $\mathcal{M}$

Given a formally successful variational principle-potential function, it is nonetheless worthwhile to critically scrutinize the particular form this takes. Specifically, for $\mathcal{M}$, one may ask the 3 closely related questions: What right or use is there, (a) to presuppose the existence of the stationary state; (b) to include kinetic-mechanistic quantities in the function rather than to "derive" them from our variational principle; and (c) to include quantities that must be evaluated at the stationary state?

In answer to (a), in this paper we explicitly limit our study to that large and important class of systems having a single (locally) stable stationary state. It is in this same spirit that we use free energy or entropy for treating (evolution of) reversible systems to known, stable, equilibrium endpoints. (Note that it is usually of little concern that

most biochemical "equilibrium" endpoints are actually only restricted or unstable equilibria since the compounds involved are commonly themselves thermodynamically unstable.)

In answer to (b), in a sense we did "derive" the included kinetic terms (16), (17) and (18). Furthermore, by their appearing simply as v_i^{st} or v^{st} , the form of these terms is quite independent of detailed mechanism, a feature long cherished for ρ within the linear domain. (One might even argue that mechanistic considerations enter into the ρ^{near} eq. even more than they do into $\mathcal{M}$; the "linear phenomenological laws," though common to all chemical systems "close enough" to equilibrium, are the actual valid rate laws so the concept of "independence of mechanism" in that domain may be somewhat misleading.) In a more general vein one may argue that the cooperative combination of rate and thermodynamic quantities lies at the very heart of the foundations of the thermodynamics of irreversible processes (c.f. De Donder's inequality: $A_T \cdot v \geq 0$, and the multi-reaction extension: $T \rho = \sum_i A_i v_i \geq 0$).¹ It also is in qualitative correspondence with the operation of the complex reaction networks of living systems, whose reaction rates must mutually adjust as part of the competition for available free energy resources.^{11,12}

Regarding question (c), perhaps the best response is simply to note that $\alpha_i = \frac{v_i^{st}}{A_i^{st}}$ is the "correct" form to assure the thermodynamic potential properties of $\mathcal{M}$, that no other such simply defined and interpretable potential function is available, and then to examine $\mathcal{M}$ to see what interesting properties and uses it may have.

In this regard a practical point may be considered. Ease in numerical evaluation of (and providing an alternative ~~route to~~ ~~desired~~ ~~desired~~ information are themselves useful attributes of a function. Calculation or measurement of the v_i^{st} and A_i^{st} is a straightforward and relatively simple algebraic exercise not requiring solution of the differential (kinetic) equations of the system. Furthermore even in large, complex networks there are always fewer v_i^{st} to determine than there are reactions (sometimes as few as one, e.g. for System I, Table 1 and its multi-variable extensions). Given the properties of $\mathcal{M}$ already discussed, plus those indicated below (e.g. its system-characterization of the "position" and evolutionary properties of far from equilibrium reaction systems; its

biological interpretation; its feature for comparison of stationary states; its possibilities (largely untested) as a stability indicator, etc.) the "interest" in the function would not seem to be in question at this moment.

In concluding this part of the discussion, another point of comparison with ρ may be noted. For near-equilibrium configurations, the "constant phenomenological coefficients" of the diagonalized ρ matrix (expressed in the affinities squared) may be given the same interpretation as our α_i ,

$$= \frac{v_i^{st}}{A_i^{st}}.$$

Significance and "Uses" of $\mathcal{M}$

From its form alone, ((2), (18)) two general properties can be stated directly: (a) as a composite function depending upon all the A_i and v_i^{st} , $\mathcal{M}$ is truly a property of the system; (b) $\mathcal{M}$ may be thought of as a "kinetically-weighted system-free-energy" quantity. Additional (even if obvious) statements follow directly from the thermodynamic-potential-associated properties: (c) for a given system and constraints, the instantaneous value of $\mathcal{M}$ (or $T\mathcal{M}$, we consider temperature constant) "locates" the system in both configuration and time space. It may also be considered to be the "cost" of a metabolic system; (d) $\Delta\mathcal{M}$ measures the tendency of a reaction system to make the indicated transition between arbitrary initial (reacting) and final (reacting) states; ($\Delta\mathcal{M} < 0$ is a criterion for spontaneous "evolution" by such a transition; $\mathcal{M}^{st} - \mathcal{M}^{init}$ measures the "maximum evolutionary potential" of the thusly-constrained system). From its interfacing property with ρ^{st} , alone, (22): (e) $\Delta\mathcal{M}^{st} = \mathcal{M}_2^{st} - \mathcal{M}_1^{st}$, measures the relative irreversibility (or $\Delta(T\mathcal{M}^{st})$, the relative dissipation) of a system in two different stationary state configurations. If one of the stationary states is in fact equilibrium, where $\mathcal{M}_2^{st} = \mathcal{M}_2^{eq} = 0$, $\mathcal{M}_1^{st}$ measures the system-configuration's "absolute irreversibility," i.e. its steady state "distance" from equilibrium.

Notwithstanding the inclusion of kinetic elements (which together with the A_i^{st} serve as the "weighting factors") since the degrees of freedom for any given system reside in the A^2 terms, we can consider $\mathcal{M}$'s dominant feature to be its "affinity" character. We may further interpret the $\mathcal{M}$ variational and time-dependent properties as indicating that

evolution towards the non-equilibrium stationary state occurs in such a way as to minimize the use of or to maximize the efficiency of use of this weighted-free-energy quantity. In an extensive current review of the experimental microbiological literature, Payne makes the intriguing suggestion of the existence of "a gene controlling the investment expenditure of energy," as one plausible explanation for certain control features observed in cell culture growth and evolution.¹² This appears generally consistent with the above interpretation (though as Payne is careful to point out, cause-effect relationships remain to be clearly sorted out from each other in interpreting the experimental data). Pardee, in discussing different regulated biochemical-pathway systems ("the networks of life") touches on energetic as well as rate aspects of such systems, but arguing biologically, particularly from a longterm evolutionary standpoint, he favors a "growth maximization" control feature.¹¹ Though this is related to the rates of the system, the exact nature of the relationship is not clear. (Recall that our $\langle v^2 \rangle_2$, (3), (30), a "pure" rate quantity was "variationally successful" for several kinetic systems, and like $\mathcal{M}$ is a state function.) Others have also discussed "velocity potentials," often of the incomplete differential type.¹⁴

Oscillations and Stability Criteria

The time independent and stable stationary states of Table 1 were noted to be representative of a large class of common homeostatic-like conditions. The relationship, $\frac{d\mathcal{M}}{dt} \leq 0$ found for these systems, demonstrates that the $\mathcal{M}$ function is a valid indicator for the "smooth" temporal evolution of these systems and also for the stability of their stationary states. (ρ clearly cannot serve this purpose, see Fig. 3.)

Other kinds of temporal endpoints obviously exist in biology, e.g. oscillatory states, covered elsewhere in this volume. In some cases one may appropriately consider such systems still to have a "stationary" state with the proviso that it be a time-averaged state, over the thermodynamic time scale suitable to the particular system, as discussed by Tykodi.¹⁵ Real physical systems commonly "maintain" a constant condition by oscillating about that condition (though the oscillations may often be sufficiently "fine-structure" in character to be disregarded) so the two concepts are perhaps not so incompatible as might seem at first sight.

(Consider, e.g., the thermostat that functions by "hunting" around its set value.) In other cases, however, one may wish to emphasize precisely the opposite theme — the non-constancy of the system's behavior at $t = \infty$. It will be interesting to explore the behavior of $\frac{d\mathcal{H}}{dt}$ for a permanent oscillatory system such as discussed by Goodwin⁵ and, alternatively, for systems known to have bistable or unstable stationary states, e.g. of the kind recently described by Gardner and Ashby.³

VI. CONCLUSION

In summary, the Affinity Squared function, $\mathcal{H}$, based on choice of α_i according to (18), is seen to have useful and satisfying properties — in its state function-thermodynamic potential, time-dependent character, and in its simplicity and smooth interfacing with $\mathcal{P}$, which in turn smoothly interfaces with entropy. One may thus regard $\mathcal{H}$ as a formal extension of $\mathcal{P}$ into the far-from-equilibrium domain of open chemical reaction systems. Questions regarding $\mathcal{H}$ which await further clarification include (1) its generality for other-than-chemical systems or for more complex chemical systems (the extension of (16) and (17) to greater than 2-variable networks with simple kinetics is trivial); (2) its possible use in characterization of reaction networks according to differences in complexity, connectivity, etc.; (3) its behavior for oscillatory and unstable and multi-stationary state systems.

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Captions:

Fig. 1. Deviation of function minima from stationary-state values, for the seven 2-variable kinetic systems of Table 1. Plotted are

$\mathcal{M}^{\min}/\mathcal{M}^{\text{st}}$, — heavy solid line;

$\rho^{\min}/\rho^{\text{st}}$, — open circles;

$\langle v^2 \rangle_2^{\min}/\langle v^2 \rangle_2^{\text{st}}$, — closed triangles;

$\langle v^2 \rangle_1^{\min}/\langle v^2 \rangle_1^{\text{st}}$, — open triangles.

For interfunction comparison on a single system, dashed lines are used for all the autocatalytic system (III) curves.

Minimum Location Program: For each constraint and function the minimum was located by evaluating the function over a 20 x 20 matrix of x and y concentration coordinates, one y-row at a time. The minimum of each row was compared with preceding rows until the smallest of the row-minima was located. This process was repeated with ranges reduced by factors of 10 until the concentration coordinates were known within errors of less than 0.1%.

Fig. 2. $\mathcal{M}$ and ρ functions in concentration space, shown for system I with $B = 10$, $A = 1$; $x^{\text{st}} = 4$, $y^{\text{st}} = 7$; $\rho^{\min} = 6.3 R$, $\mathcal{M}^{\min} = 6.9 R$. The heavy line-segment denotes the intersection of the two surfaces. The 3-dimensional figures were graphically constructed from contour maps of x-y areas near the function minima. The insert indicates the inter-relationship of the two surfaces, as seen from above.

Fig. 3. Kinetic analysis of system I. The kinetic equations for system I were solved for $x(t)$ and $y(t)$, for $B/A = 2/1$, $x_0 = 0$, and $y_0 = 2$. Pairs of x and y were calculated numerically as were the corresponding $\mathcal{M}$ and ρ function values (plotted in units of R).

Fig. 1

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DBL 711-5602

Fig. 2

DBL 711-5600

Fig. 3

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