General Mass Action Kinetics

F. HORN & R. JACKSON

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Summary

The familiar idea of mass action kinetics is extended to embrace situations more general than chemically reacting mixtures in closed vessels. Thus, for example, many reaction regions connected by convective or diffusive mass transport, such as the cellular aggregates of biological tissue, are drawn into a common mathematical scheme.

The ideas of chemical thermodynamics, such as the algebraic nature of the equilibrium conditions and the decreasing property of the free energy, are also generalized in a natural way, and it is then possible to identify classes of generalized kinetic expressions which ensure consistency with the extended thermodynamic conditions. The principal result of this work shows that there exists a simply identifiable class of kinetic expressions, including the familiar detailed balanced kinetics as a proper subclass, which ensure consistency with the extended thermodynamic conditions. For kinetics of this class, which we call *complex balanced kinetics*, exotic behavior such as bistability and oscillation is precluded, so the domain of search for kinetic expressions with this type of behavior, which is of considerable biological interest, is greatly narrowed.

It is also shown that the ideas of complex balancing and of detailed balancing are closely related to symmetry under time reversal.

1. Introduction

The study of chemical kinetics can be approached from three different points of view.

The physical chemist usually considers electrons, atoms, molecules and their interactions as primitive notions, and is interested in studying the mechanism of rearrangement of atoms into new molecules during chemical reactions. He may also explore what inferences may be drawn regarding reaction rates, possibly with the assistance of statistical mechanics.

The formal kineticist, on the other hand, takes a macroscopic viewpoint and his primitive concept is the *elementary reaction*. This is defined by a set of stoichiometric coefficients, together with a rule relating reaction rate to composition and temperature. The primary macroscopic observable is the rate of change of composition of the mixture, and an expression for this is constructed by adding the
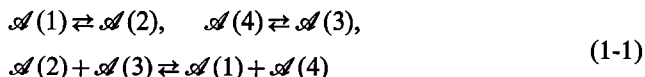
rates of the elementary reactions, each weighted by the corresponding set of stoichiometric coefficients. The elementary reactions thus provide a framework for constructing differential equations to be satisfied by the composition.

A third and still less mechanistic viewpoint is adopted by workers in modern continuum mechanics, who take the rate of change of composition itself as their primitive concept and construct a constitutive relation to express this in terms of composition, temperature, etc. The form of the constitutive relation is limited by very general considerations such as stoichiometry, which constrains the state to lie in a "*stoichiometric subspace*" of the composition space, and it is often convenient to expand the rate of change of composition in terms of a basis (in the mathematical sense) for this subspace. The members of this basis may then be referred to as reactions, but they are, of course, largely arbitrary and no particular mechanistic significance is attached to them; indeed this approach to kinetics is almost completely purged of chemistry.

We shall adopt the second viewpoint, that of formal kinetics, which has a long and well-documented history. Its basic problem is the choice of a suitable set of elementary reactions and associated rate functions to model observed kinetic behavior, and traditionally it has been guided very closely by ideas from kinetic theory and thermodynamics.

If we regard a single elementary reaction as representing an encounter and interaction between reactant molecules, kinetic theory suggests the familiar mass action form for the rate function, and it is reassuring that the condition for vanishing rate of a reaction-antireaction pair then coincides with the thermodynamic equilibrium condition, at least in an ideal mixture where simple "dilute gas" kinetic theory might be expected to be a good approximation. The link with thermodynamics can be carried further, since it can easily be shown that, in all non-equilibrium states, the Helmholtz free energy decreases with increasing time when the rate function of the reaction-antireaction pair is of the mass action form, the mixture is ideal and the system is held at constant volume. (A similar result holds for the Gibbs free energy at constant pressure.)

However, in 1902 R. WEGSCHEIDER [11] pointed out that the condition of vanishing rate does not necessarily coincide with the thermodynamic equilibrium condition when there are several linearly-dependent elementary reactions, even if their rate functions are of the mass action type. This was demonstrated by the following set of reactions:

$$\mathscr{A}(1) \rightleftarrows \mathscr{A}(2), \quad \mathscr{A}(4) \rightleftarrows \mathscr{A}(3),$$
$$\mathscr{A}(2) + \mathscr{A}(3) \rightleftarrows \mathscr{A}(1) + \mathscr{A}(4) \tag{1-1}$$

(generally we denote species by $\mathscr{A}(1)$, $\mathscr{A}(2)$ ..., a notation which will prove advantageous later) for which it is easy to show that the condition of vanishing rate coincides with the thermodynamic equilibrium conditions only if there are special relations between the rate constants.

This situation, which became known as *Wegscheider's paradox*, was invoked by LEWIS [8] as part of the justification for his very general, though rather vaguely stated "*law of entire equilibrium*", which requires that every elementary process shall have a reverse process, and that their rates must balance at equilibrium.

When applied to chemical kinetics, this principle of detailed balancing, or micro-reversibility, requires that the rate functions be constrained in such a way that the rate of each elementary reaction-antireaction pair vanishes at all kinetic equilibrium compositions. With this constraint it is not difficult to show that the condition of kinetic equilibrium with mass action rate functions always coincides with the condition of thermodynamic equilibrium in ideal mixtures, so Wegscheider's paradox never arises. It can also be shown that the free energy decreases with increasing time in all non-equilibrium states, so detailed balancing suffices to ensure complete consistency with classical thermodynamics in closed systems of ideal mixtures with mass action kinetics. Though LEWIS was apparently aware of particular examples of kinetic systems which are fully consistent with classical thermodynamics, but do not satisfy the principle of detailed balancing, he speculated about the "general" necessity of this principle in the following words: *"This (detailed balancing) is not the only way of avoiding the paradox in this particular example, but if we were to consider a great many different types of simultaneous reactions we should probably find that the only general way of avoiding the paradox, that is applicable to all cases, would be to assume that in every case of equilibrium, involving a number of simultaneous reactions, a state of equilibrium also exists for each separate reaction and its inverse."*

Among other things, we shall demonstrate in this paper that LEWIS' speculation is false; there is a much larger and simply identifiable class of mass action kinetics, including detailed balanced kinetics as a subclass, which is completely consistent with the requirements of thermodynamics. This does not necessarily imply that the principle of detailed balancing itself is false, since arguments other than thermodynamic consistency have been used in its justification. However, we shall also be interested in the formal description of certain open systems, for which such a principle would be totally inappropriate.

In the light of the above discussion we many now assert that a kinetic description of chemical reactions in closed systems with ideal mixtures, completely consistent with the requirements of stoichiometry and thermodynamics, may be obtained by satisfying the following four requirements.

a. *The rate function of each elementary reaction is of the mass action form.*

b. *The stoichiometric coefficients are such that mass is conserved in each elementary reaction.*

c. *The kinetic constants in the rate functions are constrained in such a way that the principle of detailed balancing is satisfied.*

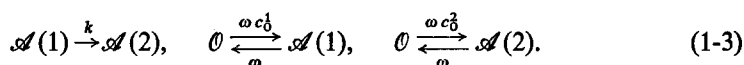d. *The stoichiometric coefficients are non-negative integers.*

There then arises the question whether anything might be gained by investigating the consequences of relaxing one or more of the conditions (b), (c) and (d); in other words, by studying **generalized mass action kinetics,** in which only (a) need be satisfied.

By relaxing *condition (b)*, requiring mass conservation in each elementary reaction, many open systems can be drawn into the formal structure of mass action kinetics. For example, when a single chemical reaction $\mathscr{A}(1) \xrightarrow{k} \mathscr{A}(2)$ takes place in a perfectly mixed flow reactor, the rate of change of composition is given

by

$$\dot{c}^1 = \omega(c_0^1 - c^1) - k c^1,$$
$$\dot{c}^2 = \omega(c_0^2 - c^2) + k c^1 \tag{1-2}$$

where c^1 and c^2 are the concentrations of $\mathscr{A}(1)$ and $\mathscr{A}(2)$ in the tank, c_0^1 and c_0^2 are the time invariant corresponding concentrations in the feed and ω is the flow rate per unit reactor volume. These relations may alternatively be regarded as the differential equations generated by the following formal set of elementary reactions, with the indicated rate constants:

$$\mathscr{A}(1) \xrightarrow{k} \mathscr{A}(2), \qquad \mathcal{O} \underset{\omega}{\overset{\omega c_0^1}{\rightleftharpoons}} \mathscr{A}(1), \qquad \mathcal{O} \underset{\omega}{\overset{\omega c_0^2}{\rightleftharpoons}} \mathscr{A}(2). \tag{1-3}$$

The symbol $\mathcal{O}$ stands for the absence of any species, or the "zero complex". It is seen that mass is conserved only in the first formal reaction, which coincides with the actual chemical reaction in the system. The remaining elementary "reactions", which include the "zero complex", represent the flow processes in and out of the reactor and their "rate constants" depend on the feed flow. Formal application of the mass action law for instance to the "reaction" $\mathcal{O} \rightarrow \mathscr{A}(1)$ yields a reaction rate which is independent of the concentrations c^1 and c^2 (these concentrations are to be raised to the power zero) corresponding to time invariant infusion of species $\mathscr{A}(1)$ into the system by convective transport. Technically, the "reaction" $\mathcal{O} \rightarrow \mathscr{A}(1)$ is *non-conservative* in a sense which will be made precise in the next section. It is easy to see that this idea can be generalized to accommodate any number of well-mixed regions, linked either by flows or by diffusive mass transfer. By formally regarding a given substance as a different species in each of the separate regions where it appears, the differential equations describing such a system can always be regarded as equivalent to those of a suitably constructed, but usually non-conservative, mass action kinetic scheme. A structure of this type can be used to model a great variety of systems, ranging from interconnected chemical reactors to biological systems with intracellular chemical reactions and intercellular transport of nutrients and waste products. In particular, in biochemistry there is considerable interest in the dynamics of isothermal systems where some of the reaction participants are kept at constant concentrations, or are infused into the system at time invariant rate or removed from it by an external mechanism though, in all other respects, the system may be regarded as closed. Formally equivalent are problems concerning the existence or nonexistence of a *quasi-steady* state for so called *Bodenstein species* and the approach to this quasi-steady state during the *initiation period* of the reaction.

Turning to *condition* (c) we have already remarked that the detailed balancing requirement in closed systems is possibly less firmly rooted than the other requirements, and that it is possible to find a more general class of kinetics which is fully consistent with the laws of thermodynamics. Furthermore, when the formal structure of generalized mass action kinetics is used to describe open systems, in the manner just outlined, it would be quite inappropriate to require detailed balancing, *i.e.*, the condition that in case of equilibrium (=stationarity) the rate of each reaction equals the rate of the corresponding antireaction. For the tank reactor example, equation (1-3) for instance, detailed balancing would require

the rate of addition of $\mathscr{A}(1)$ (corresponding to $\mathcal{O} \to \mathscr{A}(1)$) to equal the rate of removal of $\mathscr{A}(1)$ (corresponding to $\mathscr{A}(1) \to \mathcal{O}$)) in the steady state. But clearly this cannot be so, because of the chemical reaction taking place in the tank.

Obviously in open systems there is no longer any reason to require that the kinetic behavior be consistent with the requirements of thermodynamics applied to closed systems. Nevertheless, it is still of interest to identify classes of kinetic equations which behave *as though* the laws of closed system thermodynamics applied, for we are then able to say something about the uniqueness and stability of their equilibrium states. For example, in seeking a physico-chemical model to describe self-sustaining oscillations, bistability, and other phenomena of this type in biological systems, one can immediately reject any equations derivable from a mass action kinetics which satisfies such *"quasi-thermodynamic"* conditions, since the equilibria are then known to be stable and unique (in a way which will be made precise later).
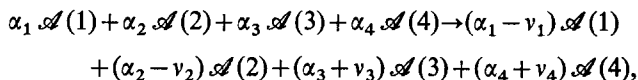
If *condition (d)* is relaxed, any kinetic expression of power law type can be reduced to mass action form. Thus an overall reaction

$$v_1 \mathscr{A}(1) + v_2 \mathscr{A}(2) = v_3 \mathscr{A}(3) + v_4 \mathscr{A}(4),$$
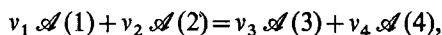
with a rate function of the form

$$k(c^1)^{\alpha_1}(c^2)^{\alpha_2}(c^3)^{\alpha_3}(c^4)^{\alpha_4}$$

(α_1, α_2, α_3, α_4 not necessarily integers or nonnegative), can be replaced by an "elementary reaction"

$$\alpha_1 \mathscr{A}(1) + \alpha_2 \mathscr{A}(2) + \alpha_3 \mathscr{A}(3) + \alpha_4 \mathscr{A}(4) \to (\alpha_1 - v_1) \mathscr{A}(1)$$
$$+ (\alpha_2 - v_2) \mathscr{A}(2) + (\alpha_3 + v_3) \mathscr{A}(3) + (\alpha_4 + v_4) \mathscr{A}(4),$$

and the rate function is of the mass action form relative to the modified reaction whose stoichiometric coefficients may be neither integers nor non-negative. Power law rate functions often arise in kinetic models from which intermediate stages have been eliminated (or they are determined empirically), and it is clearly useful to be able to include these in a common mathematical structure.

The purpose of the present paper, then, is to develop a mathematical description of **general mass action kinetics**; that is, mass action kinetics with the restrictions (b), (c) and (d) above relaxed. To such a program an adequate notation is essential, so *Section 2* is devoted to notational matters.

In *Section 3* we introduce the principle of detailed balancing and a more general concept which we call *complex balancing*, of which detailed balancing is a special case. It is shown that both ideas are related to time reversal symmetry.

The *quasi-thermostatic* and *quasi-thermodynamic* conditions, which are introduced in *Section 4*, coincide formally with the requirements of classical thermodynamics in closed systems and are shown to have similar simple consequences regarding uniqueness of equilibria. Our further investigation of these conditions hinges on a formal decomposition of the kinetic model into a set of *cycles*, so *Section 5* deals with the properties of cyclic kinetic systems. With this as a preliminary, in *Section 6* we prove our main result, that *any mass action kinetics of*

the complex balanced class satisfies both the quasi-thermostatic and quasi-thermo-dynamic conditions. Finally, in *Section 7*, the results are illustrated by a number of simple explicit examples.

2. Mathematical Description of Mass Action Systems

In this section we shall establish the mathematical frame of our theory and introduce a notation which will greatly simplify the mathematical description of complex mass action kinetics. In doing this the underlying model will be an *isothermal well mixed cell* (or reactor) with time invariant volume, in which a set of elementary reactions occur. As pointed out in the Introduction, our theory applies to more general situations, but it will be convenient to refer initially to a somewhat restricted class of physical systems.

It will be assumed that the number of different types of atoms, molecules, photons, *etc.* participating in the chemical reactions is finite and specified. The members of this set will be called *reaction participants*. There are occasions when it is useful to study systems in which the concentrations of some of the reaction participants may be regarded as time invariant. For example these participants may be supplied to or removed from the system in such a way as to maintain the respective concentrations constant. Such reaction participants will be called *external species*. All other reaction participants will be called *species*.

For instance, in biological systems it will be possible in most cases to consider water an external species, since its concentration can be regarded as time invariant because of its presence in large excess. As another example consider the infusion of a species at constant rate into an otherwise closed system. The infused species can then be regarded as the product of the first order (say) decay of a (possibly hypothetical) external species present in time invariant concentration.

It will be assumed that there are precisely m, $m \geq 1$, species in the system, and these will be denoted by

$$\mathscr{A}(1), \mathscr{A}(2), ..., \mathscr{A}(m).$$

The external species will be denoted by

$$\mathscr{B}(1), \mathscr{B}(2), ...$$

By a *genuine elementary reaction* we mean a chemical reaction equation indicating a reaction with some mechanistic significance between reaction participants (*e.g.*, collision). The term *elementary reaction* will be used for such a chemical equation after removal of the external species from the equation. For instance, if the genuine elementary reaction is

$$\mathscr{B}(1) + \mathscr{A}(1) \rightarrow 2\mathscr{A}(1), \tag{2-1}$$

the elementary reaction will be

$$\mathscr{A}(1) \rightarrow 2\mathscr{A}(1). \tag{2-2}$$
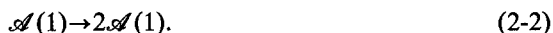
(This example represents the self-reproduction of a species $\mathscr{A}(1)$ on a substrate $\mathscr{B}(1)$.) In the case of infusion of species $\mathscr{A}(1)$ at constant rate the genuine ele-

mentary reaction may be taken as

$$\mathscr{B}(1) \to \mathscr{A}(1),$$ (2-3)

and the elementary reaction becomes

$$\mathcal{O} \to \mathscr{A}(1)$$ (2-4)

where $\mathcal{O}$ denotes the absence of any species.

In the context of this work elementary reactions are directed as indicated by an arrow. We do not consider the forward and reverse reactions together as one reaction.

The expression occurring on either the reactant or the product side of a reaction equation has the general form $\mathscr{C}$

$$\mathscr{C} = \sum_{i=1}^{m} y^i \mathscr{A}(i).$$ (2-5)

Such an expression will be called a *complex*. The numbers $y^1, \ldots y^m$ are the *molecularities* of the species $\mathscr{A}(1), \ldots \mathscr{A}(m)$ in the complex. By definition, two complexes are equal if and only if they agree in all molecularities. We shall assume that the reaction system under consideration involves n, $n \geq 2$, distinct complexes which will be denoted by

$$\mathscr{C}(1), \mathscr{C}(2), \ldots, \mathscr{C}(n).$$

Any reaction in the system can then be written in the form

$$\mathscr{C}(j) \to \mathscr{C}(i).$$ (2-6)

We now introduce two vector spaces V, $V = \mathsf{R}^m$, and W, $W = \mathsf{R}^n$, called *species space* and *complex space*, respectively. The ith natural basis vector in V (which has i^{th} coordinate equal to unity and all other coordinates zero) will be associated with species $\mathscr{A}(i)$, and similarly the jth natural basis vector W will be associated with the complex $\mathscr{C}(j)$. In addition, to each complex $\mathscr{C}(j)$ there will be assigned a vector $y(j)$ in species space V, called the jth *complex vector*, such that the coordinates of $y(j)$ are the respective molecularities of the species in $\mathscr{C}(j)$:

$$\mathscr{C}(j) = \sum_{i=1}^{m} y^i(j) \mathscr{A}(i), \quad y(j) = (y^1(j), y^2(j), \ldots, y^m(j))^T.$$ (2-7)

Complex vectors may be combined in an m by n matrix Y, called the *complex matrix*, whose columns are the complex vectors $y(1), \ldots y(n)$. Y defines a linear transformation of the complex space W into the species space V such that the jth natural basis vector in W is mapped into the complex vector $y(j)$ in V. (All vectors to be taken as column vectors.)

If we recall that the concentrations of the external species are assumed to be given and fixed, the composition of the reacting mixture is represented by a vector c in V, the coordinates of which are equal to the respective species concentrations

$$c = (c^1, c^2, \ldots, c^m)^T,$$ (2-8)

$$c^j = \text{concentration of } \mathscr{A}(j).$$

This will be called the *concentration vector* or, where misinterpretation seems impossible, simply the *concentration*. Since species concentrations must be non-negative, the concentration vector c must lie in the non-negative orthant $\bar{V}^+$ of V, that is, the subset of V consisting of all vectors having non-negative coordinates. The positive orthant of V, that is, the set of all vectors in V with positive coordinates, will be denoted by V^+.

It will be assumed that the temperature, the volume, and all other independent parameters affecting the state of the reacting mixture (apart from c) have specified magnitudes. Thus it can be assumed that the rate of the reaction $\mathscr{C}(j) \rightarrow \mathscr{C}(i)$ is a function of the concentration vector c, which will be denoted by $r_{ij}(c)$. If for a particular pair i, j there is no elementary reaction leading from $\mathscr{C}(j)$ to $\mathscr{C}(i)$, then $r_{ij} \equiv 0$. Similarly $r_{ii} \equiv 0$ by definition.

Since in our theory the term "reaction" does not refer to the net effect on the system of a pair of forward and backward reactions but to a single elementary reaction with specific direction, the reaction rates $r_{ij}(c)$ must be non-negative for all c.

The n by n matrix with elements $r_{ij}(c)$ (the first index refers to rows, the second to columns), denoted by $R(c)$, will be called the *rate matrix* at concentration c.

We define the *rate of creation* of a complex to mean the sum of the rates of all reactions which lead to the complex considered. Thus the rate of creation of complex $\mathscr{C}(i)$ is given by

$$\sum_{j=1}^{n} r_{ij}(c).$$

Similarily, the *rate of annihilation* of complex $\mathscr{C}(i)$ is defined as the sum of the rates of all reactions leading away from this complex and is thus given by

$$\sum_{j=1}^{n} r_{ji}(c).$$

The difference between the rate of creation and rate of annihilation of a complex will be called the *rate of formation* of this complex.

Note that, for each complex, both the rate of creation and the rate of annihilation must be non-negative, but no such statement can be made for the rate of formation. The rates of formation may be represented by a vector in complex space W with coordinates equal to the formation rates of the respective complexes at concentration c. This vector will be called the *complex formation vector* and denoted by $g(c)$. Clearly

$$g(c) = \left(R(c) - R^T(c) \right) e_w \tag{2-9}$$

where superscript T denotes transposition and e_w is the vector in W with all coordinates equal to unity.

The *species formation vector* $f(c)$ at concentration c will be defined by

$$f(c) = \sum_{i=1}^{n} \sum_{j=1}^{n} r_{ij}(c) \left(y(i) - y(j) \right) \tag{2-10}$$

and is seen to be a vector in species space V, whose v^{th} coordinate is the rate of formation of species $\mathscr{A}(v)$ at concentration c. By slightly rearranging the expression in (2-10) one obtains

$$f(c) = Yg(c) \tag{2-11}$$

showing that the species formation vector is the image of the complex formation vector under the transformation Y.

We shall next consider the case where the rate of each reaction is the product of a non-negative constant and a power product of the species concentrations with exponents equal to their respective molecularities in the reactant complex of the reaction. That is

$$r_{ij}(c) = k(i,j) \prod_{v=1}^{m} (c^v)^{y^v(j)} \tag{2-12}$$

for all $c \in V^+$ where $k(i,j) \geq 0$. Such a system will be said to have *mass action kinetics*, and the number $k(i,j)$ will be called the rate constant of the reaction $\mathscr{C}(j) \to \mathscr{C}(i)$. $k(i,j)$ will be set equal to zero when $i=j$ or when there is no elementary reaction from $\mathscr{C}(j)$ to $\mathscr{C}(i)$.

The rate constant, in general, is the product of a genuine rate constant and a power product of external species concentrations which, like the temperature, are assumed to be specified and time-invariant. The n by n matrix with elements $k(i,j)$ (the first argument refers to rows, the second to columns) will be called the *rate constant matrix* and denoted by K.

Any vector $x \in V$ which is the difference of two complex vectors,

$$x = y(i) - y(j) \tag{2-13}$$

where i and j are such that $k(i,j) > 0$ will be called an *elementary reaction vector*. In particular, x of equation (2-13) is the elementary reaction vector belonging to the elementary reaction $\mathscr{C}(j) \to \mathscr{C}(i)$ (if convenient, such a vector will be denoted $x(i,j)$).

The subspace of V spanned by all elementary reaction vectors will be called the *stoichiometric space* and denoted by S. s will denote the dimension of S. Any vector in S will be called a *reaction vector*.

The system under consideration will be called *conservative* if there is a vector in the orthogonal complement $S^\perp$ of S which lies in the positive orthant V^+. (Here and in what follows the inner product is to be taken as the standard inner product in $\mathbb{R}^m$ or $\mathbb{R}^n$.) Systems without external species must be conservative due to conservation of mass, since the vector in V with coordinates equal to the molecular weights of the respective species has the required properties (see also [6]). Systems with external species need not be conservative.

Next consider a vector c_0 in V^+ and the coset $c_0 + S$ of the stoichiometric space S. The intersection of such a coset with the non-negative orthant $\overline{V}^+$ will be called a *reaction simplex*, and the corresponding intersection with V^+ will be called a *positive reaction simplex*.

It can be shown (see Appendix 1) that a reaction simplex is bounded if and only if the system is conservative. Furthermore, if there is one bounded reaction simplex, then all reaction simplexes are bounded.

The algebra of mass action systems is greatly simplified by introduction of a contracted notation for certain functions defined on the domain V^+ or $V^+ \times V$, respectively.

If $c \in V^+$ and $y \in V$, then c^y will be defined by

$$c^y = \prod_{j=1}^{m} (c^j)^{y^j}. \tag{2-14}$$

If $c \in V^+$ and if Y is an m by n matrix with column vectors $y(1)$, $y(2)$, ... $y(n)$, then c^Y will be defined by

$$c^Y = (c^{y(1)}, c^{y(2)}, ..., c^{y(n)})^T. \tag{2-15}$$

The *logarithm of a vector* c in V^+ will be defined by

$$\ln c = (\ln c^1, \ln c^2, ..., \ln c^m)^T. \tag{2-16}$$

The *ratio* c/a of two vectors $c \in V$ and $a \in V^+$ will be defined by

$$\frac{c}{a} = \left(\frac{c^1}{a^1}, \frac{c^2}{a^2}, ..., \frac{c^m}{a^m} \right)^T. \tag{2-17}$$

With these definitions the following relations can easily be established:

$$\ln c^y = y \cdot \ln c, \quad \ln c^Y = Y^T \ln c \tag{2-18}$$

(here and everywhere in the paper the dot between two vectors denotes the standard inner product),

$$\ln \frac{c}{a} = \ln c - \ln a, \tag{2-19}$$

and

$$\left(\frac{c}{a} \right)^y = \frac{c^y}{a^y}, \tag{2-20}$$

$$\left(\frac{c}{a} \right)^Y = \frac{c^Y}{a^Y}. \tag{2-21}$$

With these definitions it follows from equations (2-10) and (2-12) that, for a system with mass action kinetics, the species formation vector is given by

$$f(c) = \sum_{i=1}^{n} \sum_{j=1}^{n} k(i, j) c^{y(j)} (y(i) - y(j)). \tag{2-22}$$

From this and the definition of the stoichiometric space S it follows that

$$f(c) \in S \quad (\text{all } c \in V^+). \tag{2-23}$$

For mass action kinetics, from the definitions of the rate matrix $R(c)$ and the rate constant matrix K, and from equation (2-12), it follows that

$$R(c) = K \, \mathrm{dg} \, c^Y, \tag{2-24}$$

where dg denotes the operation of transforming a vector into a diagonal matrix with diagonal elements equal to the respective coordinates of the vector. Using (2-24) in equation (2-9) for the complex formation vector, after minor rearrangements one obtains

$$g(c) = A c^Y \qquad (2\text{-}25)$$

where the *kinetic matrix* A is given by

$$A = K - \mathrm{dg}\, K^T e_w. \qquad (2\text{-}26)$$

The operation of transforming the rate constant matrix into the kinetic matrix will be denoted by ρ,

$$A = \rho K. \qquad (2\text{-}27)$$

For mass action kinetics, then, the species formation vector $f(c)$ is given by

$$f(c) = Y A c^Y. \qquad (2\text{-}28)$$

Under the assumption that the system is closed for the species (with the exception of processes already accounted for in the construction of f) one obtains the dynamical equation

$$\frac{dc(t)}{dt} = f(c(t)) \qquad (2\text{-}29)$$

where t denotes time.

In the Introduction we have pointed out that there is a large variety of systems described by mathematical relations formally identical with those for a well stirred tank in which elementary reactions with mechanistic significance occur. The results, which will be discussed in the following sections, are dependent only on certain formal structures of the investigated system. In order to emphasize this, and for convenience in notation we introduce the following definitions.

By a *kinetic system* we mean the following collection of objects: two real vector spaces V, $V = \mathsf{R}^m$ and W, $W = \mathsf{R}^n$, the *species* and *complex space*, respectively, a set of *distinct complex vectors* $y(1)$, $y(2)$, ... $y(n)$ which are specified in V, the m by n *complex matrix* Y consisting of the complex vectors as column vectors, and the n by n *rate matrix* R with specified non-negative real valued functions $r_{ij}(c)$ on V^+ as elements. By a *mass action system* we will mean a kinetic system in which an n by n *rate constant matrix* K with non-negative elements is specified and in which (2-24) holds. Clearly a mass action system is specified by Y and K, and we shall later use the notation $\langle Y, K \rangle$ to represent such a system.

If a kinetic system or a mass action system is specified, other notions which may be regarded as *primitive* in the physical theory may now be *derived*. For instance, consider the notion of an "*elementary reaction*". If a kinetic system is specified, then n is known and we may consider a set of n abstract objects, the complexes $\mathscr{C}(1)$, $\mathscr{C}(2)$, ..., $\mathscr{C}(n)$ in which we introduce the relation → (reacts to) by "$\mathscr{C}(j) \to \mathscr{C}(i)$ if and only if $r_{ij} \neq 0$". The elementary reactions become the ordered pairs of complexes which are in this relation.

Such an abstract approach serves to make our language applicable to all systems which are described by (2-26), (2-28), and (2-29) *no matter what their*

physical nature may be. Thus it is conceivable in certain cases that the "elementary reactions" of our theory could be completely abstract objects or might refer to physical objects with no relation to elementary reactions in the sense of the physical chemist. Many of our results, however, refer to the observable dynamics of a physical system (the function $c(t)$) and are therefore related to physical reality whatever may be the "true" meaning of "elementary reactions", "complex", "complex formation", and other such concepts.

3. Equilibrium and Symmetry

In this section we shall discuss definitions pertaining to the equilibrium of a system and to certain properties the rate matrix $R(c)$ may or may not possess at equilibrium.

A concentration c, $c \in V^+$, will be called an *equilibrium concentration* in a kinetic system if the species formation vector is the zero vector at this concentration. The subset of V^+ consisting of all equilibrium concentrations will be called the *equilibrium set* and will be denoted by E:

$$E = \{c \in V^+ \mid f(c) = 0\} \tag{3-1}$$

where $f(c)$ is the species formation vector. It follows from equation (2-11) that $c \in E$ if and only if

$$g(c) \in \ker Y. \tag{3-2}$$

A kinetic system will be called *complex balanced at a concentration* c, $c \in V^+$, if the complex formation vector is zero at this concentration. The set of all concentrations at which a kinetic system is complex balanced is a subset of V^+ which will be denoted by C,

$$C = \{c \in V^+ \mid g(c) = 0\}, \tag{3-3}$$

where $g(c)$ is the complex formation vector. Obviously, if $c \in C$, then $c \in E$ so that

$$C \subset E. \tag{3-4}$$

A kinetic system will be called *complex balanced* if

$$C = E \neq \phi. \tag{3-5}$$

That is, a kinetic system is complex balanced if the system is complex balanced at all equilibrium concentrations and if there is at least one such concentration.

It should be noted that in the context of this work the equilibrium set may be empty. The result obtained by Wei [12] concerning existence of at least one equilibrium point in every reaction simplex does not apply here for two reasons. First, in our definition a point of stationarity must be in the positive orthant in order to be called an equilibrium point. Hence, the mass action system $\mathscr{A}(1) \to \mathscr{A}(2)$ has no equilibrium point (though $c^1 = 0$, c^2 is a point of stationarity). Secondly, in non-conservative kinetics the reaction simplexes are unbounded and, therefore, do not satisfy one of the hypotheses in Wei's proof. For instance, the mass action system $\emptyset \to \mathscr{A}(1)$ has no equilibrium even if points at the boundary of V^+ are taken into consideration.

A kinetic system will be called *detailed balanced at c*, $c \in V^+$, if the rate matrix R is symmetric at c, *i.e.*, if

$$R(c) = R^T(c). \qquad (3\text{-}6)$$

From equation (2-9) and from the definition of complex balancing it follows that if a system is detailed balanced at c, then it is also complex balanced at c. The set of concentrations at which a kinetic system is detailed balanced is a subset of V^+ which will be denoted by D

$$D = \{c \in V^+ \mid R(c) = R^T(c)\}. \qquad (3\text{-}7)$$

Clearly

$$D \subset C \subset E. \qquad (3\text{-}8)$$

A kinetic system will be called *detailed balanced* if

$$D = C = E \neq \phi, \qquad (3\text{-}9)$$

that is, if the system is detailed balanced at all equilibrium concentrations and if there is at least one such concentration.

If a system is complex balanced at c, then the rate of creation of each complex equals its rate of annihilation at this concentration, *i.e.* the sum of the rates of reactions leading to the complex is equal to the sum of the rates of reactions leading from it. For detailed balancing the rate of each reaction $\mathscr{C}(j) \to \mathscr{C}(i)$ is equal to the rate of its antireaction $\mathscr{C}(i) \to \mathscr{C}(j)$ at each equilibrium concentration. Both conditions are special cases of a symmetry condition which can be formulated as follows. Let Ω be a function which maps n by n matrices into some set. Then Ω will be called *symmetric at c* for a kinetic system if

$$\Omega\big(R(c)\big) = \Omega\big(R^T(c)\big). \qquad (3\text{-}10)$$

Note that the transposition of R physically corresponds to reversal of time, since under this operation the rates of each reaction-antireaction pair are exchanged. Thus if Ω is symmetric at c, then the value of Ω at this concentration remains invariant under reversal of time.

If Ω is defined by

$$\Omega\big(R(c)\big) = YR(c)\,e_w, \qquad (3\text{-}11)$$

then Ω is symmetric if and only if $c \in E$; if Ω is defined by

$$\Omega\big(R(c)\big) = R(c)\,e_w, \qquad (3\text{-}12)$$

then Ω is symmetric at c if and only if $c \in C$; and if Ω is defined by

$$\Omega\big(R(c)\big) = R(c), \qquad (3\text{-}13)$$

then Ω is symmetric at c if and only if $c \in D$. Functions Ω other than those mentioned here will be investigated in a forthcoming publication. In what follows particular attention will be paid to complex balancing.

We shall consider next the sets ker Y and the image $g(V^+)$ of V^+ under g. Both are subsets of W but only the first is, in general, a subspace of W. Then the following four possibilities pertaining to the positions of these sets relative to each other, and to $\mathbf{0}$, are exhaustive (see also Fig. 1).
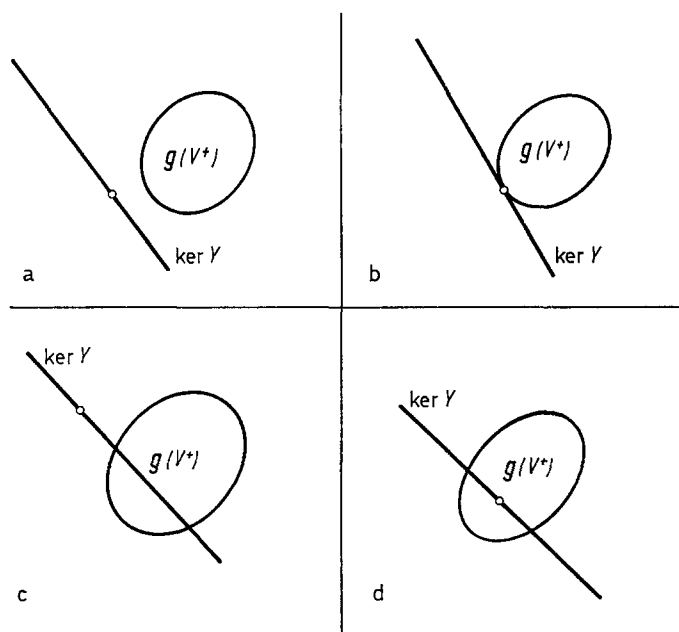
Fig. 1. Possible relations of $g(V^+)$ and ker Y. Both sets are subsets of W. The dot indicates the zero vector in W.

(a) ker Y and $g(V^+)$ do not intersect, i.e.

$$\ker Y \cap g(V^+) = \phi. \tag{3-14}$$

(b) ker Y and $g(V^+)$ intersect in 0 only:

$$\ker Y \cap g(V^+) = \{0\}. \tag{3-15}$$

(c) The intersection of ker Y and $g(V^+)$ is non-empty and does not contain 0:

$$0 \notin \ker Y \cap g(V^+) \ne \phi. \tag{3-16}$$

(d) The intersection of ker Y and $g(V^+)$ contains 0 and other vectors, i.e. $\{0\}$ is a proper subset of this intersection:

$$\{0\} \subsetneq \ker Y \cap g(V^+). \tag{3-17}$$

These four cases are represented schematically in Fig. 1, where ker Y appears as a straight line with a dot indicating the vector 0. Naturally, this is not meant to imply anything about the actual dimension of ker Y.

From equation (2-11) it follows that in *case (a)* no equilibrium concentration exists.

In *case (b)* there is at least one equilibrium concentration since $g(V^+)$ contains the zero vector. Furthermore, the complex formation vector is zero for all equilibrium concentrations so that, in case (b), the kinetic system is complex balanced.

In *case* (*c*) there is at least one equilibrium concentration but at no such concentration is the system complex balanced.

Finally, in *case* (*d*), there is at least one equilibrium concentration at which the system is complex balanced and one at which this is not the case.

Simple examples can easily be found to illustrate these four cases. In this paper examples will be defined by the usual diagrams representing reaction systems. If nothing is stated to the contrary it is implied that the set of species and complexes appearing in the diagram is complete and that an arrow is drawn if and only if the corresponding reaction rate is not the zero function on V^+. The three mass action systems represented by $\mathscr{A}(1) \to 2\mathscr{A}(1)$ (see 2-2), by $\mathcal{O} \to \mathscr{A}(1)$ (see 2-4), and by $\mathscr{A}(1) \to \mathscr{A}(2)$ correspond to case (a).

Next consider the mass action system

$$\mathscr{A}(1) \to \mathscr{A}(2) \to \mathscr{A}(3). \tag{3-18}$$

It can easily be shown that the equilibrium set E is the non-empty intersection of a one dimensional subspace of V with V^+. Clearly at every concentration in this set the system is complex balanced (though the system is not detailed balanced) since, in this case, each complex formation rate equals the corresponding species formation rate and the latter is zero on E. The system (3-18) is thus an example of case (b).

The systems $\mathscr{A}(1) \to \mathscr{A}(2)$ and (3-18) are examples of a more general situation where

$$\ker Y = \{\mathbf{0}\} \tag{3-19}$$

in which case either (3-14) or (3-15) must hold, and the kinetic system will be complex balanced if there is at least one equilibrium concentration. Equation (3-19) is satisfied if and only if the complex vectors are linearly independent. In particular, this is the case if all reactions are mono-molecular, *i.e.* if the complexes are identical with the species. In this case $n = m$ and Y is a nonsingular n by n matrix. In fact Y becomes the identity matrix if species and complexes are indexed in the obvious way, so that $\mathscr{A}(j) = \mathscr{C}(j)$.

An example of case (c) where equilibrium concentrations exist but where the kinetic system is not complex balanced at any equilibrium concentration is the mass action system

$$\mathscr{A}(1) \to \mathscr{A}(2), \quad 2\mathscr{A}(1) \leftarrow 2\mathscr{A}(2). \tag{3-20}$$

This system is closely related to the system

$$\mathscr{A}(1) \rightleftarrows \mathscr{A}(2), \quad 2\mathscr{A}(1) \rightleftarrows 2\mathscr{A}(2) \tag{3-21}$$
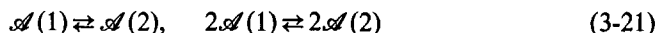
first discussed by WEGSCHEIDER [11].

In Section 6 it will be shown that for mass action kinetics case (d) is excluded. That is, for this type of kinetics, *complex balancing must occur either at all or at none of the equilibrium concentrations*. For general, non-mass action kinetics, however, this is not true, as is demonstrated in Appendix 2 by means of the reactions (3-21) with reaction rates chosen so that they do not all take mass action form.

Cases (c) and (d) can occur only if the complexes are linearly dependent. However, (a) and (b) may occur also for linearly dependent complexes as demonstrated by the system (2-4) (constant infusion), and by the system (3-21) with mass action kinetics, when the rate constant ratio of the second reaction pair equals the square of the corresponding ratio of the first pair. (See also Weg-scheider [11].)

4. The Quasithermostatic and Quasithermodynamic Conditions

In this section we shall describe two properties, called the quasi-thermodynamic and quasi-thermostatic properties which a general mass action system may or may not possess, and we shall discuss the implications of these properties with regard to the dynamic behavior. It has been stated (Shear [9]) that a property similar to our QTD property applies to *all* mass action systems, but this has been shown to be false (Higgins [2]).

A mass action system will be called *quasi-thermostatic* (QTS)* if there is a vector a in the positive orthant of species space such that c is an equilibrium concentration if and only if $\ln c - \ln a$ is in the orthogonal complement of the stoichiometric space. That is, a mass action system is QTS if and only if there is a vector a, $a \in V^+$ such that the equilibrium set E is given by

$$E = \{c \in V^+ \mid \ln c - \ln a \in S^\perp\}. \tag{4-1}$$

Also, if (4-1) is satisfied, we shall say that the system under consideration is QTS *with respect to a*.

A mass action system will be called *quasi-thermodynamic* (QTD)* if there is a vector a in V^+ such that

(a) *the system is QTS with respect to a and*

(b) *for all $c \in V^+$, $c \notin E$*

$$(\ln c - \ln a) \cdot f(c) < 0 \tag{4-2}$$

   where $f(c)$ is the species formation vector at c.

Also, if (a) and (b) are satisfied, we shall say the system is QTD *with respect to a*. It will be demonstrated later that QTS does not imply QTD though QTD implies QTS by (a). It can be shown that condition (b) alone implies QTS if it is assumed that the image of $\partial f / \partial c$ at every $c \in V^+$ is not only a subspace of S, which necessarily must be true because of (2-23), but is identical with S. Regarding this remark, the authors are grateful to M. R. Feinberg for clarifying discussions. (See also Feinberg [1].)

If a mass action system is QTS, then for any $c \in E$ and any $x \in S$

$$(\ln c - \ln a) \cdot x = 0. \tag{4-3}$$

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* Strictly speaking, the above definitions of quasi-thermostatic and quasi-thermodynamic behavior can apply to *any* kinetic system, which need not be restricted to the mass action form. They are identical with the classical thermodynamic conditions in a closed *ideal* system, and it is because the idea of mass action kinetics is physically associated with ideal mixtures that we have included the term "mass action kinetics" in the definitions. The mass action property is not required in the discussion of the pseudo-Helmholtz function below.

Since the elementary reaction vectors $x(i,j)=y(i)-y(j)$ (see 2-13) span S, the QTS condition can also be expressed in the form that $c\in E$ if and only if

$$(\ln c - \ln a) \cdot x(i,j) = 0 \tag{4-4}$$

for all elementary reactions vectors $x(i,j)$. From use of (2-18) an equivalent requirement is that $c\in E$ if and only if

$$c^{x(i,j)} = a^{x(i,j)}. \tag{4-5}$$

The right hand side of (4-5) will be called the *equilibrium constant* of the reaction $\mathscr{C}(j) \to \mathscr{C}(i)$.

Assume that a mass action system is QTS with respect to the vector a_1. Then the system is QTS with respect to a second vector a_2 if and only if

$$\ln a_1 - \ln a_2 \in S^\perp. \tag{4-6}$$

To prove this, we note first that if the system is QTS with respect to a_2, then a_2 is itself an equilibrium concentration. Thus the system can be QTS with respect to a_1 only if (4-6) is valid. Furthermore, consider the identity

$$\ln c - \ln a_2 = (\ln c - \ln a_1) - (\ln a_2 - \ln a_1); \tag{4-7}$$

if the system is QTS with respect to a_1, $\ln c - \ln a_1 \in S^\perp$, so if (4-6) is satisfied, $\ln c - \ln a_2 \in S^\perp$ also.

From this result, the definition of QTD, and (2-23) it follows that, if a mass action system is QTD with respect to a_1, (4-6) gives a necessary and sufficient condition that it should also be QTD with respect to a_2.

If S is a proper subspace of V, which is the case in particular for conservative kinetic systems, then $S^\perp$ contains infinitely many vectors. Then, if a kinetic system is QTS or QTD, there will be infinitely many vectors with respect to which it has these properties. If, on the other hand $S=V$, then $S^\perp=\{0\}$, and the system can be QTS or QTD with respect to at most one vector.

As an example consider the mass action system (3-18) with rate constants $k(2,1)$, $k(3,2)$, and $k(1,3)$. It is easily established that this system is QTS with respect to a where

$$a = \left(k^{-1}(2,1), k^{-1}(3,2), k^{-1}(1,3)\right)^T. \tag{4-8}$$

The elementary reaction vector $x(2,1)$, which corresponds to $\mathscr{A}(1) \to \mathscr{A}(2)$, is given by

$$x(2,1) = (-1,1,0)^T. \tag{4-9}$$

Thus the equilibrium constant for this reaction is $k(2,1)/k(3,2)$. That is, for any equilibrium concentration c the relation

$$\frac{c^2}{c^1} = \frac{k(2,1)}{k(3,2)} \tag{4-10}$$

must hold. This example demonstrates that if a mass action system is QTS, the equilibrium constant of the reaction $\mathscr{C}(j) \to \mathscr{C}(i)$ need not be equal to the ratio of the rate constants belonging to the forward and reverse reactions $\mathscr{C}(i) \to \mathscr{C}(j)$

and $\mathscr{C}(j) \to \mathscr{C}(i)$. For detailed balanced mass action kinetics, however, the equilibrium constant must be equal to this ratio.

In a non-conservative system the stoichiometric space S may contain one or more of the natural basis vectors of the species space V. In this case, if the system is QTS, the corresponding concentrations have fixed values everywhere in E. For example, if S contains the ith natural basis vector, it follows from (4-3) that, for all equilibrium concentrations,

$$c^i = a^i. \tag{4-11}$$

In particular, if $S = V$, then all the basis vectors are in S and (4-11) is valid for $i = 1, 2, ..., m$ at equilibrium. For an example of this type consider the system

$$\mathcal{O} \rightleftarrows \mathscr{A}(1) \tag{4-12}$$

corresponding to time invariant infusion of $\mathscr{A}(1)$ and first order decay of $\mathscr{A}(1)$. Here at equilibrium the condition

$$c^1 = \frac{k(2, 1)}{k(1, 2)} \tag{4-13}$$

must be satisfied, where the rate constants correspond to complexes defined by $\mathscr{C}(1) = \mathcal{O}$, $\mathscr{C}(2) = \mathscr{A}(1)$.

The mass action system (3-20) is an example of a system which is *not* QTS. Examples of systems which have or do not have the QTD property will be given in Section 7.

Consider now a mass action system which is QTD with respect to a, and introduce the function H,

$$H: \bar{V}^+ \to \mathsf{R} \tag{4-14}$$

defined by

$$H(c) = \sum{}' (\ln c^j - \ln a^j - 1) c^j \tag{4-15}$$

where $\sum'$ denotes the sum over all j for which $c^j \neq 0$. The sum over the empty set is to be taken equal to zero so that

$$H(0) = 0. \tag{4-16}$$

H will be called a *pseudo-Helmholtz function (PHF) with center a*. The following properties of the PHF can be derived easily from the definition (4-15).

(H1) H *is continuous everywhere in* $\bar{V}^+$.

(H2) H *is strictly convex in* $\bar{V}^+$.

(H3) H *has the following properties in the interior of its domain*:

$$H(c) = (\ln c - \ln a - e_v) \cdot c, \quad c \in V^+ \tag{4-17}$$

where e_v, $e_v \in V$, *is the vector with all coordinates equal to unity and H is continuously differentiable in* V^+ *with gradient* ∇H *given by*

$$\nabla H(c) = \ln c - \ln a. \tag{4-18}$$

(H4) *If* $c_1 \in \text{bdry } \bar{V}^+$, $c_2 \in V^+$, *then* $c_2 + \lambda (c_1 - c_2) \in V^+$ *for* $0 \leq \lambda < 1$ *and*

$$\lim_{\lambda \to 1} \frac{d}{d\lambda} H(c_2 + \lambda(c_1 - c_2)) = +\infty. \tag{4-19}$$

That is, H is increasing sufficiently close to the boundary of $\bar{V}^+$ if the boundary is approached from the interior along any straight line.

(H5) $$\lim_{|c| \to \infty} H(c) = +\infty$$ (4-20)

where $|c|$ denotes the Euclidian norm of c.

We shall now prove the following lemma.

Lemma 4A. *Given any reaction simplex, the pseudo-Helmholtz function assumes its minimum relative to this reaction simplex at a unique concentration in the positive orthant of species space.*

Proof. If the kinetic system is conservative, the reaction simplex is a non-empty, closed, and bounded subset of R^m, and the continuous function H must assume its minimum on this subset. If the system is non-conservative, the reaction simplex possesses all properties listed above except for boundedness. The existence of a minimum relative to the reaction simplex then follows from the property (H5), equation (4-20). Furthermore, a reaction simplex, by its definition, is the intersection of two convex sets and is therefore itself convex. Thus H restricted to a reaction simplex is a strictly convex function (property (H2)) and can assume its minimum relative to a reaction simplex at only one concentration. This completes the proof of the uniqueness part of the lemma. Finally, from property (H4) it follows that H cannot assume a minimum relative to a reaction simplex at a boundary point of $\bar{V}^+$.

There is a simple relation between the constrained minima of H in the reaction simplexes and the equilibrium set for a QTS system, as shown by the following lemma.

Lemma 4B. *If a mass action system is quasi-thermostatic with respect to a, then each reaction simplex contains precisely one equilibrium concentration, and the pseudo-Helmholtz function with center a assumes its minimum relative to a given reaction simplex at the equilibrium concentration contained in this simplex.*

Proof. By Lemma 4A we know that the PHF assumes a minimum relative to any given reaction simplex. The concentration c_* at which this minimum is attained lies in V^+ and, therefore, is an interior point in the relative topology of the simplex. Thus H must be stationary at c_* relative to displacements in the simplex, so at c_* the gradient of H must be orthogonal to any vector $c_* - c$, where c is in the simplex:

$$\nabla H(c_*) \in S^\perp.$$ (4-21)

It follows then from property (H3), equation (4-18), and from the definition of QTS that $c_* \in E$. This proves existence of an equilibrium and the second part of the lemma.

Next consider an equilibrium concentration c_* contained in a given simplex. By the definition of QTS

$$\ln c^* - \ln a \in S^\perp,$$ (4-22)

so the PHF is stationary at c_* relative to displacements in the simplex. However, a strictly convex function can have at most one stationary point. This proves the uniqueness part of the lemma and concludes the proof of Lemma 4 B.

Next consider the differential equation (2-29) for the function $c(t)$ of time subject to

$$c(0) = c_0 \in V^+. \tag{4-23}$$

A function $c(t)$ satisfying (2-29) and (4-23) will be called the *reaction path originating at* c_0.

We shall assume next that the kinetic system considered is of mass action type and is QTD with respect to a. Then, according to Lemma 4A, there is a unique concentration c_* in V^+ at which H, the PHF with center a, assumes its minimum on the reaction simplex containing c_0. Consider now an orthonormal basis $\{x_1, x_2, ..., x_s\}$ of the stoichiometric space and a matrix T with column vectors equal to the vectors of this basis. Then T affords a bijective linear transformation from R^s to S. Then by utilizing the relation (2-23) it is easy to show that a solution of

$$\frac{d\xi(t)}{dt} = \hat{f}(\xi(t)), \tag{4-24}$$

where $\xi(t) \in R^s$ and

$$\hat{f}(\xi(t)) = T^T f(c_* + T\xi(t)) \tag{4-25}$$

subject to

$$\xi(0) = \xi_0, \tag{4-26}$$

transforms into a solution of (2-29) and (4-23) by taking

$$c(t) = c_* + T\xi(t), \tag{4-27}$$

$$c_0 = c_* + T\xi_0. \tag{4-28}$$

We denote by P the open subset of R^s which is the inverse image of the positive reaction simplex containing c_0 and c_* under the affine transformation $\xi \mapsto c_* + T\xi$. On P the real valued function L will be defined by

$$L(\xi) = H(c_* + T\xi) - H(c_*) \quad \text{for } \xi \in P. \tag{4-29}$$

Then L has the following properties:

(L1) *L is continuously differentiable on P.* This follows immediately from the definition (4-29) and property (H3) of the PHF.

(L2) $L(\xi) \geq 0$ *on P with equality holding only for*

$$\xi = 0. \tag{4-30}$$

This follows from Lemma 4A, according to which H assumes its minimum in the positive reaction simplex only at c_*, and from the fact that $\xi \mapsto c_* + T\xi$ is bijective from P to the positive reaction simplex.

(L3) $\nabla_\xi L(\xi) \cdot \hat{f}(\xi) \leq 0 \quad on\ P$ (4-31)

with equality holding only for $\xi = 0$. This can be shown in the following way. First by utilizing (2-23) and the orthonormality of the column vectors of T one can show that

$$V_\xi L(\xi) \cdot \hat{f}(\xi) = VH(c_* + T\xi) \cdot f(c_* + T\xi). \tag{4-32}$$

According to the definition of a PHF and the definition of the QTD property, equation (4-2), the right hand side of (4-32) is non-positive and is 0 if and only if $c_* + T\xi \in E$. However, according to Lemma 4B a reaction simplex contains precisely one equilibrium concentration, which corresponds to $\xi = 0$ in our case, so that the right hand side of (4-32) is negative everywhere in P except at $\xi = 0$ where it is 0. This concludes the proof of property (L3).

The function L defined on the open subset P of R^s satisfies all conditions for a *Lyapunov function* for the differential equation (4-24) (see La Salle & Lefschetz [7]). According to the theorem of Lyapunov any solution of (4-24) originating in P remains in P and

$$\lim_{t \to \infty} \xi(t) = 0. \tag{4-33}$$

For solutions of (2-29) this has the consequence stated in the following lemma.

Lemma 4C. *If a mass action system is quasi-thermodynamic, then any reaction path $c(t)$ originating at a concentration c_0 in V^+ remains in the positive reaction simplex containing c_0. Furthermore*

$$\lim_{t \to \infty} c(t) = c_*$$

where c_* is the unique equilibrium concentration contained in this positive reaction simplex.

In systems which behave thermodynamically as ideal gas mixtures and which are genuinely closed (i.e., in the absence of external species and the zero complex), the *Helmholtz free energy function* is the product of a gas constant, temperature, volume and the *pseudo Helmholtz function* with a *particular* center a. Also, in this case, each coordinate a^j of the particular center is closely related to the *standard chemical potential* of species $\mathscr{A}(j)$:

$$-\ln a^j = \frac{\bar{\mu}_j(\theta)}{\bar{R}\theta} + \ln(\bar{R}\theta) \tag{4-34}$$

where $\bar{R}$ and θ are the gas constant and the absolute temperature, respectively, and $\bar{\mu}_j(\theta)$ is the standard chemical potential of $\mathscr{A}(j)$ at temperature θ.

As an example, consider a closed vessel at constant temperature containing, at sufficiently low pressure, Cl atoms and Cl_2 molecules. Then the mass action system corresponding to the reactions $Cl_2 \rightleftarrows 2Cl$ is QTD and there is an $a \in V^+$ such that the PHF with center a is proportional to the Helmholtz free energy function. Next consider the same system under the influence of a time invariant radiation flux with a frequency absorbed by Cl_2. Then it is easy to show that the system is still QTD, but the PHF is no longer related to the Helmholtz free

energy function, as indicated by the fact that the equilibrium constant (in our notation) of the reactions $Cl_2 \rightleftarrows 2Cl$ is changed under irradiation.

Systems which interact with the environment through external species (photons in the above example) are *not necessarily QTD*, but if they are QTD, as in the above example, the *pseudo-Helmholtz function* is *not* related to the *Helmholtz free energy function*.

5. Reaction Cycles

In this section kinetic systems called *reaction cycles* will be studied. These cycles will be of importance for the next section, where it will be shown that complex balanced mass action systems can be decomposed into reaction cycles in such a way that certain results valid for complex balanced reaction cycles are also valid for all complex balanced mass action systems.

It will be convenient in what follows to use the notation $\langle Y, K \rangle$ for the mass action system with complex matrix Y and rate constant matrix K. The symbols m and n will be used throughout to indicate the number of species and of complexes, respectively. It is always assumed that

$$m \geqq 1, \quad n \geqq 2. \tag{5-1}$$

The sets of integers $\{1, 2, ..., m\}$ and $\{1, 2, ..., n\}$ will be called *species indices* and *complex indices*, respectively. A family $v_0, v_1, ..., v_l, l \geqq 2$, of complex indices will be called a *cycle*, in particular, an *l-cycle* in $\langle Y, K \rangle$ if

$$v_0 = v_l \tag{5-2}$$

and all other members of the family are distinct, and if

$$\mathscr{C}(v_{j-1}) \to \mathscr{C}(v_j), \quad j = 1, 2, ..., l \tag{5-3}$$

are elementary reactions in $\langle Y, K \rangle$; that is,

$$k(v_j, v_{j-1}) > 0, \quad j = 1, 2, ..., l. \tag{5-4}$$

The set of reactions (5-3) will be called a *reaction cycle*, and l will be called the length of the reaction cycle.

The mass action system $\langle Y, K \rangle$, the rate constant matrix K, and the kinetic matrix ρK will be called *cyclic* if the reactions (5-3) are the *only* elementary reactions in $\langle Y, K \rangle$, that is, if all rate constants are zero except those required to be positive by (5-4).

In view of the decomposition of complex balanced mass action systems, which will be discussed in the next section, it is convenient to admit mass action systems containing complexes which are not involved in reactions. In particular, if $\langle Y, K \rangle$ is cyclic, it may be that the length l of the cycle is smaller than n, the total number of complexes in the system. Naturally, if one were exclusively interested in one particular cyclic system, one would make n equal to l and, in addition, would index the complexes so that $v_1 = 1, v_2 = 2, ..., v_l = l$.

If $\langle Y, K \rangle$ is cyclic, its species formation vector (see (2-22)) is given by

$$f(c) = \sum_{j=1}^{l} k(v_j, v_{j-1}) c^{y(v_{j-1})} (y(v_j) - y(v_{j-1})), \tag{5-5}$$

and the rate of formation of complex $\mathscr{C}(v_j)$ is given by

$$g^{v_j}(c) = k(v_j, v_{j-1}) c^{y(v_{j-1})} - k(v_{j+1}, v_j) c^{y(v_j)} \quad \text{for } j = 1, 2, ..., l. \; \star \quad (5\text{-}6)$$

It follows from (5-6) that a cyclic $\langle Y, K \rangle$ is complex balanced at a, $a \in V^+$, if and only if

$$k(v_j, v_{j-1}) a^{y(v_{j-1})} - k(v_{j+1}, v_j) a^{y(v_j)} = 0 \quad \text{for } j = 1, 2, ..., l. \; \star \quad (5\text{-}7)$$

In other words, if and only if the rates of all elementary reactions are equal at a,

$$k(v_j, v_{j-1}) a^{y(v_{j-1})} = \kappa \quad \text{for } j = 1, 2, ..., l. \quad (5\text{-}8)$$

Clearly,

$$\kappa > 0. \quad (5\text{-}9)$$

For a cyclic $\langle Y, K \rangle$ which is complex balanced at a, it follows from (5-5) and (5-8) that the species formation vector is given by

$$f(c) = \kappa \sum_{j=1}^{l} \left(\frac{c}{a}\right)^{y(v_{j-1})} (y(v_j) - y(v_{j-1})). \quad (5\text{-}10)$$

By slight rearrangement of the terms one obtains from (5-10)

$$f(c) = \kappa \sum_{j=1}^{l} y(v_j) \left(\left(\frac{c}{a}\right)^{y(v_{j-1})} - \left(\frac{c}{a}\right)^{y(v_j)}\right) \quad (5\text{-}11)$$

and correspondingly from (5-6), for the rate of formation of complex $\mathscr{C}(v_j)$,

$$g^{v_j}(c) = \kappa \left(\left(\frac{c}{a}\right)^{y(v_{j-1})} - \left(\frac{c}{a}\right)^{y(v_j)}\right). \quad (5\text{-}12)$$

We shall now prove the following lemma.

Lemma 5A. *If a cyclic mass action system is complex balanced at some concentration a, $a \in V^+$, then it is quasi-thermodynamic with respect to a.*

Proof. Let a be the concentration at which the cyclic $\langle Y, K \rangle$ is complex balanced. Then it follows from (2-19) and (5-10) that

$$(\ln c - \ln a) \cdot f(c) = \kappa \left(\ln \frac{c}{a}\right) \cdot \sum_{j=1}^{l} \left(\frac{c}{a}\right)^{y(v_{j-1})} (y(v_j) - y(v_{j-1})) \quad (5\text{-}13)$$

or, using (2-18) gives

$$(\ln c - \ln a) \cdot f(c) = \kappa \sum_{j=1}^{l} \left(\frac{c}{a}\right)^{y(v_{j-1})} \left(\ln \left(\frac{c}{a}\right)^{y(v_j)} - \ln \left(\frac{c}{a}\right)^{y(v_{j-1})}\right). \quad (5\text{-}14)$$

Conclusions regarding the sign of the right hand side of (5-14) can be reached by use of a general inequality which will now be stated. It is derived in Appendix 3. Let φ be a strictly increasing real valued function defined on a subset of the reals and $\xi_0, \xi_1, ..., \xi_l$ any real numbers in the domain of φ subject to $\xi_0 = \xi_l$, $l \geq 2$. Then

$$\sum_{j=1}^{l} \xi_{j-1} \left(\varphi(\xi_j) - \varphi(\xi_{j-1})\right) \leq 0 \quad (5\text{-}15)$$

_____
$\star \; v_{l+1} \equiv v_1.$

with equality holding if and only if

$$\xi_0 = \xi_1 = \cdots = \xi_l. \tag{5-16}$$

Now in equation (5-14), $\kappa > 0$ and the logarithmic function is a strictly increasing function of the positive reals, so if we set

$$\xi_j = \left(\frac{c}{a}\right)^{y(v_j)}, \tag{5-17}$$

it follows from (5-14) and (5-15) that

$$(\ln c - \ln a) \cdot f(c) \leqq 0 \quad \text{for all } c \in V^+ \tag{5-18}$$

with equality holding if and only if

$$\left(\frac{c}{a}\right)^{y(v_{j-1})} = \left(\frac{c}{a}\right)^{y(v_j)}, \quad j = 1, 2, \ldots, l. \tag{5-19}$$

Equation (5-19) is equivalent to

$$(\ln c - \ln a) \cdot x(j) = 0, \quad j = 1, 2, \ldots, l \tag{5-20}$$

where $x(j)$ is the reaction vector belonging to $\mathscr{C}(v_{j-1}) \to \mathscr{C}(v_j)$, namely

$$x(j) = y(v_j) - y(v_{j-1}). \tag{5-21}$$

Note that the family $x(1)$, $x(2)$, ..., $x(l)$ comprises all elementary reaction vectors of the cyclic $\langle Y, K \rangle$.

Next consider a concentration c in the equilibrium set of $\langle Y, K \rangle$. For this concentration $f(c) = 0$, so that equality applies in (5-18), and (5-20) is valid for concentration c. On the other hand, if equation (5-20) is satisfied for a certain concentration c, then (5-19) is also satisfied for this c, and according to (5-11) $f(c) = 0$. This shows that $c \in E$ if and only if (5-20) is valid, and hence that $\langle Y, K \rangle$ is QTS with respect to a. From (5-18) it then follows that $\langle Y, K \rangle$ is QTD with respect to a since equality in (5-18) implies $c \in E$, so (4-2) is satisfied. This concludes the proof of Lemma 5A.

A second result is easily established for cyclic mass action systems, namely

Lemma 5B. *If a cyclic mass action system is complex balanced at some concentration* a, $a \in V^+$, *then it is complex balanced at all equilibrium concentrations.*

Proof. Let $\langle Y, K \rangle$ be cyclic and complex balanced at a. Then if $c \in E$, equation (5-19) must hold, which implies by (5-12) that $\langle Y, K \rangle$ is complex balanced at c, concluding the proof of Lemma 5B.

Lemma 5B shows that the situation expressed by equation (3-17) and represented in Fig. 1d is excluded for cyclic mass action systems. As will be shown in the next section this situation is excluded for mass action systems in general.

By using the notation of equation (2-28) the following is an immediate consequence of the foregoing lemmas.

Corollary 5C. *If* $\langle Y, K \rangle$ *is cyclic and complex balanced at* a *and if* $A = \rho K$, *then*

$$(\ln c - \ln a) \cdot Y A c^Y \leqq 0 \quad \text{for all } c \in V^+ \tag{5-22}$$

with equality holding if and only if $c \in E$, *i.e., if and only if*

$$YA c^Y = 0.$$ (5-23)

Furthermore,

$$YA c^Y = 0 \Leftrightarrow A c^Y = 0.$$ (5-24)

6. Decomposition into Cycles

We shall prove in this section the main theorem of our paper.

Theorem 6A. *If a mass action system is complex balanced at some concentration a in the positive orthant of species space, then the system is quasi-thermodynamic with respect to a. Furthermore, the system is complex balanced at all equilibrium concentrations and is, therefore, a complex balanced mass action system.*

In the previous section it has been shown that the two statements of the theorem are valid for cyclic mass action systems. We shall prove their validity for general mass action systems using a method based on a decomposition of a general complex balanced mass action system into complex balanced cycles.

It will be useful to introduce the following notation. A *chain of complex indices* in $\langle Y, K \rangle$ is a family $\mu_0, \mu_1, ..., \mu_p, p \geq 1$, of such indices with the property that

$$k(\mu_j, \mu_{j-1}) > 0, \quad j = 1, ..., p.$$ (6-1)

That is, the reactions

$$\mathscr{C}(\mu_{j-1}) \to \mathscr{C}(\mu_j)$$ (6-2)

are elementary reactions of $\langle Y, K \rangle$.

The family of reactions (6-2) will be called a *chain of elementary reactions*, and the family of complexes $\mathscr{C}(\mu_j), j = 0, 1, ... p$, will be called a *chain of complexes* in $\langle Y, K \rangle$. The integer p will be called the *length of the chain*. μ_0 and $\mathscr{C}(\mu_0)$ will be called the *initial index* and *initial complex* of the chain respectively and μ_p and $\mathscr{C}(\mu_p)$ the *terminal index* and *terminal complex*. Each reaction cycle is a chain but not vice versa, since for a chain it is not required that initial and terminal complex be identical, nor is it necessary that the other complexes of the chain be distinct. Note, however, that because of the convention $k(i, i) = 0$ no two adjacent indices or complexes in a chain can be identical.

If the length p of a chain equals or exceeds the number n of complexes in the mass action system under consideration,

$$p \geq n,$$ (6-3)

the chain will be called a *long chain*. Since a long chain contains at least $n + 1$ complex indices, at least one idex must be repeated. In particular, there must exist a number β which is the smallest number such that one of the indices μ_0, $\mu_1, ..., \mu_{\beta-1}$ equals μ_β. Let μ_α be this index and set

$$v_0 = \mu_\alpha, \quad v_1 = \mu_{\alpha+1}, ..., v_l = \mu_\beta = \mu_{\alpha+l}.$$ (6-4)

Then the indices $v_0, v_1, ..., v_l$ are distinct except that $v_0 = v_l$, so the family of indices $v_0, v_1, ..., v_l$ is a cycle in $\langle Y, K \rangle$. Thus, if a long chain exists in $\langle Y, K \rangle$,

then there must also exist a cycle in $\langle Y, K \rangle$ (though, of course, $\langle Y, K \rangle$ need not be cyclic).

We shall now prove the following lemma.

Lemma 6B. *If $\langle Y, K \rangle$ is complex balanced at a with $K \neq 0$, then there exists a long chain and hence a cycle in $\langle Y, K \rangle$.*

(Obviously the lemma is false if $K = 0$ is not excluded. It is convenient not to require that all complexes in $\langle Y, K \rangle$ participate in reactions, so it is necessary to emphasize in the lemma the exclusion of the trivial case $K = 0$.)

Proof. The condition $K \neq 0$ implies the existence of a non-zero rate constant. Assume that

$$k(i, j) > 0. \tag{6-5}$$

Since the system is complex balanced at a, it follows that at a the rates of creation and annihilation for complex $\mathscr{C}(i)$ are equal:

$$\sum_{v=1}^{n} k(i, v) a^{y(v)} = a^{y(i)} \sum_{\mu=1}^{n} k(\mu, i). \tag{6-6}$$

(6-5) implies that the left hand side of (6-6) is positive, so the sum on the right hand side must be positive too. This implies the existence of h such that

$$k(h, i) > 0. \tag{6-7}$$

Next set $j = \mu_0$, $i = \mu_1$ and $h = \mu_2$ in (6-5); then apply the above result to $k(h, i)$, establishing the existence of a $k(l, h) > 0$, and so on. In this way an arbitrarily long chain $\mu_0, \mu_1, \mu_2, \ldots$, can be constructed. Thus there is a long chain in $\langle Y, K \rangle$, and the proof is complete.

We shall next prove the following lemma.

Lemma 6C. *If $\langle Y, K \rangle$ is complex balanced at a and if $K \neq 0$, then there exist rate constant matrices K_1 and K_1' such that*

(a) $K = K_1 + K_1'$.

(b) $\langle Y, K_1 \rangle$ *is cyclic and complex balanced at a.*

(c) $\langle Y, K_1' \rangle$ *is complex balanced at a and the number of non-zero rate constants in $\langle Y, K_1' \rangle$ is smaller than the corresponding number in $\langle Y, K \rangle$.*

(d) *The union of the elementary reactions in $\langle Y, K_1 \rangle$ and $\langle Y, K_1' \rangle$ equals the set of elementary reactions in $\langle Y, K \rangle$.*

Proof. From Lemma 6B the existence of a cycle in $\langle Y, K \rangle$ follows. Let v_0, $v_1, \ldots, v_l$ be the corresponding cycle indices and consider the reaction rates $k(v_j, v_{j-1}) a^{y(v_{j-1})}$ in this cycle. Since K is not necessarily cyclic (other reactions than those in the cycle may exist in $\langle Y, K \rangle$) these rates need not be equal, though $\langle Y, K \rangle$ is complex balanced at a. Let κ_1 be defined by

$$\kappa_1 = \min_{j=1,\ldots l} k(v_j, v_{j-1}) a^{y(v_{j-1})} \tag{6-8}$$

and $k_1(i, j)$ be defined by

$$k_1(v_j, v_{j-1}) = \kappa_1/a^{y(v_{j-1})}, \quad j = 1, 2, ..., l,$$
$$k_1(i, j) = 0 \quad \text{if} \quad (i, j) \neq (v_j, v_{j-1}) \quad \text{for all } j = 1, 2, ..., l. \tag{6-9}$$

From (6-8) and (6-9) it follows that

$$k_1(i, j) \leq k(i, j) \quad \text{all } i, j \tag{6-10}$$

with equality for at least one index pair (i, j) such that $k(i, j) \neq 0$.

Next, if we define $k'_1(i, j)$ by

$$k'_1(i, j) = k(i, j) - k_1(i, j), \tag{6-11}$$

it follows that

$$k'_1(i, j) \geq 0 \quad \text{all } i, j \tag{6-12}$$

and that the number of index pairs for which $k'_1(i, j) = 0$ is larger than the corresponding number for $k(i, j)$.

Let K_1 and K'_1 be the rate constant matrices with elements $k_1(i, j)$ and $k'_1(i, j)$, respectively, and let A_1 and A'_1 be the corresponding kinetic matrices ρK_1 and $\rho K'_1$. It is obvious then that K_1 and K'_1 satisfy part (a) of Lemma 6C. Also, from the definition of K_1, in particular from (6-9), it follows that $\langle Y, K_1 \rangle$ is cyclic and complex balanced at a, proving part (b). Furthermore, since $\langle Y, K \rangle$ and $\langle Y, K_1 \rangle$ are both complex balanced at a, $A a^Y = A_1 a^Y = 0$ (where $A = \rho K$). Since $A'_1 = A - A_1$, this implies that $A'_1 a^Y = 0$, and hence that $\langle Y, K'_1 \rangle$ is complexed balanced at a. Together with the statement following (6-12) above this completes the proof of part (c) of the lemma. Finally, part (d) of the lemma is true since $k(i, j) > 0$ is equivalent to $k_1(i, j) > 0$ and/or $k'_1(i, j) > 0$. This concludes the proof of Lemma 6C.

The result of Lemma 6C can be extended to give a complete decomposition of any mass action system complex balanced at a into cycles complex balanced at a, as follows.

Lemma 6D. *If $\langle Y, K \rangle$ is complex balanced at a and if $K \neq 0$, then there exist rate constant matrices $K_1, K_2, ..., K_\delta$ such that*

(a) $K = K_1 + K_2 + \cdots + K_\delta$;

(b) *$\langle Y, K_j \rangle$ is cyclic and complex balanced at a for $j = 1, 2, ..., \delta$;*

(c) *the union of the elementary reactions in $\langle Y, K_j \rangle$ $j = 1, 2, ..., \delta$ equals the set of elementary reactions in $\langle Y, K \rangle$.*

Proof. If the rate constant matrix K'_1 of Lemma 6C equals 0, then $\delta = 1$, and the lemma is proved. If, on the other hand, $K'_1 \neq 0$, then Lemma 6C can be applied to K'_1:

$$K'_1 = K_2 + K'_2 \tag{6-13}$$

where K_2 is cyclic and both $\langle Y, K_2 \rangle$ and $\langle Y, K'_2 \rangle$ are complex balanced at a. If $K'_2 \neq 0$, the procedure can be repeated, and so on as long as necessary. Since in each step, according to part (c) of Lemma 6C, the number of non-zero rate constants in $\langle Y, K_j \rangle$ decreases, it follows that $K'_\delta = 0$ for some δ and the process

terminates. This proves parts (a) and (b) of the lemma. Part (c) is an immediate consequence of Lemma 6C.

We are now in a position to prove the main result, Theorem 6A. Let $\langle Y, K \rangle$ be complex balanced at a, and let $f(c)$ be the species formation vector for $\langle Y, K \rangle$. Then from (2-28) and from Lemma 6D it follows that

$$(\ln c - \ln a) \cdot f(c) = \sum_{j=1}^{\delta} (\ln c - \ln a) \cdot Y A_j c^Y \qquad (6\text{-}14)$$

where A_j, $A_j = \rho K_j$, $j = 1, 2, \ldots \delta$, is cyclic and complex balanced at a. It then follows from (5-22) that each term in the sum is non-positive:

$$(\ln c - \ln a) \cdot Y A_j c^Y \leqq 0, \quad c \in V^+, \; j = 1, 2, \ldots, \delta; \qquad (6\text{-}15)$$

thus, from (6-14) and (6-15)

$$(\ln c - \ln a) \cdot f(c) \leqq 0, \quad c \in V^+. \qquad (6\text{-}16)$$

Next assume that $c \in E$ where E is the equilibrium set in $\langle Y, K \rangle$. Then $f(c) = 0$ so that equality applies in (6-16). It follows then from (6-14) and (6-15) that equality applies for each term in the sum of (6-14):

$$(\ln c - \ln a) \cdot Y A_j c^Y = 0, \quad j = 1, 2, \ldots, \delta. \qquad (6\text{-}17)$$

Since A_j is cyclic and complex balanced at a, it then follows from Corollary 5C that

$$A_j c^Y = 0, \quad j = 1, 2, \ldots, \delta \qquad (6\text{-}18)$$

and that $c \in E_j$ where E_j is the equilibrium set of $\langle Y, K_j \rangle$. However, $\langle Y, K_j \rangle$ is QTS with respect to a, so $\ln c - \ln a$ is orthogonal to all elementary reaction vectors of $\langle Y, K_j \rangle$. Since this is true for all j, $j = 1, 2, \ldots, \delta$, it follows from part (c) of Lemma 6D that $\ln c - \ln a$ is orthogonal to S, the stoichiometric space of $\langle Y, K \rangle$. Thus we have shown that

$$c \in E \Rightarrow \ln c - \ln a \in S^\perp. \qquad (6\text{-}19)$$

Clearly, the reverse implication also holds, for if $\ln c - \ln a$ is in $S^\perp$, then it is orthogonal to all elementary reaction vectors in $\langle Y, K_j \rangle$ for any j. Thus, since $\langle Y, K_j \rangle$ is QTS with respect to a, $Y A_j c^Y = 0$, which implies $Y A c^Y = 0$ and hence $c \in E$. Thus we have shown that

$$c \in E \Leftrightarrow \ln c - \ln a \in S^\perp \qquad (6\text{-}20)$$

and hence that $\langle Y, K \rangle$ is QTS. Furthermore, equality in (6-15) can apply (for each j) only if $c \in E$, since each $\langle Y, K_j \rangle$ is QTD by Lemma 5A. Thus equality in (6-16) applies only if $c \in E$, so $\langle Y, K \rangle$ is QTD, completing the proof of the first part of Theorem 6A. Recalling that $c \in E$ implies (6-18) and consequently $A c^Y = 0$, we see that $c \in E$ implies zero complex formation rate (see (2-25)) and hence complex balancing at c. This concludes the proof of Theorem 6A.

7. Examples

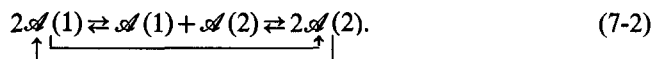In this section we shall illustrate some of the results obtained earlier by examples.

WEGSCHEIDER's [11] mass action systems (1-1) and (3-21) are easily shown not to satisfy the QTS and, consequently, the QTD conditions unless certain relations between the rate constants, known as *Wegscheider's conditions*, hold. The Wegscheider conditions imply detailed balancing and, therefore, complex balancing. The mass action systems (1-1) and (3-21) satisfy complex balancing only if they also satisfy detailed balancing. On the other hand the kinetic system (3-18) is complex balanced but not detailed balanced.

In order to state further results some terminology will be introduced. A mass action system will be called *reversible* if $k(i,j)>0$ implies $k(j,i)>0$. It will be called *weakly reversible* if the following holds: if there is a chain of elementary reactions with initial complex $\mathscr{C}(i)$ and terminal complex $\mathscr{C}(j)$, then there is also a chain of elementary reactions with initial complex $\mathscr{C}(j)$ and terminal complex $\mathscr{C}(i)$. Every reversible mass action system is also weakly reversible but not vice versa. For instance the system (3-18) is weakly reversible but not reversible. It may be shown (HORN [3]) that weak reversibility is necessary for complex balancing. A mass action system will be called *unconditionally* complex balanced (detailed balanced, QTS, QTD) if it has this property and also remains complex balanced (detailed balanced, QTS, QTD) if the positive rate constants in the system are arbitrarily changed, while remaining positive. The following can then be shown (HORN [3]). A weakly reversible mass action system is either unconditionally complex balanced, or the rate constants must satisfy certain conditions, analogous to the Wegscheider conditions for detailed balancing, in order to assure complex balancing. Also, it may be shown that there are always values for the rate constants which satisfy these conditions. It is easy to prove that every weakly reversible first order mass action system (here complexes are identical with species) is unconditionally complex balanced (see also HORN [4]). Clearly every weakly reversible two complex system must be unconditionally complex balanced since weak reversibility implies reversibility and detailed balancing in this case. However a corresponding result is not true for 3-complex systems.

A complex will be called *short* if the species molecularities in the complex are 0, 1, or 2, and if the sum of all these molecularities is 2 or less. It may then (HORN [5]) be shown that all weakly reversible mass action systems involving 3 short complexes are unconditionally complex balanced, with the exception of the two systems

$$\mathscr{O} \rightleftarrows \mathscr{A}(1) \rightleftarrows 2\mathscr{A}(1) \tag{7-1}$$

and

$$2\mathscr{A}(1) \rightleftarrows \mathscr{A}(1) + \mathscr{A}(2) \rightleftarrows 2\mathscr{A}(2). \tag{7-2}$$
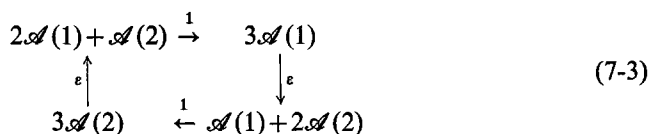
(It is to be understood here and later that some rate constants in (7-1) and (7-2) may be zero provided the weak reversibility condition is met.) Note that (7-1) is non-conservative, while (7-2) is a conservative system. The stoichiometric space of (7-2) may be represented by the overall reaction $\mathscr{A}(1)=\mathscr{A}(2)$. To see that the

mass action system (7-2) is not unconditionally complex balanced, assume that all rate constants in this system are unity with the exception of the constant belonging to $2\mathscr{A}(1) \to \mathscr{A}(1) + \mathscr{A}(2)$, which is 10. Then $a = (1, 2)^T$ is an equilibrium concentration at which the complex formation vector is not zero, since the formation rate of $2\mathscr{A}(1)$ equals -5 at a.

Even though (7-1) and (7-2) are not unconditionally complex balanced, they are unconditionally quasi-thermostatic and quasi-thermodynamic, as can be shown by straightforward computation of the equilibrium set and $\dot{H}$, the time derivative of a PHF centered at some equilibrium concentration. Thus all weakly reversible mass action systems involving 3 short complexes are unconditionally quasi-thermodynamic. Furthermore, the systems (7-1) and (7-2) demonstrate that *complex balancing is not necessary for quasi-thermodynamic behavior.*

Consider next the mass action system

$$2\mathscr{A}(1) + \mathscr{A}(2) \overset{1}{\to} \quad 3\mathscr{A}(1)$$
$$\varepsilon \uparrow \qquad\qquad \downarrow \varepsilon \qquad\qquad (7\text{-}3)$$
$$3\mathscr{A}(2) \quad \overset{1}{\leftarrow} \mathscr{A}(1) + 2\mathscr{A}(2)$$

with rate constants as indicated in the diagram. This system is not reversible but is weakly reversible for $\varepsilon > 0$. Its stoichiometric space is represented by the overall reaction $\mathscr{A}(1) = \mathscr{A}(2)$. Dynamically (7-3) is described by

$$\dot{c}^1 = -\dot{c}^2 = (c^2 - c^1)\left[2\varepsilon(c^1)^2 + (2\varepsilon - 1)c^1 c^2 + 2\varepsilon(c^2)^2\right], \qquad (7\text{-}4)$$

and it can be seen that $c \in E$ if and only if either

$$c^1 = c^2 \qquad\qquad (7\text{-}5)$$

or

$$2\varepsilon(c^1)^2 + (2\varepsilon - 1)c^1 c^2 + 2\varepsilon(c^2)^2 = 0. \qquad (7\text{-}6)$$

For $\varepsilon = 0$ and for $\varepsilon > \frac{1}{6}$ there is no $c \in V^+$ satisfying (7-6), and for $\varepsilon = \frac{1}{6}$ c satisfies (7-6) only if (7-5) is valid. The equilibrium set described by (7-5) and $c \in V^+$ clearly satisfies the QTS condition, so it can be stated that the mass action system (7-3) is QTS for $\varepsilon = 0$ and $\varepsilon \geq \frac{1}{6}$.

For $0 < \varepsilon < \frac{1}{6}$ there exist two numbers κ_1 and κ_2 with

$$0 < \kappa_1 < 1 < \kappa_2 \qquad\qquad (7\text{-}7)$$

such that (7-6) is valid in V^+ if and only if

$$\frac{c_2}{c_1} = \kappa_1 \quad \text{or} \quad \frac{c_2}{c_1} = \kappa_2. \qquad (7\text{-}8)$$

Thus (7-3) can not be QTS if $0 < \varepsilon < \frac{1}{6}$. Indeed, in this case there are three equilibrium points in each positive reaction simplex. (It is easily shown that the one belonging to $c^1 = c^2$ is unstable while the two others are locally stable.)

Let H be a pseudo-Helmholtz function centered at $(1, 1)^T$. Then $\dot{H}$ for the system (7-3) is given by

$$\dot{H}(c) = \left[2\varepsilon(c^1)^2 + (2\varepsilon - 1)c^1 c^2 + 2\varepsilon(c^2)^2\right](c^2 - c^1)\ln\frac{c^1}{c^2}. \qquad (7\text{-}9)$$

Now

$$(c^2 - c^1) \ln \frac{c^1}{c^2} \leq 0 \qquad (7\text{-}10)$$

for all $c \in V^+$, with equality holding if and only if $c^1 = c^2$. In V^+ the remaining factor in (7-9) is positive for $\varepsilon > \frac{1}{6}$, non-negative for $\varepsilon = \frac{1}{6}$ (and zero only when $c^1 = c^2$), indefinite for $0 < \varepsilon < \frac{1}{6}$, and negative for $\varepsilon = 0$. Thus the mass action system (7-3) is QTD only for $\varepsilon \geq \frac{1}{6}$. Furthermore, as can easily be checked, it is complex balanced only if $\varepsilon = 1$ and is not detailed balanced for any ε.

These results are summarized in the table below where $+$ and $-$ indicate validity and invalidity of the property stated at the top of the respective column. It can be seen that QTS does not imply QTD, and it is demonstrated again that CB is not a necessary condition for QTD.

The phenomenon of bistability (two locally stable equilibria in a positive reaction simplex), which occurs in the region $0 < \varepsilon < \frac{1}{6}$, is not restricted to non-reversible systems. It is not difficult to see that a sufficiently slight perturbation of (7-3) (for $0 < \varepsilon < \frac{1}{6}$) preserves this phenomenon even if the system is made reversible by the perturbation.

We shall now consider two mass action kinetics $\langle Y_1, K_1 \rangle$ and $\langle Y_2, K_2 \rangle$ which share the same species and, consequently, have identical species spaces V. These two kinetics will be called *macro equivalent* if the respective species formation functions f_1 and f_2 are identical, *i.e.* if

$$f_1(c) = f_2(c) \qquad \text{for all } c \in V^+. \qquad (7\text{-}11)$$

Clearly, macro-equivalent kinetics are indistinguishable by macroscopic observations. It may be shown that under very weak assumptions (*e.g.*, weak span reversibility is sufficient but not necessary) the stoichiometric space S equals the of the image of the species formation function f,

$$S = \text{span } f(V^+), \qquad (7\text{-}12)$$

so that S is then macroscopically observable*. It follows then that under these assumptions the QTD property too is macroscopically observable, and, therefore, two macro-equivalent kinetics either must both have or both not have this property. As will be demonstrated by example, the same is not true for the complex balancing property; that is, it may happen that of two macro-equivalent mass
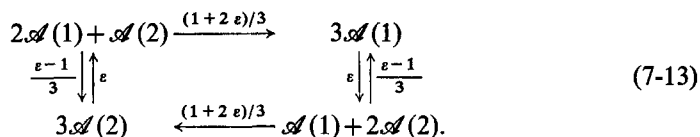
Table 1. *Properties of the mass action system (7–3) for various ε regions*

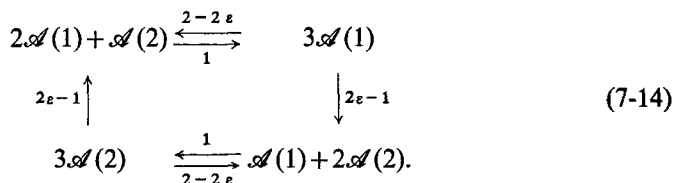|	QTS	QTD	CB	DB
$\varepsilon = 0$	$+$	$-$	$-$	$-$
$0 < \varepsilon < \frac{1}{6}$	$-$	$-$	$-$	$-$
$\frac{1}{6} \leq \varepsilon < 1$	$+$	$+$	$-$	$-$
$\varepsilon = 1$	$+$	$+$	$+$	$-$
$\varepsilon > 1$	$+$	$+$	$-$	$-$

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* An example for which (7-12) is *not* satisfied is the mass action system $\mathscr{A}(1) \rightarrow \mathscr{A}(2)$, $\mathscr{A}(1) \rightarrow \mathscr{A}(3)$.

action systems only one is complex balanced. This may be used to identify a class of quasi-thermodynamic mass action kinetics which is larger than the class of complex balanced mass action kinetics, since clearly every mass action kinetics is quasi-thermodynamic, which satisfies (7-12) and which is macro-equivalent to a complex balanced mass action kinetics.

As an example consider the mass action system (7-3) with $\varepsilon \geq 1$. This system is macro-equivalent to the complex balanced system

$$2\mathscr{A}(1)+\mathscr{A}(2) \xrightarrow{(1+2\,\varepsilon)/3} \quad 3\mathscr{A}(1)$$
$$\frac{\varepsilon-1}{3}\Big\downarrow\Big\uparrow\varepsilon \qquad\qquad\qquad \varepsilon\Big\uparrow\Big\downarrow\frac{\varepsilon-1}{3} \qquad\qquad (7\text{-}13)$$
$$3\mathscr{A}(2) \quad \xleftarrow{(1+2\,\varepsilon)/3} \quad \mathscr{A}(1)+2\mathscr{A}(2).$$

The condition $\varepsilon \geq 1$ is necessary to ensure non-negativity of all rate constants in (7-13). If $\frac{1}{2} \leq \varepsilon \leq 1$, then (7-3) is macro-equivalent to the complex balanced mass action system

$$2\mathscr{A}(1)+\mathscr{A}(2) \xrightleftharpoons[1]{2-2\,\varepsilon} \quad 3\mathscr{A}(1)$$
$$2\varepsilon-1\Big\uparrow \qquad\qquad\qquad\qquad \Big\downarrow 2\varepsilon-1 \qquad\qquad (7\text{-}14)$$
$$3\mathscr{A}(2) \quad \xrightleftharpoons[2-2\,\varepsilon]{1} \quad \mathscr{A}(1)+2\mathscr{A}(2).$$

Thus the QTD property of (7-3) follows for $\varepsilon \geq \frac{1}{2}$ from the existence of macro-equivalent complex balanced systems. Since (7-3) is not QTD for $0 \leq \varepsilon < \frac{1}{6}$, there cannot be any macro-equivalent complex balanced system in this ε range. For $\frac{1}{6} \leq \varepsilon < \frac{1}{2}$, on the other hand, such systems may possibly exist, but it can be shown that they cannot be constructed from only the four complexes appearing in the original system (7-3).

For a further example of macro-equivalence, we return to the mass action system (7-1). Consider the second order irreversible decay of a species $\mathscr{A}(1)$ taking place in a continuous flow stirred tank reactor into which $\mathscr{A}(1)$ is infused at constant rate. Such a situation corresponds to

$$\mathscr{A}(1) \rightleftarrows \mathcal{O} \leftarrow 2\mathscr{A}(1) \qquad\qquad (7\text{-}15)$$

where $\mathcal{O} \rightarrow \mathscr{A}(1)$, $\mathscr{A}(1) \rightarrow \mathcal{O}$, and $2\mathscr{A}(1) \rightarrow \mathcal{O}$ represent infusion of $\mathscr{A}(1)$, exit flow of $\mathscr{A}(1)$, and second order decay to an external species $\mathscr{B}$, respectively. (7-15) is not weakly reversible but is macro-equivalent to a weakly reversible system since some fraction of the infusion of $\mathscr{A}(1)$ may be described by $\mathcal{O} \rightarrow 2\mathscr{A}(1)$. Thus one of the two exceptional weakly reversible mass action systems involving three short complexes (see (7-1)) is realized by the well known case of a second order reaction in a flow reactor. A reaction system which is similar to the other exceptional three complex system (see (7-2)) has been discussed by KRAMBECK [6] in connection with a study of macro-equivalence (KRAMBECK uses the term "non-uniqueness") within the class of detailed balanced kinetics.

Appendix 1

We shall prove the following Lemma: *A reaction simplex is bounded if and only if the system is conservative.*

First assume that the system is conservative. Then, by definition, there exists a vector z in $S^\perp$ which has only positive coordinates. Assume that the simplex is given by $c_0 + S$ (where $c_0 \in V^+$). Then if x is in the simplex, we have that

$$z \cdot (x - c_0) = 0. \tag{A1-1}$$

From this it follows that

$$\sum_{j=1}^m z^j x^j = M > 0 \tag{A1-2}$$

where $M = z \cdot c_0$. This inner product is positive since both factors are in V^+. Next let ζ be the smallest coordinate of z,

$$\zeta = \min_j z^j. \tag{A1-3}$$

Then it follows from (A1-2) and from the fact that all x^j are non-negative that

$$\zeta \sum_{j=1}^m x^j \leqq M. \tag{A1-4}$$

Since $\zeta > 0$, it further follows that

$$0 \leqq x^j \leqq \frac{M}{\zeta} \quad \text{for all } j. \tag{A1-5}$$

Thus the coordinates of all points in the simplex are bounded, from which the boundedness of the simplex follows. This proves the "if" part of the lemma.

Next assume that the reaction simplex is bounded. Then it follows that S must not contain a non-zero vector with non-negative coordinates. For suppose that $x \neq 0$ lies in S and that $x^j \geqq 0$ for all j. Then if $c_0 + S$ is the simplex, the vector $c_0 + \lambda x$, $\lambda > 0$, is also in the simplex, which cannot be bounded, since λ can be made arbitrarily large and hence the norm of $c_0 + \lambda x$ can be made to exceed any bound. Thus if S is bounded, the following must be true:

$$x \in S, \quad x \in \bar{V}^+ \Rightarrow x = 0. \tag{A1-6}$$

Now we shall use a theorem stated by TUCKER [10]: *Let S be a subspace of a vector space V. Then there exist two vectors x and z in V such that*

$$x \in \bar{V}^+, \quad z \in \bar{V}^+, \quad x \in S, \quad z \in S^\perp, \quad \text{and} \quad x + z \in V^+. \tag{A1-7}$$

In our problem $x = 0$, so this result implies that there is a vector $z \in V^+$ which also lies in $S^\perp$. This establishes the "only if" part of the lemma.

Finally, assume that there is one bounded reaction simplex. Then, by the "only if" part of the lemma, the existence of z, $z \in V^+$, $z \in S^\perp$ follows and hence, by the "if" part of the lemma, every reaction simplex must be bounded.

Appendix 2

We wish to show that it is possible in non-mass action kinetics that the equilibrium set E contains both concentrations at which the kinetic system is complex

balanced and concentrations at which it is not complex balanced. To this purpose we shall consider the kinetic system with

$$\mathscr{C}(1) = \mathscr{A}(1), \qquad \mathscr{C}(2) = \mathscr{A}(2),$$
$$\mathscr{C}(3) = 2\mathscr{A}(1), \qquad \mathscr{C}(4) = 2\mathscr{A}(2) \tag{A2-1}$$

and

$$r_{12}(c) = c^2, \qquad r_{21}(c) = (c^1)^2,$$
$$r_{34}(c) = (c^2)^2, \qquad r_{43}(c) = c^1, \tag{A2-2}$$
$$r_{23} = r_{32} = r_{14} = r_{41} \equiv 0.$$

Clearly this system is not of mass action type. The species formation vector $f(c) = (f^1(c), f^2(c))^T$ is given by

$$f^1(c) = -(c^1)^2 + c^2 - 2c^1 + 2(c^2)^2,$$
$$f^2(c) = -f^1(c), \tag{A2-3}$$

and the components of the complex formation vector $g(c)$ are given by

$$g^1(c) = -(c^1)^2 + c^2, \qquad g^2(c) = -g^1(c),$$
$$g^3(c) = -c^1 + (c^2)^2, \qquad g^4(c) = -g^3(c); \tag{A2-4}$$

if $c^1 = c^2 = 1$, then all components of $f(c)$ and of $g(c)$ are zero. That is,

$$(1, 1)^T \in E \quad \text{and} \quad \in C. \tag{A2-5}$$

If

$$c^1 = 2 \quad \text{and} \quad c^2 = \tfrac{1}{4}(\sqrt{65} - 1), \tag{A2-6}$$

then $f(c) = 0$ but $g(c) \neq 0$. That is

$$(2, \tfrac{1}{4}(\sqrt{65} - 1))^T \in E \quad \text{but} \quad \notin C. \tag{A2-7}$$

Appendix 3

It will be useful to denote by Φ_l, $l \geq 2$, the following real valued function of l variables $\xi_1, \xi_2, ..., \xi_l$, each of which is in the domain of φ:

$$\Phi_l(\xi_1, ..., \xi_l) = \xi_l(\varphi(\xi_1) - \varphi(\xi_l)) + \xi_1(\varphi(\xi_2) - \varphi(\xi_1))$$
$$+ \cdots + \xi_{l-1}(\varphi(\xi_l) - \varphi(\xi_{l-1})). \tag{A3-1}$$

We wish to show that

$$\Phi_l(\xi_1, ..., \xi_l) \leq 0 \quad \text{all} \quad \xi_j \in \text{dom} \, \varphi \tag{A3-2}$$

and that equality applies if and only if

$$\xi_1 = \xi_2 = \cdots = \xi_l. \tag{A3-3}$$

We shall prove this by induction on l. For $l = 2$

$$\Phi_2(\xi_1, \xi_2) = (\xi_2 - \xi_1)(\varphi(\xi_1) - \varphi(\xi_2)), \tag{A3-4}$$

and it then follows easily from the fact that φ is strictly increasing, that

$$\Phi_2(\xi_1, \xi_2) \leqq 0 \tag{A3-5}$$

with equality if and only if $\xi_1 = \xi_2$. Thus the statement is true for $l = 2$. Next assume that the statement is valid for some $l \geqq 2$. Consider now a family of arguments $\xi_1, \xi_2, ..., \xi_l, \xi_{l+1}$ of Φ_{l+1}. Clearly, this family must contain a member which is larger than or equal to any other member of the family. Since Φ_l for any l is invariant under cyclic permutation of its arguments, we can assume without loss of generality that ξ_{l+1} is this member, i.e. that

$$\xi_{l+1} \geqq \xi_j, \quad j = 1, 2, ... \tag{A3-6}$$

By slight rearrangements of the terms in Φ_{l+1} one obtains

$$\Phi_{l+1}(\xi_1, \xi_2, ..., \xi_l, \xi_{l+1}) = \Phi_l(\xi_1, \xi_2, ..., \xi_l) + (\xi_{l+1} - \xi_l)(\varphi(\xi_1) - \varphi(\xi_{l+1})). \tag{A3-7}$$

The first term on the right hand side of (A3-7) is non-positive because of the induction assumption. The second term is non-positive because of (A3-6) and the fact that φ is strictly increasing. Thus

$$\Phi_{l+1}(\xi_1, \xi_2, ..., \xi_l, \xi_{l+1}) \leqq 0. \tag{A3-8}$$

Next assume that equality applies in (A3-8). Then, because of the non-positivity of the two terms mentioned above, it follows that

$$\Phi_l(\xi_1, \xi_2, ..., \xi_l) = 0 \tag{A3-9}$$

and

$$(\xi_{l+1} - \xi_l)(\varphi(\xi_1) - \varphi(\xi_{l+1})) = 0. \tag{A3-10}$$

From (A3-9), by the induction assumption

$$\xi_1 = \xi_2 = \cdots = \xi_l, \tag{A3-11}$$

and from (A3-10), by the fact that φ is strictly increasing

$$\xi_{l+1} = \xi_l \quad \text{or} \quad \xi_1 = \xi_{l+1}. \tag{A3-12}$$

(A3-11) and (A3-12) together imply that

$$\xi_1 = \xi_2 = \cdots = \xi_l = \xi_{l+1}. \tag{A3-13}$$

This concludes the proof of the inequality for Φ_{l+1}, and hence the inductive argument.

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University of Rochester
and
Rice University