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THE KINETICS OF LINEAR SYSTEMS WITH SPECIAL REFERENCE TO PERIODIC REACTIONS

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It is shown on the basis of (1) conservation of mass, (2) positive concentrations, and (3) the principle of detail balancing that periodic reactions cannot occur in a closed system described by *linear* differential equations. The matrix, A, of the rate equations must be such that $|A| = 0$, $a_{ij} > 0$ for $i \neq j$, $a_{ii} < 0$, and $VAV^{-1} = B$, where V is diagonal and B is symmetric. These properties of A imply that the latent roots are real and non-positive and that neither catalysis nor inhibition can be described by *linear* equations. It is further shown that periodic reactions cannot occur in an *open* system for which the matrix associated with the chemical reactions has the above properties and in which the *simple* law of diffusion is obeyed. The relation of these results to Onsager's reciprocal relations and to previous work on periodic and cyclic chemical reactions is discussed. The utility of certain of these results for the treatment of isotope kinetics is indicated.

1. *Introduction.* The biological occurrence of periodic phenomena is well known. It is of interest to consider whether certain cases may be explained on the basis of periodic chemical reactions. It may be said that no case has yet been so explained, in a satisfactory manner, and that the formal problem of periodic chemical reaction is not highly developed. It is reasonable to assume that the development of the formal chemical kinetics of periodic chemical reactions must precede the solution of the associated diffusion problems.

The possibility of periodic reactions was early considered (Lotka, 1910; Hirniak, 1911; Lotka, 1920) and an experimental case was shortly reported (Bray, 1921). A. J. Lotka considered a set of consecutive, autocatalytic reactions in which the concentration of the first species is constant and showed that such a system exhibits undamped oscillations, i.e., the concentrations oscillate about a "central" value. This treatment has been generalized and extended by M. J. Moore (1949). In particular it was shown that the removal of the restriction that the concentration of the first reactant be constant leads to damping of the oscillations but in no

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case, as Lotka (1920) had shown, are the oscillations simple harmonic. The treatment was extended to systems which are open but otherwise of a simplified nature. The principal, *theoretical* content of the Moore (1949) paper was anticipated by K. F. Bonhoeffer (1948) who, however, considered systems in which only two chemical species are involved.

In all of the above cases, except that of Hirniak (*loc. cit.*), the differential equations which describe the system are *non-linear*, whether or not the system is open. In fact the open nature of the system contributes no non-linear terms when the *usual* flux laws are considered. M. F. Morales (1944) has discussed periodicity in *pure diffusion systems* in which chemical reaction plays no part. The flux law, based upon an extended form of the chemical potential, assumed by Morales is non-linear and results in non-linear differential equations. In the following paragraph we refer to cases based upon *linear* equations.

N. Rashevsky (1938, 1948c) discussed a case of an open system for which the *chemical* rate laws are the *linear* equations

$$\left.\begin{aligned} \frac{dx_1}{dt} &= a_{11}x_1 + a_{12}x_2 \\ \frac{dx_2}{dt} &= a_{21}x_1 + a_{22}x_2 , \end{aligned}\right\} \tag{1}$$

where x_1, x_2 are the concentrations of the first and second chemical species and the a_{ij} are constants. A. M. Weinberg (1938) generalized the diffusion problem associated with this case and discussed solutions possessing certain symmetry properties. Rashevsky (1948a) has discussed more general solutions as well as the conditions under which the *steady state* concentration configuration exhibits *spatial* periodicity. The solutions discussed by Weinberg (1938) and Rashevsky (1948a) depend upon certain restrictions on the diffusion and permeability coefficients but the solution of the diffusion problem is otherwise exact. By forfeiting exactness in the geometric description of the system and in the formulation of the diffusion problem, an approximation method (Rashevsky 1948c, 1940) allows the restrictive condition among the diffusion and permeability coefficients to be removed. Weinberg (1939) has solved the problem in this manner with the result that the frequency of oscillation is that of the fundamental mode whereas actually, in the exact solution (Rashevsky, 1948a), the oscillations are the superposition of a countably infinite number of frequencies. Rashevsky (1948b) has discussed the method by which this defect of the approximation method is to be removed. Finally, Rashevsky (1949) has discussed the possibility of centrally asymmetric concentration configurations, which are subject to damped oscillation, leading to the division of a spherical cell and accounting for the damped pulsations which immediately precede cell division.

In the cases discussed in the above paragraph the existence of periodic solution depends *directly* (Rashevsky, 1938; Weinberg, 1939; Rashevsky, 1948b, c) or in an important manner (Weinberg, 1938; Rashevsky, 1948a, 1949) upon the properties of the coefficients in the *linear* equations, (1), for the chemical rate law.

2. *Purpose of the paper.* It is the purpose of this paper to inquire for the restrictions set, by general chemical and thermodynamic principles, upon the coefficients of the rate equations for a general *linear* chemical system. The implications of these restrictions for the existence of periodic solutions are examined and discussed for closed and open systems.

In particular it is the purpose here to show that if A is the matrix of the chemical rate equations [of which (1) is the second order case] the principle of conservation of mass and the requirement that the concentration be non-negative are sufficient to determine the signs of the elements a_{ij}. These signs are such that in no second order case can the latent roots of A be imaginary. In the general, nth order case, the principle of detail balancing (the law of entire equilibrium of G. N. Lewis) or the thermodynamic theorem that the (Gibbs) free energy is a perfect differential imposes additional restrictions upon the a_{ij} such that A can be transformed, by a similarity transformation, into a real, symmetric matrix. With these properties of A established the reality *and* non-negativeness of the roots follow at once. The relations of these results to similar, special theorems proved by I. Opatowski (1945, 1946) and to the general linear problem in chemical kinetics are discussed.

3. *The closed, uniform, homogeneous system.* By a *linear* chemical system we will mean a system consisting, in general, of n chemical species, X_i, $i = 1, 2, \ldots, n$, for which the formal chemical kinetic rate equations are

$$\dot{x}_i(t) = \sum_{j=1}^{n} a_{ij}x_j(t) , \qquad i = 1, 2, \ldots, n , \tag{2}$$

where x_i is the concentration of the ith species, X_i, the a_{ij} are constants, and $\dot{x}_i$ denotes the time derivative dx_i/dt. This terminology, of course, bears no relation to the "physical" linearity of the system; for a straight-chain, branched or cyclic system may equally well obey (2). We require only that (2) be linear. *If* the species, X_i, are converted one into another this assumption of linearity means that the chemical reactions are *first order*. They are not necessarily *unimolecular*.

We assume, initially, that the species interact in any way whatever. Then, if one species, X_k, is to influence the rate of change of another, X_i, it must do so by virtue of contributing a linear term, $a_{ik}x_k$, to the equation for $\dot{x}_i$. It will then be shown that the only real, physical interpretation of (1) is that the X_i are converted chemically one into another.

The most obvious restriction which the assumption of a closed system implies is that of the conservation of mass. This evidently requires, if the volume V of the system is constant, that there exist *positive* numbers, α_i, such that

$$\sum_{i=1}^{n} \alpha_i \dot{x}_i = \frac{d}{dt}\sum_{i=1}^{n} \alpha_i x_i = 0 . \tag{3}$$

In particular, if the x_i be expressed as mass per unit volume, rather than moles per unit volume, the value of every α_i may be taken as unity. The fact that $\alpha_i > 0$, for all i, follows from simple chemical principles: The α_i can always be chosen as multiples of molecular weights of the X_i when the x_i are in moles per unit volume. In cases of simple stoichiometry, which are most likely to obtain when (2) is valid, the α_i can be chosen as small integers which are ratios of the molecular weights.

It is worth noting here that V cannot, in principle, remain constant unless the partial molal volumes of the X_i are identical. The formal laws of chemical kinetics are, however, based upon the assumption of *dilute* solutions in which case V is essentially the volume of solvent and for most purposes, including those of this paper, V may be regarded as constant. We are clearly assuming here that, in addition to being dilute, the solutes are *perfect.*

From (2) and (3) it follows that

$$\sum_i \alpha_i \sum_j a_{ij} x_j = \sum_j \Big(\sum_i \alpha_i a_{ij} \Big) x_j = 0 . \tag{4}$$

Since (4) must be valid for *all* values of the x_j, we have proved

Statement I: The conservation of mass requires that the matrix, A, of the set (2) be singular

$$| A | = | a_{ij} | = 0 . \tag{5}$$

The linear dependence of the rows of A, or of the determinant $|a_{ij}|$, is expressible in terms of *positive* constants:

$$\begin{gathered} \sum_i \alpha_i a_{ij} = 0 , \qquad j = 1 , 2 , \ldots , n \\ \alpha_1 > 0 , \qquad i = 1, 2, \ldots , n . \end{gathered} \tag{6}$$

From (6) it is evidently impossible that all of the a_{ij} be of like sign. A more restrictive statement regarding the signs of the a_{ij} can be derived as follows. The concentrations x_i are, of necessity, non-negative. Further, their initial values are otherwise arbitrary. Let the initial conditions be

$$x_j(0) = \delta_{jm} x_j^0 \,, \qquad j = 1, 2, \ldots, n \,, \tag{7}$$

where δ_{jm} is the Kronecker delta. Then, from (2), the initial rates are

$$\dot{x}_i(0) = a_{im} x_m^0 \,, \qquad i = 1, 2, \ldots, n \,. \tag{8}$$

The implication of (7) and (8) is that if $a_{im} < 0$, $i \neq m$, then $x_i(t) < 0$ for some $t > 0$. The time, t, is of course to be reckoned non-negative. Thus (6), (7), and (8) lead to

Statement II: The requirement that the x_i be non-negative demands that the off-diagonal elements of A be non-negative

$$a_{ij} \geqslant 0 \,, \qquad i \neq j \,; \qquad i, j = 1, 2, \ldots, n \,. \tag{9}$$

This requirement, *with* that of the conservation of mass (*Statement I*), implies that the diagonal elements of A are non-positive:

$$a_{ii} = -\frac{1}{a_i} \sum_{j \neq 1} a_j a_{ji} \leqslant 0 \,, \qquad i = 1, 2, \ldots, n \,. \tag{10}$$

In particular, if any a_{ii} vanishes the column vector, in A, in which that element stands is the null-vector and the ith species is an inert solute with respect to the others.

Statements I and *II* severely restrict the possible physical interpretations of the set (2). A simple argument supports

Statement III: If (2) describes a chemical system in which mass is conserved, the only physical interpretation of (2) is that each of the chemical species, X_i, is *stoichiometrically* converted to, and formed from, the others.

For (2), (9), and (10) state that the rate of change of the ith species is the sum of one negative term and several positive terms. The negative term expresses that X_i *disappears* at a rate proportional to x_i. By (10) and (2), this rate of disappearance is, on a mass basis, numerically equal to the sum of the terms contributed by X_i to the rates of appearance of the other species X_j, ($j \neq i$). The situation is most transparent when the special initial conditions (7) and initial rates (8) are considered. It is then evident that under the conditions that every x_i is zero except one, viz., x_m, the ith species ($i \neq m$) *appears*, (9), at a rate proportional to x_m and the mth species *disappears*, (10), at a rate proportional to x_m. Moreover, by (8) and (3), the rate at which X_m disappears is, on a mass basis, the same as the sum of the rates at which the X_j, ($j \neq m$), appear.

The term "stoichiometrically," in *Statement III*, is used to imply the absence of catalysis. It has been previously noted (Morales, 1944) that the interpretation of (1), as employed by Rashevsky and by Weinberg (references in introduction), is that of catalysis *without* combination. This interpretation is, as Morales noted, plainly unrealistic and has been here excluded. Further, it has been shown that *negative* catalysis (inhibition) cannot be expressed by the linear set (2); for a negative, off-diagonal element in A implies the existence of negative concentrations (*Statement II*).

It is well known from the theory of ordinary differential equations that the nature of the solutions of (2) is determined in general by the nature of the latent roots of A. Specifically, if the roots of A are distinct, the solutions are

$$x_i = \sum_{k=1}^{n} q_{ik} e^{\lambda_k t}, \qquad i = 1, 2, \ldots, n, \tag{11}$$

where the q_{ik} depend upon the initial conditions and upon the λ_k which are the roots of the equation

$$|A - \lambda I| = 0. \tag{12}$$

Here I denotes the unit matrix of order n. If one or more pairs of the λ_j are complex, (11) can be written as a real, periodic function of t. It is to be anticipated, on the basis of physical intuition, that for a closed system the real roots and the real parts of the complex roots will be non-positive, for the $x_i(t)$ must be bounded for all t. According to (3), $\Sigma a_i x_i(t) = \Sigma a_i x_i^0 =$ constant is finite if the mass of the system is finite, and since every $a_i > 0$, every $x_i(t)$ is bounded. But this is impossible unless the real parts of the roots of A are non-positive.* Moreover, we are insured by (5) and (12) as a direct consequence of the conservation of mass of at least one zero root.† It is to be noted that condition (5) could have been secured by insisting upon the existence of non-trivial, steady state solutions of (2). This, however, would not furnish the restrictions $a_i > 0$, $i = 1, 2, \ldots, n$, of (6). Consequently, while (9) could be deduced, (10) would not follow. The conservation of mass insures, by virtue of (5), non-

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[*] Although this reasoning is sufficient it should be noted that from a known theorem [Brauer, 1946; theorem (1) p. 389] it can be shown that the real parts of all roots are non-positive.

[†] The case of an r-fold zero root requires special attention, for such a root contributes to each $x_i(t)$ a polynomial of degree $r - 1$. Unless these polynomials are constants, the $x_i(t)$ cannot be bounded. It is shown later in this paper that A can be diagonalized. Therefore if zero is an r-fold root the polynomials resulting therefrom are (positive) constants.

trivial solutions of the equations

$$\dot{x}_i = \sum_j a_{ij} x_j = 0\,, \qquad i = 1, 2, \ldots, n\,, \tag{13}$$

and in addition, by furnishing (6), affords restrictions (10). *In general* the relations (5), (6), (9), and (10) are not sufficient to completely determine the nature of the roots,* λ_j, of (12).

By a well-known theorem (Aitken, 1948; Ferrar, 1941) the roots of a real, symmetric matrix are real. By another standard theorem (Aitken, 1948; Ferrar, 1951) the roots of a matrix B are the same as those of A if

$$V A V^{-1} = B\,, \tag{14}$$

where V is non-singular but otherwise arbitrary. We therefore seek a matrix V such that B is real and symmetric. If V is the diagonal matrix

$$V = [\delta_{ij} v_i]\,, \tag{15}$$

then, from (14),

$$B = \left[\frac{a_{ij} v_i}{v_j}\right] \tag{16}$$

and if B is to be symmetric it is required that

$$b_{ij} = \frac{a_{ij} v_i}{v_j} = \frac{a_{ji} v_j}{v_i} = b_{ji}\,. \tag{17}$$

If v_k, $k = 1, 2, \ldots, n$, can be chosen such that (17) is satisfied and every b_{ij} is real it will be established that the roots of A are real and that the solutions, $x_i(t)$, of (2) are *non-periodic.*

Equations (17), $n(n-1)/2$ in number, may be considered as a set, linear and homogeneous in the n variables $\nu_k = v_k^2$. We require solutions such that every $\nu_k < 0$. The simplest manner in which to exhibit the restrictions imposed upon the a_{ij} by (17) is as follows. *It is assumed, for the present, that no* a_{ij} *vanishes.* If a variable, ν_r, is arbitrarily chosen then there can be selected, from (17), $n-1$ equations

$$a_{rj}\nu_r = a_{jr}\nu_j\,, \qquad \begin{array}{l} j = 1, 2, \ldots, n \\ \neq r \end{array} \tag{18}$$

in which ν_r appears. If ν_r is assigned the value unity, then the entire set of ν_j is given by

$$\nu_j = \frac{a_{rj}}{a_{jr}}\,, \qquad j = 1, 2, \ldots, n\,. \tag{19}$$

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* If $n = 2$, it follows at once that the non-zero root, $\lambda = a_{11} + a_{22}$, is real and negative. In the case treated by Opatowski (1945, 1946), A is a continuant matrix, every $a_i = 1$, and (6), (9), and (10) are enough to determine that every λ_i is real and non-positive.

If the ν_j from (19) are substituted into the *remaining* equations of (17),

$$a_{ij}\nu_i = a_{ji}\nu_j, \qquad j > i = 1, 2, \ldots, r-1, r+1, \ldots, n, \tag{20}$$

there results the set of relations

$$a_{ri}a_{ij}a_{jr} = a_{ir}a_{ji}a_{rj} \tag{21}$$

which are identically satisfied if any two of the subscripts, i, j, r, are identical.

For reasons immediately to become obvious we will refer to relations of the type (21) as cyclic relations. For brevity, (21) will be denoted by $(r\,i\,j)$ and a single member of the set will be called a 3-cycle. In general, a set of relations of the type (21) each of which involves σ distinct subscripts, or σ pairs of elements of A, $a_{ij} \ldots a_{st}a_{ti} = a_{ji} \ldots a_{ts}a_{it}$, will be denoted by $(i\,j \ldots s\,t)_\sigma$ and a single member called a σ-cycle. It is clear that, in (18), r can have any value except j and hence in (21), r can have any value distinct from i and j. In fact it is simple to show* that relations (21), $(n-1)(n-2)/2 = \binom{n-1}{2}$ in number where $\binom{N}{s}$ is the number of combinations of N things taken s at a time, imply the set $(i\,j\,k)$, $[i, j, k \neq r]$, which has $\binom{n-1}{3}$ members. Therefore, of the total number, $\binom{n}{3}$, of 3-cycles, $\binom{n-1}{2}$ are independent. It can further be shown that the 3-cycles $(i\,j\,k)$ imply the σ-cycles $(i\,j \ldots s\,t)_\sigma$, $\sigma = 3, 4, \ldots, n$. Therefore of the *total* number, $2^n - \binom{n+1}{2} - 1$, of cycles there are $\binom{n-1}{2}$ which are independent and this is the number of 3-cycles containing a selected subscript.

Provided that (21) can be satisfied, the problem of finding a matrix V such that B, given by (14), is real and symmetric is *mathematically* solved. The elements of V are chosen as $v_j = \sqrt{\nu_j}$, with the ν_j from (19). The elements b_{ij} are then

$$b_{ij} = a_{ij}\left(\frac{a_{ri}a_{jr}}{a_{ir}a_{rj}}\right)^{1/2} = (a_{ij}a_{ji})^{1/2} = b_{ji}. \tag{22}$$

That they are real follows at once from (9). We now consider the *physical* necessity of (21).

If the system is in the steady state, equations (13) apply and serve to fix the ratios of the steady-state values of the x_i. But for a *closed* system the steady-state is the *equilibrium state* (cf. discussion in Hearon, 1950a, b) and in addition to the requirement that every $\dot{x}_i = 0$ it is required that

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* This is discussed in detail in a forthcoming paper.

every process be balanced by its inverse. This is the familiar principle of detail balancing (e.g., Mayer and Mayer, 1947; Onsager, 1931). This additional requirement leads at once to (21). For, select from the system *any* three species X_r, X_i, and X_j, denote explicitly in the usual way their mutual interconversion,

$$\begin{tikzcd} X_r \arrow[rr, leftrightarrow] \arrow[dr, leftrightarrow] & & X_i \arrow[dl, leftrightarrow] \\ & X_j & \end{tikzcd} \tag{23}$$

and consider these transformations to be unimolecular ($\alpha_k = 1$ for all k). It is required that the rate of the process $X_r \rightarrow X_i$ be equal to that of the process $X_i \rightarrow X_r$. According to *Statement III* and the argument which immediately follows it these rates are $a_{ir}x_r$ and $a_{ri}x_i$ respectively. Similar considerations apply to the other two distinct pairs X_r, X_j and X_i, X_j. We therefore have as the conditions imposed by the principle of detail balancing,

$$\left.\begin{aligned} a_{ir}x_r &= a_{ri}x_i \\ a_{rj}x_j &= a_{jr}x_r \\ a_{ji}x_i &= a_{ij}x_j \,. \end{aligned}\right\} \tag{24}$$

The product of the three relations (24) is precisely (21). Stated otherwise, the first two equations of (24) give a relation between x_j and x_i. But this relation must be the same as the third relation of (24) and this is impossible unless (21) holds. It obviously must be true, and it is not difficult to show, that if equations (24) hold for *all* r, i, and j, the x_k so determined must satisfy (13). We will show this for the general case. If (13) is written as

$$a_{ii}x_i + \sum_{j \neq i} a_{ij}x_j = 0\,, \qquad i = 1, 2, \ldots, n \tag{25}$$

then (10) and (25) give

$$\sum_{j \neq i} \left(a_{ij}x_j - \frac{1}{\alpha_i} \alpha_j a_{ji} x_i \right) = 0\,, \qquad i = 1, 2, \ldots\ n\,. \tag{26}$$

Clearly, (26) is satisfied if

$$\alpha_i a_{ij} x_j = \alpha_j a_{ji} x_i\,, \qquad i, j = 1, 2, \ldots, n\,. \tag{27}$$

But (27) can hold only if the relations ($i\ j\ k$) hold. For (27) gives

$$x_j = \frac{\alpha_j}{\alpha_i} \frac{a_{ji}}{a_{ij}} x_i = \frac{\alpha_j}{\alpha_k} \frac{a_{jk}}{a_{kj}} x_k \tag{28}$$

and also

$$x_i = \frac{a_i}{a_k}\,\frac{a_{ik}}{a_{ki}}\,x_k\,. \tag{29}$$

It is manifestly true that (28) and (29) cannot hold simultaneously unless the 3-cycles $(i\,j\,k)$ are valid. From (27), σ-cycles, $\sigma > 3$, can be derived in the same way.

The presence in the system of cyclic chemical reactions, such as shown in (23), demands according to the principle of detail balancing, cyclic relations, such as (21). In general, if it is possible to begin with X_j, convert the species successively to $\sigma - 1$ other species, and return to X_j

$$\begin{tikzcd} X_j \arrow[r, leftrightarrow] \arrow[dd, leftrightarrow] & X_k \arrow[d, leftrightarrow] \\ & \vdots \\ X_s \arrow[r, leftrightarrow] & \cdots \end{tikzcd}$$

there must exist a σ-cycle $(j\,k\,\ldots\,s)_\sigma$. If every a_{ij} is different from zero every species can be converted to and formed from every other. The system is then said to be *completely cyclic*, for every σ-cycle, $\sigma \geqslant 3$, then exists. If some of the a_{ij} are zero the exact manner in which (17) are to be solved will be different in each case. It will now be shown that if zero elements occur symmetrically about the main diagonal of A, (17) can be satisfied if *certain* σ-cycles are satisfied. This is in contrast to the completely cyclic case in which all 3-membered chemical cycles containing a selected species, X_r, exist and (17) can be satisfied by (19) if all 3-cycles $(r\,i\,j)$ are satisfied.

Let (17) be written as

$$a_{ij}\nu_i = a_{ji}\nu_j\,, \qquad \begin{aligned} &i = 1, 2, \ldots, n \\ &i < j \leqslant n. \end{aligned} \tag{30}$$

It is assumed that if $a_{ij} = 0$, then $a_{ji} = 0$. Certain members of (30) will then be identically satisfied. For definiteness, assume that $a_{1j} = a_{j1} = 0$ for $j = m, s, t$. We exclude the trivial case (see *Statement II*) in which a_{im}, a_{is}, and a_{it} are zero for every $i \neq m, s, t$. Accordingly if ν_1 is assigned the value unity, (30) with $i = 1$ gives

$$\nu_j = \frac{a_{1j}}{a_{j1}}, \qquad j \neq m, s, t \tag{31}$$

and there are, among the remaining equations of (30), three which determine ν_j, $j = m, s, t$. Assume that there is an $r < m, s, t$ such that the members of (30) with $i = r, j = m, s, t$ are not indentically satisfied. Then (32),

$$\nu_j = \frac{a_{1r}a_{rj}}{a_{r1}a_{jr}}, \qquad j = m,\ s,\ t, \tag{32}$$

and (31) comprise a complete set of ν_j. The remaining members of (30) with $i = r$ determine the 3-cycles $(1\ r\ j), j \neq m, s, t$. Now for all k such that ν_k is given by (31) and $a_{kj} \neq 0, j = m, s, t$, the members of (30) with $j = k, i = m, s, t$, together with (32), determine the 4-cycles $(1\ r\ i\ k)$, $i = m, s, t$. The members of (30) with $j \neq m, s, t$, together with (31), determine the 3-cycles $(1\ i\ j), j \neq m, s, t$. The extension to the general case is simple: In general, (31) may fail to determine any number of ν_j. The condition on (31) is then $j \neq m, s, t, \ldots, p$. If there is an r such that (32) determines $\nu_j, j = m, s, t, \ldots, p$, the above argument goes through with the triple of indices, m, s, t, replaced everywhere by the arbitrary number ($\leqslant n - 2$) of indices $m, s, t, \ldots, p$.

If there is no *single* value of r such that the members of (30) with $i = r$, $j = m, s, t, \ldots, p$ are not identically satisfied there are two major possibilities:

(i) If values of i, (say $i = R_j, j = m, s, t, \ldots, p$) can be found such that the members of (30) with $i = R_j$ and $j = m, s, t, \ldots, p$ determine $\nu_j, j = m, s, t, \ldots, p$ where R_j may be different for each j and *is not one of the set* $m, s, t, \ldots, p$ the argument is as above, with obvious modifications. In particular, in (32) $j = m, s, t, \ldots, p$ and r is replaced by R_j. Then (30), with $j = k, i = m, s, t, \ldots, p$, together with (32), determines the 4-cycles $(1\ R_j\ j\ k), j = m, s, t, \ldots, p$ for all k such that ν_k is determined by (31).

(ii) There is always an r such that one of the $\nu_j, j = m, s, t, \ldots, p$, is determined by (32). It is no restriction to suppose that ν_m is so determined. Now it may be that the members of (30), when j has one or more of the values $s, t, \ldots, p$, are identically satisfied unless i belongs to the set $m, s, t, \ldots, p$. For example it may be that the only member of (30) which serves to determine ν_s is that with $i = m, j = s$. Then

$$\nu_s = \frac{a_{1r}a_{rm}a_{ms}}{a_{r1}a_{mr}a_{sm}}. \tag{33}$$

The remaining $\nu_j, j = t \ldots p$ may or may not be determined by (30) when i does not belong to the set $m, s, t, \ldots, p$. If they are, these remaining ν_j are determined as in (i) above. If they are not, these remaining ν_j are determined by formulae which are extensions of (33). For example, if ν_t is determined by (30) with $i = s, j = t$, then

$$\nu_t = \frac{a_{1r}a_{rm}a_{ms}a_{st}}{a_{r1}a_{mr}a_{sm}a_{ts}} \tag{34}$$

and if this situation repeatedly occurs, then finally

$$\nu_p = \frac{a_{1r}a_{rm} \ldots a_{lp}}{a_{r1}a_{mr} \ldots a_{pl}}, \tag{35}$$

where the products such as $a_{1r}a_{rm} \ldots a_{lp}$ can contain no more than $n - 1$ elements of A. The equations, if *any* remaining of (30), together with (31), (32), or its modification in (i), (33), . . . , (35) determine various σ-cycles where certain values of σ may not be represented.

Evidently, if there are no equations remaining in (30) there are no conditions (in the form of cyclic relations) upon the a_{ij} and this will occur when there are $n - 1$ equations of (30) which are not identically satisfied. This implies that when no chemical cycles occur in the system there are $2(n - 1)$ non-zero elements a_{ij} (this result is easy to prove *directly**). Further, these elements are independent, for the principle of detail balancing imposes no relations among them. A notable special case of this kind is that in which A is a continuant matrix: In (30), $i = 1, 2, \ldots, n - 1$, and $j = i + 1$. The system is a *straight chain* of consecutive reactions: $X_1 \leftrightarrows X_2 \leftrightarrows \ldots \leftrightarrows X_n$ (cf. discussion, Section 7 of this paper).

The above assumption, that if $a_{ij} = 0$ then $a_{ji} = 0$, can be justified on physical grounds: From (27), if the assumption were *not* valid the equilibrium values of certain of the x_i would be zero. This is contrary to experience and implies that certain equilibrium constants are infinite. Stated otherwise, it cannot be admitted that any chemical reaction is absolutely irreversible, in the *kinetic* sense (cf. discussion Hearon, 1950a), for by well known thermodynamic principles (see discussion, Section 7, this paper) this implies that the standard free energy change of the reaction is infinite. Of course, the assumption $a_{rs} = a_{sr} = 0$ amounts to the physical assumption that the transitions $X_r \rightarrow X_s$ and $X_s \rightarrow X_r$ do not occur. This is a familiar assumption which for practical purposes can be justified on the basis of experience although (Mayer and Mayer, 1947) in rigorous principle it is never valid and, by the same argument, no system has ever been observed to come to complete equilibrium.

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* Denote by $N(n)$ the number of non-zero a_{ij} for a non-cyclic system of n species. Then, since each additional species contributes two additional a_{ij}, $N(n + 1) - N(n) = 2$. The solution of this difference equation is $N(n) = 2n + \omega(n)$, where $\omega(n)$ is periodic with period one. Evidently $N(2) = 2$. Therefore $\omega(2) = \omega(n) = -2$ and $N(n) = 2(n - 1)$, which was to be proved.

The important features of the above arguments may now be summarized as

Statement IV: The roots of the matrix A are real and the solutions $x_i(t)$ of (2) cannot be periodic functions of time. The requirement of finite equilibrium constants, or standard free energy changes, for the allowed individual reactions of the system implies that zero elements, a_{ij}, if any, occur symmetrically about the main diagonal of A. Then, the set (30) can always be solved in such a way that a matrix V, given by (15) with $v_j = \sqrt{\nu_j}$, converts A, by a similarity transformation, into a real, symmetric matrix. For, if there are only $n - 1$ equations the ν_j are given by equations such as (31) through (35) and are, by (9), necessarily positive. If there are more than $n - 1$ equations the set (30) is consistent and equations such as (31) through (35) represent acceptable solutions if certain cyclic relations are satisfied. That these relations be satisfied is demanded by the principle of detail balancing.

It is now simple to prove that the roots of A are non-negative. In order to achieve this, and for later purposes, we prove the following

Theorem: Consider the real, symmetric matrix C. Let there be real quantities γ_k and ρ_k such that

$$\gamma_k \neq 0\,, \qquad k = 1, 2, \ldots, n \tag{36}$$

$$\sum_r \gamma_r c_{rs} = \rho_s\,, \qquad s = 1, 2, \ldots, n\,. \tag{37}$$

Then if

$$\frac{c_{ij}}{\gamma_i \gamma_j} \geqslant 0\,, \qquad i \neq j\,; \qquad i, j = 1, 2, \ldots, n \tag{38}$$

and

$$\frac{\rho_i}{\gamma_i} \leqslant 0\,, \qquad i = 1, 2, \ldots, n\,, \tag{39}$$

where at least one *inequality* in (39) holds, the matrix C is negative definite and, if the inequalities in (38) and (39) are reversed, C is positive definite. If the *equality* in (39) holds for *every* i, C is semi-definite.

Proof: Evidently, if the equality in (38) holds for all distinct i and j, the theorem is trivial, for C is then diagonal and the ratios ρ_i/γ_i are, by (37), the diagonal elements c_{ii}. We exclude this case.

The quadratic form $Q(y, y)$ associated with C can be written as

$$2Q(y, y) = \sum_i c_{ii} y_i^2 + 2 \sum_j \sum_{j \neq i} c_{ij} y_i y_j + \sum_j c_{jj} y_j^2\,. \tag{40}$$

From (36) and (37), the diagonal elements of C are

$$c_{kk} = -\frac{1}{\gamma_k}\sum_{r\neq k} \gamma_r c_{rk} + \frac{\rho_k}{\gamma_k}, \qquad k = 1, 2, \ldots, n. \tag{41}$$

If (41) is substituted in (40) and the symmetry of C is explicitly invoked, there results

$$2Q(y, y) = 2\sum_i \frac{\rho_i y_i^2}{\gamma_i} - \sum_j \sum_i c_{ij} \frac{(\gamma_j y_i - \gamma_i y_j)^2}{\gamma_i \gamma_j}. \tag{42}$$

Under the conditions of the theorem the double summation is non-negative and the single summation is non-positive for all real sets of values of the y_i. If not *every* ρ_i is zero $Q(y, y)$ is negative definite. Otherwise it is negative semi-definite. The situation is equally obvious when the inequalities in (38) and (39) are reversed.

As discussed above, the matrix B determined by (41) is real and symmetric if V is properly chosen. Further, by (17) and (9), $b_{ij} > 0$, $i \neq j$. There exist real quantities β_i, all different from zero and of like sign, such that

$$\sum_i \beta_i b_{ij} = 0\,, \qquad j = 1, 2, \ldots, n \tag{43}$$

since, by (6) and (17), the choices $\beta_i = a_i/v_i$ meet these conditions. Applying the theorem to the matrix B, condition (38) is satisfied, the equality of (39) holds for all i, and B is negative semi-definite. Thus we have

Statement V: The latent roots of the matrix A are non-negative. We will refer to a matrix which possesses the properties described in *Statements I* through *V* as an *admissible rate matrix*, or simply an *admissible matrix*.

4. *The open, uniform system.* It will be realized that if the rates of production (per unit volume) of the chemical species of an open system are linear combinations of the concentrations, the matrix of the coefficients of these linear combinations must be an admissible matrix. For the system becomes closed if it is required that the flux of every species vanishes at the surface of the system. It is easily seen that the equations of continuity then reduce to (2), if in (2) every x_i is replaced by the (spatially) mean value of the concentration of the ith species. The arguments necessary to establish the properties of an admissible matrix can be carried through without further change. The operation of closing the system (e.g., by surrounding it by an impermeable envelope) cannot effect the elements

of the matrix if we make the usual restriction that only isothermal systems are considered.

Consider an open system for which the spatially uniform internal concentrations are $x_i(t)$ and the external concentrations, spatially uniform and constant with respect to time, are C_0^i. Then the set (2) is replaced by

$$\dot{x}_i = \sum_j (a_{ij} - p_{ij})\, x_j + \sum_j p_{ij} C_0^j \,, \tag{44}$$

where the p_{ij} are the products of the generalized permeability coefficients (Hearon, 1950b) and the surface-volume ratio of the system. If the simple laws of diffusion are assumed to apply, then P is the diagonal matrix $[\delta_{ij} p_{ij}]$ and if A is an admissible matrix the roots of the matrix $A - P$ are real and non-positive. A matrix V can be found, precisely as discussed in Section 2, such that $V(A - P)V^{-1} = B - P$ is real and symmetric. The permeability coefficients are non-negative. Therefore P is positive definite or semi-definite and $B - P$ is negative definite.

The time course of the approach of the x_i to their steady-state values is governed by the solutions of the homogeneous equations associated with (44) and we have shown that these solutions cannot be periodic if P is diagonal and A is admissible.

5. *The open, non-uniform system: approximate methods.* If the simple laws of diffusion are assumed and the diffusion equation is approximated in the manner suggested by Rashevsky (1940, 1948c), then (44) is replaced by

$$\frac{d}{dt}\,\bar{x}_i = \sum_j (a_{ij} - \delta_{ij}\Lambda_i^{-1})\, \bar{x}_j + \Lambda_i^{-1} C_0^i \,, \tag{45}$$

where $\bar{x}_i$ is the *mean* concentration of X_i, Λ_i is a constant, and C_0^i is the unperturbed external concentration. The argument of Section 4 applies: P is replaced by the diagonal matrix $[\delta_{ij}/\Lambda_i]$ and $\Lambda_i > 0$.

Therefore accepting the approximation method of Rashevsky, we have only to insist that A be admissible to insure that the $\bar{x}_i$ are non-periodic functions.

A refinement of the standard approximation method has been suggested (Rashevsky, 1948b). The system is divided into regions and the diffusion equation for each species is approximated in the manner of the Householder tri-axial cell (Householder, 1942). If by C_j^i is denoted the *mean* concentration of the ith species in the jth region, the differential equations are

$$\frac{d}{dt} C_j^i = \sum_{k=1}^{n} a_{ik} C_j^k + \sum_{r=0}^{p} m_{jr}^i (C_r^i - C_j^i) \,, \tag{46}$$

where it is understood that there are p regions and n species and (46) is a set of $np = N$ equations. Here, m^i_{jr} is a parameter characteristic of regions j and r and of the substance X_i. The zeroth region is the environment and M^i_{j0} will depend also upon the permeability of the surface of the system. The quantities C^i_0 are the unperturbed external concentrations and are to be regarded as constant. Clearly, if regions j and k are not contiguous then $m^i_{jk} = m^i_{kj} = 0$ for all i. It is not difficult to see that if new variables y_k are defined by $C^i_j = y_{(j-1)+i}$, $i = 1, 2, \ldots, n, j = 1, 2, \ldots, p$, then the differential equations for the y_k, $k = 1, 2, \ldots, N$, can be written as*

$$\dot{y} = Ry + Y \, . \tag{47}$$

Here, R is the partitioned matrix

$$R = \begin{bmatrix} E_1 & M_{12} & M_{13} \ldots M_{1p} \\ M_{21} & E_2 & M_{23} \ldots M_{2p} \\ \vdots & \vdots & \vdots \quad\quad \vdots \\ M_{p1} & M_{p2} & \ldots \quad E_p \end{bmatrix} \tag{48}$$

where the sub-matrices, square and of order n, are

$$E_s = A - [\delta_{ij} m^i_s] \, , \tag{49}$$

$$M_{ij} = [\delta_{rs} m^s_{ij}] \, , \tag{50}$$

the quantities m^i_s being defined as

$$m^i_s = \sum_{r=0}^{p} m^i_{sr} \, . \tag{51}$$

By y is denoted the column vector of the y_k and the constant column vector Y is

$$Y = M_{j0} C_0 \, , \tag{52}$$

where C_0 is the column vector of the C^k_0. Now it is possible to construct a partitioned matrix $T = [\delta_{ij} T_i]$ such that TRT^{-1} is real and symmetric, provided that A is admissible. The sub-matrices on the diagonal of TRT^{-1} are $T_i E_i T_i^{-1}$ and, by (49), they are symmetric and real if $T_i = f_i V$, where f_i is any real, scalar factor and V is the matrix discussed in Section 2. The sub-matrices in the off-diagonal positions of TRT^{-1} are $V_i M_{ij} V_j^{-1}$. Since the M_{ij} are diagonal, the product TRT^{-1} is symmetric if $T_i M_{ij} T_j^{-1}$

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* It is to be noted that in equation (3) of Rashevsky (1948b) the signs of the flow terms are incorrect and that in his equation (5), which is equivalent to our (47), the constant terms have been omitted.

$= T_j M_{ji} T_i^{-1}$, or, since diagonal matrices are commutitive, if

$$f_i^2 M_{ij} = f_j^2 M_{ji} \, . \tag{53}$$

If the volume of the ith region is τ_i, it is clearly a physical necessity that $\tau_i m_{ij}^k = \tau_j m_{ji}^k$, for all i, j, and k, and hence from (50)

$$\tau_i M_{ij} = \tau_j M_{ji} \, , \qquad i, \, j = 1, \, 2, \, \ldots, \, p \, ; \qquad i \neq j \, . \tag{54}$$

According to (54), if $f_k = \sqrt{\tau_k}$, $k = 1, 2, \ldots, p$, then (53) is satisfied.

Thus it has been proved that the roots of R are real. The vector y cannot be a periodic vector. Straightforward application of the theorem of Section 2, with due respect for (49), (50), and (51), shows at once that the roots of R are negative.

6. *The open non-uniform system; general case.* If the general case

$$\sum_j D_{kj}^i \nabla^2 C_j + \sum_j a_{kj} C_j = \frac{\partial C_k}{\partial t} \, , \qquad k = 1, \, 2, \, \ldots, \, n \tag{55}$$

is considered, a definite answer to the question of the periodicity of the C_k can be supplied only if the matrix, $[D_{kj}^i]$, of the diffusion coefficients is diagonal. It can then be shown that *if* $[a_{ij}]$ *is an admissible matrix* the eigen-values of the *set* of Sturm-Liouville equations to which the Laplace transform of the set (55) gives rise are all real. This implies that the C_j cannot be periodic functions. While this demonstration depends directly upon the properties of an admissible matrix as defined here, it otherwise involves considerations very different from the subject matter of this paper. These results, which in no way depend upon the geometry of the system, will be included in a forthcoming apper (Hearon and Sangren, 1953). It may be noted in passing that it would indeed be a severe indictment of the approximate method (Rashevsky, 1940), and the refinement thereof (Rashevsky, 1948b), if (55), with $D_{kj}^i = 0$, $k \neq j$, gave rise to results *basically* different from those of Section 5.

The nature of the steady-state solutions of (55) is easily seen in the case of spherical symmetry when $D_{kj}^i = 0$, $k \neq j$. For the steady state, (55) becomes

$$D \nabla^2 C + AC = 0 \, , \tag{56}$$

where D is the *diagonal* matrix of the diffusion coefficients and C the column vector of the C_j. The transformation

$$\begin{aligned} C &= G \xi \\ G &= V^{-1} S \, , \end{aligned} \tag{57}$$

where V is the matrix discussed in Section 2 and S is the matrix which diagonalizes the symmetric matrix VAV^{-1}, gives

$$D\nabla^2\xi + \Lambda\xi = 0\,, \tag{58}$$

where $\Lambda = [\delta_{ij}\lambda_j]$ and the λ_j, the roots of A, are non-positive. The solutions of (58) are

$$\begin{gathered} \xi_i = K_i \frac{\sinh \epsilon_i r}{r} \qquad i = 2, 3, \ldots, n \\ \xi_1 = K_1\,, \end{gathered} \tag{59}$$

where $\epsilon_j = \sqrt{-\lambda_j/D_j^{i}}$ and the roots are labeled so that $\lambda_1 = 0$. Therefore,

$$\begin{aligned} C_i &= \sum_j g_{ij}\xi_j \\ &= K_1 + \sum_{j=2} g_{ij} K_i \frac{\sinh \epsilon_j r}{r}\,. \end{aligned} \tag{60}$$

The special solution, ξ_1, of (59) could have been anticipated. For if A is singular, some linear combination of the C_j is a harmonic function. If A is an admissible rate matrix this linear combination is αDC where α is the row vector of the α_k of (6). This statement, of course, does not depend upon D being diagonal.

7. *Discussion and summary.* From the standpoint of conventional chemical kinetics the arguments upon which *Statements I* and *II* are based are unnecessarily involved, for if the rate matrix for a set of chemical reactions be written down the contents of these statements can be verified by inspection. The arguments are such, however, as summarized in *Statement III* and the discussion thereof, that if a *formal* description is attempted in terms of linear equations then the only possible interpretation is the stoichiometric conversion of the X_i one into another.

The physically simple condition of the conservation of mass is mathematically a far-reaching one, for *this condition alone* is sufficient to establish that $|A| = 0$, that for any given j the a_{ij} cannot all have the same sign, that the real parts of the roots are non-positive (see first footnote) and that there are no pure imaginary roots (see below). The fact that concentrations are positive is sufficient to fix the signs of the a_{ij}, $i \neq j$. These two conditions are sufficient to insure the reality of the roots for the case $n = 2$ or for any case in which there are only $2(n-1)$ off-diagonal nonzero a_{ij}. In fact, if $n = 2$, the conservation of mass completely determines the character of the roots for one root is zero and complex roots must occur as conjugate pairs.

In general, the principle of detail balancing must be invoked in order to prove the reality of the roots. That they are non-positive then follows from the conservation of mass by physical reasoning, by the theorem of A. Brauer (1946) or by the theorem of Section 2. A necessary condition for applying the principle of detail balancing is that there exist non-trivial solutions of equations (13). As noted, this is insured by the conservation of mass. It might be questioned that these solutions actually correspond to stationary values for the x_i, i.e., if pure imaginary roots occur the $x_i(t)$ might oscillate in such a way that solutions of (13) exist although the system is not actually time independent. If the units of x_i are chosen such that every $a_i = 1$, the theorem of Brauer (*loc. cit.*) may be stated as follows: Every root of A lies in one of the circles in the complex plane with centers at a_{ii} and radii $\sum_{j \neq 1} a_{ji}$. Equations (10) then show that these circles lie in the left half-plane and are tangent to the axis of the imaginaries at the origin. There are, therefore, no pure imaginary roots, the real parts of the roots are non-positive, and the $x_i(t)$ approach true steady state values as $t \to \infty$.

From the practical point of view the argument leading from (30) to (31)–(35) perhaps requires additional comment. The hypothesis upon which the argument is based means physically that if the transition $x_r \to x_s$ occurs (i.e., $a_{sr} > 0$) then the reverse transition occurs also ($a_{rs} > 0$). The value of a_{rs} may be extremely small and for certain practical purposes it may be permissible to neglect a_{rs} with respect to a_{sr} or with respect to any other element of A. Mathematically, the hypothesis requires only that a_{sr}/a_{rs} be *finite;* the actual numerical value is irrelevant. It is well known that for practical purposes certain reactions may be considered kinetically irreversible. It cannot, however, on this basis be asserted that the hypothesis is invalid.

The history of the cyclic relations of Section 2 is of interest. Over fifty years ago R. Wegscheider (1901) published a remarkable paper in which it was pointed out that in certain cases the mass-action expression as obtained from chemical kinetics does not agree with the classical law of mass-action as derived from thermodynamics unless a certain relation among the rate constants can be assumed. This relation corresponds precisely to a 3-cycle as defined in Section 2. This situation was long known as "Wegscheider's Paradox." Nearly a quarter of a century later G. N. Lewis (1925) showed that this "paradox" could be resolved at once by the principle of detail balancing. This seems to be the first instance of the application of the principle, well known in statistical mechanics, to purely chemical considerations or to physicochemical processes such as phase changes. Six years after the appearance of the Lewis paper, L. Onsager (1931) discussed the 3-cycle as an example of the now famous Onsager reciprocal relations. He stated that such relations are not a thermodynamic necessity. However, the free energy chanage for conducting a chemical reaction around a closed cycle is of necessity zero. Further, this free energy change is equal to the *standard* free energy change for the process. If this quantity is taken to be $-RTlnK$, where K is the equilibrium constant for the cyclic reaction, it is clearly necessary that $K = 1$. But K is the product of the equilibrium constants for the individual steps in the cycle and $K = 1$ is just a σ-cycle, as defined in Section 2, if there are σ steps in the cyclic reaction. The cyclic relations could have been derived in this manner. This argument requires however the usual assumptions regarding the relation between an equilibrium constant and certain linear combinations of the standard chemical potentials as well as the relation between the equilibrium constant and the forward and reverse rate constants. While these assumptions are universally granted, the latter may be said to lie outside the framework of *classical* thermodynamics.

The relation between the present work and certain previous investigations of periodic reactions requires little discussion. The case of Section 4 is a generalization of that treated by Rashevsky (1938, 1948c). The first case of Section 5 is a generalization of that treated by Weinberg (1939), the second case a generalization of that treated by Rashevsky (1948*b*). In the more general case treated by Weinberg (1938) the characteristic equation is $|A - \lambda D| = 0$, where D is the *diagonal* matrix of the diffusion coefficients and A and D are of order 2. It follows at once that if $|A| = 0$ one root is zero. The other is necessarily real, it is $\lambda = a_{11}/D_{11} + a_{22}/D_{22}$ and therefore negative. In this case, then, the conservation of mass is definitive as regards the reality of the roots.

It is worth noting here that although the assumption of linear differential equations is very restrictive for general chemical systems there is a large class of cases in which this is valid. The concentrations of isotopically tagged species will obey linear equations provided that they are present at tracer level. If the system is stationary with respect to the normal species the coefficients in these equations are constant. The formalism of this paper then is applicable to isotope kinetics. In particular the second case of Section 5 corresponds to the diffusion of n species between p compartments with general chemical reaction in each compartment.

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