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DYNAMICS OF OPEN CHEMICAL SYSTEMS AND THE ALGEBRAIC STRUCTURE OF THE UNDERLYING REACTION NETWORK

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Abstract—While there has been a longstanding interest in stability of non-isothermal reactors there has only recently developed a comparable interest in the dynamics of open isothermal reactors with complex chemical reaction networks. In the recent literature there has been paid particular attention to the study of biological reaction systems which might exhibit sustained oscillations (biological clocks) or bistability (biological switches). Results are presented which bear upon the relationship between the algebraic structure of the underlying reaction network and the extent to which reactors might give rise to such "exotic" dynamics.

1. INTRODUCTION

In recent years there seems to have developed an interest in open chemical systems which might exhibit sustained oscillations, bistability or, more generally, behavior that might normally be regarded as "exotic". The interest seems to have its roots in biological considerations, the idea being that certain physiological functions might be borne by chemical subsystems endowed with appropriate dynamic behavior. For example, a chemical reaction network which, in an open system, gives rise to bistability might underlie a physiological switching device, while a reaction network which, in an open system, gives rise to sustained chemical oscillations might provide a basis for biological time-keeping at the cellular level.

The reader might wish to consult the comprehensive review by Higgins[1]. Of particular interest are his computer studies of the dynamics to which real biochemical reaction networks might give rise, including a demonstration of the existence of apparently sustained chemical oscillations generated by part of the biochemical mechanism wherein sugars are metabolized. Higgins also provides a brief survey of experimental work, including recent experiments by Frenkel[2] in which apparently homogeneous extracts derived from both yeast and heart muscle cells exhibited virtually sustained chemical oscillations.

It is our intention in this article to present certain results which bear upon the relationship between the algebraic structure of the underlying reaction network and the extent to which certain simple chemical systems might give rise to "exotic" dynamics. These results have their origins in three recent papers[3–5] in which may be found definitions and proofs set in a more formal and general context. Our purpose here is not to break new ground, but rather to bring together in one article some of those results and to present them in an informal manner, divorced from proof and the concomitant mathematical apparatus. We make no attempt to present results in their most general form nor to maintain consistency with the language employed in the three aforementioned articles. Sections 2–4 are preparatory to Section 5, in which our main findings are stated.

2. ENCODING OF CERTAIN OPEN SYSTEMS

In studying the dynamics of closed chemical systems, the chemist or chemical engineer often finds it useful to write down the set of elementary chemical reactions he either knows or believes to be occurring in the system under study. With the set of reactions laid out before him he can, by assuming the usual mass-action kinetics, write a set of differential equations governing species concentrations in terms of rate constants which are either known, are to be measured, or are to be approximated. The formalism for the construction of those differential equations is well known to anyone working in chemical kinetics. Hence, the written set of chemical reactions serves not only to encode the chemical processes underlying the dynamics under study but also serves as a framework for the construction of the governing differential equations.

In the case of open systems there is considerably

more to be taken into account than the chemical reactions which occur; one must incorporate into ones analysis the influx and efflux of perhaps several chemical species, each of which might be supplied or removed in a manner peculiar to itself. We suggest here that the physico-chemical makeup of many open systems might be encoded by means of a set of pseudo-reactions, much in the same manner that the chemistry of closed systems can be encoded in a written set of elementary reactions. The balance of this section is devoted to a prescription for construction of a set of pseudo-reactions for an open system that one might wish to study. In Section 4 we suggest that once constructed, the set of pseudo-reactions might serve as a framework, in the context of the formalism alluded to earlier, for the construction of the differential equations governing the open system under consideration—much as the elementary reactions serve as a guide for the construction of equations governing closed system dynamics. At first glance it would appear that all of this might have only cosmetic value; *however, we point out that the main results presented here pertain to the relationship between the algebraic structure of the set of pseudo-reactions which encode a given open system and the quality of the dynamics which that system might exhibit.*

Consider a well-stirred reactor† maintained at time invariant volume and temperature; the reactor is permitted to exchange matter with its environment in any or all of the following ways:

(A) One or more chemical species might be supplied to the reactor at constant rate.

(B) One or more chemical species might be removed from the reactor, each at a rate proportional to that species' molar concentration within the reactor.

(C) One or more chemical species might be supplied to or removed from the reactor in such a manner as to keep the molar concentration of that species within the reactor constant in time.

Situations (A) and (B) are encountered in the usual operation of continuous stirred-tank reactors familiar to chemical engineers; feed of fixed composition is supplied at a constant volumetric flow rate, the concentration of each species in the efflux being identical to its concentration in the reactor. In this case, all species present in the reactor are in the efflux; this is not essential to the theory, which we intend to be broad enough to embrace situations for which the exchange of matter between the reactor and its environment is accomplished by transport through membranes rather than by convection. (In this case some species may be denied passage outward). Situation (C) plays less of an explicit role in chemical engineering problems than it seems to play in biochemical studies. (See, for example Walter, Ch. 8[6]). Nevertheless, even in chemical engineering studies condition (C) is often implicitly involved in a *de facto* sense. For instance, this is the case in some analyses of the stability of systems in which there occur a set of highly reactive species in the presence of an excess of less reactive compounds or in circumstances in which a reactant is present in such large supply that its concentration in the reactor can, for practical purposes, be regarded as time invariant.

Open reactors of the class described above are encoded in a set of pseudo-reactions in the following manner: One begins by writing down the set of elementary reactions occurring within the reactor. Then,

(A′) if a species, say A_i, is supplied to the reactor at a constant rate a reaction $0 \rightarrow A_i$ (read "zero reacts to A_i") is added to the set of elementary reactions;

(B′) if a species, say A_j, is removed from the reactor at a rate proportional to its concentration within the reactor, one adds the reaction $A_j \rightarrow 0$ (read "A_j reacts to zero");

(C′) if a species, say B_i, is supplied or removed from the reactor in such a manner as to maintain the concentration of B_i in the reactor time-invariant then B_i is "stripped" from any reactions in which B_i appears. (For example, the reaction $A_1 + B_i \rightarrow 2A_2$ would be replaced by $A_1 \rightarrow 2A_2$, and the reaction $A_3 \rightarrow 2B_i$ would be replaced by $A_3 \rightarrow 0$.)

The resulting set of pseudo-reactions we regard as a schematic encoding of the system under study. (Clearly, for closed systems that encoding is simply the set of elementary reactions itself.) Freely adopting familiar terminology, we call the set of pseudo-reactions so constructed the *mechanism* underlying the open (or closed) system being investigated. (For closed systems the term "mechanism" takes on its usual meaning.)

†As is usual in chemical engineering literature the phrase "well-stirred" implies that composition and temperature may be taken to be independent of the position within the reactor and does not necessarily imply the presence of a mechanical stirring mechanism.

Example 1

Consider a reactor whose contents, a mixture of A_1 and A_2, are maintained homogeneous, isothermal, and of fixed volume V. In the reactor there occur only the reactions

$$2A_1 \rightleftarrows A_2.$$

Feed is supplied to the reactor at volumetric flow rate g and with molar concentrations of A_1 and A_2 equal to ${c_1}^f$ and ${c_2}^f$ respectively; g, ${c_1}^f$ and ${c_2}^f$ are time-invariant. Reactor contents are removed at volumetric flow rate g. The mechanism for this open system is

$$2A_1 \rightleftarrows A_2 \rightleftarrows 0 \rightleftarrows A_1$$

Example 2 (*the Lotka system*)

Consider a reactor whose contents, a mixture of A_1, A_2, B and D are maintained homogeneous, isothermal, and at constant volume. In the reactor there occur the reactions

$$A_1 + B \rightarrow 2A_1$$

$$A_1 + A_2 \rightarrow 2A_2$$

$$A_2 \rightarrow C.$$

Pure B is fed to the reactor in such a manner as to maintain its concentration at a fixed level C_B^*. D is removed from the reactor in a manner such as to maintain its concentration at a fixed level C_D^*. The mechanism for this open system is

$$A_1 \rightarrow 2A_1$$

$$A_1 + A_2 \rightarrow 2A_2$$

$$A_2 \rightarrow 0$$

We point out that this is sometimes called the "Lotka mechanism" and has a history rooted in ecological considerations[7], A_1 and A_2 representing two animal species†. Hence, we remark in passing that while our focus is upon chemistry, the ideas we present have applications elsewhere.

3. MECHANISMS AND THEIR CLASSIFICATION

In this section we introduce ideas and terminology pertinent to mechanism structure and classification. Throughout this section (and for the balance of this article) the word "mechanism" is used in the broad sense suggested in Section 2. Hence, encoding mechanisms might incorporate "reactions" which appear strange to the eye (e.g. $A_1 \rightarrow 2A_1$, $A_2 \rightarrow 0$) and needn't reflect compatibility with principles normally associated with "true" chemical mechanism (e.g. conservation of mass, detailed balance). In addition we take into consideration mechanisms which might be offered by the chemist as approximate in the sense that reactions which proceed at negligible rates are not displayed. As a basis for discussion we offer Table 1 in which ten mechanisms are shown. These range from the very simple Mechanism 1 to the considerably more complex Mechanism 10, which schematically encodes part of the metabolic pathway wherein sugar is degraded enzymatically.

Table 1. Examples of mechanisms

1. $2A_1 \rightarrow A_2$
2. $2A_1 \rightleftarrows A_2$
3. $2A_1 \rightarrow A_2 \rightleftarrows A_3 + A_4$
4. $2A_1$ ↗↙ ↖↘ $A_3 + A_4 \rightleftarrows A_2$
5. $2A_1$ ↗ ↘ $A_3 + A_4 \leftarrow A_2$
6. $2A_1$ ↗ ↖ $A_3 + A_4 \rightleftarrows A_2$
7. $A_1 \rightarrow A_2$, $A_1 + A_3 \rightarrow A_4$, ↖ ↙ $A_2 + A_5$
8. $A_1 \rightleftarrows A_2$, $A_1 + A_3 \rightarrow A_4$, ↖ ↙ $A_2 + A_5$
9. (Lotka) $A_1 \rightarrow 2A_1$, $A_1 + A_2 \rightarrow 2A_2$, $A_2 \rightarrow 0$
10. (Glycolysis) $o \rightarrow A_1$, $A_1 + A_2 \rightarrow A_3 + A_4$, $A_3 \rightarrow A_2 \rightleftarrows A_4 + A_5$, $A_4 + A_6 \rightarrow A_7 \rightarrow A_6$

In introducing ideas and terminology we rely heavily upon examples and refer readers interested in formal difinitions to other articles[3–5]. We proceed by means of a series of subsections.

(a) *The number of complexes in a mechanism (denoted by n)*

By the *complexes* in a mechanism we mean the set of entities appearing before or after arrows in that mechanism. Thus in Mechanisms 1 and 2 the complexes are $2A_1$ and A_2. In Mechanisms 3–6 the complexes are $2A_1$, A_2 and $A_3 + A_4$. In Mechanism 9 the complexes are A_1, $2A_1$, $A_1 + A_2$, $2A_2$, A_2 and 0. We indicate the number of complexes in a mechanism by the symbol n. Thus, for Mechanisms

†However chemical realizations of this system have also been discussed in the literature (see [8] p. 518).

3–6 $n = 3$, while for Mechanism 9 $n = 6$. For Mechanism 10 $n = 10$.

(b) *The number of linkage classes† in a mechanism (denoted by l)*

Directions of arrows aside, we point out that for Mechanisms 1–6 every complex is "linked" (either directly or indirectly) to every other complex. This is not the case for Mechanisms 7–10. For example in Mechanism 10 the set of complexes $\{A_3, A_2, A_4+A_5\}$ has the property that every complex in the set is "linked" either directly or indirectly to every other complex in that set; however, not one of these complexes is "linked" to any complex outside that threesome. We call the set $\{A_3, A_2, A_4+A_5\}$ a *linkage class* for Mechanism 10. By a linkage class in a mechanism we mean a set of complexes having the property that each complex of the set is linked (either directly or indirectly irrespective of arrow direction) to every other member of the set and such that no complex of the set is linked to any complex outside the set. Hence the remaining linkage classes in Mechanism 10 are $\{0, A_1\}$, $\{A_1+A_2, A_3+A_4\}$, $\{A_4+A_6, A_7, A_6\}$ for a total of four linkage classes in all. We denote the number of linkage classes in a mechanism by the symbol l. For Mechanisms 1–6 $l = 1$. For Mechanisms 7 and 8 $l = 2$, the linkage classes in each case being $\{A_1, A_2\}$ and $\{A_1+A_3, A_4, A_2+A_5\}$. For Mechanism 9 $l = 3$, the linkage classes being $\{A_1, 2A_1\}$, $\{A_1+A_2, 2A_2\}$ and $\{A_2, 0\}$. *Note that in the determination of linkage classes and number of complexes for a mechanism, the mechanism should be displayed in such a manner that each complex appears only once.*

Before proceeding further, it is essential that we introduce a modest mathematical framework within which the next definition might be set. For a mechanism in which there appear M species $\{A_1, A_2, \ldots, A_M\}$ we take *species space*, V, to be an M-dimensional real vector space with distinguished basis $\{\mathbf{e}_1, \mathbf{e}_2, \ldots, \mathbf{e}_M\}$. (If he wishes, the reader might take species space to be the usual vector space of "M-tuples" with $\mathbf{e}_1 \equiv [1, 0, 0, \ldots, 0]$, $\mathbf{e}_2 \equiv [0, 1, 0, 0, \ldots, 0]$, etc.). We suggest that the complexes of a mechanism have a natural representation in species space: Considering Mechanism 6 (for which $M = 4$) the complex A_3+A_4 is represented in species space by the vector $\mathbf{e}_3+\mathbf{e}_4$, the complex $2A_1$ is represented by the vector $2\mathbf{e}_1$, and the complex A_2 is represented by the vector $\mathbf{e}_2$. (The complex O, if it appears in a mechanism, is represented by the zero vector $\mathbf{O}$.) Moreover, each reaction in a mechanism might be represented vectorially by subtracting the vector corresponding to the "reactant" complex from that corresponding to the "product" complex. Hence, the set of reaction vectors for mechanism (6) is $\{2\mathbf{e}_1-\mathbf{e}_2, 2\mathbf{e}_1-(\mathbf{e}_3+\mathbf{e}_4), \mathbf{e}_2-(\mathbf{e}_3+\mathbf{e}_4), \mathbf{e}_3+\mathbf{e}_4-\mathbf{e}_2\}$. Having laid the necessary groundwork, we proceed to the next definition:

(c) *The stoichiometric subspace for a mechanism (denoted by S) and its dimension (denoted by s)*:

By the *stoichiometric subspace* for a mechanism we mean that linear subspace of V obtained by taking the span of the set of reaction vectors for that mechanism‡. We denote the stoichiometric subspace by S and denote its dimension by s. An alternative definition of s is offered which might be viewed by some as more concrete: For a mechanism, s is the number of elements in the largest *linearly independent* subset which might be taken from the set of all reaction vectors for that mechanism. In any event, s is easily computed via methods readily available in elementary texts on linear algebra. For Mechanisms 1 and 2 $s = 1$. For Mechanisms 3–6 $s = 2$. For Mechanisms 7 and 8 $s = 3$. For Mechanism 9 $s = 2$. For Mechanism 10 $s = 5$.

(d) *The deficiency of a mechanism (denoted δ)*

Having defined for a mechanism the number of complexes (n), the number of linkage classes (l), and the dimension of the stoichiometric space (s), we define the *deficiency*, δ, of a mechanism by the formula

$$\delta \equiv n-l-s.$$

Clearly for every mechanism δ is an integer, but what is less apparent is that for every mechanism, δ is non-negative [5]. Mechanism 1–8 have deficiency zero, while Mechanisms (9) and (10) have deficiency one. In short, one may classify mechanisms by assigning to each a non-negative integer called its deficiency. At this point we make a remark which does not led itself to proof, but rather which rests upon observation: It seems that an uncommonly large percentage of mechanisms which one might extract from a text on reaction kinetics are of deficiency zero. That this might be made more precise, one of us has in preparation an article in which there is ascertained the "density"

†In [4] and [5] we used the term "coarse linkage classes", while here we use the term "linkage classes".

‡The span of a set of vectors is the subspace consisting of all linear combinations of that set of vectors.

of zero deficiency mechanisms within the totality of all mechanisms of a certain large and common class. (It should be pointed out that Mechanisms (9) and (10) have been included in the examples in a sense *because* they have non-zero deficiency.) We make one further remark which does lend itself to proof: Given a mechanism, any sub-mechanism (gotten from the original mechanism by deleting arrows and/or complexes) has a deficiency which does not exceed that of the original mechanism. Hence, if a sub-mechanism has non-zero deficiency so does the "parent" mechanism.

(e) *Reversibility and weak reversibility*

Mechanisms needn't have the property that if a "reaction" appears its "anti-reaction" appears as well. For example species A_i might be removed from a reactor at a rate proportional to its concentration in the reactor (in which case $A_i \rightarrow 0$ would appear in the mechanism), but A_i might not be fed to the reactor (in which case $0 \rightarrow A_i$ would not appear†). It is sometimes held to be the case that if an elementary reaction going on *inside* a reactor is considered to occur, then the anti-reaction should be considered to occur as well (perhaps of an appreciable smaller rate); even so, chemists and chemical engineers frequently find it quite reasonable to neglect the occurrence of certain chemical reactions. For these reasons, we consider mechanisms which may or may not have the property that each reaction is "reversible".

Nevertheless, the "directedness" of mechanisms does play a role in the theory. Accordingly, we introduce some pertinent ideas and vocabulary. A mechanism is called *reversible* if for each reaction that is represented in that mechanism the anti-reaction is represented as well; thus, Mechanisms (2) and (4) are the only reversible entries in Table 1. We say that a mechanism is *weakly reversible* if it has the following property. For any pair of complexes such that there exists a directed arrow pathway (consisting of one or more arrows) "pointing" from the first complex to the second, there also exists a directed arrow pathway "pointing" from the second complex to the first. For example, in Mechanism (5), there exists a directed pathway leading from the complex $2A_1$ to the complex A_2, and there also exists a directed pathway leading from A_2 back to $2A_1$ (via complex A_3+A_4); by applying a similar test to other complex pairs, one may establish that Mechanism (5) is weakly reversible. On the other hand, Mechanism (6) is not weakly reversible; while there is a directed pathway which leads from A_2 to $2A_1$ (via A_3+A_4), there is no directed pathway which takes one from $2A_1$ back to A_2. Similarly, Mechanism (8) is weakly reversible, but Mechanism (7) is not. Mechanisms (1), (3), (7) and (10) are not weakly reversible. The reversible Mechanisms (2) and (4) are also weakly reversible; in fact, it is easily seen that *every mechanism which is reversible is also weakly reversible* (but, of course, the converse is not true).

In concluding this section we suggest that two key questions pertaining to mechanism classification are these: Given a mechanism, what is its deficiency? Is it weakly reversible?

†That is, unless $0 \rightarrow A_i$ is obtained as a result of "stripping" an elementary reaction.

4. KINETICS FOR A MECHANISM AND THE ASSOCIATED DYNAMICAL EQUATIONS

Having introduced in Section 2 the idea of a mechanism for an open system, we introduce here the idea of a *kinetics* for such a generalized mechanism. In addition we describe a formalism for constructing from a mechanism and its kinetics the differential equations which govern the system at hand. For closed systems the notion of kinetics takes on its usual meaning, and the formalism reduces to the usual one for constructing differential equations which describe closed system chemical dynamics. The ideas presented are not intended to provide a substantively new procedure for forming differential equations for open systems; this is not a particularly difficult task in the first place. Rather, the intent is to draw open and closed systems into a common mathematical framework based upon the idea of generalized mechanism, the algebraic structure of which serves as a basis for the results to be presented in Section 5.

We draw upon the vector space introduced in the last section to provide a setting for the discussion. If the species appearing in a mechanism for a system are $A_1, A_2, \ldots$ and A_M, and if at time t their molar concentrations in the reactor are, respectively, $c_1(t)$, $c_2(t)\ldots$, and $c_M(t)$, then the composition of the reactor contents might be represented vectorially in species space, V, by a vector $\mathbf{c}(t)$, where

$$\mathbf{c}(t) \equiv \sum_{i=1}^{M} c_i(t)\mathbf{e}_i \tag{4.1}$$

Molar concentrations are non-negative numbers, so $\mathbf{c}(t)$ is a vector of V which has non-negative components. We denote by $\overline{V^+}$ the set of all vectors

of V which have only non-negative components, and we denote by V^+ the set of all vectors of V which have only positive components. If $\dot{c}_1(t)$, $\dot{c}_2(t), \ldots,$ and $\dot{c}_M(t)$ are the time derivatives of the molar concentrations at time t then $\dot{\mathbf{c}}(t)$ is defined, as usual, by

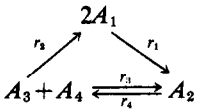
$$\dot{\mathbf{c}}(t) \equiv \sum_{i=1}^{M} \dot{c}_i(t)\mathbf{e}_i. \tag{4.2}$$

For the class of open (or closed) systems described in Section 2 it is taken to be the case that there exists a function $\mathbf{f}$ with domain $\overline{V^+}$ such that at any time

$$\dot{\mathbf{c}} = \mathbf{f}(\mathbf{c}), \tag{4.3}$$

this being the governing equation for the chemical dynamics under study. $\mathbf{f}$ is called the *overall rate function*, and a composition $\mathbf{c}$ in $\overline{V^+}$ for which $\mathbf{f}(\mathbf{c}) = \mathbf{0}$ is called here an *equilibrium composition*, there being made no terminological distinction between thermodynamic equilibria and open system steady states.

Central to the analysis is the idea that the function $\mathbf{f}$ is not arbitrary in form; rather, it bears a prescribed relationship to the mechanism which encodes the open or closed system in question. That mechanism is taken as a skeleton upon which there is built a *kinetics*, which we regard here as an assignment to each reaction in the mechanism of a scalar-valued *rate function* with domain $\overline{V^+}$. *We require that rate functions take non-negative values on* $\overline{V^+}$ *and positive values on* V^+. A mechanism taken in conjunction with an assigned kinetics suffices for the construction of the overall rate function $\mathbf{f}$ according to a formalism which is perhaps best explained by example: Consider the mechanism with reactions assigned rate functions as shown in the diagram below:



(4.4)

Then the overall rate function $\mathbf{f}$ is taken as

$$\begin{aligned}\mathbf{f}(\mathbf{c}) = {} & r_1(\mathbf{c})[\mathbf{e}_2 - 2\mathbf{e}_1] + r_2(\mathbf{c})[2\mathbf{e}_1 - (\mathbf{e}_3 + \mathbf{e}_4)] \\ & + r_3(\mathbf{c})[\mathbf{e}_2 - (\mathbf{e}_3 + \mathbf{e}_4)] + r_4(\mathbf{c})[(\mathbf{e}_3 + \mathbf{e}_4) - \mathbf{e}_2]\end{aligned} \tag{4.5}$$

That is, one forms the overall rate functions by taking a linear combination of all the reaction vectors for the mechanism, the scalar multipliers being the corresponding individual rate functions. In component form the dynamic Eqs. (4.3) and (4.5) reduce to

$$\begin{aligned}\dot{c}_1 &= 2r_2(\mathbf{c}) - 2r_1(\mathbf{c}) \\ \dot{c}_2 &= r_1(\mathbf{c}) + r_3(\mathbf{c}) - r_4(\mathbf{c}) \\ \dot{c}_3 &= \dot{c}_4 = r_4(\mathbf{c}) - r_2(\mathbf{c}) - r_3(\mathbf{c}).\end{aligned} \tag{4.6}$$

With overall rate functions formulated in this manner, the formalism ensures that composition trajectories may not wander promiscuously; rather, they must be compatible with the stoichiometry of the mechanism giving rise to the dynamics. In fact, if $\mathbf{c}(t)$ and $\mathbf{c}(t')$ are two points on a composition trajectory for which the underlying mechanism has stoichiometric subspace S, then the vector $\mathbf{c}(t) - \mathbf{c}(t')$ must reside in S. Motivated by this idea we say that for a mechanism with stoichiometric subspace S two vectors of $\overline{V^+}$, $\mathbf{c}$ and $\mathbf{c}'$, are *stoichiometrically compatible* if $\mathbf{c} - \mathbf{c}'$ lies in S. Accordingly, we may partition $\overline{V^+}$ (or V^+) into *stoichiometric compatibility classes*, (sometimes called *reaction simplices*), which may be shown to be the intersection of the parallels of S with $\overline{V^+}$ (with V^+). These ideas will be illustrated with concrete examples toward the close of this section.

Up to this point we have dealt with rate functions for individual reactions of a mechanism in general terms, requiring only that they take non-negative values on $\overline{V^+}$ and positive values on V^+. Of particular interest here is the familiar *kinetics of mass-action type*. We presume the reader to be familiar with this class of kinetics and provide here only an illustrative example. Thus, in (4.4)

$$\begin{aligned}r_1(\mathbf{c}) &\equiv k_1 c_1^2 \\ r_2(\mathbf{c}) &\equiv k_2 c_3 c_4 \\ r_3(\mathbf{c}) &\equiv k_3 c_3 c_4 \\ r_4(\mathbf{c}) &\equiv k_4 c_2\end{aligned} \tag{4.7}$$

where k_1, k_2, k_3 and k_4 are positive rate constants. The key idea is that the rate functions bear an intimate relation to the reactant complex of the reaction with which they are associated; for each reaction the rate is proportional to the product of the M species concentrations, each raised to a power given by the stoichiometric coefficient of that species in the reactant complex. We make the important point that for mass-action kinetics a reaction for which the rate constant is k and for

which the reactant complex is 0 (e.g. $0 \rightarrow A_1$) proceeds at constant rate k independent of any species concentrations, the idea being that each species concentration raised to the power zero is unity.

Consider open systems of the class described in Section 2, and suppose that the elementary chemical reactions occurring within the reactor are governed by mass-action kinetics. Then the *encoding mechanism* for such open systems can be assigned a mass-action kinetics (i.e. each "reaction" in the mechanism can be assigned a positive rate constant) such that the differential equation constructed in accord with the formalism described here is precisely the equation which emerges from application of the usual first principles. To illustrate these ideas we return to the two examples of Section 2:

Example 1

Suppose that the rate constants for the elementary reactions are those in the reaction diagram below:

$$2A_1 \underset{k'}{\overset{k}{\rightleftharpoons}} A_2 \tag{4.8}$$

Then we choose rate constants for the *encoding mechanism* as shown:

$$2A_1 \underset{k'}{\overset{k}{\rightleftharpoons}} A_2 \underset{gc_2^f/V}{\overset{g/V}{\rightleftharpoons}} 0 \underset{g/V}{\overset{gc_1^f/V}{\rightleftharpoons}} A_1 \tag{4.9}$$

In the context of mass-action kinetics the formalism described earlier applied to the encoding mechanism gives rise to the differential equations

$$\begin{aligned} \dot{c}_1 &= \frac{gc_1^f}{V} - \frac{g}{V}c_1 + 2k'c_2 - kc_1^2 \\ \dot{c}_2 &= \frac{g}{V}c_2^f - \frac{g}{V}c_2 + kc_1^2 - k'c_2 \end{aligned} \tag{4.10}$$

which are precisely the differential equations one would normally formulate for the open system of Example 1.

Example 2

Suppose that the rate constants for the elementary reactions are those indicated in the diagram below:

$$\begin{aligned} A_1 + B &\xrightarrow{k} 2A_1 \\ A_1 + A_2 &\xrightarrow{k'} 2A_2 \\ A_2 &\xrightarrow{k''} D. \end{aligned} \tag{4.11}$$

Then the rate constants for the *encoding mechanism* are taken as shown:

$$\begin{aligned} A_1 &\xrightarrow{kc_B^*} 2A_1 \\ A_1 + A_2 &\xrightarrow{k'} 2A_2 \\ A_2 &\xrightarrow{k''} 0. \end{aligned} \tag{4.12}$$

In the context of mass-action kinetics the formalism applied to the encoding mechanism gives rise to

$$\begin{aligned} \dot{c}_1 &= kc_B^* c_1 - k'c_1c_2 \\ \dot{c}_2 &= k'c_1c_2 - k''c_2. \end{aligned} \tag{4.13}$$

Hence the formalism yields the same differential equations one would normally formulate from first principles.

Now the essential point is this: Just as the dynamics of closed systems can be discussed (in the context of mass-action kinetics) in terms of mechanism and rate constants, so can open systems of the class described in Section 2 be discussed in terms of the *encoding mechanism* and rate constants, all in the context of mass-action kinetics. Hence closed and (a large class of) open systems are drawn into a common framework within which it becomes meaningful to raise questions regarding the relationship between a mechanism's structure and the statics and dynamics to which it might give rise. (For open systems these questions focus upon the structure of the *encoding* mechanism.) As a corollary it becomes meaningful to at least begin the construction of a theory which might serve to answer some of those questions. Clearly, the theory should be broad enough to embrace mechanisms with seemingly strange reactions (e.g. $0 \rightarrow A_1$, $A_2 \rightarrow 2A_2$) and for which the assigned kinetics violate conditions appropriate only to closed systems (e.g. detailed balance).

In order that certain questions might be posed, we turn to consideration of the variety of statics and dynamics to which different mechanisms might give rise when taken with mass-action kinetics. We proceed by way of examples, each mechanism involving only two species A_1 and A_2. The sample mechanisms are *not* intended to be realistic; they are merely intended to display in a simple manner features which are shared with more realistic but more complex mechanisms. There are presented four figures; in each there is shown the mechanism under consideration (with rate constants), the dynamical equations constructed in accord with

the formalism outlined earlier, and a sketch in which are indicated some reaction trajectories, some equilibrium points, the stoichiometric subspace, and some stoichiometric compatibility classes of V^+. (Of course, it is difficult to make a distinction in the figure between these and the stoichiometric compatibility classes of $\overline{V^+}$.)

Figure 1 focuses upon the simplest mechanism of Table 1—a mechanism consisting of only a single reaction. The stoichiometric subspace is which all trajectories originating in that class proceed in the limit with time. Loosely speaking, we associate this behavior with "normal" dynamics; there is a settling down to equilibrium, no species becomes entirely extinct, and initial compositions which are stoichiometrically compatible all ultimately evolve to the same equilibrium composition.

It is evident from Fig. 3 that the Lotka mechanism gives rise to considerably more "exotic"

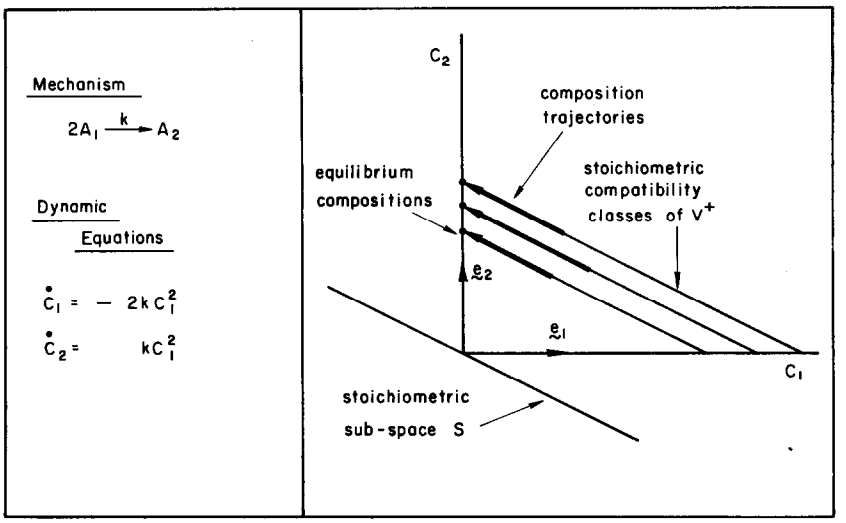


Fig. 1. Statics and dynamics of a simple irreversible mechanism.

one-dimensional and contains the reaction vector $\mathbf{e}_2 - 2\mathbf{e}_1$; the stoichiometric compatibility classes of V^+ are those parts of the parallels of S which lie in the positive orthant, V^+. (Similarly, the stoichiometric compatibility classes of $\overline{V^+}$ are those parts of the parallels of S which lie in the non-negative orthant, $\overline{V^+}$.) A composition trajectory which originates in V^+ travels progressively along the parallel of S containing the point of origin until all A_1 is depleted (i.e. until $c_1 = 0$). There are no equilibrium compositions in V^+, the dynamic equations thereby providing for the "extinction" of species A_1.

The mechanism underlying Fig. 2 is only slightly more complicated than that of Fig. 1, the reverse reaction having been added. Moving from Fig. 1 to Fig. 2, we observe that the stoichiometric subspace remains unchanged, as do the stoichiometric compatibility classes (be they of $\overline{V^+}$ or V^+). However, the dynamic situation is considerably different. We make the observation that in each stoichiometric compatibility class of V^+ there exists exactly one equilibrium composition toward

dynamics. For that mechanism the stoichiometric subspace coincides with V, and composition trajectories are not constrained as in Figs. 1 and 2 to reside in line segments. In fact, there is only one stoichiometric compatibility class of V^+ (of $\overline{V^+}$), that being V^+ ($\overline{V^+}$) itself. We note that Fig. 3 exhibits an equilibrium composition in V^+. For an initial composition in V^+, say $\mathbf{c}_0$, the trajectory emanating from $\mathbf{c}_0$ will, in a finite amount of time, return to $\mathbf{c}_0$, thereby reinitiating the cycle. Sustained chemical oscillations are a consequence, so that the Lotka mechanism might be viewed as one which provides a basis for chemical "timekeeping". We mention in passing that Higgins[1] has demonstrated via analog computation that Mechanism 10 of Table 1 also gives rise to apparently sustained oscillations, that mechanism being a schematic representation of part of the metabolic pathway for glucose degradation.

For the mechanism in Fig. 4 we have, for the sake of discussion, set rate constants for the two "vertical" reactions to unity and rate constants

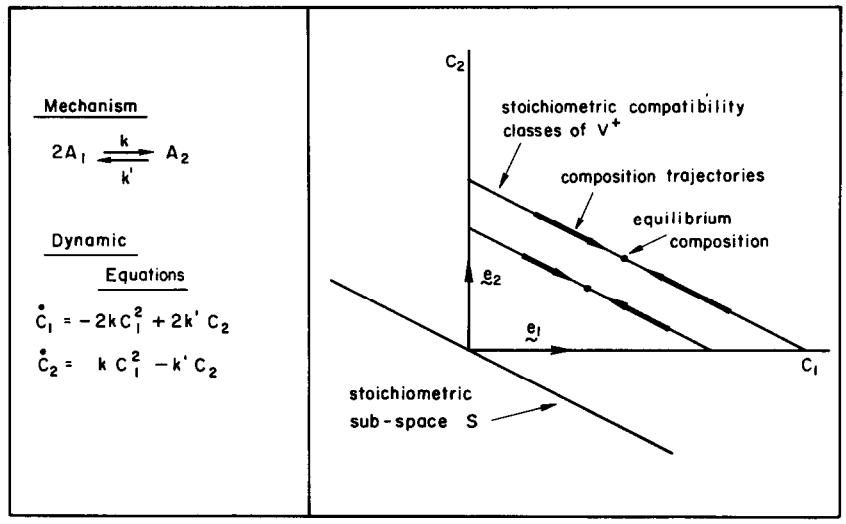


Fig. 2. Statics and dynamics of a simple reversible mechanism.

for the "horizontal" reactions to ϵ. (We consider two cases, $\epsilon \geq 1/6$ and $0 < \epsilon < 1/6$.) The mechanism gives rise to a one-dimensional stoichiometric subspace S, which contains the vector $\mathbf{e}_2 - \mathbf{e}_1$. The stoichiometric compatibility classes of V^+ are those parts of the parallels of S which reside in V^+. We note that for the case $\epsilon \geq 1/6$ there is exhibited the "normal" behavior akin to that in Fig. 2: In each stoichiometric compatibility class of V^+ there exists exactly one equilibrium point toward which all trajectories originating in that class tend with time. The situation is markedly different for the case $0 < \epsilon < 1/6$: In each stoichiometric compatibility class of V^+ there exist three equilibrium points, the center one being unstable and the two others being locally stable. Hence, two reactors (even though they might be characterized by the same stoichiometric compatibility class in V^+) might respond in markedly different ways to only slightly different initial composition settings. While the mechanism indicated in Fig. 4 is clearly unrealistic chemically for several reasons, it was chosen for its simplicity. A more realistic but more complicated mechanism which gives rise to bistability is displayed in the book by Glansdorff and Prigogine [9], p. 274).

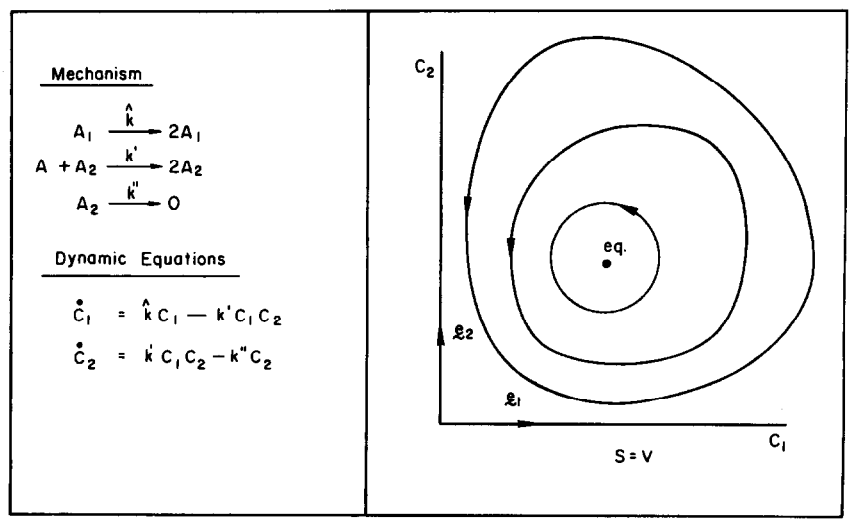


Fig. 3. Statics and dynamics of the Lotka mechanism (see Table 1).

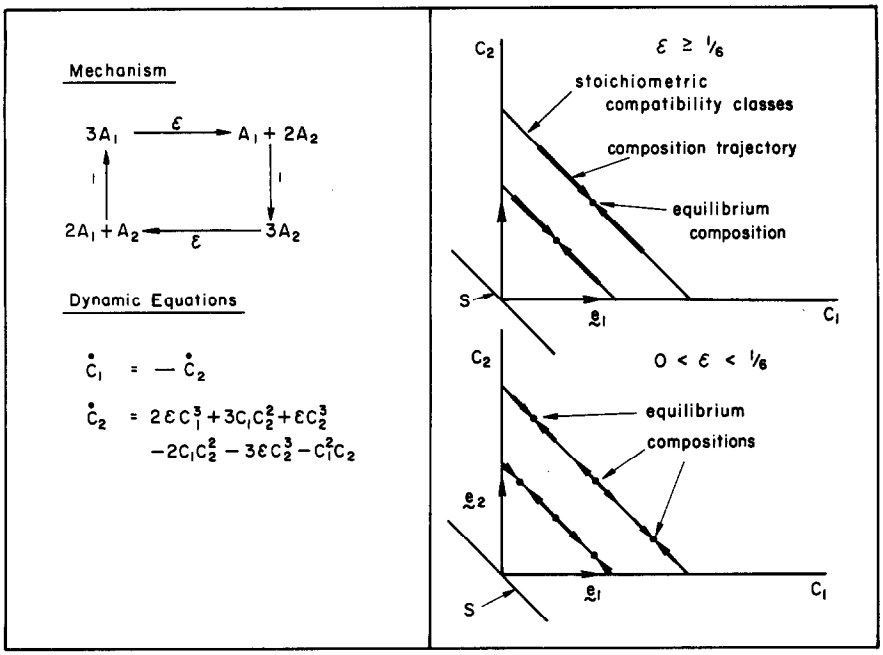


Fig. 4. Statics and dynamics of a mechanism exhibiting bistability.

Having illustrated the variety of dynamics which different mechanisms might underlie, we cite certain questions which the examples suggest.

Taken with mass-action kinetics, the mechanism in Figs. 2–4 give rise to equilibrium points in V^+, while the mechanism in Fig. 1 admits no such equilibrium point. While ones first response might be a suggestion that perhaps weak reversibility of a mechanism is essential for the existence (in the context of mass-action kinetics) of equilibrium points in V^+, Fig. 3 belies this conjecture. Hence, we ask: In the context of mass-action kinetics can one draw a relationship between mechanism structure and the existence of equilibrium compositions in V^+? In the same vein, can one make statements for *arbitrary* kinetics, restricted solely by the requirement that the rate functions take only non-negative values on $\overline{V^+}$ and only positive values on V^+?

While the mechanism of Fig. 4 gives rise to "normal" dynamics (in the context of mass-action kinetics) for *some* choices of rate constants, it is easily seen that the mechanism of Fig. 2 gives rise to "normal" dynamics for *all* choices of rate constants. Despite the fact that the latter mechanism is almost of trivial simplicity, we are led to wonder if there exists a *large class* of mechanisms for which there exists no set of rate constants which yields "exotic" dynamics. Now certain principles (e.g. detailed balance) appropriate to closed systems might place restrictions upon the class of rate constant sets which one should consider in examination of systems which are, in fact, closed. However, we remind the reader that, in the spirit of earlier remarks, we intend the theory to embrace encoding mechanisms and kinetics appropriate to open systems and view the aforementioned principles as not having *general* applicability. With this in mind, we deem all sets of positive rate constants for a mechanism as suitable for examination. Consequently we are led to pose the following question, stated in terms more suggestive than precise: Can one delineate a class of mechanisms such that for all choices of rate constants (in the context of mass-action kinetics) the corresponding differential equations give rise to "normal" dynamics?

In the next section we present a theorem which, we believe, takes one a considerable distance toward answers to these questions and bears heavily on problems concerning sustained oscillations, bistability, and other chemical "exotica".

5. THE ZERO DEFICIENCY THEOREM

Motivated by questions posed toward the end of Section 4, we draw upon the ideas of Section 3 to state the following theorem:

The zero deficiency theorem

Consider a mechanism for which the number of complexes is n, for which the number of linkage classes is l, and for which the stoichiometric subspace has dimension s. Suppose that $n-l-s=0$; that is, suppose the mechanism has deficiency zero. Then the following statements hold true:

(a) For *arbitrary* kinetics (mass action or otherwise) there can exist an equilibrium composition in V^+ only if the mechanism is weakly reversible.

(b) If the mechanism *is* weakly reversible then for *mass-action kinetics* with *any* choice of positive rate constants: There exists in each stoichiometric compatibility class of V^+ exactly one equilibrium composition; every equilibrium composition in V^+ is asymptotically stable relative to the stoichiometric compatibility class in which it resides; and the dynamic equations cannot give rise to sustained periodic solutions in V^+ (except the trivial $\mathbf{c}(t) = \text{const.}$)

In view of remarks made earlier, we suggest that the class of mechanisms to which the theorem applies (i.e. those for which $\delta = 0$) is remarkably broad in scope. With this as background, we comment on the importance of both parts (a) and (b).

We have made the suggestion that the theory we present here has application in areas other than chemistry; in fact, we have remarked that the Lotka mechanism and the associated differential equations have their roots in ecological considerations. With this in mind, we discuss (a) in ecological terms. As evidenced by the Lotka example, the differential equations governing ecological systems can often be formulated in a "mechanistic" manner—in the sense that one postulates a set of ecological "reactions", assigns to the resulting mechanism a "kinetics" (perhaps of mass-action type but not necessarily so), and, in accordance with ideas delineated in Section 3, formulates the associated dynamical equations. Given those equations, one question which might be of interest from an ecological viewpoint is this: If one begins with an ecological system in which all species under consideration are represented, can the system evolve toward an equilibrium population in which all species are represented, or is it necessarily true that whatever equilibria exist are characterized by the "extinction" of one or more species? In view of the fact that ecological mechanisms (as opposed to chemical mechanisms) might often fail to exhibit weak reversibility, part (a) of the theorem leads one to the conclusion that, for a large class of mechanisms taken with arbitrary kinetics (restricted by the requirements that the individual rate functions take positive values on V^+), the only equilibria which might exist are those which are characterized by the absence of one or more species. The nature of equilibria in more general kinetic systems than those discussed here are embraced by the theory presented in Ref. [5].

For mechanisms which encode open chemical systems of the class described in Section 2 we suggest that weak reversibility will frequently obtain. For example, suppose that all the elementary chemical reactions which occur within the reactor are reversible. Then it is easily seen that if all exchange between the reactor and its environment is governed by mode (C) of Section 2, then the encoding mechanism will be reversible (and therefore weakly reversible). The same is true if whenever a species is removed in mode (B) that same species is supplied in mode (A)—an occurrence not uncommon in the operation of continuous stirred tank reactors.

Hence, part (b) of the theorem serves to delineate a broad class of mechanisms which, taken with mass-action kinetics, must give rise to fairly mundane statics and dynamics for all choices of rate constants. To find mechanisms which, for at least some sets of rate constants, give rise to sustained oscillations in V^+ or bistability in V^+ one must search among a class which is sparse—at least among the totality of mechanisms which might loosely be described as simple.

We turn now to reconsideration of the examples presented—this time in light of the perspective afforded by the theorem. Mechanisms (1)–(8) are all of deficiency zero, and while for Mechanisms (1)–(6) at least certain of the conclusions the theorem might provide could be gotten with tools of lesser power, this is not as true of Mechanisms (7) and (8). Consequently, we use that pair for the purpose of illustration. Mechanism (7) is not weakly reversible; so it follows from the theorem that no kinetics (subject only to the weak constraints layed down earlier) can give rise to an equilibrium composition in V^+, and any equilibria which might exist are necessarily characterized by the absence of one or more species. The situation is considerably different for Mechanism (8), which *is* weakly reversible; for mass-action kinetics with any choice of rate constants there exists in every stoichiometric compatibility class of V^+ exactly one equilibrium composition, and the stability described by part (b) of the theorem

must obtain. Hence, in the context of mass action kinetics no choice of rate constants suffices to make Mechanism (8) give rise to sustained oscillations, bistability, or, more generally, chemical "exotica" in mixtures for which the concentrations of all species are positive. In light of the theorem the reader might wish to reexamine the considerably simpler mechanisms displayed in Figs. 1 and 2 in conjunction with the dynamics they exhibit.

Mechanism 9, the Lotka mechanism, serves as an example of the fact that mechanisms which are not weakly reversible but which have deficiency one may give rise to equilibrium concentrations in V^+, as is shown in Fig. 3. Moreover, the sustained oscillations shown there are not precluded by part (b) of the theorem since the mechanism is neither weakly reversible nor of deficiency zero.

The mechanism shown in Fig. 4 taken with mass-action kinetics clearly gives rise to bistability for at least some choices of rate constants. This is not precluded by the theorem; while the mechanism is weakly reversible its deficiency is easily computed to be two.

Mechanism 10 of Table 1, which has been shown by Higgins [1] via analog computation to exhibit apparently sustained oscillation, is neither weakly reversible nor of deficiency zero. Hence, it falls outside the scope of the theorem.

6. CONCLUDING REMARKS

We believe that the theorem presented in the preceding section serves to delineate a very large class of open systems which, by virtue of the algebraic structure of the encoding mechanism, behave in "non-pathological" fashion for *all* choices of rate constants (in the context of mass-action kinetics) for the "pseudo-reactions" displayed in that mechanism. Hence, the engineer has at hand a simple criterion to assure him that a reactor whose design is under consideration will behave free of eccentricities (e.g. sustained oscillations, multiple steady states) at least insofar as part (b) of the theorem obtains; on the other hand, the biologist seeking open systems endowed with complex biochemical reaction networks which might serve as physico-chemical bases for time-keeping or switching mechanisms must look *outside* the class delineated by the theorem for systems with statics and dynamics of exotic character (i.e. of character different from that described in part (b)).

While the class of open systems with encoding mechanism of deficiency zero is certainly large, there exists a wealth of systems with encoding mechanisms with deficiencies which exceed zero and are thereby not encompassed by the theorem. (For example, the very simple system described in Example 1 of Section 2 is easily seen to have an encoding mechanism of deficiency one.) Having made *ad hoc* studies of specific systems of *positive* deficiency, we know that there exist such systems for which part (b) of the Zero Deficiency Theorem remains true. Hence, it would seem that the theorem lends itself to broadening. Moreover, for those mechanisms which give rise to sustained oscillations or multiple steady states for *some* sets of rate constants, there remains the difficult problem of constructing algorithms for delineating as completely as possible those sets of rate constants for which essentially non-pathological statics and dynamics might be expected. Work is proceeding along both these lines.

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NOTATION

$A_1, A_2, \ldots, A_M$	molecular species
B_1, B_2, etc.	molecular species
c_i	concentration of species i (moles/vol)
c_i^f	feed concentration of species i (moles/vol)
$\mathbf{e}_1, \mathbf{e}_2, \ldots, \mathbf{e}_M$	basis vectors for species space
g	a volumetric flow rate (vol/time)
$k_1, k_2, k_3, k_4, k, k', k''$, etc.	rate constants
l	the number of linkage classes in a mechanism
n	the number of complexes in a mechanism
0	the "zero" or "null" complex
$r_j(\,)$	the rate function for reaction j (moles/time-volume)
S	the stoichiometric subspace for a mechanism
s	the dimension of S
t	time
V	species space
V^+	the positive orthant of V
$\overline{V^+}$	the non-negative orthant of V

Greek symbols

ϵ	a rate constant in Fig. 4 (moles^{-2}-time^{-1}-vol^{-1})
δ	the deficiency of a mechanism ($\equiv n-l-s$)

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