

Modelling of Chemical Reaction Systems

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1. The Interaction of Structure and Dynamics in Chemical Reaction Networks

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1.1 Introduction

Chemical reaction dynamics or chemical kinetics is concerned with the problem of predicting the temporal evolution of the composition of a reacting mixture, given its composition at an initial instant of time. To do this, one must know the mechanism and the rate constants of the various elementary steps, and one aspect of the problem concerns the *a priori* prediction of rate constants from bond energies and other properties of the reacting molecules. This aspect is covered in Golden's contribution to this volume (Chap. 10). Another aspect concerns the question of how the topological structure of the reaction network, by which we mean the pattern of connections between species or groups of species imposed by the reactions between them, affects the dynamical behavior of the system. More precisely, one would like to know when such phenomena as multiple steady states, temporal oscillations, and chaotic dynamics can be ruled out solely on the basis of network structure, or on the basis of network structure and some general properties of the rate laws, both for well-mixed systems and for systems in which transport occurs on the same time scale as does reaction.

The latter aspect of chemical kinetics is the subject of Feinberg's paper (Chap.5) and of this one. In closed systems, the dissipation hypothesis precludes periodic solutions and chaotic dynamics, but multiple steady states may exist in nonideal mixtures. An example of this is given in the following section. In the third section we present a graph-theoretic framework within which the foregoing questions can be dealt with for open systems. The last section deals with the problem of diffusive instabilities of a spatially uniform solution in an open system, both when the uniform solution is time-invariant and when it is time-periodic.

1.2 Closed, Spatially-Uniform Systems

Suppose that there are n reacting species M_i and $r \leq n - 1$ independent reactions amongst them, written as

$$\sum_{i=1}^n v_{ij} M_i = 0 \quad j = 1, \dots, r \quad . \quad (1.1)$$

The v_{ij} are stoichiometric coefficients that represent the relative molar proportions of the species in a reaction. For the present we assume that they are integers and that $v_{ij} > 0$ (< 0) according as species i is a product (reactant) in the j^{th} reaction. Throughout we assume that the temperature and pressure are constant and that volume changes due to reaction are negligible. Therefore, the state of the mixture is specified by the concentration vector $c = (c_1, \dots, c_n)^T$, and this must lie in R_n^+ , the nonnegative 'orthant' of an n -dimensional real vector space.

Associated with each reaction, all of which are assumed to be reversible, is a rate $R_j(c)$, and the temporal evolution of the mixture is given by the solution $c(t)$ of the differential equation

$$\frac{dc}{dt} = vR(c) \quad c(0) = c_0 \quad . \quad (1.2)$$

The $n \times r$ matrix v is the stoichiometric matrix and since the r reactions are independent, $\text{rank}(v) \equiv \rho(v) = r$. The components $R_j(c)$ of $R(c)$ are polynomials in ideal systems that follow mass action kinetics and in general are assumed to be smooth enough that the solution of (1.2) exists locally in t and is unique and nonnegative for any nonnegative c_0 .

In a closed system, the total mass and perhaps other quantities are conserved, and any such invariant combination of concentrations has the form

$$\langle \Omega_j, c(t) \rangle = \langle \Omega_j, c_0 \rangle \quad j = 1, \dots, s \quad , \quad (1.3)$$

where $v^T \Omega_j = 0$, i.e., $\Omega_j \in N(v^T)$.¹ Since $\dim R(v) < n$, the semiflow defined by (1.2) is confined to the coset of $R(v)$ defined by (1.3). The intersection of this linear manifold with R_n^+ is called the reaction simplex and is denoted $\Omega(c_0)$. Because the total mass is conserved, one of the Ω_j 's has strictly positive components, and as a result $\Omega(c_0)$ is compact. It follows from

¹ Unless specified otherwise, \langle, \rangle denotes the Euclidean inner product and $\|\cdot\|$ the associated norm. $N(A)$ and $R(A)$ are the null space and range, respectively, of the linear transformation A .

Brouwer's fixed point theorem that (1.2) always has at least one time-invariant solution, any of which we call a kinetic equilibrium point. Since $\rho(v) = r$, all kinetic equilibria are solutions of the system

$$R_i(c) = 0 \quad i = 1, \dots, r \quad . \quad (1.4)$$

If we introduce intrinsic coordinates $\{\xi_i\}$ in $\Omega(c_0)$ via

$$c - c_0 = v\xi \quad ,$$

then (1.2) can be written

$$\frac{d\xi}{dt} = R(c_0 + v\xi) \equiv \tilde{R}(\xi) \quad . \quad (1.5)$$

The thermodynamic properties of the mixture are fixed, at constant T and P, once the composition dependence of the Gibbs free energy G is prescribed. G is homogeneous of first degree in the concentrations c_i and thus can be written

$$G = \langle \mu, c \rangle \quad , \quad (1.6)$$

where

$$\mu_i = \partial G / \partial c_i \quad (1.7)$$

is the chemical potential of species i. It can be written in the form

$$\mu_i = \mu_i^0(T, P) + RT \ln \tilde{\gamma}_i(c) x_i \quad , \quad (1.8)$$

where $\tilde{\gamma}_i(c)$ is the activity coefficient of species i and x_i is its mole fraction. The solution is ideal with respect to species i if $\tilde{\gamma}_i = 1$. In any case, we require that $\tilde{\gamma}_i x_i \rightarrow 0$ as $x_i \rightarrow 0$. For convenience, we set $\gamma_i(c) = \tilde{c} \tilde{\gamma}_i(c)$ and rewrite (1.8) as

$$\mu_i = \mu_i^0(T, P) + RT \ln \gamma_i(c) c_i \quad . \quad (1.9)$$

Since the composition is restricted to lie in $\Omega(c_0)$, we restrict G(c) to $\Omega(c_0)$ by setting

$$\tilde{G}(\xi) \equiv G(c_0 + v\xi) \quad . \quad (1.10)$$

According to the classical definition [1.1], the thermodynamic equilibrium points occur at the compositions corresponding to critical points of $\tilde{G}(\xi)$, i.e., points at which the affinity

$$A_j \equiv -(\nabla \tilde{G})_j = - \sum_{i=1}^n \nu_{ij} \mu_i \quad (1.11)$$

vanishes for every reaction. Under the assumption that $\gamma_i(c) c_i \rightarrow 0$ as $c_i \rightarrow 0$ for every i , it can be shown that there is at least one thermodynamic equilibrium point in the interior of $\Omega(c_0)$ and that \tilde{G} has a minimum there. Furthermore, if the solution is ideal, the thermodynamic equilibrium point in the interior of $\Omega(c_0)$ is unique. If it is also assumed that every species participates in at least one reaction, then there are no thermodynamic equilibrium points on the boundary of $\Omega(c_0)$. There is no loss of generality in making this assumption, because when inert species are present, one can simply work in a lower-dimensional space. Of course, the dependence of the chemical potential on inert species must still be taken into account.

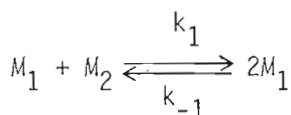
We have defined two different types of equilibria and the question arises as to when they coincide. Let us define a dissipation function ϕ as

$$\phi = \frac{-d\tilde{G}}{dt} = \langle \tilde{A}, \tilde{R} \rangle \quad (1.12)$$

and postulate that $\phi \geq 0$ along orbits or (1.5), with equality if and only if $\tilde{R} = 0$. This 'dissipation hypothesis' is the nonequilibrium generalization of the second law of thermodynamics, and under it every thermodynamic equilibrium point is a kinetic equilibrium point ($\tilde{A} = 0 \Rightarrow \tilde{R} = 0$). Furthermore, it can be shown that when this hypothesis holds,

- a) $\tilde{A} = 0$ at any kinetic equilibrium point that is positively or negatively stable (i.e., is a sink or source, respectively)
- b) $\tilde{A} = 0$ at any kinetic equilibrium point that is a saddle point if ϕ is differentiable and $\partial \tilde{R} / \partial \xi$ is nonsingular there.

Complete equivalence between thermodynamic and kinetic equilibria cannot be hoped for, because under reasonable assumptions there are no thermodynamic equilibria on the boundary of $\Omega(c_0)$, but there may be kinetic equilibria there. For instance, if the reaction is



and

$$R = k_1 c_1 c_2 - k_{-1} c_1^2 \quad ,$$

then it is easily shown that $\phi \geq 0$ if $k_1/k_{-1} = K_{eq}$, where K_{eq} is the usual equilibrium constant. Clearly there is a kinetic equilibrium point on the boundary of the simplex, and one finds that $d\phi/d\xi \rightarrow +\infty$ as $c_1 \rightarrow 0^+$ and that $\partial\tilde{R}/\partial\xi \neq 0$ there. In the terminology used by PRIGOGINE and DEFAY [1.1], points at which $\tilde{R} = 0$, but $\tilde{A} \neq 0$, are called false equilibria, and thus all boundary equilibria are false equilibria.

When the mixture is not ideal, \tilde{G} need not be globally convex and there may be more than one thermodynamic equilibrium point. Several different models of solution behavior that can lead to this phenomenon have been analyzed [1.2] and several real systems in which it might occur have been suggested [1.3]. We shall not go into details here, but will give one elementary example. Consider the reaction



in a binary regular solution for which

$$\gamma_1 = \exp[\omega(1 - x_1)^2] \quad \gamma_2 = \exp(\omega x_1^2) \quad .$$

The reaction simplex is given by $x_1 + x_2 = 1$, and there is no need to introduce ξ coordinates here. Suppose that

$$\tilde{R} = k_1\gamma_1x_1 - k_{-1}\gamma_2(1 - x_1) \quad , \quad (1.13)$$

where k_1 and k_{-1} are positive constants. The affinity for (1.13) is

$$\tilde{A} = -(\mu_2 - \mu_1) = -\Delta\mu = -\Delta\mu^0 + RT \ln \frac{\gamma_1x_1}{\gamma_2(1 - x_1)} \quad ,$$

and $\tilde{A} = 0$ implies that

$$\frac{\gamma_1x_1}{\gamma_2(1 - x_1)} = \exp(\Delta\mu^0/RT) \quad .$$

Similarly, $\tilde{R} = 0$ implies that

$$\frac{\gamma_1x_1}{\gamma_2(1 - x_1)} = \frac{k_{-1}}{k_1} \quad ,$$

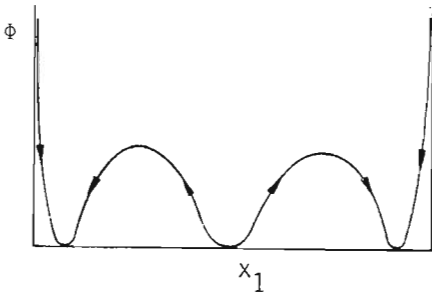
and therefore, $\tilde{A} = 0$ if and only if $\tilde{R} = 0$, provided that

$$\frac{k_{-1}}{k_1} = \exp(\Delta\mu^0/RT) \quad . \quad (1.14)$$

For simplicity suppose that $\Delta\mu^0 = 0$, and choose $\omega = 3$. A bit of computation shows that there are three equilibria, at $x_1 = 0.0709$, 0.5 and $1.0 - 0.0709$. The largest and smallest of these are positively asymptotically stable and the intermediate point is negatively asymptotically stable. The dissipation function is

$$\phi = k_1 RT \ln \left[\frac{x_1 \exp[3(1 - x_1)^2]}{(1 - x_1) \exp(3x_1^2)} \right] \left\{ \exp[3(1 - x_1)^2] x_1 - \exp(3x_1^2) (1 - x_1) \right\},$$

and a sketch of this is shown in the following diagram. The arrows indicate the evolution of ϕ as t increases. If $x_1(0)$ lies near 0.5 , ϕ passes through a maximum, while if $x_1(0)$ lies sufficiently near either of the sinks, it is monotone decreasing in t . Thus the 'excess dissipation' $\phi - \phi_{eq}$ ($= \phi$) is monotone nonincreasing only in some neighborhood of a sink, and it can only serve as a Lyapunov function in such a neighborhood.



In the foregoing example the assumed nonideality of the solution was built into the constitutive relation for the rate and the rate coefficients were restricted by (1.14) to insure coincidence of thermodynamic and kinetic equilibria. The dissipation hypothesis is obviously met in this example and one can show more generally that it will always be satisfied for rate expressions of the form

$$R_j = k_j^f \prod_{i=1}^n [\gamma_i(c) c_i]^{\alpha_{ij}} - k_j^r \prod_{i=1}^n [\gamma_i(c) c_i]^{\beta_{ij}}, \quad (1.15)$$

provided that

$$\beta_{ij} - \alpha_{ij} = \nu_{ij} \quad (1.16)$$

and

$$\frac{k_j^f}{k_j^r} = K_j \equiv \exp(-\sum \nu_{ij} \mu_i^0 / RT) \quad (1.17)$$

These conditions also ensure that kinetic and thermodynamic equilibria coincide for equilibria in the interior of $\Omega(c_0)$. Thus (1.15) provides a valid constitutive assumption for reactions that obey mass action kinetics in non-ideal solutions. The question arises whether the simpler form

$$R_j = k_j^f \prod_{i=1}^n c_i^{\alpha_{ij}} - k_j^r \prod_{i=1}^n c_i^{\beta_{ij}} \quad , \quad (1.18)$$

where k_j^r and k_j^f are constant and (1.16) and (1.17) hold, is also consistent with the dissipation hypothesis. Since kinetic equilibria are solutions of

$$K_j = \prod_{i=1}^n c_i^{\nu_{ij}}$$

and thermodynamic equilibria are solutions of

$$\prod_{i=1}^n c_i^{\nu_{ij}} = \left(\prod_{i=1}^n \gamma_i^{-\nu_{ij}} \right) \exp \left\{ -\sum_{i,j} \nu_{ij} \mu_j^0 / RT \right\} \quad ,$$

they coincide only if

$$\prod_{i=1}^n \gamma_i^{-\nu_{ij}} = 1 \quad , \quad j = 1, \dots, r \quad . \quad (1.19)$$

If this does not hold, then there is a composition at which $\tilde{A} = 0$, but $\tilde{R} \neq 0$, which violates the dissipation hypothesis. Thus (1.18) is acceptable only if the activity coefficients happen to satisfy (1.19).

Suppose that they do satisfy (1.19); then the dissipation hypothesis guarantees convergence to an equilibrium point, but doesn't determine whether the ultimate approach to equilibrium is monotonic or oscillatory in time. ONSAGER's theorem [1.4] is often invoked to prove that the phenomenological matrix associated with the linearization of (1.5) is symmetric, but one can show [1.5] that it is not applicable when the rates are given by (1.18) and the solution is nonideal. The reason for its inapplicability is that the average regression of fluctuations does not obey the same laws as the macroscopic irreversible processes, because the rate laws are not consistent with the thermodynamic model of the solution. One can still prove that the decay to equilibrium is monotonic, but Onsager's theorem cannot be invoked for this purpose. By contrast, if the rate laws are given by (1.15), the reciprocal relations are valid.

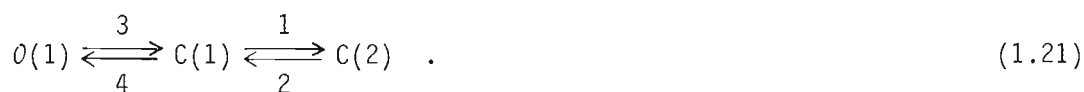
1.3 A Sketch of a Graph-Theoretic Analysis of Networks

Open systems can exhibit a greater variety of dynamical behavior because there is no universal evolution criterion similar to that provided by the dissipation hypothesis for closed systems. Their analysis is done on more of a case-by-case basis, but it is desirable to identify general classes of mechanisms for which the qualitative dynamical behavior can be readily determined. Various aspects of this problem have been discussed by others and references to some of the recent work can be found in [1.6]. Here we shall outline a graph-theoretic approach that proves useful in analyzing the separate effects of stoichiometry, network structure, and reaction phenomenology on the dynamical behavior of the network. Because the full development of our approach is presented elsewhere [1.7], we will illustrate the main ideas with a simple example.

Consider the set of reactions



where reactions 3 and 4 represent exchange of A between a reservoir of constant concentration A^0 and the reacting medium. The significant entities in (1.20), so far as the topology of the set of reactions is concerned, are not the species themselves, but rather the linear combinations of species that appear as reactants or products in the various steps. Following HORN and JACKSON [1.8], we call these combinations complexes, and clearly a species may also be a complex. Thus (1.20) can be written



A *network of reactions* consists of a set of complexes $\mathfrak{C} = \{C(1), \dots, C(p)\}$ together with a binary relation $\mathbb{R} \subset \mathfrak{C} \times \mathfrak{C}$ with the properties

- $(C(i), C(j)) \in \mathbb{R}$ if and only if there is one and only one reaction of the form $C(i) \rightarrow C(j)$,
- for every i there is a $j \neq i$ such that $(C(i), C(j)) \in \mathbb{R}$,
- $(C(i), C(i)) \notin \mathbb{R}$.

In this formulation, a reversible reaction is represented by the forward and reverse pair. The relation \mathbb{R} gives rise to a directed graph G by identifying each complex with a vertex and introducing a directed edge E_{ij} between V_i

and V_j if there is a reaction $C(i) \rightarrow C(j)$. The topology of G is in turn represented by its vertex-edge incidence matrix E , defined as follows:

$$E_{ij} = \begin{cases} +1 & \text{if } E_j \text{ is incident at } V_i \text{ and directed toward it} \\ -1 & \text{if } E_j \text{ is incident at } V_i \text{ and directed away from it} \\ 0 & \text{otherwise.} \end{cases}$$

The directed graph and incidence matrix associated with (1.21) are as follows:

$$\textcircled{3} \begin{array}{c} \xrightarrow{3} \\ \xleftarrow{4} \end{array} \textcircled{1} \begin{array}{c} \xrightarrow{1} \\ \xleftarrow{2} \end{array} \textcircled{2} \quad E = \begin{bmatrix} -1 & 1 & 1 & -1 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & -1 & 1 \end{bmatrix} \quad (1.22)$$

Since A^0 contains no species whose concentration is time-dependent, we call it a *null complex*. When the flux associated with the reaction $A^0 \rightarrow A$ is constant, it represents a time-independent input to the network. Of course, a constant species that appears in a complex that contains variable species also represents an input to the network, and these are called *implicit inputs*, as distinguished from the *explicit input* associated with A^0 .

The reaction phenomenology is accounted for by associating with each edge of G a nonnegative function $P_\rho(c)$ that represents the intrinsic rate of the ρ^{th} reaction. The rate of change of the vector $(c_1, \dots, c_n)^T$ of concentrations of the time-dependent species can now be written

$$\frac{dc}{dt} = vEP(c) \quad , \quad (1.23)$$

wherein v is an $n \times p$ stoichiometric matrix that gives the stoichiometry of the complexes and $P(c)$ is the vector of rates. For the previous example

$$v = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 1 & 0 \end{bmatrix} \quad \text{or} \quad v = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \quad ,$$

according as species C is time-dependent or not. Notice that in any case, a null complex introduces a column of zeroes into v .

It is clear from (1.23) that three separate features of a set of reactions contribute to the rate of change of the concentrations. These are the stoichiometry of the complexes, which is reflected in v , the abstract structure of the reaction network, which is embodied in the incidence matrix of G , and the reaction phenomenology contained in $P(c)$. Given the factorization of dc/dt in (1.23), we can study the separate effects of the three features

on the transient and steady-state behavior of the network and can determine, for instance, how these behaviors change when new reaction pathways are introduced into the network or old ones deleted. Some results on these questions are given later, but first we need some more terminology.

An undirected graph G^0 is obtained from G by ignoring the orientation of the edges, represented as pairs (i_j, i_k) of vertices. A path in G^0 is an open sequence $(i_1, i_2) \dots (i_{k-1}, i_k)$ of edges in which all vertices are distinct, and a cycle in G^0 is a closed path in which all but the first and last vertices are distinct. Directed paths and directed cycles are defined analogously to their counterparts in G^0 , and V_j is said to be reachable from V_i if there is a directed path from V_i to V_j . $G^0(G)$ is said to be acyclic if it contains no cycles (directed cycles). An oriented cycle in G is a cycle in G^0 with an orientation assigned by ordering of the vertices in the cycle. A cycle matrix B associated with G has elements

$$B_{ij} = \begin{cases} +1 & \text{if } E_j \text{ is in the } i^{\text{th}} \text{ oriented cycle and the cycle} \\ & \text{and edge orientation coincide} \\ -1 & \text{if } E_j \text{ is in the } i^{\text{th}} \text{ oriented cycle and the cycle} \\ & \text{and edge orientation are opposite} \\ 0 & \text{otherwise.} \end{cases}$$

It has a row in which all nonzero entries have the same sign for every directed cycle in G . A cycle matrix for the graph at (1.22) is

$$B = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix} .$$

Here and hereafter we include only independent cycles in a cycle matrix.

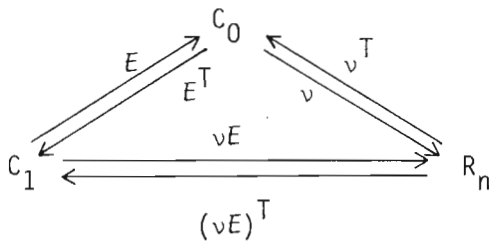
A graph is connected if every pair of vertices is connected by a path, and a component $G_1 \subseteq G$ is a connected subgraph that is maximal with respect to inclusion of edges. G is strongly connected if for every pair (V_i, V_j) , V_j is reachable from V_i and vice versa. A cutset is a set of edges whose removal increases the number of components by at least one. Cutsets can be oriented by ordering the two disjoint sets of vertices produced by the cutset and an oriented cutset matrix Q is defined by

$$Q_{ij} = \begin{cases} 1 & \text{if } E_j \text{ is in cutset } i \text{ and the orientation of the} \\ & \text{cutset and edge coincide} \\ -1 & \text{if } E_j \text{ is in cutset } i \text{ and the orientation of the} \\ & \text{cutset and edge is opposite} \\ 0 & \text{otherwise.} \end{cases}$$

It is convenient to introduce two vector spaces associated with G or G^0 as follows. Suppose that G has p vertices, q components, and r edges. Let $V(E)$ denote the vertex (edge) set of G , respectively, and let $C_0(C_1)$ denote the $p(r)$ -dimensional vector space of all real-valued functions on $V(E)$. These are both Euclidean spaces under the standard inner product and the incidence matrix E is the representation of the boundary operator $E: C_1 \rightarrow C_0$ with respect to the canonical bases.² It has rank $\rho(E) = p - q$. One can regard Q and B as transformations from C_1 to itself, and the row space of B and of Q is called the cycle and cutset subspace, respectively, of C_1 . These are of dimension $r-p+q$ and $p-q$, respectively. They are orthogonal subspaces and consequently we can write

$$\begin{aligned} C_1 &= R(B^T) \oplus R(Q^T) \\ &= N(E) \oplus R(E^T) \\ C_0 &= R(E) \oplus N(E^T) \\ &= N(v) \oplus R(v^T) \\ R_n &= R(v) \oplus N(v^T) . \end{aligned}$$

If we identify a space with its dual in the usual fashion, then the relationship amongst the various spaces and maps are as follows.



The lower leg of the triangle corresponds to the usual formulation of kinetics, in which vE is regarded as a single transformation. We shall see that there are good reasons for factoring this product through C_0 .

We call any element of C_1 a flow and for a given choice of cycles and cutsets, each flow has the representation

$$f = f^0 + f^1 \equiv B^T w + Q^T z , \quad (1.24)$$

² To simplify notation, we use the same symbol for a linear transformation and any of its representations.

where w and z are the cycle and cutset weights, respectively, associated with f . A flow is balanced when $z = 0$; cobalanced when $w = 0$; and positive, nonnegative, or strictly nonnegative according as $f > 0$, $f \geq 0$, or $f \gg 0$, respectively. In particular, the rate vector $P(c)$ is a flow for any fixed c and can be written

$$P(c) = P_1(c) + P_2(c) \quad , \quad (1.25)$$

where $P_1 \in N(E)$ and $P_2 \in R(E^T)$. Consequently, (1.23) becomes

$$\frac{dc}{dt} = vEP_2(c)$$

and so only the cutset part of any flow enters the transient equations. Said otherwise, a time-dependent flow can never be balanced.

As in closed systems, invariants may exist, but since there is no *a priori* reason that the total mass must be constant, the reaction simplex $\Omega(c_0)$ need not be compact. Indeed, one can prove that when there is at least one null complex in the network, there is no strictly positive invariant Ω and $\Omega(c_0)$ cannot be compact [1.7]. The kinematic invariants, those that are independent of the rate functions, span a subspace $I_1 \oplus I_2 \subset R_n$, where

$$I_1 \equiv \{\Omega \in R_n \mid \Omega \in N(v^T), \Omega \neq 0\}$$

$$I_2 \equiv \{\Omega \in R_n \mid v^T \Omega \in N(E^T), \langle \Omega, z \rangle = 0 \forall z \in I_1\} \quad .$$

Since $v_{ij} \geq 0$, there are no $\Omega \geq 0$ in I_1 . Furthermore,

$$I_2 = \text{preimage}[R(v^T) \cap N(E^T)] \quad ,$$

and therefore,

$$i_2 \equiv \dim[I_2] = \dim[R(v^T) \cap N(E^T)] \leq \min\{n - i_1, q\} \quad ,$$

where $i_1 \equiv \dim[I_1]$. Therefore, there can be no more independent invariants in I_2 than there are components in G . In particular, if G is connected then $i_2 \leq 1$.

The number of kinematic invariants is related to other indices of the network in the following way. Since

$$R(v^T) + N(E^T) = N(v)^\perp + R(E)^\perp = [N(v) \cap R(E)]^\perp \quad ,$$

it follows that

$$n - i_1 + q - i_2 = p - \dim[N(v) \cap R(E)] .$$

If we let $\delta = \dim[N(v) \cap R(E)]$, then

$$\delta = p - q - (n - (i_1 + i_2)) = p - q - s = \rho(E) - \rho(vE) ,$$

and thus δ is the difference between the maximal number of independent reactions based on the graph structure and the actual number of independent reactions. This number, which is clearly nonnegative, is called the deficiency by Feinberg, and when it vanishes, v does not annihilate any elements in $R(E)$. Therefore v has a left inverse \bar{N} from $R(vE)$ to $R(E)$ and the reaction subspace is isomorphic to $R(E)$. Consequently, the dynamical behavior can be described in terms of complexes alone, because the complex concentration can be defined as $\bar{c} = \bar{N}c$ and $c(t) - c(0) = v[\bar{c}(t) - \bar{c}(0)]$. This is equivalent to introducing intrinsic coordinates in $\Omega(c_0)$.

In the previous section we specifically assumed that the reactions were independent, but this is not the case for the reactions at (1.20) and it is not true in general. One may ask more generally what transformations of the complexes, reactions, and rate functions leave the dynamical behavior of the network invariant. Since that behavior is completely determined by the triple $(v, E, P(c))$, we say that two networks with $(v, E, P(c))$ and $(v', E', P'(c))$ are dynamically equivalent if

- a) the domains of $P(c)$ and $P'(c)$ are identical,
- b) $vEP(c) = v'E'P'(c)$ for all c in the domain of P .

It is shown in [1.7] that the following operations lead to equivalence transformation of a network.

- a) The identification of equal complexes.
- b) The removal of cycles in the graph.
- c) The removal of elements in $N(v) \cap R(E)$.

The first of these leaves r fixed and changes p and perhaps q , the second changes r and leaves p and q fixed, and the third changes r and perhaps p and q . By applying the first transformation one can always reduce the number of null complexes in the network to one, by applying the second transformation one can produce an acyclic graph for the transformed network, and by using the third transformation one can always produce a dynamically equivalent network for which $\delta = 0$. From a theoretical standpoint it is not

always convenient to fully reduce a network by eliminating cycles and so forth, but there may be computational advantages to doing so; this remains to be seen.

As we remarked earlier, when there are null complexes in the network, $\Omega(c_0)$ is not compact and the standard fixed point argument used to prove existence in the compact case fails. It is harder to establish existence in such cases, and in fact, it is easier to give sufficient conditions for the absence of any steady state. There are three distinct classes of steady states defined by the sets

$$S_0 \equiv \{c^S \in \overline{R_n^+} \mid P(c^S) = 0\}$$

$$S_1 \equiv \{c^S \in \overline{R_n^+} \mid EP(c^S) = 0, P(c^S) \geq 0\}$$

$$S_2 \equiv \{c^S \in \overline{R_n^+} \mid vEP(c^S) = 0, EP(c^S) \neq 0\} \quad .$$

The first set is empty when there are nonvanishing constant inputs to the network. Moreover, every rate must vanish at a $c^S \in S_0$, including the forward and reverse rate of a reversible pair. Usually this can happen only if the steady state lies on the boundary of $\Omega(c_0)$ or if some of the reactions model threshold phenomena.

Steady states in S_2 are balanced nonnegative flows, and one can prove the following theorem concerning their existence and representation [1.7].

Theorem. Let G be the graph of a reaction network with p complexes, r reactions, and q components. Then,

- a) if G is acyclic there exists no strictly nonnegative balanced flow,
- b) there exists a positive balanced flow if and only if every component G_α of G is strongly connected,
- c) any nonnegative balanced flow has the representation

$$P(c^S) = \hat{B}^T w$$

where the columns of \hat{B}^T are the *directed* cycles in G .

The flows corresponding to steady states in S_2 contain cutsets and perhaps also cycles, and therefore, $P(c^S)$ has the representation given at (1.24). Certainly $S_2 = \phi$ if $N(v) \cap R(E) = \{0\}$, i.e., when $\delta = 0$, but one can sharpen this considerably. A sharper necessary condition for the existence of a $c^S \in S_2$ is that

$$N(v) \cap \{ \{y \in C_0 \mid y = Ez, z \in C_1, z \geq 0\} - \{0\} \} \neq \emptyset .$$

It is easy to construct examples in which $\delta > 0$ but $S_2 = \emptyset$ because this condition is violated [1.7].

The foregoing leads to a general algorithm that can be used to test whether or not a system has any steady states [1.7]. In that algorithm there are tests in addition to those given here that deal with each of the components G_α separately. The algorithm is being implemented at present and tests of it will show whether there are advantages to using it over proceeding directly to an algorithm for finding steady states.

The existence problem is much harder and complete results are known in only a few cases. For instance, when the kinetics are of ideal mass-action type, every G_α is strongly connected, and the deficiency is zero, then, the steady state is unique [1.9]. Another result, which is not restricted to mass-action kinetics, is the following [1.10].

Theorem. Let G have q strong components, each of which has one explicit input, the rate of which is constant. Suppose that every nonnull complex contains only one species and that the rates satisfy

- a) $P_i: [0, \infty) \rightarrow \mathbb{R}^+$
- b) P_i is strictly monotone increasing.

Then, if $\delta = 0$ and the inputs are sufficiently small, there is a unique steady state and the flow is balanced.

1.4 Diffusive Instability of a Uniform State

When reaction and diffusion occur on comparable time scales, the governing equation for a continuous system is

$$\begin{aligned} \frac{\partial c}{\partial t} &= D\nabla^2 c + vEP(c) & \text{in } V \subset \mathbb{R}^3 \\ \eta \cdot \nabla c &= 0 & \text{on } \partial V \end{aligned} \tag{1.26}$$

when there are no explicit inputs at the boundary. Explicit inputs are manifested either as nonhomogeneous boundary conditions or as time-independent internal distributions of certain species. Implicit inputs can be manifested in the same way, and if the internal distribution in either case is non-uniform in space, the reaction term in (1.26) becomes explicitly dependent

on the space variable \underline{r} . Hereafter we assume that this is not the case if either type of input is present. Furthermore, we assume that \mathcal{D} is a diagonal matrix with nonnegative entries.

Suppose that there is a uniform steady state c^S of (1.26). One can prove that the principle of linearized stability, according to which the asymptotic stability of c^S is governed by the linearized version of (1.26), is valid here. The linear equation is

$$\begin{aligned} \frac{\partial u}{\partial t} &= \mathcal{D}\nabla^2 u + Ku \\ \underline{n} \cdot \nabla u &= 0 \quad , \end{aligned} \tag{1.27}$$

where $K \equiv vEdP(c^S)$ is the Jacobian of the kinetic terms at $c = c^S$. Thus stability is governed by the eigenvalues of the family $\{K - \mu_k \mathcal{D}\}_{k=0}^{\infty}$ of matrices, wherein μ_k is the k^{th} eigenvalue of the Laplacian on V . We say that a diffusive instability of the uniform state c^S exists whenever c^S is asymptotically stable as a solution of the kinetic equations (1.23), but for some $k > 0$ there is an eigenvalue of $K - \mu_k \mathcal{D}$ with a positive real part.

When there are reaction invariants, K is singular and u must satisfy the integral conditions

$$\int_V \langle \Omega_j, u \rangle dv = 0 \quad .$$

If we write

$$u = \sum_{k=0}^{\infty} y_k(t) \phi_k(\underline{r}) \quad ,$$

where the ϕ_k are the eigenfunctions of ∇^2 and $\phi_0 \equiv 1$, then it is necessary that

$$\langle \Omega_j, y_0(t) \rangle = 0 \quad .$$

This means that $y_0(t)$ lies in $R(vE)$ and the $y_k(t)$, $k \geq 1$, are unaffected. Thus the invariants do not affect the spectrum of $K - \mu_k \mathcal{D}$ for $k \geq 1$. However, to simplify the statement of some of the following results we assume that there are no invariants and that the spectrum of K , $\sigma(K)$, lies strictly within the left-half plane (LHP hereafter).

Some general conditions on K and \mathcal{D} under which a diffusive stability is precluded are as follows [1.10].

- a) K and \mathcal{D} are simultaneously triangularizable.
- b) \exists a diagonal matrix W with $w_j > 0 \ni \sigma(WK)^S \subset \text{LHP}$.

c) K is diagonally dominant.

d) $\min_i \mathcal{D}_i / \max_i \mathcal{D}_i > 1 - 1/m$, where m is $\exists \| \exp(Kt) \| \leq m \exp(-\gamma t)$ and $m \geq 1, \gamma > 0$.

e) The graph $G(K)$ associated with K has no cycles of length 2, 3, ..., $n - 1$.

There are numerous examples that satisfy one or more of these conditions. For example, if K is symmetric b) is satisfied. If K is the linearization for a single-loop feedback control scheme than e) is satisfied. Finally, one can show that if the kinetics are of the ideal mass-action type studied in [1.8] or [1.9], then there exists a W such that b) is satisfied whenever the steady state flow is balanced [1.10].

The foregoing provide sufficient conditions that preclude instabilities, but one is often interested in determining when they can occur, and so necessary conditions for their absence are of greater interest. The following theorem gives a set of these [1.11].

Theorem. Let \mathcal{D} be diagonal with $\mathcal{D}_i \geq 0$. In order that $\sigma(K - \mu\mathcal{D}) \subset \text{LHP}$ for all such \mathcal{D} and all $\mu \in [0, \infty)$, it is necessary that

a) $\sigma(K) \subset \text{LHP}$,

b) $\sigma(K[i_1, \dots, i_p]) \subset \overline{\text{LHP}}$ for all p^{th} -order principal submatrices $K[i_1, \dots, i_p]$ of K , where $1 \leq p \leq n - 1$.

Here we have assumed that $\mu \in [0, \infty)$, which makes the foregoing necessary conditions for the absence of instability on all smooth, simply-connected domains. Of course they may be too strong for a given, fixed domain.

To determine whether a diffusive instability is possible, one has to determine whether or not there is a subsystem that would be unstable if it were isolated from the remainder of the network. If there is one, the diffusion coefficients can be selected so that some wavelengths are unstable. The conditions in the theorem are also sufficient for $n = 2, 3$, but it is not known if they are sufficient in general.

A similar analysis can be done when the basic solution is a spatially uniform periodic solution that is orbitally asymptotically stable as a solution of (1.23), and a parallel theorem is given in [1.11]. In this case one has to check the characteristic exponents for all subsystems of the time-dependent matrix $K(t)$ that arises from linearizing around the periodic orbit.

1.5 Conclusion

The problem of determining how network structure influences the dynamics is far from solved, but the graph-theoretic formalism outlined here provides a framework within which it can be attacked systematically. Results such as the existence of a Lyapunov function for certain mass-action systems [1.8], the zero-deficiency theorem [1.9], and the stability of certain cellular systems [1.12] are very easy to prove in this framework, and numerous other results can be obtained [1.7,10]. Furthermore, our approach may lead to more efficient computational schemes for the steady state and transient analysis of reacting systems, but this remains to be seen.

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