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Monotonicity properties of chemical reactions with a single initial bimolecular step

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Arbitrary-length reversible chain reactions with a single initial bimolecular step are considered. Monotonicity properties of species concentrations with respect to initial concentrations are determined using the established theory of monotonicity with respect to closed convex cones [1–3]. Strict sign results are obtained.

1. Introduction

We consider chemical reactions of the form

$$A_1 + A_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C_2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \cdots \underset{k_{-(n-1)}}{\overset{k_{n-1}}{\rightleftharpoons}} C_{n-1} \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} C_n,$$

where the subscripted k's are positive rate constants. Assuming mass action chemical kinetics and denoting the concentration at time t of species A_i by $x_i(t)$ and the concentration at time t of species C_i by $y_i(t)$, we arrive at the system of ordinary differential equations

$$\dot{x}_1(t) = -k_1 x_1(t) x_2(t) + k_{-1} y_1(t), \tag{1.1}$$

$$\dot{x}_2(t) = -k_1 x_1(t) x_2(t) + k_{-1} y_1(t), \tag{1.2}$$

$$\dot{y}_1(t) = k_1 x_1(t) x_2(t) - (k_{-1} + k_2) y_1(t) + k_{-2} y_2(t), \tag{1.3}$$

$$\dot{y}_i(t) = k_i y_{i-1}(t) - (k_{-i} + k_{i+1}) y_i(t) + k_{-(i+1)} y_{i+1}(t), \quad i = 2, \ldots, n-1, \tag{1.4}$$

and

$$\dot{y}_n(t) = k_n y_{n-1}(t) - k_{-n} y_n(t), \tag{1.5}$$

subject to $x_i(0) = x_{i,0}$ and $y_i(0) = y_{i,0}$. We assume that both $x_{1,0} > 0$ and $x_{2,0} > 0$ or $y_{i,0} > 0$ for some i. This guarantees that all concentrations are positive for $t > 0$. Define

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$L = x_{1,0} + x_{2,0} + \sum_{j=1}^{n} y_{j,0}$ and observe that all concentrations remain in the interval $[0, L]$ for all time. Notice also that

$$x_2(t) = x_1(t) + x_{2,0} - x_{1,0}. \tag{1.6}$$

(Example 2 in [1] considered such a chain reaction of length two; here, we generalize to length n.)

We are interested in how a solution component (a concentration) changes when a single initial concentration is changed. If a solution component with a single changed initial concentration is always greater (less) than the original solution component, then we say that the component is monotone increasing (decreasing) with respect to changes in that initial concentration value. Alternatively, if the sign of the partial derivative of a concentration with respect to an initial concentration value does not change sign, then the concentration is monotone with respect to changes in the corresponding initial concentration value. We focus on obtaining this type of derivative result. Monotonicity results can enable one to predict the qualitative behaviour of a solution component relative to that same solution component with a changed initial value in some component. This knowledge can lead to an understanding of the stability of solutions under changes in initial values. Furthermore, monotonicity results can also prove useful when deciding if a given mathematical model correctly represents a physical problem of interest. For example, if examination of a proposed mathematical model does not verify certain monotonicity observed in experiments, one could conclude that the proposed model is in error.

The system (1.1)–(1.5) is not order preserving with respect to an orthant (in an order preserving system, each solution component is monotone with respect to each initial component value). We will apply the earlier-developed theory of monotonicity with respect to closed convex cones [1–3] to determine the signs of partial derivatives of reactant concentrations with respect to each initial concentration. In [4], these results were determined by using extremely long arguments based on combining the equations in the system (1.1)−(1.5). Earlier related work in this area has been abstract; practical applications of results have only looked for monotonicity with respect to an orthant.

2. Theory

The results in this section are generalizations of the Kamke–Müller theorem to closed convex expanding cones. They are stated for a general system of ordinary differential equations

$$\dot{x}(t) = f(x), \quad x \in \Omega,\ \Omega \subset \mathbb{R}^n,\ \Omega \text{ open}, \tag{2.1}$$

with flow φ_t. We note that the related comparison results require that Ω is convex. We let $\mathrm{D}f$ represent the Jacobian matrix with ijth entry $\partial f_i/\partial x_j$.

A set $K \subseteq \mathbb{R}^n$ is a *cone* if $\forall x \in K$ and $\alpha \geqslant 0$, $\alpha x \in K$. This usage of cones in a Banach space appears in [3], for example. Cones in [5] are assumed to be convex. For a convex cone and for $x, y \in \mathbb{R}^n$, we write $x \leqslant_K y$ (or $y \geqslant_K x$) if and only if $y - x \in K$;

we write $x <_K y$ (or $y >_K x$) if $y - x \in \mathit{relint}(K)$, where $\mathit{relint}(K)$ denotes the interior of K relative to the smallest subspace containing K.

$K(t)$ is an expanding cone if $K(t_1) \subseteq K(t_2)$ whenever $0 \leqslant t_1 \leqslant t_2$ and if the smallest subspace containing $K(t)$ for each t is the same for all t.

The following nonstrict sign result was obtained in [1].

Theorem 1. Suppose that $f(x)$ is continuously differentiable on Ω, φ is the flow for (2.1), $\varphi_t(x_0) \in \Omega$ for $t \geqslant 0$, $x_0 \in \Omega$, Ω open, and that $\exists l$ such that

$$\mathrm{D}f\big(\varphi_t(x_0)\big) + lI : K(t) \mapsto K(t), \quad \forall t \geqslant 0, \tag{2.2}$$

where $K(t)$ is a closed convex expanding cone in $\mathbb{R}^n$. Then

$$\frac{\partial \varphi_t}{\partial k}(x_0) \geqslant_{K(t)} 0, \quad \forall t \geqslant 0,$$

for any unit vector $k \in K(0)$.

A related strict sign result was presented in [2]. The following extra theory is needed.

A vector x generates an extreme ray (or generator) of K if $0 \leqslant_K y \leqslant_K x \Rightarrow y$ is a nonnegative multiple of x. A cone K is pointed if $K \cap \{-K\} = \{0\}$. A closed convex cone is polyhedral if and only if it is the intersection of finitely many halfspaces each containing the origin on its boundary. F is a face of K if

$$x \in F \text{ and } 0 \leqslant_K y \leqslant_K x \quad \Rightarrow \quad y \in F.$$

For $k \in K$, F_k is the smallest face of K containing k.

For each fixed t, the generators of the polyhedral expanding cone of constant dimension $K(t)$ may be labelled e_i, $i = \{1, \ldots, n_K\}$. The directed multigraph $G_{K(t)}(\mathrm{D}f(x))$ is constructed on the vertices $\{g_1, \ldots, g_{n_K}\}$ as follows. For each i, let $k_i = (\mathrm{D}f(x) + (l+1)I)e_i$, where l is chosen so (2.2) holds. Draw a directed edge from g_i to g_j, $i \neq j$, if $e_j \in F_{k_i}$, $\forall x \in \mathcal{O}$, the nonnegative orthant.

Theorem 2. Suppose that $f(x)$ is continuously differentiable in x on Ω, φ is the flow for (2.1), $\varphi_t(x_0) \in \Omega$ for $t \geqslant 0$, $x_0 \in \Omega$, Ω open, and that $\exists l$ such that

$$\mathrm{D}f\big(\varphi_t(x_0)\big) + lI : K(t) \mapsto K(t), \quad \forall t \geqslant 0,$$

where $K(t)$ is a pointed polyhedral expanding cone in $\mathbb{R}^n$. Pick some unit vector $k \in K(0)$ and $t_0 \geqslant 0$. Suppose that for each $e_j(t_0) \notin F_k(t_0)$ and for some $e_i(t_0) \in F_k(t_0)$ there is a directed (g_i, g_j)-path in $G_{K(t_0),1}(\mathrm{D}f(\varphi_{t_0}(x_0)))$. Then

$$\frac{\partial \varphi_t}{\partial k}(x_0) >_{K(t)} 0,$$

for $t > t_0$ ($t \geqslant t_0$ if $k >_{K(t_0)} 0$). (If the graph-theoretic condition does not hold for $t_0 = 0$ but does hold for t_0 arbitrarily close to 0, the result holds for $t > 0$.)

3. Results

Table 1 gives the signs of partial derivatives of concentrations with respect to initial concentrations. A $+$ ($++$, $-$) entry means that the associated partial derivative is positive for $t > 0$ (positive for $t \geqslant 0$, negative for $t > 0$). The $/+$ entry means that the associated partial derivative is positive for $t > 0$ if $x_{1,0} \leqslant x_{2,0}$ and $\dot{x}_1(t) < 0$ and positive for $t > 0$ if $x_{1,0} = x_{2,0}$. Symmetry of $x_1(t)$ and $x_2(t)$ gives analogous sign results with respect to $x_{2,0}$. These results are proved by using three separate closed convex cones, applying theorems 1 and 2 to obtain nonstrict and strict sign results, respectively.

We first consider the proper cone K_1 with $n+1$ extreme rays in $\mathbb{R}^{n+2}$ given by $e_1 = (1, 1, 0, \dots, 0)^T$ and $e_i = (0, 0, \dots, 0, 1, 0, \dots, 0)^T$, $2 \leqslant i \leqslant n+1$, where the $(i+1)$st component in e_i equals 1. Note that $l_1 = 2L - x_1(t) - x_2(t)$ and $l_2 = 2L + x_1(t) + x_2(t)$ are both nonnegative $\forall t \geqslant 0$. It is easy to check that the Jacobian matrix $\mathrm{D}f$ generated by (1.1)–(1.5) satisfies

$$(\mathrm{D}f + 2k_1LI)e_1 = k_1l_1e_1 + k_1l_2e_2, \tag{3.1}$$

$$\bigl(\mathrm{D}f + (k_{-(i-1)} + k_i)I\bigr)e_i = k_{-(i-1)}e_{i-1} + k_ie_{i+1}, \quad 2 \leqslant i \leqslant n, \tag{3.2}$$

and

$$(\mathrm{D}f + k_{-n}I)e_{n+1} = k_{-n}e_n. \tag{3.3}$$

With

$$l = \max_{2\leqslant i\leqslant n-1}\{2k_1L, k_{-(i-1)} + k_i, k_{-n}\}, \tag{3.4}$$

(2.2) is satisfied; theorem 1, with k in the theorem equal to any of e_2 to e_{n+1}, gives that the partial derivative of any concentration with respect to $y_{i,0}$ is nonnegative, $1 \leqslant i \leqslant n$. Consider the associated multigraph $G_{K_1}(\mathrm{D}f(\varphi_t(x_0)))$ on vertices $\{g_1, \dots, g_{n+1}\}$. The nonnegative span of any subset of extreme rays of K_1 forms a face of K_1 since all of the extreme rays are orthogonal. Thus, (3.1) induces a directed edge from g_1 to g_2; (3.2) induces directed edges from g_i to g_{i-1} and to g_{i+1}, $2 \leqslant i \leqslant n$; and (3.3) induces a directed edge from g_{n+1} to g_n. $G_{K_1}(\mathrm{D}f(\varphi_t(x_0)))$ is strongly connected, and theorem 2 applies, with the same choices for k, to give the strict sign results in the final two rows of table 1.

Next, if $x_{1,0} < x_{2,0}$ let $e_{n+2} = (x_1(t), -x_2(t), 0, \dots, 0)^T$, and define the proper expanding cone of constant dimension $K_2(t)$ with extreme rays $e_1, \dots, e_{n+2}$. By considering the x_1x_2-plane, using (1.6), one can see that $K_2(t)$ is expanding when

Table 1
Signs of partial derivatives of concentrations with respect to initial concentrations; $1 \leqslant i \leqslant n-1$.

	$x_1(t)$	$x_2(t)$	$y_i(t)$	$y_n(t)$
$x_{1,0}$	$++$	$-$	$/+$	$+$
$y_{i,0}$	$+$	$+$	$++$	$+$
$y_{n,0}$	$+$	$+$	$+$	$++$

$x_{1,0} < x_{2,0}$ and $\dot{x}_1(t) < 0$. Since $(\mathrm{D}f)e_{n+2} = 0$, (2.2) is satisified. By theorem 1 with $k = (1, 0, \dots, 0) \in K_2$, we conclude that for $1 \leqslant i \leqslant n-1$

$$\frac{\partial y_i}{\partial x_{1,0}} \geqslant 0, \quad \forall t \geqslant 0, \text{ if } x_{1,0} < x_{2,0} \text{ and } \dot{x}_1(t) < 0. \tag{3.5}$$

If $x_{1,0} = x_{2,0}$ we can let $e_{n+2} = (1, -1, 0, \dots, 0)^T$ to get the same conclusion without the extra condition. The multigraph $G_{K_2}(\mathrm{D}f(\varphi_t(x_0)))$ has one extra vertex g_{n+2} but contains only the edges of $G_{K_1}(\mathrm{D}f(\varphi_t(x_0)))$. With $F_k = \mathrm{span}^+\{e_1, e_{n+2}\}$, the nonnegative span of the two vectors, the graph theoretic hypothesis of theorem 2 is satisfied since there is a directed (g_1, g_j)-path for $j = 2, \dots, n+1$. Theorem 2 then gives that the partial derivatives in (3.5) are positive for $t > 0$.

Finally, we define the $n+1$ vectors $e_1 = (1, 0, \dots, 0)^T$, $v_1 = (-1, -1, 1, \dots, 0)^T$, and $v_i = (0, 0, \dots, 0, -1, 1, 0, \dots, 0)^T$, $2 \leqslant i \leqslant n$, where the -1 entry in v_i is in the $(i+1)$st position. For $n > 1$, we can calculate that

$$(\mathrm{D}f)e_1 = k_1 x_2(t) v_1, \tag{3.6}$$
$$(\mathrm{D}f)v_1 = -\bigl(k_1\bigl(x_1(t) + x_2(t)\bigr) + k_{-1}\bigr)v_1 + k_2 v_2, \tag{3.7}$$
$$(\mathrm{D}f)v_i = k_{-(i-1)}v_{i-1} - (k_i + k_{-i})v_i + k_{i+1}v_{i+1}, \quad 2 \leqslant i \leqslant n-1, \tag{3.8}$$

and

$$(\mathrm{D}f)v_n = k_{-(n-1)}v_{n-1} - (k_n + k_{-n})v_n. \tag{3.9}$$

(If $n = 1$ we only need e_1 and v_1; (3.6)–(3.9) simplify in this case.) Let $w_i = \sum_{j=1}^n a_j^i v_j$, $1 \leqslant i \leqslant 2^n$, where $a_j \in \{0, 1\}$, $\forall j$. The tips of the vectors $\{w_i\}$ in $\mathbb{R}^{n+2}$ are images of the vertices of the unit hypercube under the linear transformation $T = (v_1|v_2|\cdots|v_n) : \mathbb{R}^n \mapsto \mathbb{R}^{n+2}$. The parallelotope P with vertices $\{e_1 + w_i\}$ is a linearly transformed hypercube translated by e_1.

We claim that $K_3 = \mathrm{span}^+\{e_1 + w_i \mid 1 \leqslant i \leqslant 2^n\}$ is a proper cone with extreme rays $\{e_1 + w_i \mid 1 \leqslant i \leqslant 2^n\}$. The extreme rays claim would be true if for each i

$$0 \leqslant_{K_3} y \leqslant_{K_3} e_1 + w_i \quad \Rightarrow \quad y = \alpha(e_1 + w_i), \quad \alpha > 0.$$

Because $y \in K_3$ means $y = \sum_{j=1}^n \lambda_j(e_1 + w_j)$, $\lambda_j \geqslant 0$, and $e_1 + w_i - y \in K_3$ means $e_1 + w_i - y = \sum_{j=1}^n \mu_j(e_1 + w_j)$, $\mu_j \geqslant 0$, we have that

$$e_1 + w_i = \sum_{j=1}^n (\lambda_j + \mu_j)(e_1 + w_j).$$

Since $e_1 + w_i$ is an extreme point of the parallelotope, this means that $\lambda_j + \mu_j = 0$, $j \neq i$, and $\lambda_i + \mu_i = 1$; hence, $y = \lambda_i(e_1 + w_i)$.

Now, using (3.6)–(3.9), for each i

$$(\mathrm{D}f)(e_1 + w_i) = \bigl[k_1\bigl(x_2(t)\bigl(1 - a_1^i\bigr) - a_1^i x_1(t)\bigr) + k_{-1}\bigl(a_2^i - a_1^i\bigr)\bigr]v_1$$

$$
\begin{aligned}
&+ \sum_{j=2}^{n-1} \bigl[k_j \bigl(a^i_{j-1} - a^i_j \bigr) + k_{-j} \bigl(a^i_{j+1} - a^i_j \bigr) \bigr] v_j \\
&- a^i_n (k_n + k_{-n}) v_n,
\end{aligned} \tag{3.10}
$$

where $a^i_j \in \{0, 1\}$, $\forall j$. In each term in (3.10), if $a^i_m = 0$ write $v_m = (e_1 + w_i + v_m) - (e_1 + w_i)$, noticing that in this case $w_i + v_m$ is some other w_p. If $a^i_m = 1$ write $v_m = (e_1 + w_i) - (e_1 + w_i - v_m)$, where $w_i - v_m$ is some other w_p in this case. The rewritten equation has nonnegative coefficients on every $e_1 + w_p$ vector except possibly the $e_1 + w_i$ term. Hence, by picking l large enough, $\mathrm{D}f + lI : (e_1 + w_i) \mapsto K_3$, for each i, so condition (2.2) is satisfied. By theorem 1, with $k = e_1$, we conclude that

$$
\frac{\partial x_1}{\partial x_{1,0}} \geqslant 0, \quad \frac{\partial x_2}{\partial x_{1,0}} \leqslant 0, \quad \frac{\partial y_n}{\partial x_{1,0}} \geqslant 0, \qquad \forall t \geqslant 0. \tag{3.11}
$$

The associated graph $G_{K_3}(\mathrm{D}f(\varphi_t(x_0)))$ on vertices $\{g_1, \ldots, g_{2^n}\}$ seems difficult to analyze in general. To conclude that the partial derivatives in (3.11) are strictly positive we only need to show that there is a directed path from g_1 to all other vertices in $G_{K_3}(\mathrm{D}f(\varphi_t(x_0)))$. Labeling $e_{i+1} = e_1 + v_i$ for $i = 1, \ldots, n$, we see that $1/n \sum_{i=1}^n e_{i+1}$ is in the interior of the parallelotope P. In other words, $F_{e_1 \cup e_2 \cup \cdots \cup e_{n+1}} = K$. Thus, if there is a directed path from g_1 to g_j, $j = 2, \ldots, n + 1$, in $G_{K_3}(\mathrm{D}f(\varphi_t(x_0)))$ then there must be a directed path from g_1 to all other vertices in $G_{K_3}(\mathrm{D}f(\varphi_t(x_0)))$. By considering (3.6)$-$(3.9), we see that $G_{K_3}(\mathrm{D}f(\varphi_t(x_0)))$ has directed (g_i, g_{i+1})-paths for $i = 1, \ldots, n - 1$, giving the desired result. Theorem 2, once again with $k = e_1$, tells us that the partial derivatives in (3.11) are strictly positive.

References

[1] H. Kunze and D. Siegel, Monotonicity with respect to closed convex cones II, Applicable Analysis 77 (2001) 233–248.

[2] H. Kunze and D. Siegel, A graph theoretic approach to strong monotonicity with respect to polyhedral cones, Positivity 6 (2002) 95–113.

[3] E. Zeidler, *Nonlinear Functional Analysis and its Applications*, Vol. 1 (Springer, Berlin, 1986).

[4] H. Kunze, Monotonicity properties of systems of ordinary differential equations, Master's thesis, University of Waterloo (April 1992).

[5] A. Berman, M. Neumann and R. Stern, *Nonnegative Matrices in Dynamic Systems* (Wiley, New York, 1989).