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Monotonicity in chemical reaction systems

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This paper discusses the question of when the dynamical systems arising from chemical reaction networks are monotone, preserving an order induced by some proper cone. The reaction systems studied are defined by the reaction network structure while the kinetics is only constrained very weakly. Necessary and sufficient conditions on cones preserved by these systems are presented. Linear coordinate changes which make a given reaction system cooperative are characterised. Also discussed is when a reaction system restricted to an invariant subspace is cone preserving, even when the system fails to be cone preserving on the whole of phase space. Many of the proofs allow explicit construction of preserved cones. Numerous examples of chemical reaction systems are presented to illustrate the results.

Keywords: Chemical reactions; monotone dynamical systems; cones; order preserving systems; stability

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1. Introduction

The primary task of this paper is to discuss when reaction systems give rise to order preserving flows in the sense of [1, 2], with the orders of interest being generated by proper cones in $\mathbb{R}^n$, not necessarily orthants. A subset of monotone reaction systems are those which can be recoordinatised via a linear change of coordinates to give a cooperative system, preserving the nonnegative orthant. These systems will be fully characterised.

The dynamical implications of monotonicity include, for example, the nonexistence of attracting periodic periodic orbits, and, with additional assumptions, generic convergence of orbits to the set of equilibria. Rather than discussing the dynamical implications, which are extensively treated in [1, 2] for example, it is the **identification** of monotone reaction systems which is discussed here. For example the results will allow us to claim that the system of two reactions

$$A + B \rightleftharpoons C, \quad A \rightleftharpoons B$$

is monotone for essentially arbitrary kinetics, even though it cannot be recoordinatised to give a cooperative dynamical system.

Monotonicity in chemical reaction systems was the subject of [3, 4], while reaction-diffusion systems were discussed in [5, 6]. Extensions of the general theory

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of monotone dynamical systems to cones which are not necessarily proper, and to expanding cones, can be found in [7, 8] which also contain examples drawn from chemical dynamics. A graph-theoretic approach to irreducibility and hence strong monotonicity was presented in [9] and applied to chemical reaction systems.

From the chemist's point of view, these results all belong in a tradition of work drawing conclusions about reaction network dynamics primarily from the network *structure*. Early work in this direction is exemplified by [10] and [11], with more recent strands including discussions of monotonicity detailed above and also discussions of injectivity [12–14]. Although the reaction systems discussed in examples mostly have mass action kinetics, an important feature of [4] and [14] was that the kinetics was constrained more weakly. The aim of this paper is to discuss monotonicity of reaction systems which satisfy only these weak constraints. Sections 2 to 4 introduce basic concepts and prove lemmas needed for the later development; Sections 5 to 7 contain the main results; Section 8 contains a number of examples illustrating the results.

2. Reaction systems

We start with some basic material on reaction systems, following [14]. A chemical reaction system in which n reactants participate in m reactions has dynamics governed by the ordinary differential equation

$$\dot{x} = Sv(x). \tag{1}$$

$x = [x_1, \ldots, x_n]^T$ is the nonnegative vector of reactant concentrations, $v = [v_1, \ldots, v_m]^T$ is the vector of reaction rates, assumed to be C^1, and S is the (constant) $n \times m$ **stoichiometric matrix**. The subspace of $\mathbb{R}^n$ spanned by the columns of S is called the **stoichiometric subspace**. Assuming that when $x_i = 0$, then $\dot{x}_i \geq 0$, (1) defines a dynamical system on $\mathbb{R}^n_+$, the nonnegative orthant in $\mathbb{R}^n$, which we note is convex. The jth column of S, termed S_j, is the **stoichiometric vector** for the jth reaction, and a stoichiometric matrix is defined only up to an arbitrary signing of its columns. In other words, given any signature matrix D (i.e. any diagonal matrix with diagonal entries ± 1), we could regard SD as the stoichiometric matrix and $Dv(x)$ as the rate vector.

Some further terminology: A **complex** is any combination of reactants, corresponding to a nonnegative vector in $\mathbb{R}^n$. A special kind of reaction is an **interconversion** whose stoichiometric vector has exactly two nonzero entries, one positive, and one negative. A reaction system is **indecomposable** when the set of reactions cannot be divided into two sets of reactions with no substrates in common. In general, assuming that reaction systems are indecomposable entails no loss of generality, because where they are decomposable, results can be applied to each indecomposable subset of the reactions. A set of reactions is **linearly independent** if their stoichiometric vectors form a linearly independent set. A set of reactions is **pairwise independent** if no stoichiometric vector is a linear multiple of another.

(1) may represent an open system where there is some inflow/outflow of reactions. We will refer to reactions not involving any inflow or outflow as **true** reactions and assume that a set of true reactions has the following property arising from the law of atomic balance [15]: If S is the stoichiometric matrix of the reactions, and $\mathcal{S}$ is the stoichiometric subspace, then there is at least one strictly positive vector $E \in \mathcal{S}^\perp \equiv \ker(S^T)$ – i.e. there is a strictly positive vector $E \in \mathbb{R}^n$ such that $E^T S = 0$. This also means that $\mathcal{S}$ cannot contain a nonnegative vector.

Defining $V_{ij}(x) \equiv \frac{\partial v_i}{\partial x_j}$ gives us an $m \times n$ matrix $V(x)$, which our assumptions guarantee is continuous in x. For notational convenience we will generally write V instead of $V(x)$. The Jacobian of (1) is then just $SV : \mathbb{R}^n \to \mathcal{S}$. A very reasonable, but weak, assumption about many reaction systems is that reaction rates are monotonic functions of substrate concentrations as assumed in [4, 14, 16]. We use the following definition provided in [14]:

> A reaction system is **nonautocatalytic** (**NAC**) if the stoichiometric matrix S and the matrix V^T have opposite sign structures in the following sense: $S_{ij}V_{ji} \leq 0$ for all i and j, and $S_{ij} = 0 \Rightarrow V_{ji} = 0$.

In more intuitive terms, if a substrate is used up (created) in a reaction, then increasing the concentration of this substrate, while holding all others constant, cannot cause the reaction rate to decrease (increase). Further, if a substrate does not participate in a reaction, then it does not influence the reaction rate. As we allow $V_{ji} = 0$, even when $S_{ij} \neq 0$, irreversible reactions are allowed by this definition. As discussed in [14], all reasonable reaction kinetics (including mass action and Michaelis-Menten kinetics for example) give rise to NAC systems provided that reactants never occur on both sides of a reaction.

2.1. *The physical context of a reaction system*

Reactions take place in some physical setting, which determines the inflow and outflow of reactants. It is useful to refer to an important experimental and theoretical setting – a so called Continuous Flow Stirred Tank Reactor (CFSTR) as presented in [12]. The reactions take place in a closed chamber, substrates are fed into this chamber (with possibly zero inflow rates), and outflow of all substrates occurs at a constant rate.

Using S to refer to the stoichiometric matrix of the reactions in a CFSTR (excluding the outflow from the CFSTR itself), the dynamical system arising from a CFSTR can be written:

$$\dot{x} = q(x_{in} - x) + Sv(x). \tag{2}$$

q, the flow rate through the reactor, is generally assumed to be positive, but we allow $q = 0$ so that (1) becomes a special case of (2). $x_{in} \in \mathbb{R}^n$ is a nonnegative vector representing the "feed" concentration. As (1) preserves the positive orthant, then so does (2). The Jacobian of (2) is $J = SV - qI$. Since $SV : \mathbb{R}^n \to \mathcal{S}$, any linear subspace containing $\mathcal{S}$ is left invariant by J. Later it will be shown that the techniques for checking monotonicity work for arbitrary fixed q.

From here on, a "reaction system" defined by a stoichiometric matrix S will mean the system (2) with $q \geq 0$, and with Jacobian SV satisfying the NAC condition. To see that such systems generally have invariant subspaces, consider any vector $E \in \mathcal{S}^{\perp}$. Left multiplying (2) by E^T gives:

$$\frac{\mathrm{d}(E^T x)}{\mathrm{d}t} = q(E^T x_{in} - E^T x)$$

With $q > 0$, $E^T x$ approaches the value $E^T x_{in}$ monotonically, and all trajectories converge to the hyperplane defined by the equation $E^T x = E^T x_{in}$. Since this is true for every $E \in \mathcal{S}^{\perp}$, all trajectories converge exponentially to a *coset* of $\mathcal{S}$ – i.e.

to an affine subspace parallel to $\mathcal{S}$. When $q = 0$, we get

$$\frac{\mathrm{d}(E^T x)}{\mathrm{d}t} = 0$$

for any $E \in \mathcal{S}^\perp$. This time *all* cosets of $\mathcal{S}$ are invariant.

In both cases, given $\mathcal{S}'$, an invariant coset of $\mathcal{S}$, any affine subspace containing $\mathcal{S}'$ is itself invariant: Any such subspace is defined by a set of equations of the form $q(E_i^T x_{in} - E_i^T x) = 0$ where each $E_i \in \mathcal{S}^\perp$. So any set of vectors $\{E_i\} \subset \mathcal{S}^\perp$ defines a linear subspace of $\mathcal{S}^\perp$, and the orthogonal complement of this subspace, say $\mathcal{V}$, (which contains $\mathcal{S}$) has some coset(s) invariant under the dynamics. Given such a coset, say $\mathcal{V}'$, the tangent space to $\mathcal{V}'$ at each point can be identified with $\mathcal{V}$, and so the Jacobian of the system restricted to $\mathcal{V}'$ is a linear transformation on $\mathcal{V}$. Under the assumptions in this paper, we know no more about $J(x)|_{x\in\mathcal{V}'}$ than about $J(x)$, so examining the action of $J(x)|_{x\in\mathcal{V}'}$ on $\mathcal{V}$ is the same as examining the action of $J(x)$ on $\mathcal{V}$.

Associated with invariant subspaces are linear coordinate transformations. Assume that $\dim(\mathcal{S}) = m < n$. Choose any set Z of $k \leq n - m$ linearly independent vectors lying in $\mathcal{S}^\perp$, and a set Y consisting of $n - k$ vectors such that $Z \cup Y$ spans $\mathbb{R}^n$. Treating the vectors in Y as the rows of an $(n-k)\times n$ matrix T, and the vectors in Z as the rows of an $k \times n$ matrix T_0 gives us an invertible linear transformation

$$T_{tot} = \left[\frac{T}{T_0}\right].$$

Defining $y = Tx \in \mathbb{R}^{n-k}$, $z = T_0 x \in \mathbb{R}^k$ and $y_{tot} = T_{tot}x \in \mathbb{R}^n$, we get the skew-product system

$$\begin{aligned}\dot{y} &= q(Tx_{in} - y) + TSv(T_{tot}^{-1} y_{tot})\\ \dot{z} &= q(T_0 x_{in} - z).\end{aligned}$$

$\dot{z}$ decays to zero and all trajectories approach the subspace defined by $z = T_0 x_{in}$. On this subspace z is constant, so $\dot{y}$ can be seen as a function of y alone. In this coordinate system, the reduced Jacobian is $TSVT' - qI_{n-k}$, where T' is the matrix composed of the first $n - k$ columns in T_{tot}^{-1}, so that $TT' = I_{n-k}$, the identity in $\mathbb{R}^{n-k}$.

3. Sign-structured classes of matrices

Given a matrix M it is possible to define several classes of matrices of the same dimensions as M, dependent on the sign structure of M alone[1]. In this section five such classes will be defined, $\mathcal{Q}(M)$, $\mathcal{Q}_0(M)$, $\mathcal{Q}_1(M)$, $\mathcal{Q}_2(M)$ and $\mathcal{Q}_3(M)$, and basic results needed for later development will be proved. We will often refer to the closure or interior of a set of matrices: In this case a real $n \times m$ matrix is being regarded as a point in $\mathbb{R}^{nm}$ with the Euclidean or any equivalent topology.

Firstly, a real matrix M determines the qualitative class $\mathcal{Q}(M)$ [17] of all matrices with the same sign pattern as M. Explicitly, $\mathcal{Q}(M)$ consists of all matrices X with

[1]Note that as vectors and scalars can be regarded as special cases of matrices, the definitions carry over naturally to these objects.

the same dimensions as M and satisfying $\text{sign}(X_{ij}) = \text{sign}(M_{ij})$, i.e. $M_{ij} > 0 \Rightarrow X_{ij} > 0$, $M_{ij} < 0 \Rightarrow X_{ij} < 0$ and $M_{ij} = 0 \Rightarrow X_{ij} = 0$.

Define $\mathcal{Q}_0(M) \equiv \text{cl}(\mathcal{Q}(M))$, the closure of $\mathcal{Q}(M)$. $\mathcal{Q}_0(M)$ consists of all matrices X such that $M_{ij} > 0 \Rightarrow X_{ij} \geq 0$, $M_{ij} < 0 \Rightarrow X_{ij} \leq 0$ and $M_{ij} = 0 \Rightarrow X_{ij} = 0$. With this definition, a reaction system is NAC if $V \in \mathcal{Q}_0(-S^T)$.

The next class we define is $\mathcal{Q}_1(M) \supseteq \mathcal{Q}_0(M)$. $\mathcal{Q}_1(M)$ consists of all matrices X such that $M_{ij} > 0 \Rightarrow X_{ij} \geq 0$, $M_{ij} < 0 \Rightarrow X_{ij} \leq 0$. When y is a vector in $\mathbb{R}^n$, we have the geometrical fact that

$$\mathcal{Q}_1(y) = \{x \in \mathbb{R}^n : x^T w \geq 0 \quad \text{for all} \quad w \in \mathcal{Q}_0(y)\}. \tag{3}$$

$\mathcal{Q}_1(M)$ can thus be thought of as the dual of $\mathcal{Q}_0(M)$. When M has no zero entries, then $\mathcal{Q}_1(M) = \mathcal{Q}_0(M)$. Unlike $\mathcal{Q}(M)$ and $\mathcal{Q}_0(M)$ which may have empty interior, $\mathcal{Q}_1(M)$ always has nonempty interior $\text{int}(Q_1(M))$ consisting of matrices X satisfying the two constraints: $M_{ij} > 0 \Rightarrow X_{ij} > 0$ and $M_{ij} < 0 \Rightarrow X_{ij} < 0$.

Lemma 3.1: *Let $M' \in \mathcal{Q}(M)$, and $N \in \mathcal{Q}_1(M)$. Then $M' + N \in \text{int}(Q_1(M))$.*

Proof: From the definitions, if $\text{sign}(M_{ij}) \neq 0$, then $\text{sign}((M' + N)_{ij}) = \text{sign}(M_{ij})$. The result follows. □

Lemma 3.2: *Let $M' \in \mathcal{Q}(M)$, and $N \in \mathcal{Q}_1(-M)$. Then there exists $\delta > 0$ such that $N + \delta M' \in \text{int}(Q_1(M))$.*

Proof: Choose

$$\delta_0 > \max_{M'_{ij} \neq 0} \frac{|N_{ij}|}{|M'_{ij}|}$$

Then for $\delta > \delta_0$, whenever $M_{ij} \neq 0$, then $\delta |M'_{ij}| > |N_{ij}|$ and hence $\text{sign}(N_{ij} + \delta M'_{ij}) = \text{sign}(M'_{ij}) = \text{sign}(M_{ij})$, i.e. $N + \delta M' \in \text{int}(Q_1(M))$. □

Note that for two matrices M_1 and M_2, $M_1 \in \mathcal{Q}_1(M_2) \Leftrightarrow M_2 \in \mathcal{Q}_1(M_1)$. The next useful set is $\mathcal{Q}_2(M) \equiv \mathcal{Q}_1(M) \cap \mathcal{Q}_1(-M)$. Clearly $\mathcal{Q}_2(M) = \mathcal{Q}_2(-M)$, and when $y \in \mathbb{R}^n$, we have the geometrical interpretation:

$$\mathcal{Q}_2(y) = \{x \in \mathbb{R}^n : x^T w = 0 \quad \text{for all} \quad w \in \mathcal{Q}_0(y)\} \tag{4}$$

$\mathcal{Q}_2(y)$ is a linear subspace of $\mathbb{R}^n$, and its dimension is precisely the number of zero entries in the vector y. If y has no zero coordinates, then $\mathcal{Q}_2(y)$ consists only of the zero vector.

Note that $\mathcal{Q}(-M) = -\mathcal{Q}(M)$ and similarly $\mathcal{Q}_i(-M) = -\mathcal{Q}_i(M)$ for $i \in \{0, 1, 2\}$. All the classes defined so far are convex cones (more on this in the next section). Further, all the definitions have been componentwise, and so it makes sense to state that $X \in \mathcal{Q}(M) \Leftrightarrow X_{jk} \in \mathcal{Q}(M_{jk})$ for all j, k, and similarly

$$X \in \mathcal{Q}_i(M) \Leftrightarrow X_{jk} \in \mathcal{Q}_i(M_{jk}) \quad \text{for all} \quad j, k \quad (i = 0, 1, 2)$$

Lemma 3.3: *Let y be a nonzero vector. Then $y \notin \mathcal{Q}_1(-y)$.*

Proof: $y \in \mathcal{Q}_0(y) \subset \mathcal{Q}_1(y)$, so if $y \in \mathcal{Q}_1(-y)$, then $y \in \mathcal{Q}_2(y)$. But by (4) $\mathcal{Q}_0(y) \cap \mathcal{Q}_2(y) = 0$. So $y \in \mathcal{Q}_1(-y)$ iff $y = 0$. □

Since, by Lemma 3.1, given any vector $y \in \mathbb{R}^n$, the sets $\mathcal{Q}_1(y)$ and $\mathcal{Q}_1(-y)$ have nonempty interior in $\mathbb{R}^n$, these sets must span $\mathbb{R}^n$. It follows that:

Lemma 3.4: *Given any nonzero vector $y \in \mathbb{R}^n$, we can choose a set of n linearly independent vectors consisting of y and $n-1$ vectors in $\mathcal{Q}_1(-y)$.*

Proof: When choosing a set of basis vectors from $\mathcal{Q}_1(-y)$, the first vector is arbitrary. So choose any basis set consisting of $-y$ and $n-1$ other vectors from $\mathcal{Q}_1(-y)$. Now replace $-y$ with y to get the desired basis. □

Lemma 3.5: *Let $\{x_i\} \subset \mathbb{R}^n$ be some set of vectors satisfying $x_i \in \mathcal{Q}_2(x_j)$ for every $i \neq j$. Let*

$$y \in \mathcal{Q}_0\left(\sum_i \alpha_i x_i\right)$$

where α_i are scalars. Then $\langle y, x_i\rangle \in \mathcal{Q}_0(\alpha_i)$.

Proof: As mentioned above, it makes sense to talk about the $\mathcal{Q}_0(\alpha_i)$.

(1) If $\alpha_i = 0$ then $\mathcal{Q}_0(\sum_i \alpha_i x_i) \subset \mathcal{Q}_2(x_i)$, so $y \in \mathcal{Q}_2(x_i)$ and thus $\langle y, x_i\rangle = 0$.
(2) If $\alpha_i > 0$ then $\mathcal{Q}_0(\sum_i \alpha_i x_i) \subset \mathcal{Q}_1(x_i)$, so $y \in \mathcal{Q}_1(x_i)$ and thus $\langle y, x_i\rangle \geq 0$.
(3) If $\alpha_i < 0$ then $\mathcal{Q}_0(\sum_i \alpha_i x_i) \subset \mathcal{Q}_1(-x_i)$, so $y \in \mathcal{Q}_1(-x_i)$ and thus $\langle y, x_i\rangle \leq 0$.

Together these three statements are equivalent to $\langle y, x_i\rangle \in \mathcal{Q}_0(\alpha_i)$. □

A final class of matrices with the same dimensions as M, useful primarily to simplify notation, is

$$\mathcal{Q}_3(M) \equiv \text{the set of all matrices not in } \mathcal{Q}_1(M) \cup \mathcal{Q}_1(-M)$$

Where $y \in \mathbb{R}^n$, $\mathcal{Q}_3(y) = \mathbb{R}^n \backslash (\mathcal{Q}_1(y) \cup \mathcal{Q}_1(-y))$. The set $\mathcal{Q}_3(M)$ is not convex, but consists of entire lines minus the origin – i.e. if $N \in \mathcal{Q}_3(M)$, then $\alpha N \in \mathcal{Q}_3(M)$ for all $\alpha \neq 0$. As a corollary of the definition of $\mathcal{Q}_1(y)$ we get:

Lemma 3.6: *Consider a nonzero vector $y \in \mathbb{R}^n$ and another vector $w \in \mathbb{R}^n$. Then $w \in \mathcal{Q}_3(y)$ iff there exist vectors $y_1, y_2 \in \mathcal{Q}_0(y)$ (or $y_1, y_2 \in \mathcal{Q}_0(-y)$) such that*

$$\frac{\langle w, y_1\rangle}{\langle w, y_2\rangle} = -1$$

Proof: From (3), if $w \notin \mathcal{Q}_1(y) \cup \mathcal{Q}_1(-y)$ then there exist vectors $y_1, y_2 \in \mathcal{Q}_0(y)$ (or $y_1, y_2 \in \mathcal{Q}_0(-y)$) such that $\langle w, y_1\rangle > 0$ and $\langle w, y_2\rangle < 0$. By scaling one of y_1 or y_2 if necessary we get $\langle w, y_1\rangle / \langle w, y_2\rangle = -1$. On the other hand, suppose there exist vectors $y_1, y_2 \in \mathcal{Q}_0(y)$ such that $\langle w, y_1\rangle / \langle w, y_2\rangle = -1$. Then either $\langle w, y_1\rangle < 0$ or $\langle w, y_2\rangle < 0$, implying, by (3), that $w \notin \mathcal{Q}_1(y)$. Similarly, either $\langle w, y_1\rangle > 0$ or $\langle w, y_2\rangle > 0$ implying that $w \notin \mathcal{Q}_1(-y)$. The argument when $y_1, y_2 \in \mathcal{Q}_0(-y)$ is similar. □

The following geometrical property of $\mathcal{Q}_3(y)$ follows:

Lemma 3.7: *Given a nonzero vector $y \in \mathbb{R}^n$ with $n \geq 3$, and a vector $w \in \mathcal{Q}_3(y)$, there is a line passing through w and contained in $\mathcal{Q}_3(y)$.*

Proof: Consider the point $w \in \mathcal{Q}_3(y)$. By Lemma 3.6, there exist $y_1, y_2 \in \mathcal{Q}_0(y)$ such that $\langle y_1, w\rangle = -\langle y_2, w\rangle > 0$. Choose a nonzero vector $z \in y_1^\perp \cap y_2^\perp$ (such a vector exists because $n \geq 3$). Consider the line $w + tz$, $t \in \mathbb{R}$. For every t, $\langle y_1, w + tz\rangle = \langle y_1, w\rangle = -\langle y_2, w\rangle = -\langle y_2, w + tz\rangle$, which implies, by Lemma 3.6, that $w + tz \in \mathcal{Q}_3(y)$ for every t. □

Note that if y has only one nonzero coordinate, so that $\mathcal{Q}_0(y)$ is a half line, then $\mathcal{Q}_1(y) \cup \mathcal{Q}_1(-y) = \mathbb{R}^n$ and so $\mathcal{Q}_3(y)$ is empty.

Given two vectors, $w, x \in \mathbb{R}^n$, we will be interested in the line segment

$$[w, x] \equiv \{(1-\alpha)w + \alpha x \mid 0 \leq \alpha \leq 1\}.$$

In the next few lemmas, some geometrical facts about line segments, and spanning sets of vectors are proved for later use.

Lemma 3.8: *Consider a vector y and two vectors $y_1 \in \mathcal{Q}_1(y)$ and $y_2 \in \mathcal{Q}_1(-y)$. Then $[y_1, y_2]$ either intersects $\mathcal{Q}_2(y)$, or intersects $\mathcal{Q}_3(y)$, but not both.*

Proof: If one of y_1 or y_2 lies in $\mathcal{Q}_2(y)$, then by convexity of these regions, $[y_1, y_2]$ lies entirely in $\mathcal{Q}_1(y)$ or $\mathcal{Q}_1(-y)$ (and hence does not intersect $\mathcal{Q}_3(y)$). So assume that $y_1 \in \mathcal{Q}_1(y) \backslash \mathcal{Q}_1(-y)$ and $y_2 \in \mathcal{Q}_1(-y) \backslash \mathcal{Q}_1(y)$. The line segment $[y_1, y_2]$ is connected, and hence must intersect $\mathcal{Q}_2(y) \cup \mathcal{Q}_3(y)$ which separates $\mathcal{Q}_1(y) \backslash \mathcal{Q}_1(-y)$ and $\mathcal{Q}_1(-y) \backslash \mathcal{Q}_1(y)$. If $[y_1, y_2]$ intersects $\mathcal{Q}_2(y)$, then it does not intersect $\mathcal{Q}_3(y)$, because if $(1-\lambda_0)y_1 + \lambda_0 y_2 \in \mathcal{Q}_2(y)$ for some $\lambda_0 \in (0,1)$, then by convexity of $\mathcal{Q}_1(y)$ and $\mathcal{Q}_1(-y)$, $(1-\lambda)y_1 + \lambda y_2 \in \mathcal{Q}_1(y)$ for $\lambda \in [0, \lambda_0]$, and $(1-\lambda)y_1 + \lambda y_2 \in \mathcal{Q}_1(-y)$ for $\lambda \in [\lambda_0, 1]$. □

A general fact is the following:

Lemma 3.9: *Consider two linear subspaces $\mathcal{X}, \mathcal{Y}$ of $\mathbb{R}^n$ with $\dim(\mathcal{Y}) \leq \dim(\mathcal{X}) - 2$. Consider a set of vectors $\{y_i\}$ spanning $\mathcal{X}$ and any vector $\overline{y} \in \mathbb{R}^n$. Then there exists a vector $y_k \in \{y_i\}$ such that $y_k + \alpha\overline{y} \notin \mathcal{Y}$ for any scalar α.*

Proof: Suppose on the contrary, that for each j, there exists α_j such that $y_j + \alpha_j \overline{y} \in \mathcal{Y}$. Since $\{y_i\}$ spans $\mathcal{X}$, and $\mathcal{Y}$ is a subspace, this means that any vector $w \in \mathcal{X}$ satisfies $w + \alpha_w \overline{y} \in \mathcal{Y}$ for some scalar α_w. In other words, $\{\overline{y}\} \cup \mathcal{Y}$ must span $\mathcal{X}$. But this is impossible since $\dim(\mathcal{Y}) \leq \dim(\mathcal{X}) - 2$. □

A particular case is:

Lemma 3.10: *Consider a nonzero vector $y \in \mathbb{R}^n$, some vector $\overline{y}$, and a set of vectors $\{y_i\}$ spanning $\mathbb{R}^n$. If $\dim(\mathcal{Q}_2(y)) \leq n-2$ (i.e. y has at least two nonzero entries), then there exists a vector $y_k \in \{y_i\}$ such that $y_k + \alpha\overline{y} \notin \mathcal{Q}_2(y)$ for any scalar α.*

Proof: This follows from Lemma 3.9 with $\mathcal{X} = \mathbb{R}^n$, and $\mathcal{Y} = \mathcal{Q}_2(y)$. □

Lemma 3.11: *Consider a nonzero vector $y \in \mathbb{R}^n$, and a set of vectors $\{y_i\} \subset \mathcal{Q}_1(y) \cup \mathcal{Q}_1(-y)$ spanning $\mathbb{R}^n$ with at least one vector in $\mathcal{Q}_1(y) \backslash \mathcal{Q}_1(-y)$ and at least one vector in $\mathcal{Q}_1(-y) \backslash \mathcal{Q}_1(y)$. Assume that $\dim(\mathcal{Q}_2(y)) \leq n-2$. Then there exists a pair of vectors $y_{k_1} \in \mathcal{Q}_1(y)$, $y_{k_2} \in \mathcal{Q}_1(-y)$ such that $[y_{k_1}, y_{k_2}]$ intersects $\mathcal{Q}_3(y)$.*

Proof: Consider the sets

$$\mathcal{W} \equiv \{y_i\} \cap (\mathcal{Q}_1(y) \backslash \mathcal{Q}_1(-y)) \quad \text{and} \quad \mathcal{X} \equiv \{y_i\} \cap (\mathcal{Q}_1(-y) \backslash \mathcal{Q}_1(y))$$

which are both nonempty by assumption. By Lemma 3.8, given any $w \in \mathcal{W}$, $x \in \mathcal{X}$, the segment $[w, x]$ must either intersect $\mathcal{Q}_2(y)$, or $\mathcal{Q}_3(y)$. Suppose, contrary to the claim of the theorem, $[w, x]$ intersects $\mathcal{Q}_2(y)$ for every pair of vectors $w \in \mathcal{W}$, $x \in \mathcal{X}$. Choose any $\overline{w} \in \mathcal{W}$. Then any $x \in \mathcal{X}$ can be written $x = x^{(0)} + \beta_x \overline{w}$, where $x^{(0)} \in \mathcal{Q}_2(y)$, and β_x is some nonzero scalar. In turn, fixing some $\overline{x} \in \mathcal{X}$, any $w \in \mathcal{W}$ can be written $w = w^{(0)} + \beta_w \overline{x}$, where $w^{(0)} \in \mathcal{Q}_2(y)$, and β_w is some scalar. Putting these together, fixing *any* vector $\overline{y} \in \mathcal{W} \cup \mathcal{X}$, every vector $y_k \in \{y_i\}$ satisfies $y_k + \beta_k \overline{y} \in \mathcal{Q}_2(y)$, where β_k is some scalar, which is impossible by Lemma 3.10.

□

4. Order preserving dynamical systems

The importance of identifying a system as order preserving stems from the fact that these dynamical systems display restricted behaviour, discussed in detail in [1, 2]. In some situations, for example when there is a unique equilibrium, bounded trajectories, and an appropriate phase space [4], monotonicity implies convergence of *all* orbits to an equilibrium. In this paper our primary concern is with the *identification* of monotone chemical reaction systems, and the dynamical *implications* of monotonicity will not be explored.

For elementary definitions and results concerning cones we follow [18]. Throughout we work in the context of $\mathbb{R}^n$ and linear subspaces of $\mathbb{R}^n$. A cone K is a subset of $\mathbb{R}^n$ satisfying $x \in K \Rightarrow \alpha x \in K$ for any positive scalar α. K is **pointed** if $K \cap -K = \{0\}$. Closed, pointed, convex cones with nonempty interior in $\mathbb{R}^n$ will be referred to as **proper cones**. Where $\mathcal{V}$ is some linear subspace of $\mathbb{R}^n$, closed, pointed, convex cones with nonempty relative interior in $\mathcal{V}$ will be referred to as **$\mathcal{V}$-proper** cones. A proper ($\mathcal{V}$-proper) cone K induces a partial order on $\mathbb{R}^n$ ($\mathcal{V}$), where $y \overset{K}{\leq} x \Leftrightarrow x - y \in K$.

A subset F of a cone K is a **face** of K when $x \in F$ and $0 \overset{K}{\leq} y \overset{K}{\leq} x$ implies that $y \in F$. Faces of a convex cone are themselves convex. Given a face F, the the smallest linear subspace of $\mathbb{R}^n$ in which F lies is referred to as $\text{span}(F)$, or $F - F$. For a proper cone $(F - F) \cap K = F$. One dimensional faces of a cone are called **extremal rays** and consist of **extremal vectors**. We can identify extremal rays with unit extremal vectors, which we will also refer to (in a slight abuse of notation) as extremals. When F is one dimensional (i.e. an extremal ray), then we refer to $F - F$ as an **extremal line**.

A proper cone in $\mathbb{R}^n$ has at least n extremals and is generated by its extremals in the sense that every vector in the cone can be written as a nonnegative combination of its extremals. A **polyhedral cone** is *finitely generated* – i.e. has a finite number of extremal rays. A proper cone in $\mathbb{R}^n$ with exactly n extremal rays is called a **simplicial** cone. Any set of n linearly independent vectors in $\mathbb{R}^n$ defines a simplicial cone. When $\mathcal{V}$ is some linear subspace of $\mathbb{R}^n$, a $\mathcal{V}$-proper cone with exactly $\dim(\mathcal{V})$ extremal rays, all in $\mathcal{V}$, will be called a **$\mathcal{V}$-simplicial** cone.

Given any set of vectors in $\mathbb{R}^n$, the set generated by finite nonnegative combinations of these vectors is a closed, convex cone, but may not be pointed or have nonempty interior in $\mathbb{R}^n$. To claim that the cone is proper ($\mathcal{V}$-proper) requires checking that it is pointed and has nonempty interior in $\mathbb{R}^n$ (relative interior in $\mathcal{V}$).

Given an arbitrary proper cone K, the definition and implications of calling a dynamical system **K-cooperative** were clarified in [19]. In this paper we are concerned with a related condition which we term **K-quasipositivity**: A matrix J is K-quasipositive if there is some scalar α such that $J + \alpha I : K \mapsto K$. If such an α exists then it can be chosen to be positive so we can assume $\alpha > 0$. When K is a proper polyhedral cone, and the matrices arise as the Jacobians of a dynamical system, then the dynamical system is K-cooperative iff the Jacobians are K-quasipositive. This equivalence follows from Theorem 8 in [20]. In the case of nonpolyhedral cones the condition that the Jacobians are K-quasipositive is sufficient, but not necessary (Example 1 in [20]) to ensure that the dynamical system is K-cooperative. Given a reaction system, a cone K such that the Jacobians

of the system are K-quasipositive will be referred to as a **preserved** cone[1].

On this same theme, when we refer to a cone "preserved by a reaction system" we mean a cone preserved by *all possible instances of the reaction system* – i.e. all possible dynamics satisfying the NAC condition. If any allowed Jacobian does not preserve K, then we will say that K is not preserved. For a cone K and any scalar q, the matrix $J - qI$ is K-quasipositive iff the matrix J is. So embedding a system of reactions in a CFSTR makes no difference to whether K is preserved. If there is a simplicial proper cone K preserved by a reaction system, then the extremals of K can be chosen as the basis of a new coordinate system in which the system is cooperative. So systems preserving a simplicial proper cone are precisely those which can be made cooperative by a linear coordinate change.

It is not infrequent that a reaction system preserves no cones, but has some invariant affine subspaces as described in Section 2.1 restricted to which it is cone-preserving. The modifications to the theory developed below required to deal with this situation are minor and are discussed in Section 7 and Appendix A.

The following lemmas are all elementary and will prove useful later. In each case K is a cone in $\mathbb{R}^n$.

Lemma 4.1: *Consider the extremals $\{y_i\}$ of K. If $\{y_i\}$ forms a linearly independent set, then K is pointed.*

Proof: If K is not pointed, then there is some vector v such that $v, -v \in K$. We can write $v = \sum_i p_i y_i$ and $-v = \sum_i q_i y_i$, where $p_i, q_i \geq 0$, and not all are zero. Adding gives $0 = \sum_i (p_i + q_i) y_i$. Since not all $p_i + q_i$ are zero, the set $\{y_i\}$ is linearly dependent. □

As a partial converse to Lemma 4.1:

Lemma 4.2: *Consider the set $\{y_i\}$ of extremals of K. If we can write $\sum_i p_i y_i = 0$, where $p_i \geq 0$, and at least one is nonzero, then K is not pointed.*

Proof: Assume $\sum_i p_i y_i = 0$ and let p_k be nonzero. Rearranging gives $y_k = -\sum_{i \neq k} \frac{p_i}{p_k} y_i$, i.e. $-y_k \in K$. Since K contains both y_k and $-y_k$, it is not pointed. □

Lemma 4.3: *Let K have extremals $\{y_i\}$, $i \in \mathcal{I}$. If there is a subset of $\{y_i\}$ which*

(1) are linearly dependent,
(2) all satisfy $y_i \in \mathcal{Q}_1(-y_j)$ for each $i \neq j$,

then K is not pointed.

Proof: If some subset of $\{y_i\}$ form a linearly dependent set, then we can write $\sum_{i \in \mathcal{I}_1} p_i y_i = \sum_{i \in \mathcal{I}_2} p_i y_i$ where p_i are *positive* constants and $\mathcal{I}_1, \mathcal{I}_2 \subset \mathcal{I}$ are disjoint with at least one nonempty. Consider the kth component of this equation:

$$\sum_{i \in \mathcal{I}_1} p_i y_i^{(k)} = \sum_{i \in \mathcal{I}_2} p_i y_i^{(k)}. \tag{5}$$

Since $y_i \in \mathcal{Q}_1(-y_j)$ for each $i \neq j$, no more than two vectors can have a nonzero entry in kth place, and if this is the case then these entries must be of opposite signs. This means that no member of $\{y_i\}_{i \in \mathcal{I}_1}$ can have a nonzero entry in the same place as some member of $\{y_i\}_{i \in \mathcal{I}_2}$, because then (5) would necessarily be violated. Thus $\{y_i\}_{i \in \mathcal{I}_1}$ and $\{y_i\}_{i \in \mathcal{I}_2}$ are linearly independent and (5) can only be satisfied

[1]The reader should bear in mind that if we write that a system "preserves no cones", it is still possible that the system is K-cooperative for some nonpolyhedral cone K. There is no such ambiguity if we write that a system "preserves no polyhedral cones" or "preserves no simplicial cones".

if $\sum_{i\in\mathcal{I}_1} p_i y_i = 0 = \sum_{i\in\mathcal{I}_2} p_i y_i$. Since at least one of $\mathcal{I}_1$ or $\mathcal{I}_2$ is nonempty, it now follows from Lemma 4.2 that K is not pointed. □

Lemma 4.4: *Let F be a face of K, $v_1, v_2 \in F$, and $w \in \mathbb{R}^n$. If there exist $\alpha, \beta > 0$ such that $v_1 + \alpha w \in K$ and $v_2 - \beta w \in K$, then $w \in \text{span}(F)$.*

Proof: Define $y_1 \equiv v_1 + \alpha w \in K$ and $y_2 \equiv v_2 - \beta w \in K$. Then $y_3 \equiv y_1 + (\alpha/\beta) y_2 = v_1 + (\alpha/\beta) v_2 \in F$. Since $y_3 - y_1 = (\alpha/\beta) y_2 \in K$, we can write $0 \overset{K}{\leq} y_1 \overset{K}{\leq} y_3$. By the definition of a face, this implies that $y_1 \in F$. So $w = (y_1 - v_1)/\alpha \in \text{span}(F)$. □

5. A single chemical reaction

The first major result will be to characterise cones preserved by a single chemical reaction. The results can then easily be applied to systems with an arbitrary number of chemical reactions. Consider a set of n reactants and a single reaction involving some subset of these reactants. $S, V^T \in \mathbb{R}^n$, so SV is an $n \times n$ rank 1 matrix. We want to characterise cones K such that $SV - qI$ is K-quasipositive, i.e. cones such that SV is K-quasipositive. The next theorem defines necessary conditions any such cone must satisfy. Applicability of these conditions will be illustrated via examples in Section 8.

Theorem 5.1: *Let $S \in \mathbb{R}^n$ be the stoichiometric vector of a reaction, and K a proper cone with extremals $\{y_i\}$ preserved by the reaction system. Then*

(1) If F is a face of K intersecting $\mathcal{Q}_3(S)$, then $S \in \text{span}(F)$.
(2) $\{y_i\} \subset \mathcal{Q}_1(S) \cup \mathcal{Q}_1(-S)$.
(3) If $S \in K \cup -K$, then S lies on an extremal line of K.
(4) If $S \in K$, then exactly one member of $\{y_i\}$ lies in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$. Similarly if $S \in -K$, then exactly one member of $\{y_i\}$ lies in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$.
(5) If S has more than one nonzero coordinate (i.e. the reaction involves two or more substrates), then $K \not\subset \mathcal{Q}_1(S)$, and $K \not\subset \mathcal{Q}_1(-S)$.
(6) If S has more than one nonzero coordinate and $n \geq 3$, then the boundary of K intersects $\mathcal{Q}_3(S)$.

Proof: Let $\mathcal{I}$ be the index set of the extremals $\{y_i\}$. A vector $z \in K$ iff we can write $z = \sum_i a_i y_i$ where $a_i \geq 0$ for all i, and a finite number of a_i are nonzero. If $J = SV$ preserves K for all $V \in \mathcal{Q}_0(-S^T)$, then

$$\exists\, \alpha(V) \geq 0 \text{ s.t. } Jz + \alpha(V) z = \left(\sum_i a_i V y_i \right) S + \alpha(V) z \in K. \tag{6}$$

Choosing $z = y_k$ gives the necessary requirement that for each $V \in \mathcal{Q}_0(-S^T)$

$$\exists\, \alpha(V) \geq 0 \text{ s.t. } \alpha(V) y_k + (V y_k) S \in K \tag{7}$$

When K is polyhedral, the existence of such a scalar for each extremal is also sufficient – if there is such an $\alpha_k(V)$ for each $k \in \mathcal{I}$, then we can choose $\alpha(V) = \max_k \{\alpha_k(V)\}$ to get $SV + \alpha(V) I : K \mapsto K$.

(1) Given a face F of K which intersects $\mathcal{Q}_3(S)$, consider any vector $w \in F \cap \mathcal{Q}_3(S)$. By Lemma 3.6 we can choose $V_1, V_2 \in \mathcal{Q}_0(-S^T)$, such that $V_1 w = -V_2 w > 0$. From Condition 6 there exist $\alpha_1, \alpha_2 \geq 0$ such that $\alpha_1 w + (V_1 w) S \in K$ and $\alpha_2 w + (V_2 w) S \in K$, i.e. $\alpha_1 w + (V_1 w) S \in K$ and $\alpha_2 w - (V_1 w) S \in K$. By Lemma 4.4 $S \in \text{span}(F)$.

(2) Assume that $y_k \in \mathcal{Q}_3(S)$ for some index k. Extremal rays are 1D faces of a cone, so the previous result implies that S must be collinear with y_k, i.e. $S \in \mathcal{Q}_3(S)$ (since $\mathcal{Q}_3(S)$ consists of entire lines minus the origin), which is of course impossible since $S \in \mathcal{Q}_1(S)$.
(3) Suppose $S \in K$. This means that S can be written as a nonnegative combination of $\{y_i\}$, and so, by the previous part of the theorem combined with Lemma 3.3, at least one extremal $y_k \in \mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$. We can then choose $V \in \mathcal{Q}_0(-S^T)$ such that $Vy_k < 0$. Now by Condition 7, there exists $\alpha \geq 0$ such that $\alpha y_k + Vy_k S \in K$, and since $S \in K$, we also have $\alpha y_k - Vy_k S \in K$. By Lemma 4.4, $S \in \text{span}(y_k)$, and, since $S \in K$, S is a positive multiple of y_k. If K is preserved then so is $-K$. So, if $-S \in K$, then we can repeat the argument using $-K$ instead of K. Thus S lies on an extremal line of K.
(4) Assume that $S \in K$ and there are two extremals, $y_{k_1}, y_{k_2} \in \mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$. Then by Part (3), S lies on y_{k_1} and y_{k_2}, which is impossible. The same argument holds if $S \in -K$ and there are two extremals $y_{k_1}, y_{k_2} \in \mathcal{Q}_1(-S)\backslash\mathcal{Q}_1(S)$.
(5) We prove the claim by contradiction. Assume $K \subset \mathcal{Q}_1(S)$. Since $\mathcal{Q}_1(S)$ is convex, all of K lies in $\mathcal{Q}_1(S)$ iff all its extremals lie in $\mathcal{Q}_1(S)$. Since the reaction involves two or more substrates, by Lemma 3.10 we can choose some extremal $y_k \in \mathcal{Q}_1(S)$ such that $y_k + \delta S \notin \mathcal{Q}_2(S)$ for any scalar δ. Define

$$\delta_0 = \sup\{\delta : y_k - \delta S \in K\}.$$

δ_0 exists since by Lemma 3.2, for large enough $\delta > 0$, $y_k - \delta S \in \text{int}(\mathcal{Q}_1(-S))$, so $y_k - \delta S \notin \mathcal{Q}_1(S)$. As K is closed, $w \equiv y_k - \delta_0 S$ lies on the boundary of K, and also $w \in \mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$. By the definition of w, $w - \delta S \notin K$ for any $\delta > 0$, and consequently $\alpha w - \delta S \notin K$ for any $\alpha > 0$ and any $\delta > 0$. Since $w \in \mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$, there exists $V \in \mathcal{Q}_0(-S^T)$ such that $Vw < 0$. But from Condition 6 there exists positive α such that $\alpha w + (Vw)S \in K$, contradicting $\alpha w - \delta S \notin K$ for any $\alpha > 0$ and any $\delta > 0$. Whenever K is preserved, so is $-K$, so similar arguments lead to $K \not\subset \mathcal{Q}_1(-S)$.
(6) Part (5) tells us that K has at least one extremal in $\mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$ and at least one in $\mathcal{Q}_1(-S)\backslash\mathcal{Q}_1(S)$. Since the reaction involves two or more substrate, it follows by Lemma 3.11 that K intersects $\mathcal{Q}_3(S)$. Consider some point $w \in K \cap \mathcal{Q}_3(S)$. By Lemma 3.7, there is a line $L \subset \mathcal{Q}_3(S)$ passing through w. Since a proper cone cannot contain an entire line, L must intersect the boundary of K. This proves that the boundary of K intersects $\mathcal{Q}_3(S)$.

□

To summarise some of the key restrictions on K:

(1) K has extremals in $\mathcal{Q}_1(S) \cup \mathcal{Q}_1(-S)$ and nowhere else,
(2) If S has more than one nonzero coordinate, K certainly has extremals in $\mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$ and in $\mathcal{Q}_1(-S)\backslash\mathcal{Q}_1(S)$,
(3) Either S lies on an extremal line of K or S lies outside $K \cup -K$,
(4) S lies in the span of all faces of K intersecting $\mathcal{Q}_3(S)$.

One physically natural but important observation is the following:

Theorem 5.2: *If a reaction with stoichiometric vector S preserves a cone K, then given any $r \neq 0$, so does the reaction with stoichiometric vector $S' = rS$.*

Proof: Assume the reaction with stoichiometric vector S preserves a cone K. This means that for each $V \in \mathcal{Q}_0(-S^T)$ there exists $\alpha(V) \geq 0$ such that $\alpha(V)z + (Vz)S \in K$ for all $z \in K$. We now show that this implies that given any $V' \in \mathcal{Q}_0(-S'^T)$

there exists $\alpha^{'}(V^{'}) \geq 0$ such that $\alpha^{'}(V^{'})z + V^{'}zS^{'} \in K$.

(1) If $r > 0$, then $\mathcal{Q}_0(-S^{'}) = \mathcal{Q}_0(-S)$. Given any $V^{'} \in \mathcal{Q}_0(-S^T)$, define $V = V^{'}$ and $\alpha^{'}(V) = r\alpha(V)$. Then $\alpha^{'}(V^{'})z + V^{'}zS^{'} = r(\alpha(V)z + (Vz)S) \in K$.
(2) If $r < 0$, then $\mathcal{Q}_0(-S^{'}) = \mathcal{Q}_0(S)$. Given any $V^{'} \in \mathcal{Q}_0(S^T)$, define $V = -V^{'}$ and $\alpha^{'}(V^{'}) = -r\alpha(V) \geq 0$. Then $\alpha^{'}(V^{'})z + V^{'}zS^{'} = -r(\alpha(V)z + (Vz)S) \in K$.

Thus in both cases the reaction with stoichiometric vector $S^{'}$ preserves K. □

Since the cones K constructed in Theorem 5.1 can be divided into those for which $S \in K \cup -K$ (and hence S lies on an extremal line of K), and those for which $S \notin K \cup -K$, it is useful to treat these two cases separately from now on. First we look at the case $S \in K \cup -K$.

5.1. *Cones for which $S \in K \cup -K$*

The main result is that when $S \in K \cup -K$, the necessary conditions placed on K in Parts (2) and (4) of Theorem 5.1 are sufficient to ensure that the reaction system preserves K. We prove this by explicitly constructing α such that $J + \alpha I : K \mapsto K$.

Theorem 5.3: *Let S be the stoichiometric vector of a reaction. Consider any cone K with extremals $\{y_i\}$ such that $S = ry_k$ for some k and some $r \neq 0$, and*

(1) if $r > 0$, then $y_j \in \mathcal{Q}_1(-S)$ for $j \neq k$,
(2) if $r < 0$, then $y_j \in \mathcal{Q}_1(S)$ for $j \neq k$.

Then K is preserved by the system.

Proof: Let $J = SV$ and $\tau = -VS \geq 0$. Then given any scalar α and $z = \sum a_i y_i$:

$$Jz + \alpha z = \frac{a_k}{r} SVS + S\sum_{i \neq k} a_i V y_i + \alpha \frac{a_k}{r} S + \alpha \sum_{i \neq k} a_i y_i$$

$$= \left(a_k(\alpha - \tau) + r\sum_{i \neq k} (a_i V y_i) \right) y_k + \sum_{i \neq k} \alpha a_i y_i$$

The assumptions of the theorem imply that $r\sum_{i \neq k}(a_i V y_i) \geq 0$. Thus choosing $\alpha \geq \tau$ ensures that the coefficient of y_k is nonnegative, and $Jz + \alpha z \in K$. □

Note that choosing $\alpha = \tau$ means that α is continuous in V, which in turn is continuous in x, and hence α is bounded on any compact subset of $\mathbb{R}^n$. From Lemma 3.4 combined with Lemma 4.1, the set of proper cones defined by Theorem 5.3 is certainly not empty. Many proper cones can be defined in this way, including simplicial cones.

5.2. *Cones for which $S \notin K \cup -K$*

We now look at the second category of cones – those for which S lies outside $K \cup -K$, but lies in the span of any faces intersecting $\mathcal{Q}_3(S)$. This set of cones is harder to characterise completely, but it is possible to find some sufficient conditions on such cones, and simplicial cones falling into this category can be completely characterised. First a sufficient condition:

Theorem 5.4: *Let S be the stoichiometric vector of a reaction. Consider a cone K generated by extremals $\{y_i\}$ satisfying $y_1 \in \mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$, $y_2 \in \mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$*

and $y_i \in \mathcal{Q}_2(S)$ for $i \neq 1,2$. Assume that $S \notin K \cup -K$ and $S \in \text{span}(y_1, y_2)$. Then K is preserved by the system.

Proof: Since $S \in \text{span}(y_1, y_2)$, but $S \notin K \cup -K$, this means that it can be written $S = r_1 y_1 - r_2 y_2$ where $r_1, r_2 > 0$. Then with $z = \sum a_i y_i$:

$$\begin{aligned} Jz + \alpha z &= (a_1 V y_1 + a_2 V y_2) S + \sum_{i \neq 1,2} a_i V y_i S + \alpha \sum a_i y_i \\ &= (a_1 V y_1 + a_2 V y_2)(r_1 y_1 - r_2 y_2) + \alpha \sum a_i y_i \end{aligned}$$

The fact that $V \in \mathcal{Q}_0(-S)$ and $y_i \in \mathcal{Q}_2(S)$ for all $i \neq 1,2$ was used. The last expression gives, after a little rearranging:

$$\begin{aligned} Jz + \alpha z = a_1(r_1 V y_1 + \alpha) y_1 + a_2(\alpha - r_2 V y_2) y_2 \\ + a_2 V y_2 r_1 y_1 - a_1 V y_1 r_2 y_2 + \alpha \sum_{i \neq 1,2} a_i y_i \end{aligned}$$

Here, since $V y_1 \leq 0$, and $V y_2 \geq 0$, the only possibly negative coefficients are $a_1(r_1 V y_1 + \alpha)$ and $a_2(\alpha - r_2 V y_2)$, but clearly by choosing $\alpha \geq \max\{|r_1 V y_1|, r_2 V y_2\}$, they can be made nonnegative, ensuring that $J + \alpha I : K \mapsto K$. □

Again $\alpha = \max\{|r_1 V y_1|, r_2 V y_2\}$ is continuous in x. We now show that the conditions on K proved to be sufficient in Theorem 5.4 are also necessary when K is simplicial, completing the characterisation of simplicial cones preserved by a single reaction.

Theorem 5.5: *Let $S \in \mathbb{R}^n$ be the stoichiometric vector of a reaction involving at least two substrates, K a preserved* **simplicial** *proper cone with extremals $\{y_i\}$, and $S \notin K \cup -K$. Then K has exactly one extremal (say y_1) in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$, one (say y_2) in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$, and all others in $\mathcal{Q}_2(S)$. Moreover S can be written $S = r_1 y_1 - r_2 y_2$ where $r_1, r_2 > 0$.*

Proof: We know from Parts (2) and (5) of Theorem 5.1 that K has at least one extremal in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$ and at least one in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$. Let $y_1 \in \mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$ and fix some $V \in \mathcal{Q}_0(-S^T)$ such that $V y_1 < 0$. Choose $\alpha > 0$ such that $\alpha y_1 + V y_1 S \in K$. Writing $\alpha y_1 + V y_1 S = \sum p_i y_i$ where $p_i \geq 0$ for all i, and solving gives

$$S = \frac{\sum p_i y_i - \alpha y_1}{V y_1} \equiv \sum r_i y_i$$

In other words, S has a representation $S = \sum_i r_i y_i$ where $r_i \leq 0$ for all $i \neq 1$. Now if we assume that K is simplicial, then this representation of S is unique.

If K has two extremals in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$, say y_1 and y_k, then this implies that the unique representation of S satisfies $r_i \leq 0$ for all $i \neq 1$, and $r_i \leq 0$ for all $i \neq k$, i.e. $r_i \leq 0$ for all i. In other words, $S \in -K$, contradicting our assumption that $S \notin K \cup -K$. So S cannot have two extremals in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$. A similar argument applied to $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$ tells us that K must have exactly one extremal (say y_2) in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$.

So the unique representation of S satisfies $r_i \leq 0$ for all $i \neq 1$, and $r_i \geq 0$ for all $i \neq 2$. This implies that $r_i = 0$ for $i \neq 1,2$. The fact that $S \in \mathcal{Q}_1(S)$ along with the stipulation that $S \notin K \cup -K$ further implies that $r_1 > 0$ and $r_2 < 0$. □

The restrictions in Theorem 5.5 only apply to simplicial cones. Later in Example 8.3 in Section 8 a nonsimplicial cone will be constructed satisfying $S \notin K \cup -K$ with two extremals in $\mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$, and two in $\mathcal{Q}_1(-S)\backslash\mathcal{Q}_1(S)$. Cones with nonempty interior in $\mathbb{R}^n$ fulfilling the conditions of Theorem 5.5 arise only in one situation:

Corollary 5.6: *Let $S \in \mathbb{R}^n$ be the stoichiometric vector of a reaction involving at least two substrates, K a simplicial proper cone with extremals $\{y_i\}$ preserved by the reaction, and $S \notin K \cup -K$. Then S has no more than two nonzero entries – i.e. the reaction involves exactly two substrates.*

Proof: By Theorem 5.5 K has exactly one extremal, say y_1 in $\mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$, one, say y_2, in $\mathcal{Q}_1(-S)\backslash\mathcal{Q}_1(S)$, and all others in $\mathcal{Q}_2(S)$. If S involves more than two substrates, then $\dim(\mathcal{Q}_2(S)) < n-2$. So $\dim(\text{span}(\{y_1, y_2\} \cup \mathcal{Q}_2(S))) < n$, and hence K cannot have nonempty interior in $\mathbb{R}^n$. □

We will see later in Section 7 that for a reaction system to behave like a monotone dynamical system, the requirement for the preserved cone to have nonempty interior in $\mathbb{R}^n$ is in general unnecessarily strong.

5.3. *Summary on cones preserved by a single reaction*

Consider a proper cone K with extremals $\{y_i\}$, and a reaction with stoichiometric vector S, and define the following possibilities:

A) There exists an index k, and $r \neq 0$ such that $S = ry_k$, and
- If $r > 0$, then $y_j \in \mathcal{Q}_1(-S)$ for all $j \neq k$.
- If $r < 0$, then $y_j \in \mathcal{Q}_1(S)$ for all $j \neq k$.

B) There exist indices i_1 and i_2 and $r_1, r_2 > 0$, such that $S = r_1 y_{i_1} - r_2 y_{i_2}$. Moreover, $y_{i_1} \in \mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$, $y_{i_2} \in \mathcal{Q}_1(-S)\backslash\mathcal{Q}_1(S)$ and $y_j \in \mathcal{Q}_2(S)$ for all $j \notin \{i_1, i_2\}$.

Some previous results can be conveniently summarised in the following corollary:

Corollary 5.7: *Consider S and K as above.*

(1) If S and K fulfil either condition A or B, then K is preserved by the system.
(2) If $S \in K \cup -K$ and K is preserved by the system then S and K must fulfil condition A.
(3) If $S \notin K \cup -K$, and K is a simplicial cone preserved by the system, then S and K must fulfil condition B.

Proof: Theorems 5.3 and 5.4 establish the first claim. Parts (2), (3) and (4) of Theorem 5.1 establish the second. Theorem 5.5 establishes the third. □

Incidentally none of the above results require the reactions to be true reactions. Only a few later corollaries require this stipulation.

The fact that single reactions necessarily give rise to monotone dynamical systems is not of great importance in itself, as we can use a variety of techniques to prove convergence of orbits for a single reaction. However, the main power of our results for a single reaction is that they allow us to make claims about monotonicity in systems of reactions which is the task of the next section.

6. Monotone systems of chemical reactions

In this section the results are extended to arbitrary systems of chemical reactions. Consider an NAC reaction system with n reactants and m reactions with Jacobian $SV-qI$. The first result is that the set of cones preserved by a system of reactions is precisely the intersection of the sets of cones preserved by the individual reactions (this intersection may of course be empty). This might at first appear surprisingly restrictive, but it arises because $V \in \mathcal{Q}_0(-S^T)$ is a weak assumption on the reaction kinetics.

Theorem 6.1 : *Consider a system of m reactions with S_j being the stoichiometric vector for the jth reaction, and $S = [S_1|S_2|\cdots|S_m]$. Let K be a cone with extremals $\{y_i\}$. Then the system preserves K iff each individual reaction preserves K.*

Proof : Assume K is preserved by each reaction. Let $J = SV$ where $V \in \mathcal{Q}_0(-S^T)$. Define $V^{(j)}$ to be the jth row of V, and $J^{(j)} = S_j V^{(j)}$ so that $J = \sum_{j=1}^m J^{(j)}$. For any fixed V there exist $\alpha_j \geq 0, j = 1, \ldots, m$ such that $J^{(j)} + \alpha_j I : K \mapsto K$. Choosing $\alpha = \sum_{j=1}^m \alpha_j$, we get $J + \alpha I = \sum_{j=1}^m (J^{(j)} + \alpha_j I) : K \mapsto K$.

Now assume K is preserved by the reaction system so that there exists $\alpha(V) \geq 0$ such that $J + \alpha(V)I : K \mapsto K$. Consider an arbitrary $z \in K$. Then:

$$Jz + \alpha(V)z = \sum_{j=1}^{m} J^{(j)}z + \alpha(V)z \in K \tag{8}$$

Choose $\overline{j} \in \{1, \ldots, m\}$ and set $V^{(j)} = 0$ for all $j \neq \overline{j}$, to get $J^{(j)}(V)z + \alpha(V)z \in K$ confirming that each reaction preserves K. □

By Theorem 5.2, adding a reaction to a system with stoichiometric vector parallel to some existing stoichiometric vector (e.g. writing a single reaction as two irreversible reactions) makes no difference to whether the system preserves a cone K or not. On the other hand, this is not generally true if we add a dependent reaction to the system – i.e. a reaction whose stoichiometric vector is a multiple of existing stoichiometric vectors – but which is not a linear multiple of any *one* other stoichiometric vector, as illustrated by a number of the examples in Section 8.

Theorem 6.1 implies:

Corollary 6.2: *Consider a system of reactions. Let K be a proper cone with extremals $\{y_j\}$. Then K is preserved by the system if each stoichiometric vector S_j fulfils either condition A or condition B in Section 5.3.*

Proof : Part (1) of Corollary 5.7 showed that each individual reaction preserves K provided that S and K fulfil either condition A or condition B. It then follows from Theorem 6.1 that the whole system preserves K. □

The condition that each individual reaction must fulfil either condition A or condition B becomes necessary when K is simplicial:

Corollary 6.3: *Consider a system of reactions each involving two or more substrates. Let K be a simplicial proper cone with extremals $\{y_j\}$. Then K is preserved by the system iff each stoichiometric vector S_j fulfils either condition A or condition B in Section 5.3.*

Proof : Sufficiency follows from Corollary 6.2. Parts (2) and (3) of Corollary 5.7 showed that if K was a simplicial preserved cone for a reaction then the stoichiometric vector of the reaction must fulfil either condition A or B. The result now follows from Theorem 6.1. □

The remaining corollaries in this section lead to important practical restrictions which simplify the process of deciding whether a cone is preserved or not.

Corollary 6.4: *Suppose there are two reactions with stoichiometric vectors S_1 and S_2, both involving substrates k_1 and k_2, so that $S_{1,k_1}, S_{2,k_1}, S_{1,k_2}, S_{2,k_2} \neq 0$. Suppose further that* $\text{sign}(S_{1,k_1}) = \text{sign}(S_{2,k_1})$ *and* $\text{sign}(S_{1,k_2}) \neq \text{sign}(S_{2,k_2})$. *Then any cone K preserved by both reactions satisfies $S_1 \notin K \cup -K$ and $S_2 \notin K \cup -K$.*

Proof: The assumptions imply that $S_1 \in \mathcal{Q}_3(S_2)$ and $S_2 \in \mathcal{Q}_3(S_1)$. The result now follows from Part (2) of Theorem 5.1. □

The next corollary places restrictions on applying constructions A and B simultaneously to find preserved simplicial cones for a reaction system.

Corollary 6.5: *Consider two reactions each involving at least two reactants and sharing at least one substrate, with stoichiometric vectors S_1 and S_2. Assume there is some simplicial cone K preserved by both reactions, and $S_1 \in K \cup -K$, but $S_2 \notin K \cup -K$. Then $S_2 \in \text{int}(\mathcal{Q}_1(S_1)) \cup \text{int}(\mathcal{Q}_1(-S_1))$.*

The meaning of $S_2 \in \text{int}(\mathcal{Q}_1(S_1)) \cup \text{int}(\mathcal{Q}_1(-S_1))$ is that reaction 2 involves all the substrates involved in reaction 1 (plus possibly more), and if two substrates occur on the same side of reaction 1 then they occur on the same side of reaction 2.

Proof: As usual, let $\{y_i\}$ be the extremals of K. Let $S_1 = q_1 y_1$, where $q_1 > 0$ (following the case with $q_1 < 0$ is similar), so that by Part (4) of Theorem 5.1, $y_k \in \mathcal{Q}_1(-S_1)$ for all $k \neq 1$. Since $S_2 \notin K \cup -K$, by Theorem 5.5, there is exactly one extremal vector in $\mathcal{Q}_1(S_2)\backslash\mathcal{Q}_1(-S_2)$, and one in $\mathcal{Q}_1(-S_2)\backslash\mathcal{Q}_1(S_2)$ with the remainder in $\mathcal{Q}_2(S_2)$. Since the reactions share a substrate, $y_1 \notin \mathcal{Q}_2(S_2)$, and so either $y_1 \in \mathcal{Q}_1(S_2)\backslash\mathcal{Q}_1(-S_2)$, or $y_1 \in \mathcal{Q}_1(-S_2)\backslash\mathcal{Q}_1(S_2)$. Assume that $y_1 \in \mathcal{Q}_1(S_2)\backslash\mathcal{Q}_1(-S_2)$. Labelling the unique vector in $\mathcal{Q}_1(-S_2)\backslash\mathcal{Q}_1(S_2)$ as y_2, we can then write $S_2 = r_1 S_1 - r_2 y_2$ for some $r_1, r_2 > 0$. Note that y_2 is also in $Q_1(-S_1)$, so by Lemma 3.1 $S_2 \in \text{int}(\mathcal{Q}_1(S_1))$. Assuming that $y_1 \in \mathcal{Q}_1(-S_2)\backslash\mathcal{Q}_1(S_2)$ leads similarly to $S_2 \in \text{int}(\mathcal{Q}_1(-S_1))$ proving the result. □

For brevity, we will refer to indecomposable reaction systems all involving at least two substrates, with at least one reaction involving three or more substrates as "non-interconversion" systems. The previous result leads to:

Corollary 6.6: *Consider any non-interconversion system preserving a simplicial proper cone K. All stoichiometric vectors lie on extremal lines of K.*

Proof: By Corollary 5.6, all reactions involving three or more substrates have stoichiometric vectors lying on extremal lines of K. Term this set of reactions R_0. Any reaction not in R_0 must involve exactly two substrates. By Corollary 6.5, any such reaction not in R_0 but sharing substrates with reactions from R_0 must have stoichiometric vectors lying on extremal lines of K. Term this set R_1. We can continue in this way to construct further sets of reactions R_2, R_3, etc, and all reactions in each such set must have stoichiometric vectors lying on extremal lines of K. Because the system is indecomposable, the process will only terminate when all reactions have been counted. □

The last result means that when constructing simplicial preserved cones for any non-interconversion system, we can ignore construction B in Section 5.3 and insist that each stoichiometric vector lies on an extremal line of the cone, and hence, by Part (4) of Theorem 5.1, that there is some signing of S such that $S_i \in \mathcal{Q}_1(-S_j)$ for every $i \neq j$. Next, a few more easy results, starting with a result on interconversions.

Corollary 6.7: *Any system of interconversions preserves $K = \mathbb{R}^n_+$ (the nonnegative orthant in $\mathbb{R}^n$).*

Proof: $K = \mathbb{R}^n_+$ is a proper cone with extremals e_i. By the definition of an interconversion, the stoichiometric vector of an interconversion can be written in the form $S = r_1 e_{i_1} - r_2 e_{i_2}$ with $r_1, r_2 > 0$. Further $e_{i_1} \in \mathcal{Q}_1(S)\backslash\mathcal{Q}_1(-S)$, $e_{i_2} \in \mathcal{Q}_1(-S)\backslash\mathcal{Q}_1(S)$ and $e_i \in \mathcal{Q}_2(S)$ for $i \notin \{i_1, i_2\}$. Thus when $K = \mathbb{R}^n_+$, each stoichiometric vector fulfils condition B. From Corollary 6.2 any interconversion system preserves $\mathbb{R}^n_+$. □

Systems of interconversions, subject to considerably weaker flow requirements than a CFSTR, were analysed in [16] where it was shown that if these systems have an equilibrium, then it is unique and globally attracting. Corollary 6.7 is included more for completeness than practical importance.

Corollary 6.8: *Suppose that a non-interconversion system has two reactions, each involving three or more substrates, with stoichiometric vectors S_1 and S_2, and*

(1) S_1 and S_2 are linearly independent,
(2) $S_2 \in \mathcal{Q}(S_1) \cup \mathcal{Q}(-S_1)$. (I.e. up to a choice of signing, the stoichiometric vectors lie in the same qualitative class.)

Then the system preserves no simplicial proper cones.

Proof: From Corollary 6.6 all stoichiometric vectors must lie on extremal lines of any preserved cone K. Since S_1 and S_2 are linearly independent, they do not lie on the same extremal line of K. By Part (4) of Theorem 5.1, K cannot have two extremals in $\mathcal{Q}_1(S_1)\backslash\mathcal{Q}_1(-S_1)$ or two extremals in $\mathcal{Q}_1(-S_1)\backslash\mathcal{Q}_1(S_1)$. So K must have exactly one extremal in each of these sets, with all others in $\mathcal{Q}_2(S_1)$. Since $\dim(\mathcal{Q}_2(S_1)) < n-2$, K cannot have nonempty interior in $\mathbb{R}^n$. □

Although by Corollary 6.8 systems with two reactions in the same qualitative class cannot be recoordinatised to make them cooperative, Example 8.10 in Section 8 will show that they can behave asymptotically as monotone systems.

Corollary 6.9: *Suppose that a non-interconversion system has two reactions with stoichiometric vectors S_1 and S_2, and that both reactions involve substrates k_1 and k_2, so that $S_{1,k_1}, S_{2,k_1}, S_{1,k_2}, S_{2,k_2} \neq 0$. Further suppose that $\operatorname{sign}(S_{1,k_1}) = \operatorname{sign}(S_{2,k_1})$, $\operatorname{sign}(S_{1,k_2}) \neq \operatorname{sign}(S_{2,k_2})$. Then the system preserves no simplicial proper cone K.*

Proof: From Corollary 6.6 all stoichiometric vectors must lie on extremal lines of K. However from Corollary 6.4, S_1 and S_2 cannot lie on extremal lines of K. □

Corollary 6.10: *Consider a reaction system with a substrate which figures in three reactions, which are pairwise independent. Then there is no preserved proper cone K such that all the stoichiometric vectors lie on extremal lines of K. If the system is a non-interconversion system, then it preserves no simplicial cones.*

Proof: Suppose the contrary. Since the reactions are pairwise independent, their stoichiometric vectors S_i lie on *distinct* extremal lines of K, and hence corresponding to each S_i is a unique extremal y_i of K. By Part (4) of Theorem 5.1, these $\{y_i\}$ must satisfy $y_i \in \mathcal{Q}_1(-y_j)$ for every $i \neq j$. It then follows that for some choice of signing the stoichiometric vectors must satisfy $S_i \in \mathcal{Q}_1(-S_j)$ for every $i \neq j$. Assume that the kth substrate is shared by three reactions, and consider the kth coordinate in each of the three corresponding stoichiometric vectors. Given any choice of signing, at least two of the three vectors must have a nonzero element of the same sign in the kth position, contradicting $S_i \in \mathcal{Q}_1(-S_j)$.

If the system is a non-interconversion system and K is a simplicial preserved cone, then by Corollary 6.6 all the stoichiometric vectors must lie on extremal lines of K, which has just been shown to be impossible. □

Similarly:

Corollary 6.11: *Consider a reaction system, which has, as some subset of the reactions, N reactions with stoichiometric vectors S_i that are*

(1) pairwise independent but
(2) linearly dependent (i.e. they span a subspace of dimension less than N).

Then there is no preserved proper cone K such that all the stoichiometric vectors lie on extremal lines of K. If the system is a non-interconversion system, then it preserves no simplicial cones.

Proof: Assume the contrary so that S_i, $i = 1, \ldots, N$ lie on extremal lines of K. Pairwise independence implies that they lie on *distinct* extremal lines, and hence corresponding to each S_i is a unique extremal y_i of K. By Part (4) of Theorem 5.1, these $\{y_i\}$ must satisfy $y_i \in \mathcal{Q}_1(-y_j)$ for every $i \neq j$. Moreover they are linearly dependent since the S_i are linearly dependent. But from lemma 4.3 this implies that K is not pointed.

If the system is a non-interconversion system and K is a simplicial preserved cone, then by Corollary 6.6 all the stoichiometric vectors must lie on extremal lines of K, which has just been shown to be impossible. □

It follows that a non-interconversion system with n reactants and $N \geq n$ pairwise independent *true* reactions preserves no simplicial cone K. This is because the stoichiometric subspace has dimension at most $n - 1$ and hence the $N \geq n$ stoichiometric vectors must be linearly dependent. Interconversion systems are not subject to this restriction.

7. Systems which are monotone when restricted to an invariant subspace

Our effort so far has been focussed on choosing proper cones preserved by dynamical systems on $\mathbb{R}^n_+$. However, as detailed in Section 2.1 all trajectories either remain on, or approach, cosets of the stoichiometric subspace. Thus from the point of view of asymptotic dynamics, our requirement that a reaction system must preserve a cone on all of phase space is unnecessarily strong. All we need to know is whether the dynamical system restricted to some (attracting or neutrally stable) invariant subspace is cone preserving. The majority of results can be restated and re-proved in this context without great difficulty. This task is carried out in Appendix A. Application of these generalisations are presented in Section 8.

7.1. *Reactions involving independent complexes in a CFSTR*

A particular case is where some reactants only participate in reactions in particular combinations – in other words where they only figure as part of complexes. In this case it is possible to make a rather strong and general claim.

Complexes can be identified with nonnegative vectors in $\mathbb{R}^n$, and a set of complexes $\{C_i\}$ are independent if no two of them have a positive entry in the same place, or more succinctly, $C_i \in \mathcal{Q}_2(C_j)$ for every i and j. The main result, proved in Appendix B, is that the system contains one (when $q > 0$) or many (when $q = 0$) invariant subspaces with the following property: As long as the original system is

an NAC reaction system, then the system restricted to these invariant subspaces behaves formally as an NAC reaction system, so that any results on NAC reaction systems can be applied. Moreover this restricted system is exactly the system we would get *if we treated each complex as an individual reactant*. For example, the reaction system

$$A \rightleftharpoons B + C, \quad B + C \rightleftharpoons D$$

embedded in a CFSTR (possibly with zero flow rate) asymptotically has the same dynamics as the system

$$A \rightleftharpoons B, \quad B \rightleftharpoons D.$$

The result has wider application than simply deciding whether a system is asymptotically monotone: Any results on NAC reaction systems (including for example the results in [14] on injectivity) can be applied to the new system.

8. Examples

8.1. *The reaction* $A + B \rightleftharpoons C$

This reaction has stoichiometric vector $S = [1, 1, -1]^T$, and $\mathcal{Q}_2(S) = 0$. We know from Section 5 that a single reaction preserves many proper cones K for which $S \in K \cup -K$. However the reaction also preserves a proper cone K such that $S \notin K \cup -K$ (which by Corollary 5.6 must necessary be nonsimplicial). Given a vector $x = [x_1, x_2, x_3]^T \in \mathbb{R}^3$ we can define K via: $x \in K$ iff

$$x_3 \leq 0, \quad x_1 + x_3 \leq 0, \quad x_2 + x_3 \leq 0, \quad x_1 + x_2 + x_3 \leq 0.$$

K is pointed and has nonempty interior, and has four extremals

$$y_1 = \begin{bmatrix} 1 \\ 0 \\ -1 \end{bmatrix}, \quad y_2 = \begin{bmatrix} 0 \\ -1 \\ 0 \end{bmatrix}, \quad y_3 = \begin{bmatrix} 0 \\ 1 \\ -1 \end{bmatrix}, \quad y_4 = \begin{bmatrix} -1 \\ 0 \\ 0 \end{bmatrix}.$$

Note that $y_1, y_3 \in \mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$ and $y_2, y_4 \in \mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$. K has four 2D faces F_{12}, F_{24}, F_{34}, F_{13} defined by the pairs of extremals (y_1, y_2), (y_2, y_4), (y_3, y_4) and (y_1, y_3) respectively. F_{12} and F_{34} intersect $\mathcal{Q}_3(S)$, and $S \in \text{span}(F_{12})$, $S \in \text{span}(F_{34})$, fulfilling the necessary condition in Part (1) of Theorem 5.1. Defining $V = [-a, -b, c]$ with $a, b, c \geq 0$, and $\alpha = a + b + c$, it is a simple task to check (for example using the computer algebra package Maxima [21]) that for each extremal y_i, the vector $(SV + \alpha I)y_i$ lies in K.

8.2. *The system* $A + B \rightleftharpoons C, \quad 2B \rightleftharpoons C$

There are two possible signings of the stoichiometric matrix

$$S = \begin{bmatrix} 1 & 0 \\ 1 & 2 \\ -1 & -1 \end{bmatrix} \quad \text{and} \quad S = \begin{bmatrix} 1 & 0 \\ 1 & -2 \\ -1 & 1 \end{bmatrix}$$

Define $S_1 = [1, 1, -1]^T$ and $S_2 = [0, -2, 1]^T$. From Part (1) of Theorem 5.1 this reaction system does not preserve the cone K defined in the previous example, because F_{12} intersects $\mathcal{Q}_3(S_2)$, but $S_2 \notin \text{span}(F_{12})$. However $S_1 \in \mathcal{Q}_1(-S_2)$, and we can choose a third vector – $[1, 0, 0]^T \in \mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(-S_2)$ which together with S_1 and S_2 spans $\mathbb{R}^3$. So the system preserves the simplicial cone generated by extremals $[-1, -1, 1]^T, [0, 2, -1]^T$ and $[1, 0, 0]^T$, which can be used as the basis of a coordinate transformation making the system cooperative.

8.3. *The system* $A + B \rightleftharpoons C$, $A \rightleftharpoons B$

There are two possible signings of the stoichiometric matrix

$$S = \begin{bmatrix} 1 & 1 \\ 1 & -1 \\ -1 & 0 \end{bmatrix} \quad \text{and} \quad S = \begin{bmatrix} 1 & -1 \\ 1 & 1 \\ -1 & 0 \end{bmatrix}$$

By Lemma 6.9, there are no coordinate transformations which will make the system cooperative. The next task is to check if there is any $\mathcal{S}$-proper cone K preserved by the system restricted to invariant cosets of $\mathcal{S}$, the stoichiometric subspace. Note that $\mathcal{S}$ is two dimensional (orthogonal to the vector $[1, 1, 2]^T$). Consider an $\mathcal{S}$-proper cone K with extremals in $\mathcal{S}$ preserved by the restricted system. K must be 2D and hence $\mathcal{S}$-simplicial. Term the extremals of K y_1 and y_2. By Corollary A.10 S_1 and S_2 must lie outside $K \cup -K$. It is easy to see that $\dim(\mathcal{Q}_2(S_1) \cap \mathcal{S}) = 0 = \dim(\mathcal{S}) - 2$, and $\dim(\mathcal{Q}_2(S_2) \cap \mathcal{S}) = 0 = \dim(\mathcal{S}) - 2$, fulfilling the conditions of Part (5) of Theorem A.2. So, by parts (2) and (5) of Theorem A.2, there are (up to a renaming of y_1 and y_2) two possibilities: $y_1 \in \mathcal{Q}_1(S_1) \cap \mathcal{Q}_1(S_2)$ and $y_2 \in \mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(-S_2)$; or $y_1 \in \mathcal{Q}_1(S_1) \cap \mathcal{Q}_1(-S_2)$ and $y_2 \in \mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(S_2)$. Examining the forms of these intersections it is easy to see that two such vectors cannot span $\mathcal{S}$. Thus there is no $\mathcal{S}$-proper cone K preserved by the system restricted to cosets of $\mathcal{S}$.

Finally, consider the nonsimplicial cone K defined in Example 8.1. With $S_2 = [1, -1, 0]^T$, and the extremals y_i and the faces F_{ij} defined as in Example 8.1, we have $y_1, y_2 \in \mathcal{Q}_1(S_2)$, $y_3, y_4 \in \mathcal{Q}_1(-S_2)$, $S_2 \in \text{span}(F_{13})$, and $S_2 \in \text{span}(F_{24})$. Indeed the second reaction preserves K (as can be checked by hand or using Maxima [21]). Since we have already seen in Example 8.1 that the first reaction preserves K, the reaction system as a whole preserves K. Thus this provides an interesting example of a system which preserves no simplicial cones, *not even when restricted to invariant subspaces*, but nevertheless preserves a nonsimplicial cone.

8.4. *The system* $A \rightleftharpoons B$, $B \rightleftharpoons C$

The system has stoichiometric matrix

$$S = \begin{bmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{bmatrix}$$

Clearly $S_1 \in \mathcal{Q}_1(-S_2)$ and $S_2 \in \mathcal{Q}_2(-S_1)$. Further a vector $[1, 0, 0]^T$, or $[0, 0, -1]^T$ can be chosen as a third independent vector (along with S_1 and S_2) to generate a simplicial cone preserved by the reaction system. Since this system is an interconversion system, by Corollary 6.7 it also preserves $\mathbb{R}^3_+$.

8.5. *The system* $A \rightleftharpoons B$, $B \rightleftharpoons C$ $C \rightleftharpoons A$

The system has stoichiometric matrix

$$S = \begin{bmatrix} -1 & 0 & 0 \\ 1 & -1 & -1 \\ 0 & 1 & 1 \end{bmatrix}$$

for example. Here, regardless of any choice of signing, there are three stoichiometric vectors, pairwise linearly independent, which only span a two dimensional subspace $\mathcal{S}$ of $\mathbb{R}^3$. So, by Corollary 6.11, all three cannot lie on extremal lines of a preserved cone K. However, again, by Corollary 6.7 the system preserves $\mathbb{R}^3_+$.

It is interesting that the system restricted to cosets of $\mathcal{S}$ does not preserve any $\mathcal{S}$-proper cones. $\mathcal{S}$ consists of vectors orthogonal to $[1,1,1]^T$ and from this it follows that $\dim(\mathcal{Q}_2(S_i) \cap \mathcal{S}) = 0 = \dim(\mathcal{S}) - 2$ for $i = 1,2,3$, and so the conditions of Theorem A.3 are fulfilled for each reaction. Since any cone K on $\mathcal{S}$ is simplicial with two extremals – say y_1 and y_2 – this means for each i that if $y_1 \in \mathcal{Q}_1(S_i)\backslash\mathcal{Q}_1(-S_i)$, then $y_2 \in \mathcal{Q}_1(-S_i)\backslash\mathcal{Q}_1(S_i)$ and vice versa. Examining the possibilities reveals that there must be some $j \in \{1,2,3\}$ such that $y_{1,j} = y_{2,j} = 0$. Clearly such a pair of extremals does not span $\mathcal{S}$.

8.6. *The system* $A + B \rightleftharpoons 2C$, $A \rightleftharpoons C$, $B \rightleftharpoons C$

The system has stoichiometric matrix

$$S = \begin{bmatrix} -1 & -1 & 0 \\ -1 & 0 & -1 \\ 2 & 1 & 1 \end{bmatrix}$$

Without even writing down the stoichiometric matrix, we can see that reactant C participates in three pairwise independent reactions. Hence, by Corollary 6.10, there exists no recoordinatisation making the system cooperative. However, the system restricted to cosets of $\mathcal{S}$ does preserve an $\mathcal{S}$-proper cone. Consider the two vectors $y_1 = [1,0,-1]^T$ and $y_2 = [0,-1,1]^T$, spanning $\mathcal{S}$. $y_1 \in \mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(-S_2) \cap \mathcal{Q}_1(-S_3)$, while $y_2 \in \mathcal{Q}_1(S_1) \cap \mathcal{Q}_1(S_2) \cap \mathcal{Q}_1(S_3)$. Moreover $S_1 = y_2 - y_1$, $S_2 = -y_1$, and $S_3 = y_2$. Thus each stoichiometric vector fulfils either condition A or condition B in Section 5.3, and so, by Theorem A.6, the cone is preserved by the restricted system.

8.7. *The system* $A + B \rightleftharpoons C$, $A \rightleftharpoons B$, $2A \rightleftharpoons C$

The system has stoichiometric matrix

$$S = \begin{bmatrix} -1 & -1 & -2 \\ -1 & 1 & 0 \\ 1 & 0 & 1 \end{bmatrix}$$

This system shares two reactions and the same stoichiometric subspace $\mathcal{S}$ with the system in Example 8.3, and so, as in that example, it preserves no simplicial cones in $\mathbb{R}^3$ and no cones on $\mathcal{S}$. We can also check that the third reaction with stoichiometric vector $S_3 = [-2,0,1]^T$ does not preserve the nonsimplicial cone defined in Example 8.1. This follows from Part (1) of Theorem 5.1 because the face

F_{34} intersects $\mathcal{Q}_3(S_3)$, but $S_3 \notin \text{span}(F_{34})$. Whether the reaction system preserves any other nonsimplicial cones is an open question.

8.8. *The system* $A \rightleftharpoons B + C$, $2B + C \rightleftharpoons D$

Defining $S_1 = [-1, 1, 1, 0]^T$ and $S_2 = [0, -2, -1, 1]^T$, we see that $S_1 \in \mathcal{Q}_1(-S_2)$. Here $\mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(-S_2)$ consists of vectors of the form $[a, 0, 0, -b]$ where $a, b \geq 0$. The vectors $y_1 \equiv [1, 0, 0, 0]^T$ and $y_2 \equiv [0, 0, 0, -1]$ provide two further vectors in $\mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(-S_2)$, such that S_1, S_2, y_1 and y_2 spans $\mathbb{R}^4$, and the system can be recoordinatised to make it cooperative.

Now consider the apparently similar reaction system $A \rightleftharpoons B + C$, $B + C \rightleftharpoons D$ with $S_1 = [-1, 1, 1, 0]^T$ and $S_2 = [0, -1, -1, 1]^T$. Again $S_1 \in \mathcal{Q}_1(-S_2)$, and $\mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(-S_2)$ consists of vectors of the form $[a, 0, 0, -b]$ where $a, b \geq 0$. However it is now impossible to choose two further vectors y_1 and y_2 in $\mathcal{Q}_1(-S_1) \cap \mathcal{Q}_1(-S_2)$ such that the set $\{S_1, S_2, y_1, y_2\}$ spans $\mathbb{R}^4$. Thus this system cannot be recoordinatised to make it cooperative.

This fact appears to contradict results in [4], but this is not the case. By the results in Section 7.1 and Appendix B when considering dynamics restricted to an invariant subspace, we can treat an equivalent system of the form

$$A \rightleftharpoons X, \quad X \rightleftharpoons D$$

which preserves a number of cones as shown in Example 8.4. Thus the system restricted to invariant subspaces is indeed monotone.

8.9. *Any set of interconversions between complexes*

As a generalisation of the previous example, and following [4], consider any set of m independent complexes $\{C_i\}$, and any set of interconversions between the complexes of the form

$$C_i \rightleftharpoons C_j \tag{9}$$

These interconversions need not form a chain. Assume that the reactions are embedded in a CFSTR with possibly zero flow rate. By the results in Section 7.1 when considering asymptotic dynamics, we can treat the equivalent system

$$A_i \rightleftharpoons A_j \tag{10}$$

where each A_i is a substrate. This system is simply an interconversion system and hence by Corollary 6.7 preserves $\mathbb{R}^m_+$.

This example also provides a partial answer to questions left open in [16] on interconversion networks involving complexes. From results in Appendix B, in a CFSTR with nonzero outflow rate, any system involving complexes has an invariant subspace $\mathcal{C}$ attracting all trajectories, such that the system restricted to $\mathcal{C}$ is formally an NAC reaction system. When the outflow rate is zero there is a whole family of such subspaces, all neutrally stable. In either case, on any such subspace the complex-interconversion system in (9) reduces formally to the substrate-interconversion system in (10). Injectivity and global convergence results in [14] and [16] can be applied, so each invariant subspace contains a unique equilibrium, and all trajectories *on the subspace* converge to this unique equilibrium. When

$q > 0$ the invariant subspace is itself unique and asymptotically attracting, so in fact the equilibrium is unique and all trajectories converge to it.

The complete generalisation of results in [16] would involve the generalisation of the discussion in Section 7.1 beyond the case of a CFSTR, an easy task for future work.

8.10. *The system* $A + B \rightleftharpoons 2C$, $2A + B \rightleftharpoons 3C$

Let $S_1 = [-1, -1, 2]^T$ and $S_2 = [-2, -1, 3]^T$. Since $\mathcal{Q}(S_1) = \mathcal{Q}(S_2)$. By Corollary 6.8 there is no simplicial cone with nonempty interior in $\mathbb{R}^3$ preserved by the system. Let the stoichiometric subspace be $\mathcal{S}$. Certainly $y_1 = S_1$ and $y_2 = -S_2$ generate an $\mathcal{S}$-proper cone, satisfying the conditions in Theorem 5.3, and hence preserved by the system, so the system restricted to invariant cosets of $\mathcal{S}$ is monotone.

Preserved cones can also be constructed in other ways: For example, $y_1 = S_1$ and $y_2 = S_1 - S_2 \in \mathcal{Q}_1(-S_1)$ together generate an $\mathcal{S}$-proper preserved cone K such that $S_1 \in K \cup -K$ while $S_2 \notin K \cup -K$. Of course $S_2 \in \text{int}(\mathcal{Q}_1(S_1)) \cup \text{int}(\mathcal{Q}_1(-S_1))$ as required by Corollary A.9. The same techniques could be used for any pair of reactions with stoichiometric vectors in the same qualitative class.

8.11. *The system* $2A \rightleftharpoons B + C$, $2B \rightleftharpoons A + C$, $2C \rightleftharpoons A + B$

The system has stoichiometric matrix

$$S = \begin{bmatrix} -2 & 1 & 1 \\ 1 & -2 & 1 \\ 1 & 1 & -2 \end{bmatrix}$$

The stoichiometric subspace $\mathcal{S}$ is orthogonal to $[1, 1, 1]^T$ and so we can regard this as a system of true reactions. Let K be a proper cone preserved by the system. By Part (2) of Theorem 5.1, every extremal of K must lie in some intersection of the form

$$\mathcal{Q}_1(\pm S_1) \cap \mathcal{Q}_1(\pm S_2) \cap \mathcal{Q}_1(\pm S_3).$$

A quick check reveals that these intersections are all contained within the coordinate axes. Since all extremals of K must lie on the coordinate axes, K can have no more than three extremals – i.e. K must be simplicial. But by Lemma 6.9, there is no simplicial cone K with nonempty interior in $\mathbb{R}^3$ preserved by the system. So there are no proper cones preserved by the system – simplicial or otherwise.

We can also show that there are no $\mathcal{S}$-proper cones preserved by the system restricted to cosets of $\mathcal{S}$, for if K is such a cone, then by Part (2) of theorem A.2, all extremals of K must lie on the coordinate axes. But no two vectors on the coordinate axes can span $\mathcal{S}$. This example illustrates that it is possible for a system with a 2D stoichiometric subspace to preserve no cones.

9. Conclusions

We have characterised the set of cones preserved by an NAC reaction system, possibly embedded in a CFSTR. The characterisation of simplicial preserved cones – i.e. the identification of reaction systems which can be made cooperative by

a linear change of coordinates – is complete. Necessary and sufficient conditions have been placed on general preserved cones. The subject of reaction systems with invariant affine subspaces has also been tackled.

The examples presented are sometimes surprising, and have illustrated that it is possible for reaction systems to:

(1) Preserve simplicial cones when restricted to invariant subspaces, but no simplicial cones on all of $\mathbb{R}^n$ (Examples 8.6 and 8.8);
(2) Preserve cones on all of $\mathbb{R}^n$ but no cones when restricted to invariant subspaces (Examples 8.3 and 8.5);
(3) Preserve nonsimplicial cones, but no simplicial cones either on all of $\mathbb{R}^n$ or on some invariant subspace (Example 8.3);
(4) Preserve no cones (Example 8.11).

There are also examples (e.g. Example 8.7) where large classes of cones can be ruled out by our techniques, but we cannot definitively state that the system preserves no cones. Such examples clearly point the way for one strand of future work – to complete the process of drawing conclusions from the necessary and sufficient conditions in Section 5. In particular a more complete study of the geometrical implications of Condition 7 and its corollaries (particularly Part (1) of Theorem 5.1) is required, examining the possible ways in which a cone can lie in phase space while fulfilling these conditions.

There are also several other open questions, and tasks for future work. Are there simple characterisations of the set of nonsimplicial cones preserved by a single reaction? We have seen that a system of two reactions may preserve no simplicial cones and no cones when restricted to the stoichiometric subspace; We have also seen that a system of three reactions with a 2D stoichiometric subspace may preserve no cones; But are systems of two true reactions always cone preserving?

Importantly, the dynamical implications of monotonicity have not been explored. Going from monotonicity to convergence of orbits generally requires additional assumptions (the dynamical system needs to be strongly monotone or strongly order preserving, [1, 2]). Examining the conditions for K-irreducibility of the Jacobians, and hence for strong monotonicity, in [9] and applying them in the context of NAC systems would be a useful way forward.

In this paper only static cones have been explored. However in [8] an expanding cone is used in one chemical reaction example. An important is question is to what extent the class of order-preserving reaction systems grows if we allow expanding cones.

In [14] injectivity was discussed both for general NAC systems and for the more restricted class of mass action systems, for which weaker conditions were required for injectivity. It is an open question whether a similar weakening of the conditions on preserved cones – and hence an enlargement of this set – takes place when the kinetics are assumed to be mass action.

An important practical observation is that in various contexts – particularly biological contexts – the assumptions of a CFSTR are too strong. Instead quantities may have different outflow rates, and there may be some quantities subject to no inflow and outflow at all. The theory developed in this paper could be applied by treating each outflow process as a separate reaction. There is room for systematic study in this direction.

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Appendix A. Systems restricted to invariant subspaces

In this appendix we restate and where necessary reprove several results when we are interested in the dynamics restricted to an invariant subspace rather than the whole of $\mathbb{R}^n$. Throughout this section we will assume that $\mathcal{V} \subset \mathbb{R}^n$ is a linear subspace of $\mathbb{R}^n$ containing the stoichiometric subspace $\mathcal{S}$ and hence with some coset(s) invariant under the dynamics. The "restricted system" will mean the system restricted to any invariant coset of $\mathcal{V}$. The terms $\mathcal{V}$-proper and $\mathcal{V}$-simplicial were defined in Section 4.

The preliminary lemmas in Sections 3 and 4 are mostly independent of whether K has nonempty interior in $\mathbb{R}^n$ or only in some subspace of $\mathbb{R}^n$. Only results which depended fundamentally on the dimensionality of certain sets need reworking. In particular certain results required a reaction to involve two or more substrates (i.e. $\dim(\mathcal{Q}_2(S)) \leq n-2$) so that at least two vectors from any set spanning $\mathbb{R}^n$ lay outside $\mathcal{Q}_2(S)$. The appropriate generalisation of this condition is that $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$. If $\dim(\mathcal{Q}_2(S)) \leq n-2$, and $\mathcal{Q}_2(S)$ and $\mathcal{V}$ are in general position then $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$; But it is possible to construct examples where $\dim(\mathcal{Q}_2(S)) \leq n-2$, but $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) > \dim(\mathcal{V}) - 2$. For example the two stoichiometric vectors $S_1 = [1,-1,0,0]^T, S_2 = [1,-1,1,-1]^T$ together define a stoichiometric subspace $\mathcal{S}$ which is not in general position with $\mathcal{Q}_2(S_1)$, and $\dim(\mathcal{Q}_2(S_1) \cap \mathcal{S}) = 1 = \dim(\mathcal{S}) - 1$.

We start with the generalisation of Lemma 3.10.

Lemma A.1: *Consider a subspace $\mathcal{V} \subset \mathbb{R}^n$, a nonzero vector $y \in \mathbb{R}^n$, some vector $\overline{y} \in \mathcal{V}$, and a set of vectors $\{y_i\} \subset \mathcal{V}$ spanning $\mathcal{V}$. If $\dim(\mathcal{Q}_2(y) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$, then there exists a vector $y_k \in \{y_i\}$ such that $y_k + \alpha\overline{y} \notin \mathcal{Q}_2(y)$ for any scalar α.*

Proof: From Lemma 3.9, replacing $\mathcal{X}$ with $\mathcal{V}$, and $\mathcal{Y}$ with $\mathcal{V} \cap \mathcal{Q}_2(S)$ we find the existence of $y_k \in \{y_i\}$ such that $y_k + \alpha\overline{y} \notin \mathcal{V} \cap \mathcal{Q}_2(y)$ for any scalar α. Since $\overline{y} \in \mathcal{V}$, $y_k + \alpha\overline{y} \in \mathcal{V}$ for every α, so this implies that $y_k + \alpha\overline{y} \notin \mathcal{Q}_2(y)$ for any α. □

With this preliminary, we can restate parts 1 to 5 of Theorem 5.1. The first four parts are identical to the original statements, and the proofs require no modification – indeed the statements are only included for completeness. When it comes to proving that $K \not\subset \mathcal{Q}_1(-S)$ we require a slight modification of the assumptions and proof in Theorem 5.1.

Theorem A.2: *Let $S \in \mathbb{R}^n$ be the stoichiometric vector of a reaction and K a $\mathcal{V}$-proper cone with extremals $\{y_i\} \subset \mathcal{V}$ preserved by the restricted system. Then*

(1) If F is a face of K intersecting $\mathcal{Q}_3(S)$, then $S \in \text{span}(F)$.
(2) $\{y_i\} \subset \mathcal{Q}_1(S) \cup \mathcal{Q}_1(-S)$.
(3) Hence, if $S \in K \cup -K$, then S lies on an extremal line of K.
(4) If $S \in K$, then exactly one member of $\{y_i\}$ lies in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$. Similarly if $S \in -K$, then exactly one member of $\{y_i\}$ lies in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$.
(5) If $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$, then $K \not\subset \mathcal{Q}_1(S)$, and $K \not\subset \mathcal{Q}_1(-S)$.

Proof: The preliminaries are identical to those in the proof of Theorem 5.1. We are again led to Conditions 6 and 7. The proofs of parts 1. to 4. are identical to those in Theorem 5.1.

Proof of statement 5. We prove the claim by contradiction. Since $\mathcal{Q}_1(S)$ is convex, all of K lies in $\mathcal{Q}_1(S)$ iff all its extremals lie in $\mathcal{Q}_1(S)$. Assume $K \subset \mathcal{Q}_1(S)$. Since $\{y_i\}$ spans $\mathcal{V}$, $S \in \mathcal{V}$, and $\dim(\mathcal{Q}_2(y) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$, by Lemma A.1 we can choose some extremal $y_k \in \mathcal{Q}_1(S)$ such that $y_k + \delta S \notin \mathcal{Q}_2(S)$ for any scalar δ. Define

$$\delta_0 = \sup\{\delta : y_k - \delta S \in K\}.$$

δ_0 exists because K is closed and by Lemma 3.2, for large enough $\delta > 0$, $y_k - \delta S \in \text{int}(\mathcal{Q}_1(-S))$. The vector $w \equiv y_k - \delta_0 S$ lies on the boundary of K, and also $w \in \mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$. By the definition of w, $w - \delta S \notin K$ for any $\delta > 0$, and consequently $\alpha w - \delta S \notin K$ for any $\alpha > 0$ and any $\delta > 0$. Since $w \in \mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$, there exists $V \in \mathcal{Q}_0(-S^T)$ such that $Vw < 0$. But from Condition 6 there exists α (which can be chosen positive) such that $\alpha w + (Vw)S \in K$, contradicting the statement that $\alpha w - \delta S \notin K$ for any $\alpha > 0$ and any $\delta > 0$. Whenever K is preserved, so is $-K$, so we can apply the same argument to claim that $K \not\subset \mathcal{Q}_1(-S)$. □

Theorem 5.2 states that any cone preserved by a reaction with stoichiometric vector S is also preserved by a reaction with stoichiometric vector $S' = rS$ where r is any nonzero scalar. The theorem nowhere requires K to have nonempty interior in $\mathbb{R}^n$, and so the result is immediately applicable to cones preserved by the restricted system. Theorems 5.3 and 5.4 which provide sufficient conditions for a cone to be preserved also nowhere require the cone to have nonempty interior in $\mathbb{R}^n$. Theorem 5.5 becomes:

Theorem A.3: *Let $S \in \mathbb{R}^n$ be the stoichiometric vector of a reaction and K a $\mathcal{V}$-simplicial cone with extremals $\{y_i\}$. Assume that the restricted system preserves K, and $S \notin K \cup -K$. Assume also that* $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$. *Then K has exactly one extremal in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$, one in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$, and all others in $\mathcal{Q}_2(S)$.*

Proof: First note that $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$ implies that $\dim(\mathcal{V}) \geq 2$, and so K must have at least two extremals. Then, from Parts (2) and (5) of Theorem A.2, K must have at least one extremal in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$ and at least one in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$. Let $y_k \in \mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$ and fix some $V \in \mathcal{Q}_0(-S^T)$ such that $Vy_k < 0$. Choose $\alpha > 0$ such that $\alpha y_k + (Vy_k)S \in K$. Writing $\alpha y_k + (Vy_k)S = \sum p_i y_i$ where $p_i \geq 0$ for all i, and solving for S gives that S has a representation $S = \sum_i r_i y_i$ where $r_i \leq 0$ for all $i \neq k$. Now since K has exactly $\dim(\mathcal{V})$ extremals spanning $\mathcal{V}$, this representation of S is unique. The argument from here on is identical to that in the proof of Theorem 5.5. □

Corollary 5.6 followed from Theorem 5.5 and stated that if S had two or more nonzero entries, and K was a simplicial preserved cone with $S \notin K \cup -K$ then S must have exactly two nonzero entries (i.e. $\dim(\mathcal{Q}_2(S)) = n - 2$). This condition generalises as follows:

Corollary A.4: *Let $S \in \mathbb{R}^n$ be the stoichiometric vector of a reaction, and K a $\mathcal{V}$-simplicial cone preserved by the restricted system with extremals $\{y_i\}$, such that $S \notin K \cup -K$. Assume that* $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$. *Then* $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) = \dim(\mathcal{V}) - 2$.

Proof: By Theorem A.3 K has exactly one extremal, say y_1 in $\mathcal{Q}_1(S) \backslash \mathcal{Q}_1(-S)$, one, say y_2, in $\mathcal{Q}_1(-S) \backslash \mathcal{Q}_1(S)$, and all others in $\mathcal{Q}_2(S)$. If $\dim(\mathcal{Q}_2(S) \cap \mathcal{V}) < \dim(\mathcal{V}) - 2$, then $\dim(\text{span}(\{y_1, y_2\} \cup (\mathcal{Q}_2(S) \cap \mathcal{V}))) < \dim(\mathcal{V})$, and hence K cannot have nonempty interior in $\mathcal{V}$. □

In practice, the condition $\dim(\mathcal{Q}_2(S)\cap\mathcal{V}) = \dim(\mathcal{V})-2$ is quite different from the condition that a reaction involves exactly two substrates, as illustrated by several of the examples. Corollary 5.7 involving conditions A and B in Section 5.3 becomes:

Corollary A.5: *Consider a reaction with stoichiometric vector S and some $\mathcal{V}$-proper cone K.*

(1) If S and K fulfil either condition A or B, then K is preserved by the restricted system.
(2) If $S \in K \cup -K$ and K is preserved by the restricted system then S and K must fulfil condition A.
(3) If $S \notin K \cup -K$, and K is a $\mathcal{V}$-simplicial cone preserved by the restricted system, then S and K must fulfil condition B.

Proof: Theorems 5.3 and 5.4 establish the first claim. Parts (2), (3) and (4) of Theorem A.2 establish the second. Theorem A.3 establishes the third. □

Theorem 6.1 tells us that a cone is preserved by a reaction system if and only if it is preserved by each reaction in the system. The proof nowhere requires K to have nonempty interior in $\mathbb{R}^n$. Corollaries 6.2 and 6.3 generalise easily.

Corollary A.6: *Consider a system of reactions. Let K be a $\mathcal{V}$-proper cone with extremals $\{y_j\}$. Then K is preserved by the restricted system if each stoichiometric vector S_j satisfies either condition A or condition B in Section 5.3.*

Proof: Part (1) of Corollary A.5 showed that each individual reaction (restricted to cosets of $\mathcal{V}$) preserves K provided that S and K fulfil either condition A or condition B. □

It immediately follows that:

Corollary A.7: *Consider a system of reactions with stoichiometric subspace $\mathcal{S}$ containing stoichiometric vectors S_i which can be signed such that for each i, j, either*

- *S_i and S_j are collinear, or*
- *S_i and S_j are not collinear, but $S_i \in \mathcal{Q}_1(-S_j)$*

Assume further that every subset of $\{S_i\}$ either

- *contains a collinear pair of vectors, or*
- *is linearly independent*

Then there is an $\mathcal{S}$-simplicial cone K preserved by the restricted system with the stoichiometric vectors lying on extremals of K.

Proof: We can write $S_i \sim S_j$ if S_i and S_j are collinear and confirm that this is an equivalence relation. If the relation partitions $\{S_i\}$ into m equivalence classes, then by the assumptions of the theorem $\dim(\mathcal{S}) = m$. We can now choose one vector from each equivalence class to generate an extremal of a cone K. K is pointed by Lemma 4.1 and it is $\mathcal{S}$-simplicial since it has exactly m linearly independent extremals in $\mathcal{S}$. Each stoichiometric vector satisfies condition A in Section 5.3, and so, by Corollary A.6, K is preserved by the restricted system. □

Corollary 6.3 becomes

Corollary A.8: *Consider a system of reactions with stoichiometric vectors S_j. Let K be a $\mathcal{V}$-simplicial cone with extremals $\{y_j\}$. Then K is preserved by the restricted system iff each stoichiometric vector S_j satisfies either condition A or condition B in Section 5.3.*

Proof: Sufficiency follows from Corollary A.6. Parts (2) and (3) of Corollary A.5 showed that if K was a $\mathcal{V}$-simplicial preserved cone for a reaction then the stoichiometric vector of the reaction must fulfil either condition A or B. □

Corollary 6.5 restricted the simultaneous application of conditions A and B when constructing simplicial cones. Its generalisation to $\mathcal{V}$-simplicial cones is:

Corollary A.9: *Consider two reactions sharing at least one substrate, with stoichiometric vectors S_1 and S_2. Assume there is some $\mathcal{V}$-simplicial cone K preserved by both reactions, and that $S_1 \in K$, but $S_2 \notin K \cup -K$. Assume that* $\dim(\mathcal{Q}_2(S_2) \cap \mathcal{V}) \leq \dim(\mathcal{V}) - 2$. *Then* $S_2 \in \mathrm{int}(\mathcal{Q}_1(S_1)) \cup \mathrm{int}(\mathcal{Q}_1(-S_1))$.

Proof: The proof follows from Part (4) of Theorem A.2 and Theorem A.3 and is formally identical to that of Theorem 6.5. □

Corollary 6.4 generalises without change:

Corollary A.10: *Suppose there are two reactions with stoichiometric vectors S_1 and S_2, both involving substrates k_1 and k_2, so that $S_{1,k_1}, S_{2,k_1}, S_{1,k_2}, S_{2,k_2} \neq 0$. Suppose further that* $\mathrm{sign}(S_{1,k_1}) = \mathrm{sign}(S_{2,k_1})$, $\mathrm{sign}(S_{1,k_2}) \neq \mathrm{sign}(S_{2,k_2})$. *Then $S_1, S_2 \notin K \cup -K$ for any $\mathcal{V}$-proper cone K preserved by the restricted system.*

Proof: The assumptions imply that $S_1 \in \mathcal{Q}_3(S_2)$ and $S_2 \in \mathcal{Q}_3(S_1)$. The lemma now follows from Part (2) of Theorem A.2. □

Similarly Corollary 6.11 generalises to:

Corollary A.11: *Consider a reaction system, which has, as some subset of the reactions, N reactions with stoichiometric vectors S_i that are*

(1) pairwise independent but
(2) linearly dependent (i.e. they span a subspace of dimension less than N).

Then there is no $\mathcal{V}$-proper cone K preserved by the restricted system such that all the stoichiometric vectors lie on extremal lines of K.

Proof: Assume the contrary, so that, by pairwise independence, all the S_i lie on *distinct* extremal lines of K, and hence corresponding to each S_i is a unique extremal y_i of K. By Part (4) of Theorem A.2, these $\{y_i\}$ must satisfy $y_i \in \mathcal{Q}_1(-y_j)$ for every $i \neq j$. Moreover they are linearly dependent since the S_i are linearly dependent. But from lemma 4.3 this implies that K is not pointed. □

This completes the restatement of many of the main results in a context of systems restricted to invariant subspaces. Some results have not been generalised, either because there is no generalisation, or because their generalisations would require additional theory and would not necessarily be easy to apply.

Appendix B. Reactions involving complexes

To say that a set of complexes $\{C_i\}$ are independent means $C_i \in \mathcal{Q}_2(C_j)$ for every i and j. Define $\mathcal{I}_i$ as the index set of nonzero entries in C_i, and $\mathcal{S}(C_i) \equiv \mathrm{span}(\mathcal{Q}_0(C_i)) = \mathcal{Q}_2(C_i)^\perp$ (i.e. the set of all vectors with zeros in the same places as C_i). Clearly $\mathcal{S}(C_i) \perp \mathcal{S}(C_j)$ for every i and j. For each i define $C_i^\perp$ as the orthogonal complement of C_i in $\mathcal{S}(C_i)$: If C_i consists of k substrates, then $C_i^\perp$ is a $k-1$ dimensional subspace of $\mathcal{S}(C_i)$. For each i, choose an orthogonal basis for

$C_i^{\perp}$ consisting of vectors $C_i^j, j = 1, \ldots, k-1$. Letting $n_i = |C_i|^2$, define the sets

$$Y = \bigcup_i \left\{ \frac{C_i}{n_i} \right\} \quad \text{and} \quad Z = \bigcup_{i,j} \{C_i^j\}.$$

If there are m complexes, then Y has m members and Z has $n-m$ members. All vectors in Z are orthogonal to every complex C_i, and hence to every stoichiometric vector, and hence to the stoichiometric subspace. Further, all vectors in Y are orthogonal to each other and to all vectors in Z, so $Y \cup Z$ forms an orthogonal set spanning $\mathbb{R}^n$. As in Section 2.1, we can define a matrix T with rows from Y and a matrix T_0 with rows from Z, which together define an invertible coordinate transformation T_{tot}. Defining $y = Tx$, $z = T_0 x$, and $y_{tot} = T_{tot} x$ we have the dynamical system

$$\begin{aligned} \dot{y} &= q(Tx_{in} - y) + TSv(T_{tot}^{-1} y_{tot}) \\ \dot{z} &= q(T_0 x_{in} - z) \end{aligned}$$

From the point of view of asymptotic dynamics we are only interested in the y coordinates as z is asymptotically constant. Consider invariant subspaces defined by equations of the form $z = C$ where C is some constant vector in $\mathbb{R}^{n-m}$. In the case where $q > 0$ there is one such subspace defined by $z = T_0 x_{in}$, while if $q = 0$, any equation of the form $z = C$ defines such a subspace.

The key point is this: Any invariant subspace $\mathcal{C}$ defined by an equation $z = C$ is special because the system restricted to $\mathcal{C}$ is itself, formally, an NAC reaction system embedded in a CFSTR. Firstly, the recoordinatised system preserves $\mathbb{R}_+^n$ since

$$y_i = 0 \Rightarrow x_k = 0 \ (k \in \mathcal{I}_i) \ \Rightarrow \dot{x}_k \geq 0 \ (k \in \mathcal{I}_i) \ \Rightarrow \dot{y}_i \geq 0.$$

Secondly, the reduced Jacobian fulfils the requirements on an NAC reaction system in a CFSTR (as long as the original system fulfils these requirements). The Jacobian of the reduced system takes the form $J_{red} = TSVT' - qI$, where T' is the matrix composed of the first m columns in T_{tot}^{-1}. Explicitly, the ith column of T' is simply C_i since the ith row of T is C_i/n_i. To see that $TSVT'$ fulfils the NAC condition, we define the constant matrix $\tilde{S} = TS$ and the variable matrix $\tilde{V} = VT'$ and examine the properties of these two matrices.

Define s_{ij} to be the total amount of complex i produced by the jth reaction (i.e. the number of units of complex i on the right hand side of the reaction minus the number on the left). Then S_j, the stoichiometric vector of the jth reaction can be written $S_j = \sum_k s_{kj} C_k$. Using the Kronecker delta defined by $\delta_{ii} = 1, \delta_{ij} = 0$ if $i \neq j$, we have

$$\tilde{S}_{ij} = T^{(i)} S_j = \langle C_i/n_i, \sum_k s_{kj} C_k \rangle = \sum_k s_{kj} \frac{\langle C_i, C_k \rangle}{n_i} = \sum_k s_{kj} \delta_{ik} = s_{ij}$$

Now we examine $\tilde{V}_{ji} = V^{(j)} T_i'$. Note that by the definition of an NAC system,

$$V^{(j)} \in \mathcal{Q}_0(-S_j^T) = \mathcal{Q}_0 \left(\sum_k -s_{kj} C_k^T \right)$$

Consequently, by Lemma 3.5, $V^{(j)}C_i \in \mathcal{Q}_0(-s_{ij})$. Since $\tilde{V}_{ji} = V^{(j)}T_i' = V^{(j)}C_i$ and $\tilde{S}_{ij} = s_{ij}$, we have $\tilde{V}_{ji} \in \mathcal{Q}_0(-\tilde{S}_{ij})$, i.e. $\tilde{V} \in \mathcal{Q}_0(-\tilde{S}^T)$. Thus clearly $\tilde{S}\tilde{V}$, the Jacobian after recoordinatisation, fulfils the requirements on the Jacobian of an NAC system being the product of a constant matrix $\tilde{S}$ and a variable matrix $\tilde{V} \in \mathcal{Q}_0(-\tilde{S}^T)$.

The practical conclusion is that whenever we deal with an NAC reaction system involving complexes embedded in a CFSTR, and we are only interested in the dynamics restricted to invariant subspaces, we can consider each complex as though it were a single substrate, and then examine the reduced system. This conclusion goes beyond discussions of monotonicity and could for example be applied to discuss injectivity of the reduced system using techniques in [14] or global convergence of interconversion systems as discussed in [16].

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