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Translation-invariant monotone systems, and a global convergence result for enzymatic futile cycles ☆

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Abstract

Strongly monotone systems of ordinary differential equations which have a certain translation-invariance property are shown to have the property that all projected solutions converge to a unique equilibrium. This result may be seen as a dual of a well-known theorem of Mierczyński for systems that satisfy a conservation law. As an application, it is shown that enzymatic futile cycles have a global convergence property.

Keywords: Enzymatic futile cycles; Monotone systems; Global stability; Chemical reaction networks

1. Introduction and motivations

This paper has two motivations: to show the global convergence of solutions in enzymatic futile cycles, which constitute a chemical reaction of great interest in contemporary cell biology, and to prove a general theorem which provides a context for this result. The general theorem may be viewed as a dual to a well-known theorem on monotone dynamical systems, and is in itself of considerable interest. We briefly discuss next these two motivations.

1.1. Chemical reactions and enzymatic cycles

An important theme in molecular systems biology is the understanding of the dynamics of cell behavior in terms of cascades and feedback interconnections of elementary "modules" or subsystems, which are re-used in different pathways [25]. One of the most common components in such pathways are the *enzymatic futile cycles*, illustrated in Fig. 1. An excellent discussion can be found in [22], which also points out that futile cycles play a central role in signaling processes ranging from GTPase cycles [7] and mitogen-activated protein cascades [9,18] to glucose mobilization [17], actin treadmilling [4], bacterial two-component systems and phosphorelays [11,3] and division or apoptosis [27] and cell-cycle checkpoint control [20], as well as in metabolic control [26]. Other names for futile cycles are [22] substrate

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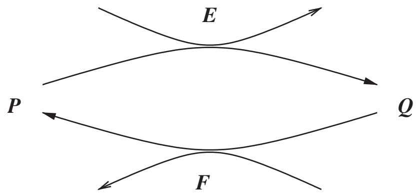

Fig. 1. Enzymatic futile cycle: the substrate P is converted into the product Q under the action of enzyme E; backward conversion is facilitated by another enzyme F.

cycles, enzymatic cycles, or enzymatic interconversions, depending on the context. Mathematical models of futile cycles amount to sets of linear/quadratic differential equations (mass-action kinetics) associated to the following reactions:

$$E + P \leftrightarrow C \rightarrow E + Q,$$

$$F + Q \leftrightarrow D \rightarrow F + P$$

with coefficients (kinetic constants) which depend on the particular enzymes and substrates participating in the reaction. There are conserved quantities (e.g., the sum of the amounts of enzyme E plus complex C remains constant as a function of time), but in each affine subspace defined by these constraints, all solutions converge to a unique equilibrium, as we will show. The proof will be a corollary of a more general set of results on monotone systems, as we describe next. (For other applications of monotone systems theory to establishing properties of chemical networks, see also [1,2] and references there.)

1.2. Monotone systems

Recall that a dynamical system is said to be *monotone* whenever its state space X is endowed with a partial order $\succcurlyeq$ and the forward flow preserves the order. In other words, for each ordered pair of initial conditions $\xi_1 \succcurlyeq \xi_2$, solutions remain ordered: $\varphi_t(\xi_1) \succcurlyeq \varphi_t(\xi_2)$ for all $t \geqslant 0$. See [24] for a discussion and many basic theorems, as well as the recent excellent exposition [15]. A special and most interesting case is when the partial order is induced by a positivity cone, i.e. a closed subset K of a Banach space B containing X such that $K + K \subset K$, $K \subset \alpha K$ for all $\alpha \geqslant 0$, and $K \cap (-K) = \{0\}$. In this case, one defines a partial order by the rule that $\xi_1 \succcurlyeq \xi_2$ whenever $\xi_1 - \xi_2 \in K$. Strict versions of the order are also possible, and particularly useful whenever K has non-empty interior: one defines $\xi_1 \succ \xi_2$ if $\xi_1 \succcurlyeq \xi_2$ and $\xi_1 \neq \xi_2$, and the following even stronger notion: $\xi_1 \gg \xi_2$ if $\xi_1 - \xi_2 \in \operatorname{int}(K)$. A *strongly* monotone system is one for which the following holds:

$$\xi_1 \succ \xi_2 \Rightarrow \varphi_t(\xi_1) \gg \varphi_t(\xi_2) \quad \forall t > 0, \quad \forall \xi_1, \xi_2 \in X. \tag{1}$$

A key foundational result is Hirsch's Generic Convergence Theorem [12–15,24], which guarantees that, if solutions of such systems are bounded, then, generically, they converge to the set of equilibria. Roughly speaking, more complex asymptotic behaviors are possible, but are (if they exist at all) confined to a zero-measure set of initial conditions.

Remarkably, under suitable additional assumptions, generic convergence to equilibria can be made global, as is the case if, for instance, the equilibrium is unique [24], sometimes not requiring strong monotonicity [16,6], if the system is cooperative and tridiagonal [23] or if, there exists a positive first-integral for the system, as shown in Mierczyński's paper [21]. Our main result may be viewed as a dual of the latter result, and applies to strongly monotone systems which have the property of translation invariance with respect to a positive vector. Equilibria of such systems are never unique. The result is roughly as follows. For systems evolving on Euclidean spaces $\mathbb{R}^n$, we will assume that for some $v \in \operatorname{int}(K)$, and for all $\lambda \in \mathbb{R}$, the following is true:

$$\varphi_t(\xi + \lambda v) = \varphi_t(\xi) + \lambda v \tag{2}$$

for all nonnegative $t \in \mathbb{R}$ and all $\xi \in X$. Under strong monotonicity, we show that convergence to equilibria is global for a suitable projection of the system. We also show that for competitive systems, i.e. systems that are strongly monotone under time-reversal, the same result holds. Statements and proofs are in Section 2.

We were originally motivated by proving a global convergence result for the futile cycle as well as more generally chemical reaction systems which are not necessarily monotone. There has been much interest in recent years in establishing such global results, see for instance [8,28,19,10,25,1,5]. In Section 3, we show how to associate, to any chemical reaction system, a new system of differential equations, evolving on a different space (of "reaction coordinates") for which our techniques may sometimes be applied, and we illustrate with the futile cycle application.

In the last section, we make some remarks on extensions and comment on the duality with Mierczyński's theorem.

2. Main result

We consider nonlinear dynamical systems of the following form:

$$\dot{x} = f(x) \tag{3}$$

with states $x \in X \subset \mathbb{R}^n$, for some closed set X which is the closure of its interior, and some locally Lipschitz vector field $f : X \to \mathbb{R}^n$. For each initial condition $\xi \in X$, we denote by $\varphi_t(\xi)$ the corresponding solution, and we assume that $\varphi_t(\xi)$ is uniquely maximally defined (as an element of X) for $t \in I_\xi$, where I_ξ is an interval in $\mathbb{R}$ which contains $[0, +\infty)$ in its interior. (In other words, the system is assumed to be forward—but not necessarily backward—complete.)

Furthermore, a closed cone $K \subset \mathbb{R}^n$ is given, with non-empty interior, and the corresponding non-strict and strict partial orders are considered: $\succcurlyeq, \succ, \gg$. In particular, we assume that (3) is *strongly monotone* as in (1) and that solutions enjoy the translation invariance property (2) for some $v \in \text{int}(K)$, which we take, without loss of generality, to have norm one.

Because of property (2) it is natural to assume, and we will do so, that the state space is invariant with respect to translation by v, namely:

$$x \in X \Rightarrow x + \lambda v \in X \quad \forall \lambda \in \mathbb{R}. \tag{4}$$

In order to state our main result, we require an additional definition. Given any unit vector v, we introduce the linear mapping:

$$\pi_v : \mathbb{R}^n \to \mathbb{R}^n : x \mapsto x - (v'x)v$$

(prime indicates transpose), which amounts to subtracting the component along the vector v, that is, an orthogonal projection onto $v^\perp$. Since $(v'x)v = (vv')x$, we can also write

$$\pi_v x = (I - vv')x.$$

Note that $\pi_v v = 0$.

Definition. Let $\xi \in X$ be given and consider the corresponding solution $\varphi_t(\xi)$. We say that $\varphi_t(\xi)$ *is bounded modulo* v if $\pi_v(\varphi_t(\xi))$ is bounded as a function of t, for $t \geqslant 0$.

Note that we are not asking for precompactness of $\varphi_t(\xi)$ (which, in examples, will typically fail), but only of its projection. We will view $\pi_v(\varphi_t(\xi))$ as a trajectory of the projected system $\dot{\tilde{x}} = (I - vv')f(\tilde{x})$ (see (8) below for more details).

Remark. Equivalently, the solution $\varphi_t(\xi)$ is bounded modulo v if and only if there exists some scalar function $\beta(\xi, t) : X \times [0, +\infty) \to \mathbb{R}$ such that $\varphi_t(\xi) - \beta(\xi, t)v$ is bounded as a function of time t. (Recall that X is invariant under translations by all multiples of v, so this difference is again an element of X.) One direction is clear, using $\beta(\xi, t) = v'\varphi_t(\xi)$. Conversely, suppose that there is any such β. Then:

$$v'(\beta(\xi, t)v) = \beta(\xi, t)v'v = \beta(\xi, t)|v|^2 = \beta(\xi, t),$$

so $\pi_v(\beta(\xi, t)v) = \beta(\xi, t) - (v'(\beta(\xi, t)v)v) = 0$. Since X is closed, the assumption is that the closure of $\{\varphi_t(\xi) - \beta(\xi, t)v, t \geqslant 0\}$ is compact. Thus, since π_v is continuous, the same holds for $\pi_v(\varphi_t(\xi)) = \pi_v(\varphi_t(\xi) - \beta(\xi, t)v)$.

We are now ready to state our main result.

Theorem 1. *Consider a forward complete nonlinear system* (3), *strongly monotone on* X, *having the property of positive translation invariance as in* (2), *with respect to some vector* $v \in \operatorname{int}(K)$. *The state space* X *is closed and invariant with respect to translation by* v *as in* (4). *Then, every solution which is bounded modulo* v *is such that* $\pi_v(\varphi_t(\xi))$ *converges to an equilibrium. Moreover, there is a unique such equilibrium.*

Before addressing the technical steps of the proof, it is useful to provide an infinitesimal characterization of translation invariance. This is a routine exercise, but we include a proof for ease of reference.

Lemma 2.1. *A system* (3) *enjoys the translation invariance property* (2) *with respect to* $v \in \mathbb{R}^n$ *if and only if*:

$$x_1, x_2 \in X, \quad x_1 - x_2 \in \operatorname{span}\{v\} \Rightarrow f(x_1) = f(x_2). \tag{5}$$

Note that, for differentiable f, yet another characterization is that $v \in \ker f_*(x)$ (Jacobian) at all states x.

Proof. If the system satisfies (2), and $x_2 = x_1 + \lambda v$, then $\varphi_t(x_2) - \varphi_t(x_1) = \lambda v$. Taking $(\mathrm{d}/\mathrm{d}t)|_{t=0}$, we obtain $f(x_1) = f(x_2)$. We now show the sufficiency of the condition. More generally, suppose that L is a linear subspace of $\mathbb{R}^n$ such that $x_1 - x_2 \in L \Rightarrow f(x_1) = f(x_2)$; we will prove that $\varphi_t(x_2) - \varphi_t(x_1)$ is constant if $x_1 - x_2 \in L$.

We first change coordinates with a linear map T in such a manner that L gets transformed into the span of the first $\ell = \dim L$ canonical vectors $\tilde{L} = \{e_1, \ldots, e_\ell\}$. The transformed equations are $\dot{\tilde{x}} = \tilde{f}(\tilde{x})$, where $\tilde{f}(\tilde{x}) = Tf(T^{-1}\tilde{x})$ and $\tilde{x} = Tx$. We partition the state as $\tilde{x} = (y', z')'$, with y of size ℓ, and write the transformed equations in block form:

$$\dot{y} = \tilde{f}_1(y, z),$$
$$\dot{z} = \tilde{f}_2(y, z).$$

Suppose that two vectors $\tilde{x}_1$ and $\tilde{x}_2$ are such that $z_1 = z_2$. This means that $\tilde{x}_1 - \tilde{x}_2 \in \tilde{L}$. Then, letting $x_i := T^{-1}\tilde{x}_i$, we have that $x_1 - x_2 \in L$, and therefore, $f(x_1) = f(x_2)$ by assumption. Thus also $\tilde{f}(\tilde{x}_1) = Tf(x_1) = Tf(x_2) = \tilde{f}(\tilde{x}_2)$. In other words, $\tilde{f}$ is independent of y, and the transformed equations in block form read

$$\dot{y} = \tilde{f}_1(z),$$
$$\dot{z} = \tilde{f}_2(z).$$

Now pick any $x_1, x_2 \in X$ such that $x_1 - x_2 \in L$. Then, $\tilde{x}_1 - \tilde{x}_2 \in \tilde{L}$, i.e., $z_1 = z_2$. Let $y_i(t)$ and $z_i(t)$ denote the components of the solution of the transformed differential equation with respective initial conditions $\tilde{x}_i$, $i = 1, 2$. Then, $z_1(t) = z_2(t)$ for all $t \geqslant 0$ (same initial conditions for the second block of variables), which implies that $\dot{y}_1(t) = \dot{y}_2(t)$ for all t. Therefore, also $\dot{\tilde{x}}_1(t) = \dot{\tilde{x}}_2(t)$ for all t, and back in the original coordinates we have that $(\mathrm{d}/\mathrm{d}t)(\varphi_t(x_2) - \varphi_t(x_1)) = 0$, as desired. □

In order to carry out the proof we first need the following lemma.

Lemma 2.2. *Let* $v \in \operatorname{int}(K)$ *be given, such that* $|v| = 1$. *Then, the function*:

$$V(x) := \inf\{\alpha \in \mathbb{R} : x \preccurlyeq \alpha v\}$$

is well defined and Lipschitz for $x \in \mathbb{R}^n$.

Proof. We show first that for all x there exists α such that $\alpha v \succcurlyeq x$. We may equivalently check that $v \succcurlyeq x/\alpha$ for some $\alpha \neq 0$. Since $x/\alpha \to 0$ as $\alpha \to +\infty$, we may conclude that this is the case, since, as is well-known, $(-v, v) := \{x : v \gg x \gg -v\}$ is an open neighborhood of the origin, for all $v \gg 0$ (in other words the topology induced by a positivity cone with non-empty interior is equivalent to the standard topology in $\mathbb{R}^n$). On the other hand, $\alpha v \prec x$ for all sufficiently large negative α (as $\alpha \to -\infty$, $(-x)/(-\alpha) \to 0$, so $(-x)/(-\alpha) \prec v$, that is, $-x \prec -\alpha v$). Therefore, $V(x)$ is well defined. Moreover, since K is closed and the feasible set of α's is bounded from below, the infimum is achieved and is actually a minimum, which implies that $V(x)$ is a continuous function. We can prove, moreover, that V is Lipschitz, as follows.

We first pick an $\varepsilon > 0$ such that $\varepsilon z \prec v$ for all unit vectors z. (Such an ε exists, because $\varepsilon z \to 0$ uniformly on the unit sphere, and $(-v, v)$ is a neighborhood of zero.) Therefore, for each two vectors $x \neq y$, applying this observation to $z = 1/|x-y|(x-y)$, we have that $x - y \preccurlyeq k|x-y|v$, where $k := 1/\varepsilon$, and the same holds if $x = y$. Now, given any two x, y, we write

$$x = x - y + y \preccurlyeq k|x-y|v + V(y)v = (k|x-y| + V(y))v$$

which means that $V(x) \leqslant k|x-y| + V(y)$, and therefore

$$V(x) - V(y) \leqslant k|x-y|.$$

Since x and y were arbitrary, this proves that V is Lipschitz with constant k. □

The next lemma is crucial for proving our main result.

Lemma 2.3. *Let ξ_1 and ξ_2 in X be arbitrary, and V be defined according to the previous Lemma* 2.2. *Then, for all $t > 0$ it holds that*

$$V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) \leqslant V(\xi_1 - \xi_2) \tag{6}$$

and the inequality is strict whenever $\xi_1 - \xi_2 \notin \operatorname{span}\{v\}$.

Proof. Let ξ_1 and ξ_2 be arbitrary. By definition of V, we have

$$\xi_1 \preccurlyeq \xi_2 + V(\xi_1 - \xi_2)v.$$

By translation invariance and monotonicity, then

$$\varphi_t(\xi_1) \preccurlyeq \varphi_t(\xi_2 + V(\xi_1, \xi_2)v) = \varphi_t(\xi_2) + V(\xi_1, \xi_2)v.$$

It follows that $V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) \leqslant V(\xi_1 - \xi_2)$, as claimed. In particular, whenever $\xi_1 - \xi_2 \notin \operatorname{span}\{v\}$ we have $\xi_1 \prec \xi_2 + V(\xi_1 - \xi_2)v$ and therefore, exploiting strong monotonicity:

$$\varphi_t(\xi_1) \lll \varphi_t(\xi_2 + V(\xi_1 - \xi_2)v) = \varphi_t(\xi_2) + V(\xi_1 - \xi_2)v.$$

In particular, then, $V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) < V(\xi_1 - \xi_2)$. □

Note that, by the semigroup property for flows, Lemma 2.3 implies that the function $t \mapsto V(\varphi_t(\xi_1) - \varphi_t(\xi_2))$ is nondecreasing.

We also prove a result for systems that are strongly monotone in reversed time, meaning that for every pair ξ_1, ξ_2 and every time $t < 0$ such that $\varphi_t(\xi_1)$ and $\varphi_t(\xi_2)$ are well-defined the following implication holds:

$$\xi_1 \succ \xi_2 \Rightarrow \varphi_t(\xi_1) \ggg \varphi_t(\xi_2).$$

Corollary 2.4. *Let ξ_1 and ξ_2 in X be arbitrary, and V be defined according to the previous Lemma* 2.2. *Assume that system* (3) *be forward-complete, strongly monotone in reversed time over X, and translation invariant with respect to some $v \in \operatorname{int}(K)$; then, for all $t > 0$ it holds that*

$$V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) \geqslant V(\xi_1 - \xi_2) \tag{7}$$

and the inequality is strict whenever $\xi_1 - \xi_2 \notin \operatorname{span}\{v\}$.

We are now ready to prove the main result.

2.1. Proof of main result

Let $\xi \in X$ be such that $\varphi_t(\xi)$ is bounded modulo v. That is, $\tilde{x}(t) := \pi_v(\varphi_t(\xi)) = (I - vv')\varphi_t(\xi)$ is a bounded function of t. Note that $\tilde{x}$ satisfies the following differential equation:

$$\dot{\tilde{x}} = (I - vv')f(\varphi_t(\xi)) = (I - vv')f(\tilde{x}), \tag{8}$$

where the last equality follows by translation invariance. This is a new dynamical system, with state space

$$\tilde{X} := \{\tilde{x} \in v^\perp : \exists \lambda \in \mathbb{R} : \tilde{x} + \lambda v \in X\},$$

viz. the projection along v of X onto the vector-space $v^\perp$, and we will denote by $\tilde{\varphi}_t$ the corresponding flow. Note that π (we omit the subscript v from now on), φ_t and $\tilde{\varphi}_t$ are related in the following sense:

$$\pi \circ \varphi_t = \tilde{\varphi}_t \circ \pi.$$

Moreover, by translation invariance of X, we have $\tilde{X} = X \cap v^\perp$ and $X = \tilde{X} \oplus \mathrm{span}\{v\}$.

By the above considerations, it makes sense to speak about the ω-limit set $\omega(\tilde{x})$ of solutions of (8), which by the boundedness assumption, will be a compact, non-empty invariant set we would like to show that $\omega(\tilde{x})$ is a single equilibrium.

We show uniqueness first. An equilibrium $\widetilde{x}$ of (8) satisfies that $f(\widetilde{x})$ belongs to the span of v, let us say $f(\widetilde{x}) = rv$. Therefore, the function $z(t) = \widetilde{x} + tf(\widetilde{x})$ is a solution of the system $\dot{x} = f(x)$, since its derivative satisfies:

$$\dot{z}(t) = f(\widetilde{x}) = f(\widetilde{x} + (rt)v) = f(z(t)),$$

where the second inequality holds by (the infinitesimal characterization of) translation invariance. Since $z(0) = \widetilde{x}$, we have that $\varphi_t(\widetilde{x}) = \widetilde{x} + tf(\widetilde{x})$ for all t. Assuming that $\tilde{x}_1$ and $\tilde{x}_2$ are two distinct equilibria for (8), we have that $\varphi_t(\tilde{x}_i) = \tilde{x}_i + tf(\tilde{x}_i)$ (for $i = 1, 2$). Hence, for all $t > 0$

$$V(\tilde{x}_1 - \tilde{x}_2) > V(\varphi_t(\tilde{x}_1) - \varphi_t(\tilde{x}_2)) = V(\tilde{x}_1 - \tilde{x}_2 + [f(\tilde{x}_1) - f(\tilde{x}_2)]t). \tag{9}$$

By a symmetric argument, however

$$V(\tilde{x}_2 - \tilde{x}_1) > V(\tilde{x}_2 - \tilde{x}_1 + [f(\tilde{x}_2) - f(\tilde{x}_1)]t) \tag{10}$$

which should hold again for all $t > 0$. It is straightforward, from the definition of $V(x)$, that the function is increasing with respect to (positive) translations along v. Hence, the inequality in (9) implies $f(\tilde{x}_1) - f(\tilde{x}_2) \prec 0$, while, the second inequality gives $f(\tilde{x}_1) - f(\tilde{x}_2) \succ 0$. But this is clearly a contradiction.

Let $\tau > 0$ be arbitrary; consider the solutions of (3) corresponding to ξ and $\varphi_\tau(\xi)$. We claim that $\varphi_t(\varphi_\tau(\xi)) - \varphi_t(\xi)$ is bounded. In fact, denoting by $\tilde{\varphi}_t$ the corresponding projections onto $\tilde{X}$ and exploiting Lemma 2.1, we obtain

$$\varphi_t(\varphi_\tau(\xi)) - \varphi_t(\xi) = \varphi_\tau(\varphi_t(\xi)) - \varphi_t(\xi) = \int_t^{t+\tau} f(\varphi_s(\xi))\,\mathrm{d}s = \int_t^{t+\tau} f(\tilde{\varphi}_s(\pi(\xi)))\,\mathrm{d}s \tag{11}$$

and so $|\varphi_t(\varphi_\tau(\xi)) - \varphi_t(\xi)| \leqslant \tau M$, where M is an upper bound on the magnitude of the vector field f on a compact set that contains the trajectory $\pi_v(\varphi_t(\xi))$.

Hence, $V(\varphi_t(\varphi_\tau(\xi)) - \varphi_t(\xi))$ is lower-bounded, and, by virtue of Lemma 2.3, is decreasing. Therefore, it admits a limit $\bar{V} > -\infty$ as $t \to +\infty$. We claim that

$$\varphi_t(\varphi_\tau(\xi)) - \varphi_t(\xi) \to \mathrm{span}\{v\}. \tag{12}$$

Suppose that this claim is false. Then, since, as we just proved, $\varphi_t(\varphi_\tau(\xi)) - \varphi_t(\xi)$ is bounded, there will be a sequence of times $t_n \to \infty$ and an $\delta_0 \notin \mathrm{span}\{v\}$ such that

$$\varphi_{t_n}(\varphi_\tau(\xi)) - \varphi_{t_n}(\xi) \to \delta_0.$$

Moreover, by precompactness of $\pi \circ \varphi_t(\xi)$, we can pick a subsequence of $\{t_n\}$, which we denote without loss of generality in the same way, such that $\pi \circ \varphi_{t_n}(\xi) \to \tilde{x}_0$, for some vector $\tilde{x}_0$.

So the pair $[\tilde{x}_0, \delta_0]$ belongs to the following set

$$\Omega = \{[\tilde{x}, \delta] : \exists t_n \to +\infty : \pi \circ \varphi_{t_n}(\xi) \to \tilde{x} \text{ and } \varphi_{t_n}(\varphi_\tau(\xi)) - \varphi_{t_n}(\xi) \to \delta\}. \tag{13}$$

We show next that Ω satisfies the following invariance property:

$$\forall [\tilde{x}, \delta] \in \Omega, \quad \forall t \geqslant 0, \ \ [\tilde{\varphi}_t(\tilde{x}), \varphi_t(\tilde{x} + \delta) - \varphi_t(\tilde{x})] \in \Omega. \tag{14}$$

Pick any $[\tilde{x}, \delta] \in \Omega$ and some sequence $\{t_n\}$ as in the definition of Ω, as well as any fixed $t > 0$. From $\tilde{x} = \lim_{n \to +\infty} \pi \circ \varphi_{t_n}(\xi)$ and continuity of the flow, we have

$$\tilde{\varphi}_t(\tilde{x}) = \lim_{n \to +\infty} \tilde{\varphi}_t(\pi \circ \varphi_{t_n}(\xi)) = \lim_{n \to +\infty} \pi \circ \varphi_{t+t_n}(\xi). \tag{15}$$

Moreover,

$$\begin{aligned} \delta &= \lim_{n \to +\infty} \varphi_{t_n}(\varphi_\tau(\xi)) - \varphi_{t_n}(\xi) \\ &= \lim_{n \to +\infty} \varphi_\tau(\varphi_{t_n}(\xi)) - \varphi_{t_n}(\xi) \\ &= \lim_{n \to +\infty} \varphi_\tau(\tilde{\varphi}_{t_n}(\pi(\xi)) + [v'\varphi_{t_n}(\xi)]v) - \tilde{\varphi}_{t_n}(\pi(\xi)) - [v'\varphi_{t_n}(\xi)]v, \end{aligned}$$

where the last equality follows from

$$\tilde{\varphi}_t(\pi(\xi)) = \pi(\varphi_t(\xi)) = \varphi_t(\xi) - [v'\varphi_t(\xi)]v$$

applied at $t = t_n$. Finally, from the equality $\varphi_\tau(\zeta + \lambda v) = \varphi_\tau(\zeta) + \lambda v$ applied to $\zeta = \tilde{\varphi}_{t_n}(\pi(\xi))$ and $\lambda = v'\varphi_{t_n}(\xi)$, this last expression gives that

$$\delta = \lim_{n \to +\infty} \varphi_\tau(\tilde{\varphi}_{t_n}(\pi(\xi))) - \tilde{\varphi}_{t_n}(\pi(\xi)) = \varphi_\tau(\tilde{x}) - \tilde{x}, \tag{16}$$

that is, $\tilde{x} + \delta = \varphi_\tau(\tilde{x})$. Therefore,

$$\varphi_t(\tilde{x} + \delta) - \varphi_t(\tilde{x}) = \varphi_t(\varphi_\tau(\tilde{x})) - \varphi_t(\tilde{x}) = \lim_{n \to +\infty} \varphi_{t+\tau}(\pi \circ \varphi_{t_n}(\xi)) - \varphi_t(\pi \circ \varphi_{t_n}(\xi)). \tag{17}$$

Now, by translation invariance, we have that

$$\varphi_{t+\tau}(\pi(\varphi_{t_n}(\xi))) = \varphi_{t+\tau}(\varphi_{t_n}(\xi) - [v'\varphi_{t_n}(\xi)]v) = \varphi_{t+\tau}(\varphi_{t_n}(\xi)) - [v'\varphi_{t_n}(\xi)]v$$

and similarly

$$\varphi_t(\pi(\varphi_{t_n}(\xi))) = \varphi_t(\varphi_{t_n}(\xi) - [v'\varphi_{t_n}(\xi)]v) = \varphi_t(\varphi_{t_n}(\xi)) - [v'\varphi_{t_n}(\xi)]v$$

so that

$$\varphi_{t+\tau}(\pi(\varphi_{t_n}(\xi))) - \varphi_t(\pi(\varphi_{t_n}(\xi))) = \varphi_{t+\tau}(\varphi_{t_n}(\xi)) - \varphi_t(\varphi_{t_n}(\xi))$$

so, substituting into (17), we have

$$\varphi_t(\tilde{x} + \delta) - \varphi_t(\tilde{x}) = \lim_{n \to +\infty} \varphi_{t+\tau}(\varphi_{t_n}(\xi)) - \varphi_t(\varphi_{t_n}(\xi)) = \lim_{n \to +\infty} \varphi_{t+t_n}(\varphi_\tau(\xi)) - \varphi_{t+t_n}(\xi). \tag{18}$$

Hence, (14) follows combining (15) and (18) (using the new sequence $\{t + t_n\}$).

Recall that $V(\varphi_t(\varphi_\tau(\xi)) - \varphi_t(\xi))$ decreases to its limit $\bar{V}$ as $t \to \infty$. On the other hand, for any $[\tilde{x}, \delta] \in \Omega$, by definition of Ω we have that $\varphi_{t_n}(\varphi_\tau(\xi)) - \varphi_{t_n}(\xi) \to \delta$ as $n \to \infty$. Because of continuity of V, this implies that $V(\delta) = \bar{V}$. Moreover, by invariance of Ω, $V(\varphi_t(\tilde{x} + \delta) - \varphi_t(\tilde{x})) = \bar{V}$, independently of t. Hence, application of Lemma 2.3 gives $\delta \in \operatorname{span}\{v\}$ for any $[\tilde{x}, \delta] \in \Omega$. This contradicts the assumption that $\delta_0 \notin \operatorname{span}\{v\}$. Therefore, (12) is true.

Projecting (12) onto the $\tilde{X}$ space shows

$$\lim_{t \to +\infty} \tilde{\varphi}_t(\tilde{\varphi}_\tau(\pi(\xi))) - \tilde{\varphi}_t(\pi(\xi)) = 0.$$

We next claim that every element of $\omega(\tilde{x})$ is an equilibrium. Indeed, suppose that $\tilde{\varphi}_{t_n}(\pi(\xi)) \to p$ then, for any τ

$$\tilde{\varphi}_\tau(p) = \tilde{\varphi}_\tau\left(\lim_{t_n\to+\infty} \tilde{\varphi}_{t_n}(\pi(\xi))\right) = \lim_{t_n\to+\infty} \tilde{\varphi}_\tau(\tilde{\varphi}_{t_n}(\pi(\xi))) = \lim_{t_n\to+\infty} \tilde{\varphi}_{t_n}(\pi(\xi)) = p.$$

Hence, the result follows by uniqueness of the equilibrium for the projected system $\dot{\tilde{x}} = (I - vv')f(\tilde{x})$.

Corollary 2.5. *Let a system as in* (3) *be strongly monotone in reverse time and enjoy the translation invariance property with respect to some vector* $v \in \mathrm{int}(K)$. *Then, every solution which is bounded modulo* v *has a projection which converges to an equilibrium. Moreover, there is a unique such equilibrium.*

Proof. The proof is entirely analogous, once Corollary 2.4 is used in place of Lemma 2.3. □

3. An Application to chemical reactions

In this section, we show how our result may be applied to conclude global convergence to steady states, for certain chemical reactions. A standard form for representing (well-mixed and isothermal) chemical reactions by ordinary differential equations is

$$\dot{S} = \Gamma R(S), \tag{19}$$

evolving on the nonnegative orthant $\mathbb{R}^n_{\geqslant 0}$, where S is an n-vector specifying the concentrations of n chemical species, $\Gamma \in \mathbb{R}^{n\times m}$ is the *stoichiometry matrix*, and $R : \mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^m$ is a function which provides the vector of reaction rates for any given vector of concentrations. We assume that R is locally Lipschitz, so uniqueness of solutions holds, and that the positive orthant $\mathbb{R}^n_{\geqslant 0}$ is invariant, and that it is forward complete: every solution is defined for all $t \geqslant 0$.

To each system of the form (19) and each fixed vector $\sigma \in \mathbb{R}^n_{\geqslant 0}$, we associate the following system

$$\dot{x} = f_\sigma(x) = R(\sigma + \Gamma x) \tag{20}$$

evolving on the state-space

$$X_\sigma = \{x \in \mathbb{R}^m | \sigma + \Gamma x \geqslant 0\}.$$

The ith component x_i of the vector x is sometimes called the “extent” of the ith reaction. We will derive conclusions about (19) from the study of (20).

Note that X_σ is a closed set which is the closure of its interior (it is, in fact, a polytope), and also that X_σ *is invariant with respect to translation* by any $v \in \ker \Gamma$, because $x \in X_\sigma$ means that $\sigma + \Gamma x \geqslant 0$, and therefore also $x + \lambda v \in X_\sigma$ for all $\lambda \in \mathbb{R}$, because $\sigma + \Gamma(x + \lambda v) = \sigma + \Gamma x \geqslant 0$.

As an illustrative example, consider the following set of chemical reactions

$$\begin{aligned} &E + P \leftrightarrow C \to E + Q, \\ &F + Q \leftrightarrow D \to F + P \end{aligned} \tag{21}$$

which may be thought of as a model of the activation of a protein substrate P by an enzyme E; C is an intermediate complex, which dissociates either back into the original components or into a product (activated protein) Q and the enzyme. The second reaction transforms Q back into P, and is catalyzed by another enzyme (a phosphatase denoted by F). A system of reactions of this type is sometimes called a “futile cycle”, and reactions of this type are ubiquitous in cell biology. The mass-action kinetics model is obtained as follows. Denoting concentrations with the same letters (P, etc.) as the species themselves, we introduce the species vector

$$S = (P, Q, E, F, C, D)'$$

and these stoichiometry matrix Γ and vector of reaction rates $R(S)$

$$\Gamma = \begin{bmatrix} -1 & 0 & 0 & 1 \\ 0 & 1 & -1 & 0 \\ -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}, \quad R(S) = \begin{bmatrix} k_1 EP - k_{-1}C \\ k_2 C \\ k_3 FQ - k_{-3} D \\ k_4 D \end{bmatrix}.$$

The reaction constants k_i, with $i = -1, 1, 2, 3, -3, 4$, are arbitrary positive real numbers, and they quantify the speed of the different reactions. This gives a system (19). Explicitly, we have in this example that $f_\sigma(x) = R(\sigma + \Gamma x)$ is the following function:

$$f_\sigma(x) = \begin{pmatrix} k_1(\sigma_3 + x_2 - x_1)(\sigma_1 + x_4 - x_1) - k_{-1}(\sigma_5 + x_1 - x_2) \\ k_2(\sigma_5 + x_1 - x_2) \\ k_3(\sigma_4 + x_4 - x_3)(\sigma_2 + x_2 - x_3) - k_{-3}(\sigma_6 + x_3 - x_4) \\ k_4(\sigma_6 + x_3 - x_4) \end{pmatrix}.$$

Note that, along all solutions, one has that

$$P(t) + Q(t) + C(t) + D(t) \equiv \text{constant}$$

because $(1, 1, 0, 0, 1, 1)\Gamma = 0$. Since the components are nonnegative, this means that, for any solution, each of $P(t)$, $Q(t)$, $C(t)$, and $D(t)$ are upper bounded by the constant $P(0) + Q(0) + C(0) + D(0)$. Similarly, we have two more independent conservation laws

$$E(t) + C(t) \quad \text{and} \quad F(t) + D(t)$$

are also constant along trajectories, so also E and F remain bounded. Therefore, all solutions are bounded, and hence, in particular, are defined for all $t \geqslant 0$. The system of equations (19) in this example is not monotone, at least with respect to any orthant order. (See [2] for more on this example, as well as an alternative way to study it.) We will prove, as a corollary of our main theorem, that every solution that starts with $E(0) + C(0) \neq 0$ and $F(0) + D(0) \neq 0$ converges to a steady state, which is unique with respect to the conservation relations.

Lemma 3.1. *The system* (20) *is forward complete: every solution is defined for all $t \geqslant 0$ and remains in X_σ. Furthermore, if it holds that every solution of* (19) *is bounded, then, for every solution $x(t)$ of* (20), *$\Gamma x(t)$ is bounded.*

Proof. Pick any $x_0 \in X_\sigma$, and let $S_0 := \sigma + \Gamma x_0 \in \mathbb{R}^n_{\geqslant 0}$. Consider the solution $S(t)$ of the initial value problem $\dot S = \Gamma R(S)$, $S(0) = S_0$, which is well-defined and satisfies $S(t) \geqslant 0$ for all $t \geqslant 0$. Let, for $t \geqslant 0$

$$x(t) := x_0 + \int_0^t R(S(\tau))\, \mathrm{d}\tau. \tag{22}$$

Note that $\dot x(t) = R(S(t))$ for all t. We claim that x is a solution of $\dot x = f_\sigma(x)$. Since $x(0) = x_0$ and x is defined for all t, uniqueness of solutions (f_σ is locally Lipschitz) will prove the first statement of the lemma. To prove the claim, we first introduce the new vector function

$$P(t) := \sigma + \Gamma x(t).$$

Differentiating with respect to time we obtain that

$$\dot P(t) = \Gamma \dot x(t) = \Gamma(R(S(t))) = \dot S(t)$$

for all $t \geqslant 0$. Therefore, $P - S$ is constant. Since $P(0) = \sigma + \Gamma x_0 = S(0)$, it follows that $P \equiv S$. In other words, S satisfies $S(t) = \sigma + \Gamma x(t)$. Thus,

$$\dot x(t) = R(S(t)) = R(\sigma + \Gamma x(t)) = f_\sigma(x(t)),$$

as claimed.

To prove the second statement, we simply remark that, as already proved, for every solution x of (20), there is a solution S of (19) such that $S(t) = \sigma + \Gamma x(t)$. Therefore, $\Gamma x(t) = S(t) - \sigma$ is bounded if $S(t)$ is. □

Note that the futile cycle example discussed earlier satisfies the assumptions of this lemma. We now specialize further, imposing additional conditions also satisfied by the example.

Lemma 3.2. *Suppose that the matrix Γ has rank exactly $m - 1$, its kernel spanned by some positive unit vector v. Let $x(t)$ be a solution of* (20). *Then, $\Gamma x(t)$ is bounded if and only if $\pi_v x(t)$ is bounded.*

Proof. Since $\Gamma \pi_v x = \Gamma(x - (v'x)v) = \Gamma x$, one implication is clear. Let M be the restriction of Γ to the space $v^\perp$ orthogonal to the vector v, i.e. the image of π_v. As $\Gamma \pi_v x = \Gamma x$, the images of Γ and M are the same. The map M is one-to-one: suppose that $x \in v^\perp$ is so that if $Mx = 0$. Then, $\Gamma x = 0$, so x is in the kernel of Γ, i.e., it is also in the span of v. Thus, $x = 0$. Let M^{-1} be the inverse of M, mapping the image of Γ into $v^\perp$. Thus, if a trajectory is such that $\Gamma x(t)$ is bounded, then also

$$M^{-1}\Gamma x(t) = M^{-1}\Gamma \pi_v x(t) = M^{-1} M \pi_v x(t) = \pi_v x(t)$$

is bounded. □

Observe that the spaces X_σ are translation invariant with respect to any v as in the statement of this lemma.

Corollary 3.3. *Suppose that*:

1. *the matrix Γ has rank $m - 1$, with kernel spanned by some positive unit vector*;
2. *every solution of* (19) *is bounded*;
3. *$\sigma \in \mathbb{R}^n_{\geqslant 0}$ is so that the system $\dot{x} = f_\sigma(x)$ is strongly monotone.*

Then, there is a $\zeta = \zeta_\sigma \in \mathbb{R}^n_{\geqslant 0}$ with the following property: *for each $\rho \in \mathbb{R}^n_{\geqslant 0}$ such that $\rho - \sigma \in$* Image(Γ), *the solution S of* (19) *with $S(0) = \rho$ satisfies $S(t) \to \zeta$ as $t \to \infty$.*

Proof. We let the kernel of Γ be spanned by the positive unit vector v. By Lemmas 3.1 and 3.2, $\pi_v x(t)$ is bounded, for every solution of (20). By Theorem 1, there is a unique equilibrium ξ of the projected system $\dot{\tilde{x}} = (I - vv')f(\tilde{x})$ so that every solution x of $\dot{x} = R(\sigma + \Gamma x)$ is such that $\pi_v(x(t)) \to \xi$ as $t \to \infty$. We next show that $\zeta = \sigma + \Gamma\xi$ satisfies the requirements.

Pick $\rho \in \mathbb{R}^n_{\geqslant 0}$ so that $\rho - \sigma = \Gamma a$, $a \in \mathbb{R}^m$, and let S be the solution of $\dot{S} = \Gamma R(S)$ with initial condition $S(0) = \rho$. Uniqueness of solutions of (19) gives that $S(t) = \rho + \Gamma x(t)$, where $\dot{x} = R(\rho + \Gamma x)$, $x(0) = 0$.

Introduce the function $z(t) = x(t) + a$. Then,

$$\dot{z} = \dot{x} + 0 = R(\rho + \Gamma x) = R(\sigma + \Gamma z)$$

with $z(0) = a$. Since $\sigma + \Gamma z(0) = \sigma + \Gamma a = \rho \geqslant 0$, it follows that $z(0) \in X_\sigma$, and therefore $z(t)$ is a solution of $\dot{x} = R(\sigma + \Gamma x)$ on X_σ. Therefore, $\pi_v z(t) \to \xi$. As $x(t) = z(t) - a$, this means that $\pi_v x(t) \to \xi - \pi_v a$. Since for every vector x it holds that $\Gamma \pi_v x = \Gamma x$, applying Γ to the above gives

$$\Gamma x(t) = \Gamma \pi_v x(t) \to \Gamma\xi - \Gamma a.$$

Therefore, $S(t) = \rho + \Gamma x(t) \to \rho + \Gamma\xi - \Gamma a = \sigma + \Gamma\xi = \zeta$ as $t \to \infty$. □

In the futile cycle example, we may take $v = \left(\frac{1}{4}, \frac{1}{4}, \frac{1}{4}, \frac{1}{4}\right)'$, and consider the following set:

$$\Sigma = \{\sigma = (P, Q, E, F, C, D) \in \mathbb{R}^n_{\geqslant 0} | E + C > 0, F + D > 0\}.$$

The system $\dot{x} = f_\sigma(x)$ is strongly monotone for $\sigma \in \Sigma$. To see this, we compute the Jacobian of $R(\sigma + \Gamma x(t))$ with respect to x

$$\begin{pmatrix} * & * & 0 & k_1 E \\ & * & 0 & 0 \\ 0 & k_3 F & * & * \\ 0 & 0 & * & * \end{pmatrix},$$

where the stars represent strictly positive elements when in the off-diagonals (and strictly negative when on the diagonals), and where E, F are the E and F coordinates of $\sigma + \Gamma x$, or, more explicitly:

$$\begin{pmatrix} * & * & 0 & k_1(\sigma_3 + (x_2 - x_1)) \\ & * & 0 & 0 \\ 0 & k_3(\sigma_4 + (x_4 - x_3)) & * & * \\ 0 & 0 & * & * \end{pmatrix}.$$

Thus, the system is cooperative (i.e., monotone with respect to the main orthant). It is strongly monotone if this matrix is irreducible almost everywhere along trajectories (see e.g. [15], Section 3.2), which amounts, because f_σ is a real-analytic function, to asking that $\sigma_3 + x_2 - x_1 \not\equiv 0$ and $\sigma_4 + x_4 - x_3 \not\equiv 0$ along any solution. Let us prove now that this is the case, assuming that $\sigma \in \Sigma$, that is, that $\sigma_3 + \sigma_5 \neq 0$ and $\sigma_4 + \sigma_6 \neq 0$. Suppose that $\sigma_3 + x_2 - x_1 \equiv 0$, so that $\dot{x}_1 - \dot{x}_2 \equiv 0$ and $x_1 - x_2 \equiv \sigma_3$. The equations for (20) give

$$\dot{x}_1 - \dot{x}_2 = k_1(\sigma_3 + x_2 - x_1)(\sigma_1 + x_4 - x_1) - (k_{-1} + k_2)(\sigma_5 + x_1 - x_2)$$

so

$$0 \equiv -(k_{-1} + k_2)(\sigma_3 + \sigma_5)$$

which contradicts $\sigma_3 + \sigma_5 \neq 0$. Similarly for $\sigma_4 + x_4 - x_3 \equiv 0$. So the system is indeed strongly monotone.

We conclude that every solution of our example with an initial condition in the set Σ converges to an equilibrium. Moreover, there is a unique such equilibrium in each stoichiometry class $\sigma + \mathrm{Image}(\Gamma)$.

When initial conditions do not belong to Σ, one has a standard enzymatic Michaelis–Menten type of reaction, and the same conclusion holds. This is very easy to show. (Indeed, take for instance the case when $E(0) = C(0) = 0$. As $\dot{P} = k_4 D$, $P(t)$ is nondecreasing, so (since it is upper bounded) we know that P converges. Consider the function $y = Q + D$. Since $P + y$ is constant, y converges, too. Since $\dot{y}$ has a bounded derivative (it can be expressed in terms of bounded variables), and its integral is convergent, it follows ("Barbălat's lemma") that $\dot{y} = -k_4 D$ converges to zero, so D must converge and therefore, again using that $P + Q + D$ is constant, Q converges as well. Finally, since $D + F$ is constant, F converges, too.)

4. Remarks on duality and possible extensions

As pointed out in the introduction, our main result stated in Theorem 1 can be seen as a dual to Mierczyński's global convergence theorem for strongly cooperative systems with a positive first integral, published in [21]. We discuss this informally in this section. Strictly speaking, duality of 1 only holds provided that we consider the following special case of Mierczyński's Theorem: *Consider a system of ordinary differential equations in* $\mathbb{R}^n_+$, *defined by a* $\mathscr{C}^1$ *vector field* $f : \mathbb{R}^n_+ \to \mathbb{R}^n$, *such that*: $f(0) = 0$, $\partial f_i/\partial x_j > 0$ *for all* $i \neq j$, *and*:

$$\text{there exists a vector } c \in (\mathbb{R}_+)^n \text{ such that } c' f(x) = 0 \text{ for all } x \in (\mathbb{R}_+)^n. \tag{23}$$

Then, *every solution is bounded and converges to an equilibrium.* This is a special case of Mierczyński's result, which had already appeared in several previous publications, in that *linear* positive first integrals are considered; namely the quantity $c'x$ is preserved along solutions of the system. For simplicity, we actually strengthened one of the original assumptions by asking that $\partial f_i/\partial x_j > 0$ for all $i \neq j$, rather than a strict monotonicity condition with respect to all off-diagonal entries as the theorem is stated in [21].

The duality with Theorem 1 is evident if we express the conditions in terms of the Jacobian of the vector field. A linear positive first integral amounts to having a constant left-eigenvector relative to the dominant zero eigenvalue for the Jacobian matrix $Df(x)$; in particular, $c'Df(x) = 0$ for all x in the state-space. On the other hand, translation invariance by a positive vector v (over a given state-space X) can be stated in terms of the Jacobian matrix by asking that $Df(x)v=0$ for all $x \in X$; i.e., the existence of a constant right-eigenvector relative to the dominant zero eigenvalue of the Jacobian matrix $Df(x)$. As a further remark, we note that our main result does not need the strict monotonicity condition as stated above, but only asks for strong-monotonicity of the resulting flow (this is in fact weaker than assuming strictly positive off-diagonal entries of the Jacobian; for instance a much tighter sufficient condition for strong monotonicity of the flow, can be formulated by asking that the Jacobian matrix have *non-negative* off-diagonal entries and be *irreducible*).

A more general version of Mierczyński's Theorem than stated above does not assume linearity of the first integral. In particular, assumption (23) is replaced by the existence of a $\mathscr{C}^1$ function $H(x) : \mathbb{R}^n_+ \to \mathbb{R}$, such that $DH(x) \cdot f(x) = 0$ and $DH(x) \in \mathbb{R}^n_+$ for all $x \in \mathbb{R}^n_+$. This condition does not allow an elegant interpretation in terms of Jacobians of $Df(x)$, but nevertheless, one may state a nonlinear dual of the theorem provided that we understand translation invariance in the following more general sense. Let us say that a flow is *invariant with respect to translation by a strictly increasing flow* $\tilde{\varphi}$ (meaning that its solutions are such with respect to t) if for all t_1,t_2 in $\mathbb{R}$ the following holds:

$$\varphi_{t_1}(\tilde{\varphi}_{t_2}(x_0)) = \tilde{\varphi}_{t_2}(\varphi_{t_1}(x_0))$$

and moreover, for each $x_1, x_2 \in X$ there exists $t \in \mathbb{R}$ so that $x_2 \succcurlyeq \tilde{\varphi}_t(x_1)$. This property generalizes our previous concept: translation invariance with respect to a constant vector v is exactly the property of invariance with respect to translation by the increasing flow $\tilde{\varphi}$ induced by the system of differential equations $\dot{x} = v$. Invariance with respect to non-trivial general flows as in this definition is not easy to check in concrete examples, however, at least in principle, an infinitesimal characterization of the property is as follows. Let $f(x) : X \to \mathbb{R}^n$ and $v(x) : X \to \mathbb{R}^n$ be $\mathscr{C}^1$ vector-fields. The flow induced by the system $\dot{x} = f(x)$ commutes with respect to the strictly increasing flow induced by $\dot{x} = v(x)$ if and only if

$$Df(x)v(x) = Dv(x)f(x).$$

Moreover, if there exists a compact set $P \subset \text{int}(K)$ so that $v(x) \in P$ for all $x \in X$, then the flow induced by $v(x)$ is strictly increasing and for any x_1 and x_2 in X there exists $t \in \mathbb{R}$ so that $x_2 \succcurlyeq \tilde{\varphi}_t(x_1)$.

Accordingly, we have to redefine the notion of boundedness modulo translation by $\tilde{\varphi}$ by asking that solutions are bounded if there exists $M > 0$ such that for all $x_0 \in X$ and all $t \in \mathbb{R}$, there exists τ with the property that $|\tilde{\varphi}_\tau(\varphi_t(x_0))| \leqslant M$. While this definition is rather natural, there is not, however, a natural counter-part to the space $\tilde{X} = X \cap v^\perp$. One should let $\tilde{X}$ be defined as a quotient space of $X/\sim$, under the following equivalence relation: $x_1 \sim x_2$ if and only if $\tilde{\varphi}_t(x_1) = x_2$ for some $t \in \mathbb{R}$. This definition of $\tilde{X}$ and the commutativity of $\tilde{\varphi}$ and φ allow us to define a flow on equivalence classes of $[x]$ of $\tilde{X}$ in the obvious way: $\varphi_t([x]) := [\varphi_t(x)]$. There are several technical difficulties involved in this construction, however: in order to define "boundedness" one needs to be precise about a metric in the quotient space chosen so that boundedness of a solution in the space $\tilde{X}$ becomes equivalent to boundedness modulo translation as given above. Under an appropriate definition, our main result would then be translated into the following statement in the current set-up: "Consider a forward complete, strongly monotone nonlinear system (3) with translation invariance with respect to a strictly increasing flow. Then, every solution which is bounded is such that $\varphi_t([x])$ admits a limit as $t \to +\infty$." The correct formulation will depend on a concrete example that requires this generality, of which we have none at the present time. We leave this as a subject for further research.

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