A Global Convergence Result for Strongly Monotone Systems with Positive Translation Invariance

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July 31, 2018

Abstract
We show that strongly monotone systems of ordinary differential equations which have a certain translation-invariance property are so that all solutions converge to a unique equilibrium. The result may be seen as a dual of a well-known theorem of Mierczyn ski for systems that satisfy a conservation law. An application to a reaction of interest in biochemistry is provided as an illustration.

Keywords: monotone systems, global stability, chemical reaction networks

1 Introduction and Motivations
We recall that a dynamical system is said to be monotone whenever its state space $X$ is endowed with a partial order $\geq$ and the forward flow preserves the order. In other words, for each ordered pair of initial conditions $\xi_1 \geq \xi_2$, solutions remain ordered: $\varphi_t(\xi_1) \geq \varphi_t(\xi_2)$ for all $t \geq 0$. See [15] for a discussion and many basic theorems, as well as the recent excellent exposition [10]. 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 $\alpha \geq 0$.

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and $K \cup -K = \{0\}$. In this case, one defines a partial order by the rule that $\xi_1 \succeq \xi_2$ 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 $\xi_1 \succeq \xi_2$ and $\xi_1 \neq \xi_2$, and the following even stronger notion: $\xi_1 \gg \xi_2$ if $\xi_1 - \xi_2 \in \text{int}(K)$. A strongly monotone system is one for which the following holds:

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

A key foundational result is Hirsch’s Generic Convergence Theorem ([7, 8, 9, 10, 15]), 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 [15], sometimes not requiring strong monotonicity [11, 4], if the system is cooperative and tridiagonal [14] or if, there exists a positive first-integral for the system, as shown in Mierczinski’s paper [13]. 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 $v \in \text{int}(K)$, and for all $\lambda \in \mathbb{R}$, the following is true:

$$\varphi_t(\xi + \lambda v) = \varphi_t(\xi) + \lambda v \quad (2)$$

for all $t \in \mathbb{R}$ 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 certain chemical reaction systems which are not necessarily monotone. There has been much interest in recent years in establishing such global results, see for instance [5, 17, 12, 6, 16, 11, 3]. 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 a system of interest in biochemistry.

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

## 2 Main Result

We consider nonlinear dynamical systems of the following form:

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

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 $I_\xi$ 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.)

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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: $\preceq, >, \gg$. 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:

$$x \in X \Rightarrow x + \lambda v \in X \quad \forall \lambda \in \mathbb{R}.$$  \hspace{1cm} (4)

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

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

(prime indicates transpose), which amounts to subtracting the component along the vector $v$, that is, an orthogonal projection onto $v^\perp$. Since $(v^t x)v = (v v^t)x$, we can also write $\pi_v x = (I - vv^t)x$. 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 $t \geq 0$.

Notice that we are not asking for precompactness of $\varphi_t(\xi)$ (which, in examples, will typically fail), but only of its projection.

**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 $v$, so this difference is again an element of $X$.) One direction is clear, using $\beta(\xi, t) = v^t \varphi_t(\xi)$. Conversely, suppose that there is any such $\beta$. Then: $v'(\beta(\xi, t)v) = \beta(\xi, t)v^t v = \beta(\xi, t)|v|^2 = \beta(\xi, t)$, so $\pi_v(\beta(\xi, t)v) = \beta(\xi, t) - (v^t(\beta(\xi, t)v)v = 0$, Since $X$ is closed, the assumption is that the closure of $\{\varphi_t(\xi) - \beta(\xi, t)v, t \geq 0\}$ is compact. Thus, since $\pi_v$ 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, strongly monotone on $X$. Let (3) enjoy positive translation invariance as in (4) with respect to some vector $v \in \text{int}(K)$, and so that 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:

$$x_1, x_2 \in X, \ x_1 - x_2 \in \text{span}\{v\} \Rightarrow f(x_1) = f(x_2).$$  \hspace{1cm} (5)
Notice that, for differentiable \( f \), yet another characterization is that \( v \in \ker f_*(x) \) (Jacobian) at all states \( x \).

**Proof.** If the system is translation-invariant by \( v \), and \( x_2 = x_1 + \lambda v \), then \( \varphi_t(x_2) - \varphi_t(x_1) = \lambda v \). Taking \( (d/dt)|_{t=0} \), 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 \( L = \{e_1, \ldots, e_\ell\} \). The transformed equations are \( \tilde{x} = \tilde{f}(\tilde{x}) \), where \( \tilde{f}(\tilde{x}) = T f(T^{-1} \tilde{x}) \) and \( \tilde{x} = Tx \). We partition the state as \( \tilde{x} = (y', z')' \), with \( y \) of size \( \ell \), and write the transformed equations in block form:

\[
\begin{align*}
\dot{y} &= \tilde{f}_1(y, z) \\
\dot{z} &= \tilde{f}_2(y, z).
\end{align*}
\]

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:

\[
\begin{align*}
\dot{y} &= \tilde{f}_1(z) \\
\dot{z} &= \tilde{f}_2(z).
\end{align*}
\]

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 \( t \geq 0 \) (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 \( \dot{x}_1(t) = \dot{x}_2(t) \) for all \( t \), and back in the original coordinates we have that \( (d/dt)(\varphi_t(x_2) - \varphi_t(x_1)) = 0 \), as desired.

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

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

\[
V(x) := \inf\{\alpha \in \mathbb{R} : x \preceq \alpha v\}
\]

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

**Proof.** We show first that for all \( x \) there exists \( \alpha \) such that \( \alpha v \succeq x \). We may equivalently check that \( v \succeq x/\alpha \) 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 small \( \alpha \) (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 \( \alpha \)’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 \( \varepsilon z < v \) for all unit vectors \( z \). (Such an \( \varepsilon \) 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 \( z = \frac{1}{|x-y|}(x-y) \), we have that \( x - y \leq k|x-y|v \), where \( k := 1/\varepsilon \), and the same holds if \( x = y \). Now, given any two \( x, y \), we write

\[
x = x - y + y \leq k|x-y|v + V(y)v = (k|x-y| + V(y))v
\]

which means that \( V(x) \leq k|x-y| + V(y) \), and therefore \( V(x) - V(y) \leq k|x-y| \). 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 \( \xi_1 \) and \( \xi_2 \) in \( X \) be arbitrary, and \( V \) be defined according to the previous Lemma 2.2. Then, for all \( t > 0 \) it holds that:

\[
V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) \leq V(\xi_1 - \xi_2),
\]

and the inequality is strict whenever \( \xi_1 - \xi_2 \notin \text{span}\{v\} \).

**Proof.** Let \( \xi_1 \) and \( \xi_2 \) be arbitrary. By definition of \( V \), we have: \( \xi_1 \leq \xi_2 + V(\xi_1 - \xi_2)v \). By translation invariance and monotonicity then: \( \varphi_t(\xi_1) \leq \varphi_t(\xi_2 + V(\xi_1, \xi_2)v) = \varphi_t(\xi_2) + V(\xi_1, \xi_2)v \). It follows that \( V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) \leq V(\xi_1 - \xi_2) \), as claimed. In particular, whenever \( \xi_1 - \xi_2 \notin \text{span}\{v\} \) we have \( \xi_1 < \xi_2 + V(\xi_1 - \xi_2)v \) and therefore, exploiting strong monotonicity: \( \varphi_t(\xi_1) \ll \varphi_t(\xi_2 + V(\xi_1 - \xi_2)v) = \varphi_t(\xi_2) + V(\xi_1 - \xi_2)v \). In particular, then \( V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) < V(\xi_1 - \xi_2) \).

Notice 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 \( \xi_1, \xi_2 \) and every time \( t < 0 \) such that \( \varphi_t(\xi_1) \) and \( \varphi_t(\xi_2) \) are well-defined the following implication holds:

\( \xi_1 \triangleright \xi_2 \Rightarrow \varphi_t(\xi_1) \triangleright \varphi_t(\xi_2) \).

**Corollary 2.4** Let \( \xi_1 \) and \( \xi_2 \) 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 \( v \in \text{int}(K) \); then, for all \( t > 0 \) it holds that:

\[
V(\varphi_t(\xi_1) - \varphi_t(\xi_2)) \geq V(\xi_1 - \xi_2),
\]

and the inequality is strict whenever \( \xi_1 - \xi_2 \notin \text{span}\{v\} \).

We are now ready to prove the main result.

**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 \( t \). Notice that \( \tilde{x} \) satisfies the following differential equation:

\[
\dot{\tilde{x}} = (I-vv')f(\varphi_t(\xi)) = (I-vv')f(\tilde{x})
\]
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. Notice that \( \pi \) (we omit the subscript \( v \) from now on), \( \varphi_t \) 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 \( \tilde{X} = \tilde{X} \oplus \text{span}\{v\} \).

By the above considerations, it makes sense to speak about the \( \omega \)-limit set \( \omega(\tilde{x}) \) of solutions of \( \tilde{X} \), 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 \( \tilde{x} \) of \( \tilde{X} \) satisfies that \( f(\tilde{x}) \) belongs to the span of \( v \), let us say \( f(\tilde{x}) = rv \). Therefore, the function \( z(t) = \tilde{x} + tf(\tilde{x}) \) is a solution of the system \( \dot{\tilde{x}} = f(\tilde{x}) \), since its derivative satisfies:

\[
\dot{z}(t) = f(\tilde{x}) = f(\tilde{x} + (rt)v) = f(z(t)),
\]

where the second inequality is by (the infinitesimal characterization of) translation invariance. Since \( z(0) = \tilde{x} \), we have that \( \varphi_t(\tilde{x}) = \tilde{x} + tf(\tilde{x}) \) for all \( t \). Assuming that \( \tilde{x}_1 \) and \( \tilde{x}_2 \) are two distinct equilibria for \( \tilde{X} \), 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 definition of \( V(x) \), that the function be increasing with respect to (positive) translations along \( v \). Hence, the inequality in (9) implies \( f(\tilde{x}_1) - f(\tilde{x}_2) < 0 \), while, the second inequality gives \( f(\tilde{x}_1) - f(\tilde{x}_2) > 0 \). But this is clearly a contradiction.

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

\[
\varphi_t(\varphi_t(\xi)) - \varphi_t(\xi) = \varphi_t(\varphi_t(\xi)) - \varphi_t(\xi) = \int_t^{t+\tau} f(\varphi_s(\xi)) ds = \int_t^{t+\tau} f(\tilde{\varphi}_s(\pi(\xi))) ds \tag{11}
\]

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

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

\[
\varphi_t(\varphi_t(\xi)) - \varphi_t(\xi) \to \text{span}\{v\}. \tag{12}
\]

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

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

We show next that \( \Omega \) satisfies the following invariance property:

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

Pick any \([\tilde{x}, \delta] \in \Omega\) and some sequence \( \{t_n\} \) as in the definition of \( \Omega \), 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:

\[
\varphi_t(\tilde{x}) = \lim_{n \to +\infty} \varphi_t(\pi \circ \varphi_{t_n}(\xi)) = \lim_{n \to +\infty} \pi \circ \varphi_{t+t_n}(\xi).
\] (15)

Moreover,

\[
\delta = \lim_{n \to +\infty} \varphi_{t_n}(\varphi_t(\xi)) - \varphi_{t_n}(\xi)
\]

\[
= \lim_{n \to +\infty} \varphi_t(\varphi_{t_n}(\xi)) - \varphi_{t_n}(\xi)
\]

\[
= \lim_{n \to +\infty} \varphi_t(\tilde{\varphi}_{t_n}(\pi(\xi)) + [\varphi'(\varphi_{t_n}(\xi))]v) - \varphi_{t_n}(\pi(\xi)) - [v']\varphi_{t_n}(\xi)\]

where the last equality follows from \( \tilde{\varphi}_t(\pi(\xi)) = \pi(\varphi_t(\xi)) = \varphi_t(\xi) - [v']\varphi_{t_n}(\xi)v \) applied to \( t = t_n \).

Finally, from the equality \( \varphi_t(\xi + \lambda v) = \varphi_t(\xi) + \lambda v \) applied to \( \xi = \tilde{\varphi}_{t_n}(\pi(\xi)) \) and \( \lambda = v'\varphi_{t_n}(\xi) \), this last expression gives that

\[
\delta = \lim_{n \to +\infty} \varphi_t(\tilde{\varphi}_{t_n}(\pi(\xi))) - \tilde{\varphi}_{t_n}(\pi(\xi)) = \varphi_t(\tilde{x}) - \tilde{x},
\] (16)

that is, \( \tilde{x} + \delta = \varphi_t(\tilde{x}) \). Therefore:

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

Now, by translation invariance, we have that:

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

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:

\[
\varphi_{t+t_n}(\pi(\varphi_{t_n}(\xi))) - \varphi_t(\pi(\varphi_{t_n}(\xi))) = \varphi_{t+t_n}(\varphi_{t_n}(\xi)) - \varphi_t(\varphi_{t_n}(\xi))
\]

so, substituting into (17), we have:

\[
\varphi_t(\tilde{x} + \delta) - \varphi_t(\tilde{x}) = \lim_{n \to +\infty} \varphi_{t+t_n}(\varphi_{t_n}(\xi)) - \varphi_t(\varphi_{t_n}(\xi)) = \lim_{n \to +\infty} \varphi_{t+t_n}(\varphi_t(\xi)) - \varphi_{t+t_n}(\xi).
\] (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 \([\bar{x}, \delta] \in \Omega\), by definition of \( \Omega \) we have that \( \varphi_{tn}(\varphi_\tau(\xi)) - \varphi_{tn}(\xi) \to \delta \) as \( n \to \infty \). Because of continuity of \( V \), this implies that \( V(\delta) = \bar{V} \). Moreover, by invariance of \( \Omega \), \( V(\varphi_t(\bar{x} + \delta) - \varphi_t(\bar{x})) = \bar{V} \), independently of \( t \). Hence, application of Lemma 2.3 gives \( \delta \in \text{span}\{v\} \) for any \([\bar{x}, \delta] \in \Omega\). Therefore, (12) is true.

Projecting (12) onto the \( \bar{X} \) 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 \( \omega(\bar{x}) \) is an equilibrium. Indeed, suppose that \( \varphi_{tn}(\pi(\xi)) \to p \); then, for any \( \tau \):
\[
\varphi_\tau(p) = \varphi_\tau\left(\lim_{t_n \to +\infty} \varphi_{tn}(\pi(\xi))\right) = \lim_{t_n \to +\infty} \varphi_\tau(\varphi_{tn}(\pi(\xi))) = \lim_{t_n \to +\infty} \varphi_{tn}(\pi(\xi)) = p.
\]

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 \( v \in \text{int}(K) \). 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:
\[
\dot{S} = \Gamma R(S),
\]  
(19)
evolving on the nonnegative orthant \( \mathbb{R}^n_{\geq 0} \), 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 \( R : \mathbb{R}^n_{\geq 0} \to \mathbb{R}^m \) 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 \( \mathbb{R}^n_{> 0} \) is invariant, and that it is forward complete: every solution is defined for all \( t \geq 0 \).

To each system of the form (19) and each fixed vector \( \sigma \in \mathbb{R}^n_{\geq 0} \), we associate the following system:
\[
\dot{x} = f_\sigma(x) = R(\sigma + \Gamma x)
\]
(20)
evolving on the state-space
\[
X_\sigma = \{ x \in \mathbb{R}^m | \sigma + \Gamma x \geq 0 \}.
\]
The $i$th component $x_i$ of the vector $x$ is sometimes called the “extent” of the $i$th reaction. We will derive conclusions about (19) from the study of (20).

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

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

$$
\begin{align*}
E + P &\leftrightarrow C \rightarrow E + Q \\
F + Q &\leftrightarrow D \rightarrow F + P,
\end{align*}
$$

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:

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

and these stoichiometry matrix $\Gamma$ and vector of reaction rates $R(S)$:

$$
\Gamma = \begin{bmatrix}
-1 & 0 & 0 & 1 \\
0 & 1 & -1 & 0 \\
-1 & 1 & 0 & 0 \\
0 & 0 & -1 & 1 \\
1 & -1 & 0 & 0 \\
0 & 0 & 1 & -1
\end{bmatrix}, \quad R(S) = \begin{bmatrix}
k_1EP - k_{-1}C \\
k_2C \\
k_3FQ - k_{-3}D \\
k_4D
\end{bmatrix}.
$$

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

\[
x(t) := x_0 + \int_0^t R(S(\tau)) d\tau.
\]

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 (\( f_\sigma \) 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 \( t \geq 0 \). 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 \( \Gamma \) has rank exactly \( n - 1 \), 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 \( \Gamma \) to the space \( v^\perp \) orthogonal to the vector \( v \), i.e. the image of \( \pi_v \). As \( \Gamma \pi_v x = \Gamma x \), the images of \( \Gamma \) 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 \( \Gamma \), 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 \( \Gamma \) 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. \( \blacksquare \)

Observe that the spaces \( X_\sigma \) are translation invariant with respect to any \( v \) as in the statement of this Lemma.

**Corollary 3.3** Suppose that:

1. the matrix \( \Gamma \) has rank \( n - 1 \), with kernel spanned by some positive unit vector;
2. every solution of (19) is bounded;
3. \( \sigma \in \mathbb{R}^n_{\geq 0} \) is so that the system \( \dot{x} = f_\sigma(x) \) is strongly monotone.
Then, there is a \( \zeta = \zeta_\sigma \in \mathbb{R}_{\geq 0}^n \) with the following property: for each \( \rho \in \mathbb{R}_{\geq 0}^n \) such that \( \rho - \sigma \in \text{Image}(G) \), the solution \( S \) of (19) with \( S(0) = \rho \) satisfies \( S(t) \to \zeta \) as \( t \to \infty \).

Proof. We let the kernel of \( \Gamma \) 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 11 there is a unique equilibrium \( \xi \) of the projected system \( \ddot{x} = (I - vv')f(\dot{x}) \) so that every solution \( x \) of \( \ddot{x} = R(\sigma + \Gamma x) \) 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 \( \rho \in \mathbb{R}_{\geq 0}^n \) 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 \( S(0) = \rho \). Arguing as in the proof of Lemma 3.1, we have 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 \( \sigma + \Gamma z(0) = \sigma + \Gamma a = \rho \geq 0 \), it follows that \( z(0) \in X_\sigma \), and therefore \( z(t) \) is a solution of \( \dot{x} = R(\sigma + \Gamma x) \) on \( X_\sigma \). 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 \( \Gamma \) 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 \( v = (1/4, 1/4, 1/4, 1/4)' \), and consider the following set:

\[
\Sigma = \{ \sigma = (P, Q, E, F, C, D) \in \mathbb{R}_{\geq 0}^n \mid E + C > 0, F + D > 0 \}.
\]

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. [10], Section 3.2), which amounts, because \( f_\sigma \) is a real-analytic function, to asking that \( \sigma_3 + x_2 - x_1 \neq 0 \) and \( \sigma_4 + x_4 - x_3 \neq 0 \) 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 $\Sigma$ converges to an equilibrium. Moreover, there is a unique such equilibrium in each stoichiometry class $\sigma + \text{Image}(\Gamma)$.

When initial conditions do not belong to $\Sigma$, 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 (“Barbalat’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 Mierczynski’s global convergence theorem for strongly cooperative systems with a positive first integral, published in [13]. We discuss this informally in this section. Strictly speaking, duality of 1 only holds provided that we consider the following special case of Mierczynski’s Theorem: Consider a system of ordinary differential equations in $\mathbb{R}^n_+$, defined by a $C^1$ vector field $f : \mathbb{R}_+^n \to \mathbb{R}_+^n$, such that:

\[
\frac{\partial f_i}{\partial x_j} > 0 \quad \text{for all } i \neq j,
\]

there exists a vector $c \in (\mathbb{R}_+)^n$ such that $c^t f(x) = 0$ for all $x \in (\mathbb{R}_+)^n$. \hspace{1cm} (23)

Then, every solution is bounded and converges to an equilibrium. This is a special case of Mierczynski result, which had already appeared in several previous publications, in that linear positive first integrals are considered; namely the quantity $c^t x$ is preserved along solutions of the system. For simplicity, we actually strengthened one of the original assumptions by asking that $\frac{\partial f_i}{\partial x_j} > 0$ for all $i \neq j$, rather than a strict monotonicity condition with respect to all off-diagonal entries as the Theorem is stated in [13].

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, $c^t Df(x) = 0$ 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 Mierczinski Theorem than stated above does not assume linearity of the first integral. In particular, assumption \[23\] is replaced by the existence of a \(C^1\) 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 would 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 \(\tilde{\varphi}\) 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 \(x_2 \succeq \tilde{\varphi}_t(x_1)\). 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 \(C^1\) 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 (meaning that its solutions are such with respect to \(t\)) and for any \(x_1\) and \(x_2\) in \(X\) there exists \(t \in \mathbb{R}\) so that \(x_2 \succeq \tilde{\varphi}_t(x_1)\).

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 \(\tau\) with the property that \(|\tilde{\varphi}_\tau(\varphi_t(x_0))| \leq M\). While this definition is rather natural, there is not, however, a natural counter-part to the space \(\tilde{X} = X \cap v^+\). Hence, we may as well let \(\tilde{X}\) be defined as a quotient space of \(X/\sim\) under the 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 \(\varphi\) allow us to define a flow on equivalence classes of \([x]\) of \(\tilde{X}\) in the natural way: \(\varphi_t([x]) := [\varphi_t(x)]\). Boundedness of a solution in the space \(\tilde{X}\) is equivalent to boundedness modulo translation given above. 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 \(t \to +\infty\).
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