Multistability in systems with counter-clockwise Input-Output dynamics

David Angeli
Dip. Sistemi e Informatica
Università di Firenze

Abstract— The notion of Counter-Clockwise (ccw) Input-Output dynamics is extended and used for the global analysis of multistability in positive feedback interconnections. A library of examples is provided to illustrate the usefulness of this concept and help recognizing ccw dynamics in specific applications, especially those arising in systems biology.

I. Motivations and basic definitions

Although there is no general agreement on the matter, and precise definitions may vary according to the field of interest, roughly speaking a multistable system can be defined as a dynamical system for which almost all solutions converge to the asymptotically stable equilibria (which are actually more than one). In particular, since the pioneering works by Delbrück, [8], bistability and more in general multistability, have been recognized as a fundamental dynamical behaviour associated to many cell subsystems and playing a crucial role in phenomena such as cell differentiation, development, and also in the insurgence of periodic behaviours due to the combination of an hysteretic system in conjunction with a negative feedback loop around it (typically much slower), giving rise to what the property amounts to. In addition, it has very close connection with classical passivity and it can be interpreted as asking for passivity of the system through the output channel \( y \) (see [1] for more details on this). Convergence in positive feedback loops is guaranteed, under mild technical assumptions, whenever trajectories are bounded, (see Theorem 4 in [1]). In this paper we show how the results in [1] can be used in order to predict multistability in positive feedback interconnections of ccw systems (see Theorem 2). This result, in particular, is the analog for ccw systems of a similar theorem which is proven in [5] for the case of monotone Input-Output systems (see also [6]). Together they provide an effective tool for designing and analyzing multistable systems.

In addition, we provide a number of “off-the-shelf” examples suitable for several domains of application and especially meant for molecular biology models. They fall within the class of systems for which the signs of the Jacobian matrices are entrywise constant throughout the state space. Of course, such systems include linear ones, but also many other interesting examples of nonlinear dynamics which are often encountered in modeling chemical reaction networks due to a large prevalence of monotone nonlinearities in such models.

While in the theory of electrical networks and in mechanics there are conjugate quantities which can naturally play the role of inputs and outputs of the system (voltages and currents, forces and positions) giving rise to the desired passivity properties, in the context of molecular biology there is no natural choice of in-
puts and outputs of a system; even more fundamentally, there is no need for measuring a certain quantity in a linear scale, rather than, for instance, in a logarithmic scale (pH concentrations) or in possibly any other nonlinear scale. Having said that, the definition of counter-clockwise Input-Output dynamics as given in [1], which, we recall here for the sake of completeness, involves computation of the area encircled by the input-output trajectory in the \((u, y)\) plane, may appear rather arbitrary. In this respect, it becomes clear, especially for SISO nonlinear systems, that a further degree of flexibility can be introduced by considering the area defined on the \((u, y)\) plane, viz. \(\rho : \mathbb{R}^2 \rightarrow \mathbb{R}_{>0}\). This makes the new definitions compatible with a fully nonlinear Input-Output paradigm, that is what biological systems often entail.

Before giving precise definitions we recall that, at this level of abstraction, it is enough to consider a dynamical system as a map: 
\[
\psi : \mathbb{R} \times X \times U \rightarrow Y \text{ which, to each initial condition } \xi \in X \text{ and each input signal } u(\cdot) \in U \text{ (}U\text{-valued Lebesgue measurable locally essentially bounded functions) associates the output at time } t, \text{ according to } y(t) = \psi(t, \xi, u), \text{ where } X \text{ is any topological space and } U, Y \subset \mathbb{R}^m \text{ are, respectively, the input and output space.}
\]

The most typical examples of such I/O maps are those induced by considering nonlinear differential equations of the following type:
\[
\begin{align*}
\dot{x} &= f(x, u) \\
y &= h(x)
\end{align*}
\]

in which the state space \(X \subset \mathbb{R}^n\) is a closed set and \(f : X \times U \rightarrow \mathbb{R}^n\) is a locally Lipschitz map; similarly, \(h : X \rightarrow Y\) is locally Lipschitz and \(\psi(t, \xi, u)\) is defined, for each \(\xi \in X\) and each input signal \(u\), by letting \(\psi(t, \xi, u) = h(x(t, \xi, u))\), where \(x(t, \xi, u)\) denotes the solution at time \(t\) of (1) with initial condition \(\xi \in X\) and input \(u\). Another situation of interest arises when static I/O maps are considered, viz. \(\psi\) is independent of \(\xi\), and only depends upon the value of \(u\) at time \(t\): 
\[
\psi(t, u) = h(u(t)) \quad \text{for some Lipschitz function } h : U \rightarrow Y.
\]

We emphasize that \(\psi(t, \xi, u)\) need not be defined for all \(t \geq 0\); however, for each \(\xi \in X\) and each \(u \in U\) there exists \(T_{\xi,u} \in (0, +\infty]\) so that \(\psi(t, \xi, u)\) is well defined for all \(t \in [0, T_{\xi,u})\).

It is useful to define the following subsets of \(X \times U\):
\[
\begin{align*}
S_{\text{fc}} &= \{(\xi, u) \in X \times U : T_{\xi,u} = +\infty\} \\
S_{\text{bd}} &= \{(\xi, u) \in X \times U : T_{\xi,u} = +\infty \text{ and } u(\cdot), \psi(\cdot, \xi, u) \text{ are bounded}\}
\end{align*}
\]

where ‘fc’ comes from the commonly adopted term forward complete, used to denote global existence of solutions forward in time. We assume, without loss of generality that \(0 \in U\), and that \(U = U_1 \times U_2 \ldots \times U_m\) and \(Y = Y_1 \times Y_2 \ldots \times Y_m\) for some non-empty intervals \(U_i, Y_i \subset \mathbb{R}\). We are now ready to detail our main definitions.

**Definition I.1:** We say that \(\rho : U \times Y \rightarrow \mathbb{R}^m\) is a density function if it satisfies the following properties:
1. \(\rho(u, y) = [\rho_1(u_1, y_1), \rho_2(u_2, y_2), \ldots, \rho_m(u_m, y_m)]\) for scalar functions \(\rho_i : U_i \times Y_i \rightarrow \mathbb{R}\)
2. \(\rho_i(u_i, y_i) > 0\) for almost all \((u_i, y_i) \in U_i \times Y_i\) (according to Lebesgue measure) and all \(i \in \{1 \ldots m\}\)
3. \(\rho\) is a measurable and locally summable function (jointly in \(u\) and \(y\))

**Definition I.2:** We say that a system has ccw Input-Output dynamics with respect to the density function \(\rho(u, y)\) if for any \((\xi, u) \in S_{\text{bd}}\) the following inequality holds:
\[
\liminf_{T \rightarrow +\infty} \int_0^T \int_0^{\rho(t)} \mu(t) \ d\mu dt > -\infty.
\]

where \(y(t) = \psi(t, \xi, u)\) is assumed to be absolutely continuous.

For certain classes of systems a much stronger property may hold. In particular, the inequality of ccw dynamics could be satisfied regardless of the density function \(\rho\). This justifies the following definition.

**Definition I.3:** We say that a system has ccw Input-Output dynamics with respect to arbitrary density functions, if for all density functions \(\rho(u, y)\) and all pairs \((\xi, u) \in S_{\text{bd}}\), the inequality (3) holds.

A few remarks are in order.

**Remark I.4:** Notice that (3) is only required to hold on bounded input-output pairs. This is different from classical passivity literature where conditions are typically assumed on arbitrary Input-Output pairs. Especially in the context of systems biology, it makes sense to keep analytical conditions for convergence distinct from those ensuring boundedness (which often are much more simple to deal with, for instance many of the state spaces of interest are already bounded to start with). Therefore, we decided to relax definitions by only asking for the inequalities to hold on the class of inputs which are relevant to our subsequent analysis, viz. bounded input-output pairs. These are in fact the class of inputs (and outputs) that arise within a system when a closed-loop interconnection is considered and a bounded asymptotic behaviour is observed.

Strict versions of the property are possible and useful, in analogy to those defined in [1].
Definition I.5: A system has strict ccw Input-Output dynamics with respect to arbitrary density functions if for any density function \( \rho(u,y) \) there exists a positive definite function \( \tilde{\rho} \) of \( t \) and \( \gamma \in \mathcal{K} \) so that for all pairs \((\xi, u) \in S_{bd}\) the following inequality holds:
\[
\liminf_{t \to \infty} \int_0^T \dot{y}(t) \int_0^{u(t)} \rho(\mu, y(t)) \, d\mu - \frac{\tilde{\rho}(\dot{y}(t))}{1 + \gamma(\vert \xi(t) \vert)} \, dt > -\infty
\]
where \( y(t) = \psi(t, \xi, u) \) is absolutely continuous. \( \Box \)

Notice, in definition I.5, that the “positivity margin” \( \tilde{\rho} \) may vary according to the density function \( \rho \) itself. A further relaxation of the notion in Definition I.5 is to allow \( \tilde{\rho} \) to possibly depend upon \( u \) and/or \( \xi \). This is still a strong enough version of the property in order to yield convergence results when combined with the notion given in Definition I.2.

Remark I.6: For MIMO systems, viz. in the case of \( u, y \in \mathbb{R}^m \) and \( \rho : \mathbb{R}^m \times \mathbb{R}^m \to \mathbb{R}^m \), the integral \( \int_0^u \rho(\mu, y) \, d\mu \) denotes the vector \( [\int_0^{u_1} \rho_1(\mu_1, y_1) \, d\mu_1, \ldots, \int_0^{u_m} \rho_m(\mu_m, y_m) \, d\mu_m]' \). A special case arises whenever the density function \( \rho \) is separable, viz. \( \rho(u,y) = \rho_u(u) \cdot \rho_y(y) \) (component-wise in the case of MIMO systems). In this case, it can be shown that considering the area weighted through the density function \( \rho \) is equivalent to looking at the standard area (viz. for \( \rho = 1 \)), with respect to rescaled inputs and outputs, viz. by letting \( \tilde{y} = \int_0^y \rho_y(\eta) \, d\eta \) and \( \tilde{u} = \int_0^u \rho_u(\mu) \, d\mu \). \( \Box \)

II. Multistability in positive feedback loops

The goal of this Section is to show how multistability can occur in positive feedback loops of systems with ccw dynamics. By a bistable (or multistable) system we mean, in this context, a system satisfying the following requirements:
1. existence of two or more equilibria in the state space;
2. all solutions converge to one of these equilibria;
3. almost all solutions converge to asymptotically stable equilibria.

To this end, a fundamental technical step will be the derivation of a generalization of Theorem 4 in [1]. This is stated next; for the sake of completeness we recall some of the relevant terminology introduced in [1].

Definition II.1: A system as in (1) admits a well defined Steady state response if for all constant input signal \( u(t) \equiv u \), and all initial conditions \( \xi \) the corresponding solution exists and admits a limit as \( t \to +\infty \). In particular the steady-state Input-State response \( k_x \) is the map (possibly multivalued)
\[
k_x(u) = \bigcup_{\xi} \lim_{t \to +\infty} x(t, \xi, u)
\]
We also define Input-Output steady state response \( k_y \) as follows: \( k_y := h \circ k_x \). Moreover, if for all \( u \in U \), \( k_x \) is single-valued and the corresponding equilibrium \( k_x(u) \) is globally asymptotically stable we call it the Input-State static characteristic (correspondingly \( k_y \) is called the Input-Output static characteristic). If, in addition, \( k_x(u) \) is exponentially stable and \( f(x, u) \) of class \( C^\infty \), we say that \( k_x \) is hyperbolic. \( \Box \)

Definition II.2: A system is Input-Output observable at steady state if for any pair of Input-Output values \( (\bar{u}, \bar{y}) \) the set \( \{x : f(x, \bar{u}) = 0, \bar{y} = h(x, \bar{u})\} \) is either empty or a singleton. \( \Box \)

Notice that, for systems with Input-State characteristics, the property of Input-Output observability at steady-state trivially holds.

Definition II.3: A system has detectable constant trajectories if the following implication holds:
\[
u(t) = \bar{u}, \quad y(t) = \bar{y} \Rightarrow x(t) \equiv \bar{x}
\]
for some \( \bar{x} \in \mathbb{R}^n \) (\( \bar{x} \) possibly depending upon the initial condition, and of course \( \bar{u} \) and \( \bar{y} \)). \( \Box \)

Theorem 1: Consider the positive feedback interconnection of two finite-dimensional nonlinear systems with strictly ccw Input-Output dynamics with respect to the density functions \( \rho_1(u_1, y_1) \) and \( \rho_2(u_2, y_2) \):
\[
\dot{x}_1 = f_1(x_1, u_1) \\
y_1 = h_1(x_1) \\
\dot{x}_2 = f_2(x_2, u_2) \\
y_2 = h_2(x_2)
\]
with \( f_i : X_i \times U_i \to \mathbb{R}^{n_i} \) locally Lipschitz functions and \( h_i : X_i \to Y_i \subset \mathbb{R}^{m_i} \) output functions of class \( C^\infty \) (\( i = 1, 2 \)).

Assume further that the following symmetry holds
\[
U_1 = Y_2, \quad Y_1 = U_2 \quad \forall u \in U_1, \quad \forall y \in Y_1.
\]
Then, for any initial condition \( [\xi_1, \xi_2] \) giving rise to a bounded solution (forward in time), we have \( u_1(t) = y_2(t) \to 0 \) and \( y_1(t) = u_2(t) \to 0 \) as \( t \to +\infty \). Moreover
1. if both systems admit well defined Steady State responses then, for any pair of initial conditions \( (\xi_1, \xi_2) \), we have that \( \omega([\xi_1, \xi_2]) \) is the union of forward converging orbits (some of which are clearly just equilibria);
2. if, in addition, the equilibria are isolated, then \( \lim_{t \to +\infty} y_i(t) \) exist, \( i = 1, 2 \);
3. if, in addition, the systems are Input-Output observable at steady-state, then \( \omega([\xi_1, \xi_2]) \) is the union of a
single equilibrium and possibly a set of forward converging orbits;
4. if, in addition, the systems have constant detectable trajectories, then \( \omega(\xi_1, \xi_2) \) is a single equilibrium.

**Remark II.4:** Before proving the result, we remark that the symmetry condition in (5) is trivially satisfied if, for instance, one of the systems enjoys the CCW property with respect to arbitrary density functions, and the other with respect to some density function. □

**Proof:** Consider the feedback interconnection (4). By assumption, each of the subsystems has strictly CCW I-O dynamics, hence, taking any bounded solution of (4), \([x_1(t), x_2(t)' \) and denoting by \( y_1(t) := h_1(x_1(t)) = u_2(t) \) and \( y_2(t) := h_2(x_2(t)) = u_1(t) \), we have:

\[
\lim_{T \to +\infty} \inf \int_0^T y_1 \rho_1(\mu, y_1) d\mu - \frac{\rho(|y_1|)}{1 + \gamma(|x_1|)} dt > -\infty.
\]

\[
\lim_{T \to +\infty} \inf \int_0^T y_2 \rho_2(\mu, y_2) d\mu - \frac{\rho(|y_2|)}{1 + \gamma(|x_2|)} dt > -\infty.
\]

Taking sums in both sides of the inequalities above and exploiting the conditions \( u_1 = y_2 \) and \( u_2 = y_1 \), as well as symmetry of \( \rho_1 \) and \( \rho_2 \) we obtain:

\[
\lim_{T \to +\infty} \inf \int_0^T C(t) - \frac{\rho(|y_1|)}{1 + \gamma(|x_1|)} - \frac{\rho(|y_2|)}{1 + \gamma(|x_2|)} dt > -\infty
\]

where we defined \( C(t) := c(y_1(t), y_2(t)) \) where \( c : Y_1 \times Y_2 \to \mathbb{R} \) is the function:

\[
c(y_1, y_2) = \sum_{i=1}^m \int_{y_1}^{y_1} \int_{y_2}^{y_2} \rho_1(\mu, \eta) d\mu d\eta.
\]

Therefore, since solutions are bounded and by continuity of the function \( c \),

\[
\limsup_{T \to +\infty} \int_0^T \rho(|y_1|) + \frac{\rho(|y_2|)}{1 + \gamma(|x_2|)} dt < +\infty
\]

We are now in a position which is analogous to equation (19) in [1]; from now on the proof follows along the same lines.

The following result, is a consequence of the previous theorem which can be proved along the same lines as the corresponding corollary in [1].

**Corollary II.5:** Consider the positive feedback interconnection of two systems with strictly counter-clockwise I-O dynamics with respect to symmetric density functions, as in (4) and (5). Assume that both systems admits well-defined I-O static characteristics which intersect in a finite number of points. Then, any bounded solution of the closed-loop system converges to a single equilibrium. □

Before stating our main result concerning occurrence of multistability in positive feedback loops we state a lemma (of independent interest and whose proof is postponed to the appendix) which will be used in the proof of the Main Result.

**Lemma II.6:** Let \( x_e \) be an hyperbolic equilibrium, corresponding to the constant input \( u_c \) relative to a \( C \in \mathbb{R}^n \) dynamical system as in (1). Assume that the system has CCW Input-Output dynamics with respect to some density function \( \rho(u, y) \) of class \( C \). Then, the linearized system at \( x_e, u_c \)

\[
\dot{x}_L = \frac{\partial f}{\partial x}|_{x=x_e,u=u_c} x_L + \frac{\partial f}{\partial u}|_{x=x_e,u=u_c} u
\]

enjoys the CCW dynamics property (with respect to the density function \( \rho = 1 \)). □

**Remark II.7:** Even assuming strict CCW dynamics for the nonlinear system in Lemma II.6, we were not able to prove strict CCW dynamics for the linearized system. Indeed we conjecture that such a conclusion is in general not possible. However, the set \( N^* \) of asymptotically stable SISO linear systems for which CCW dynamics hold in a non-strict sense is a zero-measure set in the Euclidean space of coefficients \( (A, B, C) \) characterizing a linear system according to the usual equations \( \dot{x} = Ax + Bu, y = Cx \). In fact, letting

\[
S_{CCW} := \{(A, B, C) \in \mathbb{R}^{n \times n} \times \mathbb{R}^{n \times 1} \times \mathbb{R}^{1 \times n} : A \text{ is Hurwitz and Im}[C(j\omega I - A)^{-1}B] < 0, \forall \omega > 0\}
\]

by Theorems 1 and 2 of [1] it follows: \( N^* \subset S_{CCW} \cap \{(A, B, C) : A \text{ is Hurwitz}\} \). In particular, by the Routh-Hurwitz criterion and the KYP Lemma (see for instance [22]), \( S_{CCW} \) is open and semialgebraic (it can be seen as the projection of a set defined on some extended space by polynomial inequalities, hence by quantifier elimination it is itself a semialgebraic set). As a consequence, \( \dim(\partial S_{CCW}) < \dim(S_{CCW}) \), (see page 52, paragraph I.2.9.2 of [28] ). As clarified in [1], asymptotically stable linear systems with CCW I-O dynamics may present a non-empty set of critical frequencies, \( \Omega_c = \{\omega > 0 : \text{Im}[C(j\omega I - A)^{-1}B] = 0\} \). By the above considerations, however, the possibility of having \( \Omega_c \) non-empty is a degenerate situation, so that generally the conclusions of Lemma II.6 may be strengthened to strict CCW dynamics. □

We are now ready to state our main result concerning occurrence of multistability in positive feedback loops:
Theorem 2: Consider the following positive feedback interconnection of SISO finite-dimensional nonlinear systems:

\[
\begin{align*}
\dot{x}_1 &= f_1(x_1, u_1) \\
y_1 &= h_1(x_1) \\
\dot{x}_2 &= f_2(x_2, u_2) \\
y_2 &= h_2(x_2) \\
u_1 &= y_2 & u_2 &= y_1
\end{align*}
\] (9)

and in turn \( y_1 = k_1(u_1) = k_1(y_2) = k_1(k_2(u_2)) = k_1 \circ k_2(y_1) \). Therefore \( y_1 \) at equilibrium can be computed by looking at the fixed points of the map \( k_1 \circ k_2 \). Let \( y_{1e} \) denote any such fixed point. The equilibria of the original system are then computed according to: \( x_e = [k_21(k_2(y_{1e}))', k_22(y_{1e})']' \). Hence equilibria are in one-to-one correspondence with the fixed points of \( k_1 \circ k_2 \).

Step 3: The next step consists in a local stability analysis of the equilibria in question. By Lemma II.6, under the hyperbolicity assumption, also the linearized \( x_1 \) and \( x_2 \) subsystems have CCW I-O dynamics, though, possibly in a non-strict sense. By Assumption 3., however, at least one of the two linearized subsystems has an empty set of critical frequencies, so that we may apply Theorem 5 of [1]. This, in turn, provides necessary and sufficient conditions for exponential stability and instability of the linearized system (8) at the equilibrium \( x_e \) in terms of DC-gains of the individual subsystems. In particular, since slopes of I-O characteristics compute the DC-gain of the linearized system at the corresponding equilibrium, we have, under the assumption of transversality between the diagonal and \( k_1 \circ k_2 \), that

\[
G_1(0) \cdot G_2(0) \neq 1
\]

where we denoted by \( G_1(s) \) and \( G_2(s) \) the transfer functions of the linearized \( x_1 \) and \( x_2 \) subsystems. Therefore, we may apply items 1 or 2 of Corollary V.2 of [1] in order to conclude that fixed-points for \( [k_1 \circ k_2]' \neq 1 \) are asymptotically stable for the linearized system, and hence locally exponentially stable for the original nonlinear system. Conversely, \( G_1(0) \cdot G_2(0) > 1 \) implies, by item 2 in Corollary V.2 of [1], existence of an exponentially unstable equilib-rium which, therefore, is such also as far as the original nonlinear system is concerned. This concludes the local stability analysis, based on slopes of I-O characteristics.

Step 4: We already established that all solutions converge; we only need to prove that solutions converging to unstable equilibria are non generic, viz. correspond to a zero-measure set of initial conditions. The fact that stable manifolds of an exponentially unstable equilib-rium (not necessarily hyperbolic) have zero-measure is an easy consequence of Theorem 2.1 in [21]. This concludes the proof of our main result.

Remark II.8: The analog of Theorem 2 which holds for monotone Input-Output systems has a very simple frequency domain interpretation in the case of linear systems. Monotonicity, in fact, yields the following important property: \( G(\omega) \geq |G(j\omega)| \) for all \( \omega \in \mathbb{R} \) (where \( G(s) \) denotes the transfer function of the system). In other words, the DC-gain of the system also coincides with the \( L_2 \rightarrow L_2 \) induced gain. Under such premises it becomes clear why stability or instability of positive feedback interconnections can be determined just by
looking at the corresponding Nyquist diagram. If \( G_1(0) \cdot G_2(0) < 1 \) gives asymptotic stability and \( G_1(0) \cdot G_2(0) > 1 \) implies exponential instability. Similarities between Theorem 2 of the present paper and Theorem 3 in [5] clearly hint at the possibility that a broader class of systems, comprising ccw systems on one hand and monotone systems on the other, could exist so that a statement analogous to Theorem 2 still holds. At least for the linear case, a class of systems with this feature can be easily identified by requiring ccw behaviour over a certain range of frequencies, and, complementarily, a monotone-like behaviour for higher frequencies, namely:

- \( \text{Im}[G(j\omega)] < 0 \) for all \( \omega \in (0, \bar{\omega}) \);
- \( |G(j\omega)| < G(0) \) for all \( \omega \in [\bar{\omega}, +\infty) \).

We emphasize that such a property is really a natural requirement for many dynamical systems of interest [19]; as a matter of fact, the natural filtering capabilities of integrators tend to result in low gains at high frequencies; similarly, the phase-lag introduced at low frequencies is often limited in the range \([-\pi, 0]\). It is intuitive that closed-loop stability of the feedback interconnection of two such systems can be performed by looking at the corresponding Nyquist diagram. If \( \bar{\omega} \) is the same for both systems, then the only intersections with the real axis may happen at frequency 0 or \( \omega = \bar{\omega} \). Therefore, since for \( \omega > \bar{\omega} \) we have \( |G_i(j\omega)| < G_i(0) \) for both subsystems, stability or instability is again governed just by the product of static gains. It is an open question if a similar argument can be extended to nonlinear systems by making use of suitable time-domain interpretations of the above properties. \( \Box \)

**Remark II.9:** Thanks to the considerations expressed in Remark II.7, assumption 3. of Theorem 2 is extremely mild. We may argue that it is generically fulfilled. Indeed, this assumption is the price to pay for choosing a notion of strict ccw dynamics that is nonuniform and “nonlinear” in spirit (it makes in fact use of positive definite and class \( \mathcal{K}_{\infty} \) functions), whereas for linear systems, strict dissipation inequalities always take the form of quadratic dissipation rates. This gap, between arbitrary dissipation rates versus quadratic dissipation rates (which, preferably, are adopted in standard passivity literature), is responsible for a weaker statement of Theorem 2. Under the assumption of quadratic dissipation rates for strict ccw dynamics, linearization at hyperbolic equilibria turns out to preserve strict ccw dynamics as well (see Lemma A.2), so that Theorem 2 can be restated under this additional assumption dropping assumption 3. \( \Box \)

**Remark II.10:** It is worth pointing out that the analogous of Theorems 1 and 2 hold for feedback interconnections of the following type:

\[
\begin{align*}
\dot{x} &= f(x, u) \\
y &= h(x) \\
u &= k_2(y)
\end{align*}
\] (12)

in which the \( x \)-subsystem has strictly ccw I-O dynamics from \( u \) to \( y \) with respect to some density function \( \rho \), whereas the system in feedback is static and described therefore by its static I-O characteristic \( k_2 \), provided that \( k_2 \) be a function with ccw I-O dynamics. It will be shown in the next Section that scalar nonlinearities always satisfy the property with respect to arbitrary density functions. \( \Box \)

III. Examples of systems with ccw I-O dynamics

In general, finding Lyapunov functions which allow to test ccw dynamics may be a very difficult task; this is particularly true if models are only approximately known and involve uncertain parameters as is often the case in systems biology. For this reason, it is useful to have a library of examples for which the property holds, irrespectively of parameters or even of the particular shape of nonlinearities involved. A broad class of systems which enjoy the property because of their very structure is the class of Hamiltonian Systems. This is a well-known fact, already pointed out in the companion paper [1], and we only recall it here for the sake of completeness. However, mathematical models in other fields of science and engineering, are often not nearly as structured. Before starting the discussion of specific cases, it is useful to consider the following Lemma which, due to space limitations, is stated without proof.

**Lemma III.1:** Let \( g(x) : X \to \mathbb{R}_{\geq 0} \) be a continuous function, satisfying the implication below:

\[ h(x) \neq 0 \implies g(x) > 0 \quad \forall x \in X \]

for some continuous function \( h(x) : X \to \mathbb{R}^m \) and some closed set \( X \subset \mathbb{R}^n \). Then, there exists \( \rho \) positive definite and \( \gamma \) of class \( \mathcal{K} \) such that:

\[ g(x) \geq \frac{\rho(|h(x)|)}{1 + \gamma(|x|)} \quad \forall x \in X. \] (13)

Moreover, for compact \( X \), the class \( \mathcal{K} \) function \( \gamma \) can be taken equal to 0 without loss of generality. \( \Box \)

The above Lemma will be used in order to establish strict ccw dynamics. It shows that the dissipation margin adopted in the definition of ccw dynamics (viz. \( \rho(|y|)/[1 + \gamma(|x|)] \) ) is actually equivalent to the minimal requirement that the dissipation inequalities characterizing ccw dynamics be strict whenever \( \dot{y} \neq 0 \) (at least in the case of systems with relative degree higher than 1; if the relative degree equals one then the positivity
follows that under the assumption that $k$ is continuous of a certain given compact set included in $\mathbb{R}^n$. Interconnections of $\mathbb{R}^n$ hold with respect to arbitrary Input-Output pairs. If, in addition, $\lim \inf_{t \to \infty} |k'(u)| > 0$ then $\mathbb{R}^n$ is intervals of the real line. The nonlinear system are intervals of the real line. The nonlinear system

\begin{align*}
\dot{y}(t) &= \psi(t, \xi, u(t)) \\
\dot{u}(t) &= k(u(t))
\end{align*}

is again $\mathbb{R}^n$ for arbitrary density functions as long as solutions of (14) exist and are sufficiently smooth. Let $(\xi, u) \in \mathcal{S}_{1\|T}$ be arbitrary and $y(t) = \psi(t, \xi, u)$ absolutely continuous, where $\psi$ and $\mathcal{S}_{1\|T}$ both refer to the closed-loop system (14). We want to estimate the integral (3) along trajectories. We have:

\begin{align*}
\int_0^T \tilde{\psi}(t) \int_0^{u(t)} \rho(\mu, y(t)) \, d\mu \, dt &= \int_0^T \tilde{\psi}(t) \int_0^{u(t)} \rho(\mu, y(t)) \, d\mu \, dt \\
&= \int_0^T \tilde{\psi}(t) \int_0^{u(t)} \rho(\mu, k(y(t))) \, d\mu \, dt
\end{align*}

Proof: Let us express the area spanned on the $(u, y)$ plane through the following equation:

\begin{align*}
\int_0^T \tilde{\psi}(t) \int_0^{u(t)} \rho(\mu, k(u(t))) \, d\mu \, dt &= \tilde{\psi}(t) \int_0^{u(t)} \rho(\mu, k(u(t))) \, d\mu \\
&= F(u(T)) - F(u(0))
\end{align*}

where $F(u) = \int_0^u \tilde{k}(s) \int_0^s \rho(\mu, k(s)) \, d\mu \, ds$. Then, letting $T \to +\infty$ for bounded inputs $u(\cdot)$ and exploiting continuity of $F$ yields the desired property. Moreover, under the assumption that $k'$ be positive on the complement of a certain given compact set included in $\mathcal{U}$, it follows that $F(u)$ is lower-bounded, and therefore, $\mathbb{R}^n$ dynamics can be concluded for arbitrary inputs.

B. Interconnections of $\mathbb{R}^n$ systems with static nonlinearities

Unlike the notion of $\mathbb{R}^n$ Input-Output dynamics given in [1], which, thanks to bilinearity, is preserved under parallel and positive feedback interconnections, the case of $\mathbb{R}^n$ dynamics with respect to some or arbitrary density functions appears to be more complex. It is still an open question to what extent such interconnections preserve the property or not. However, the case of SISO systems in connection with static scalar nonlinearities is relatively simpler to derive. Interconnections with scalar monotone systems will be addressed later on in the Section.

C. Feedback interconnections

Let us consider the following interconnection of dynamical systems:

\begin{align*}
y_1(t) &= \psi(t, \xi_1, u_1) \\
y_2(t) &= k(u_2(t)) \\
u_1 &= y_2 + u \\
y &= y_1 + u.
\end{align*}

We assume that the dynamical system $\psi$ is SISO and enjoys $\mathbb{R}^n$ Input-Output dynamics with respect to arbitrary density functions, while $k : \mathbb{R} \to \mathbb{R}$ is continuous. We show that the resulting closed-loop system

\begin{align*}
y_1(t) &= \psi(t, \xi_1, u_1) \\
y_2(t) &= k(u_2(t)) \\
u &= u \\
y &= y_1 + u
\end{align*}

Both functions are strictly monotone, $\mathbb{R}^n$ and invertible. Hence, without loss of generality we may prove the result for the case an invertible $\mathbb{R}^n$ function $k$. We
have through tedious but straightforward calculations:
\[ \int_0^T \dot{y}(t) \int_0^{y(t)} \rho(\mu, y(t)) \, d\mu \, dt \]
\[ = \int_{y(0)}^{y(T)} \int_0^{\kappa^{-1}(\eta - y_1(t))} \rho(\mu, \eta) \, d\mu \, d\eta \]
\[ + \int_0^T \dot{y}(t) \int_0^{y(t)} \rho(\mu, k(\mu) + y_1(t)) \, d\mu \, dt \]
\[ + \int_{y(1)}^{y(T)} \int_{-\eta}^{0} \rho(k^{-1}(\lambda), \lambda + \eta) [k'(k^{-1}(\lambda))]^{-1} \, d\lambda \, d\eta. \]

Notice that \( u \) and \( y \) bounded implies, by continuity of \( k \), that \( y_1 \) is also bounded. Hence, the claim follows by taking lim inf in both sides of the previous equations and exploiting CCW dynamics of \( \psi \) with respect to arbitrary density functions \( \rho \). The same argument applies in order to show that the parallel of a scalar nonlinearity with a system with CCW Input-Output dynamics with respect to some density function \( \tilde{\rho} \) is again CCW with respect to the density function \( \rho \) (possibly different), defined as \( \rho(u, y) = \tilde{\rho}(u, y - k(u)) \).

**E. Scalar monotone systems**

Consider the scalar nonlinear system:
\[ \dot{x} = f(x, u) \quad y = h(x) \]  \hspace{1cm} (16)

with \( x \in X \subset \mathbb{R} \) a closed invariant interval for the system dynamics and \( u \in U \subset \mathbb{R} \) a closed bounded interval (the case of \( U \) unbounded follows as a corollary from the case of \( U \) bounded). Assume that \( f(x, \cdot) \) is strictly increasing for any given \( x \in X \) with respect to \( u \in U \subset \mathbb{R} \) and that \( h \) be differentiable almost everywhere and such that \( \partial h / \partial x > 0 \) for almost all \( x \in X \). Then, the system has strictly CCW I-O dynamics with respect to arbitrary density functions \( \rho \).

**Proof:** Let us define \( \gamma(x) = \arg\min_{u \in U} |f(x, u)|^2 \). \hspace{1cm} (17)

By continuity and strict monotonicity of \( f \) with respect to \( u \), \( \gamma(x) \) is well-defined, single-valued and continuous. By monotonicity of \( f \) with respect to \( u \) we have that \( \dot{y}(t) \geq 0 \) implies \( u(t) \geq \gamma(x(t)) \), (and similarly \( \dot{y}(t) \leq 0 \Rightarrow u(t) \leq \gamma(x(t)) \)). Moreover, inequalities are strict whenever \( \dot{y}(t) \neq 0 \) and \( u(t) \in \text{int}(U) \). Hence, taking the area from time 0 to \( T \) yields:
\[ \int_0^T \dot{y}(t) \int_0^{u(t)} \rho(\mu, y(t)) \, d\mu \, dt \]
\[ \geq \int_0^T \dot{z}(t) \int_0^{\gamma(x(t))} \rho(x, y(t)) \, d\mu \, dt \]
\[ = F(x(T)) - F(x(0)) \]  \hspace{1cm} (18)

where \( F(x) = \int_0^x \partial h(\xi) \int_0^{\rho(\mu, h(x))} \, d\mu \, d\xi \). Since \( F \) is continuous, the function \( F(x(t)) \) is bounded along any bounded trajectory, and therefore the system has CCW Input-Output dynamics with respect to arbitrary density functions; moreover, since the inequality in (18) is strict if and only if \( \dot{y}(t) \neq 0 \), CCW dynamics hold in the strict sense by virtue of Lemma III.1 for any input signal taking values in any compact interval included in \( \text{int}(U) \).

\[ \text{Fig. 1. Relative degree 2 systems with } \rho \text{ CCW dynamics} \]

**F. Planar systems of relative degree 2**

Consider the following nonlinear bidimensional system:
\[ \dot{x} = f_1(x, y, u) \]
\[ \dot{y} = f_2(x, y) \]  \hspace{1cm} (19)

with output \( y \), input \( u \in U \subset \mathbb{R} \) a closed interval and state \((x, y) \in X \subset \mathbb{R}^2 \) a closed invariant set, with the property that \( X \cap [\mathbb{R} \times \{y_0\}] \) is an interval (possibly empty) for all \( y_0 \in \mathbb{R} \). We assume that \( f_1 \) and \( f_2 \) are locally Lipschitz functions and that the following monotonicity conditions hold:

1. \( f_1 \) is increasing in \( u \) and decreasing in \( x \)
2. \( f_2 \) is increasing in \( x \) and decreasing in \( y \); moreover \( \partial f_2 / \partial y(x, y) \) can be upperbounded, for all \( y \) in any compact set, by a locally summable function of \( x \).

Then, the system has strict CCW dynamics with respect to some density function \( \rho(u, y) \) whose explicit expression will be given later in the proof, provided that the Bounded Input-Output Bounded State Property holds.

**Proof:** Let us define the function \( g_x(y, \dot{y}) \) as follows:
\[ g_x(y, \dot{y}) := \arg\min_{x \in X : (x, y) \in X} [f_2(x, y) - \dot{y}]^2. \]  \hspace{1cm} (20)

\( \text{(notice that for definition (20) to make sense it must hold } (x, y) \in X \text{ for at least some scalar } x) \text{. Moreover, since any section of } X \text{ at a specific value of } y \text{ is an interval, and } f_2 \text{ is (strictly) increasing with respect to } x, \text{ then (20) is uniquely defined. The function } g_x \text{ enjoys certain monotonicity properties. In fact, monotonicity of } f_2 \text{ yields } g_x \text{ is non-decreasing with respect to } \dot{y} \text{ (viz. with respect to its second argument) and non-decreasing with respect to } y. \text{ Notice that } f_2(x, y) \geq 0 \text{ implies } x = g_x(y, f_2(x, y)) \geq g_x(y, 0) \text{ and therefore } f_1(x, y, u) \leq f_1(g_x(y, 0), y, u). \text{ A symmetric inequality holds whenever } f_2(x, y) \leq 0 \text{ so that combining the 2 cases we have:} \]
\[ f_2(x, y)[f_1(x, y, u) - f_1(g_x(y, 0), y, u)] \leq 0. \]
This will be used in the next series of inequalities. Let us first define $\rho(u, y)$:

$$
\rho(u, y) = \frac{\partial f_1}{\partial u} (g_x(y, 0), y, u). \tag{21}
$$

By strict monotonicity of $f_1$ with respect to $u$, this is indeed a positive function almost everywhere. We then proceed to estimate the area spanned along solutions:

$$
\begin{align*}
\dot{y}(t) & \cdot \int_0^{\eta(t)} \rho(\mu, y(t)) \, d\mu \\
& \geq \dot{y}(t) \cdot \int_0^{\eta(t)} \rho(\mu, y(t)) \, d\mu \\
& = \dot{y}(t) \cdot \int_0^{\eta(t)} \frac{\partial f_1}{\partial u} (g_x(\eta, 0), \eta, y) \, d\eta \\
& = \frac{d}{dt} \left[ \int_0^{\eta(t)} f_1(\xi, y(t)) \, d\xi - \int_0^{\eta(t)} f_1(\xi, y(0), y(0)) \, d\eta \right] \\
& - \int_0^{\eta(t)} \left[ \frac{\partial f_1}{\partial y} (\xi, y(t)) \right] \cdot \dot{y}(t) \\
& \geq \frac{d}{dt} \left[ \int_0^{\eta(t)} f_1(\xi, y(t)) \, d\xi - \int_0^{\eta(t)} f_1(\xi, y(0), y(0)) \, d\eta \right] \\
& - \int_0^{\eta(t)} \left[ \frac{\partial f_1}{\partial y} (\xi, y(t)) \right] \cdot \dot{y}(t)
\end{align*}
$$

which holds and is well defined by virtue of Lebesgue Dominated Convergence Theorem, under the summability assumptions on $\partial f_2/\partial y$. Moreover, since for any \((x(t), y(t)) \in \text{int}(X)\) we have $\dot{y}(t) > 0$ \Rightarrow $x(t) > g_x(y(t), 0)$, and similar inequalities hold for the symmetric case $\dot{y}(t) < 0$, the second inequality in (22) is actually strict whenever $\dot{y}(t) \neq 0$ and \((x(t), y(t)) \in \text{int}(X)\). Therefore, by virtue of Lemma III.1, ccw dynamics hold in a strict sense provided that trajectories are bounded away from $\partial X$, viz. there exists a compact $K_X \subset \text{int}(X)$ such that $x(t) \in K_X$ for all sufficiently large $t$.

Notice that we did not assume any sign definiteness for $\frac{\partial f_1}{\partial y}$. The result applies in particular to the cooperative case $\frac{\partial f_1}{\partial y} \geq 0$ and also to the “predator-prey” case, $\frac{\partial f_1}{\partial y} \leq 0$. As a consequence of the previous discussion, just by letting $\dot{x} = -x$, we also obtain similar results for the competitive case. A complete list of the sign patterns which are allowed is shown in Fig. III-P with the convention that a solid edge denotes a positive value in the corresponding entry of the Jacobian, while a dashed line stands for a negative entry (notice that the list includes all and only the sign patterns which comprise an even number of negative edges in the directed path from $u$ to $y$).

**G. Tridiagonal cooperative systems of relative degree 1**

In this paragraph we consider $n$-dimensional tridiagonal systems of the following form:

$$
\begin{align*}
\dot{x}_1 &= f_1(x_1, x_2, u) \\
\dot{x}_2 &= f_2(x_1, x_2, x_3) \\
& \vdots \\
\dot{x}_n &= f_n(x_{n-1}, x_n) \\
y &= x_1
\end{align*}
$$

where we assume that the $f_i$s are $C^\infty$ functions and satisfying the following monotonicity properties:

1. $f_1$ is increasing with respect to $x_2$ and $u$; in particular $\partial f_1/\partial u > 0$
2. $f_i$ is increasing with respect to $x_{i-1}$ and $x_{i+1}$, for all $i = 2 \ldots n - 1$ and in particular $\partial f_1/\partial x_{i-1} > 0$
3. $f_n$ is increasing with respect to $x_{n-1}$ and in particular $\partial f_n/\partial x_{n-1} > 0$

We claim that system (23) has strictly ccw Input-Output dynamics with respect to arbitrary density functions $\rho$, defined in the $u, y$ plane, provided it satisfies the Bounded Input-Output Bounded State Property. The proof is similar in spirit and generalizes the one pursued in [12]. We show the result by induction. For $n = 1$ the result boils down to the scalar case and was proved in the previous subsection. The induction argument is based on the following Lemma.

**Lemma III.2:** Consider a monotone scalar system ($y$-subsystem below) connected in positive feedback to a system with ccw I-O dynamics with respect to arbitrary density functions ($x$-subsystem):

$$
\begin{align*}
\dot{y} &= f_1(y, v, u) \\
\dot{x} &= f_2(x, y) \\
v &= h_2(x),
\end{align*}
$$

where $y \in \mathbb{R}$, $x \in \mathbb{R}^n$, $v \in \mathbb{R}$ and $f_1 : \mathbb{R}^3 \to \mathbb{R}$ is increasing with respect to $u$ and $v$; moreover $\partial f_1/\partial u$ is positive. Then, the resulting closed-loop system (24) has Counter-Clockwise I-O dynamics (from $u$ to $y$) with respect to arbitrary density functions provided that the overall system satisfies the Bounded Input-Output Bounded State property. Moreover, the property is strict provided that $u(t) \in K$ for all $t \geq 0$, given some compact $K \subset \text{int}(U)$.

**Proof:** Let us consider any initial condition $\xi$ for the closed-loop system, and any input signal $u$, so that $(\xi, u) \in S_{[0]}$; let $y(t)$ be the output of (24). We denote by $x(t)$ the corresponding solution for the $x$-subsystem and $\nu(t) := h_2(x(t))$ the relative output. By boundedness of $u(t)$ we may define $u_{\min} = \min_{t \geq 0} u(t)$ and $u_{\max} = \max_{t \geq 0} u(t)$. Monotonicity of $f_1$ ensures the existence of an inverse function $g_u(y, v, \dot{y}) : \mathbb{R}^3 \to \mathbb{R}$.
so that $g_u(y, v, f_1(y, v, u)) = u$. Since $g_u$ may not be defined for all $y, v$ and $\hat{y}$ we extend it as follows:

$$\hat{g}_u(y, v, \hat{y}) := \arg \min_{\nu \in [\min, \max]} |f_1(y, v, u) - \hat{y}|^2 \quad (25)$$

By the implicit function theorem $g_u$ is $C^\infty$ whenever defined, moreover, by monotonicity of $f_1$, it is increasing with respect to $y$ and decreasing with respect to $\hat{y}$. Accordingly, $\hat{g}_u$ is non-decreasing with respect to $y$ and non-increasing in $v$. By strict positivity of $\partial f_1/\partial u$ and the implicit function Theorem, $\partial g_u/\partial v$ is a continuous function, and hence locally integrable in $y$ and $v$. As a consequence, local integrability of $\partial \hat{g}_u/\partial v$ also follows (since $\hat{g}_u$ is just a saturated version of $g_u$).

$$\int_0^y \int_0^v \hat{g}_u(\xi, v(t), 0, \xi) \frac{\partial \hat{g}_u}{\partial v}(\xi, v(t), 0) d\xi dt. \quad (26)$$

where $F$ is defined according to:

$$F(y, v) = \int_0^y \int_0^v \hat{g}_u(\xi, v, 0) \partial f_u(\mu, v) \partial u d\xi$$

and is therefore a continuous function. Since $\frac{\partial \hat{g}_u}{\partial v}$ exists almost everywhere (in the domain of $\hat{g}_u$) and is less than 0 whenever it exists we may regard

$$\hat{\rho}(y, v) := -\rho(\hat{g}_u(y, v, 0), y) \frac{\partial \hat{g}_u}{\partial v}(y, v, 0)$$

as a density function in the $(y, v)$-plane. Thus, for arbitrary density functions $\rho(u, y)$ the following holds:

$$\int_0^y \int_0^v \hat{g}_u(\xi, v(t), 0, \xi) \frac{\partial \hat{g}_u}{\partial v}(\xi, v(t), 0) d\xi dt \geq \int_0^y \int_0^v \hat{\rho}(\xi, v(t), 0) d\xi dt$$

By assumption the $x$ subsystem has CCW dynamics with respect to arbitrary density functions, hence: equation $(27)$, boundedness of $y$ and $v$ together with continuity of $F$ yield the desired result for any dimension $n$.

**H. Feedback interconnections with scalar systems**

The induction argument in the previous subsection is based on the fact that positive feedback with scalar monotone systems preserves CCW dynamics with respect to arbitrary density functions. The next natural question is to investigate if a similar result holds for systems which are CCW with respect to some density function. This is actually the case as shown in the next Lemma, under some additional technical assumption.

**Lemma III.3:** Consider the positive feedback interconnection in (24), where $y, u, v$ are scalar variables and $x \in \mathbb{R}^n$. Let $f_1 : \mathbb{R} \times V \times U \to \mathbb{R}$ be a $C^\infty$ function, increasing with respect to $u$ and $v$, in particular with $\partial f_1/\partial u > 0$, and unbounded as $u \to \pm \partial U$ for any $y$ and $v$. Assume further that the $x$-subsystem has CCW I-O dynamics with respect to some density function $\rho(v, y)$, from input $y$ to output $v$. Then, the resulting closed-loop system (24) from $u$ to $y$ enjoys CCW I-O dynamics with respect to some density function $\rho$, (possibly different from $\rho$).

**Proof:** Consider the inequalities in (26) where $\hat{g}_u : \mathbb{R}^3 \to \mathbb{R}$ is defined according to (25) and always satisfies $f_1(y, \hat{g}_u(y, v, \hat{y}), v) = \hat{y}$ for any $\hat{y}$ in $\mathbb{R}$ and any $y, v$ because of the unboundedness assumption with respect to $u$. Let $\hat{\rho} : \mathbb{R}^2 \to \mathbb{R}_{>0}$ be a suitable density function which will be defined later. In order to estimate the area in (26) we set $\hat{\rho}$ according to

$$\hat{\rho}(u, v) = -\frac{\rho(g_u(y, u, 0), y)}{\partial g_u/\partial v}(y, u, 0) \quad (28)$$

where $g_u : \mathbb{R}^3 \to \mathbb{R}$ is uniquely defined by the following implicit equation: $g_u(y, u, f_1(y, v, u)) = v$. Notice that $\partial g_u/\partial v < 0$ almost everywhere and this is why $\hat{\rho}$ is non-negative and well defined.

Since $\hat{\rho}(\hat{g}_u(y, v(t), 0), y) \frac{\partial \hat{g}_u}{\partial v}(y, v(t), 0) = \rho(v, y)$, we have (27) holds. Therefore, taking integrals and limits in both sides of such inequality yields the claim (thanks to the CCW assumption on the $x$-subsystem).

**IV. AN EXAMPLE OF MULTISTABILITY**

The application of the theorems discussed so far is illustrated through an example which, though not related to any specific biological model, is designed by having in mind the typical nonlinearities which are met in such systems (see [2] for a biologically meaningful example). It is of sufficiently high dimension to make it interesting, yet feasible for rigorous analysis. We consider the following systems of equations:

$$\begin{align*}
\dot{s}_1 &= -k_1 s_1 + k_2 s_2 + 9.2 \frac{s_1^5}{s_1 + z_1^3} \\
\dot{s}_2 &= -(k_2 + k_3) s_2 + k_1 s_1 + k_4 s_3 \\
\dot{s}_3 &= -(k_4 + k_5) s_3 + k_5 s_2 \\
\dot{z}_1 &= -z_1^3 + \frac{s_1^5}{s_1 + z_1^3 + z_2} \\
\dot{z}_2 &= -z_2^3 + \frac{s_1^5}{s_1 + z_1^3 + z_2} + 0.5 \frac{0.2 + 0.001 s_1^2}{1 + 0.001 s_1^2}
\end{align*} \quad (29)$$

where the parameters are chosen as follows: $k_1 = 0.2$, $k_2 = 0.3$, $k_3 = 1$, $k_4 = 0.2$, $k_5 = 0.1$. Notice, first of all, that the positive orthant is invariant for (29). Hence, we may take $\mathbb{R}_{\geq 0}^5$ as the state space of our system.
Moreover, the Jacobian matrix is sign-definite throughout the state-space; the corresponding sign-pattern is graphically represented in Fig. 2, using the convention that a positive entry in an off-diagonal position of the Jacobian can be represented by a solid edge in the corresponding graph, while dashed ones stand for a negative entry. This representation is useful to realize that, due to the presence of a negative loop (viz. a loop comprising an odd number of dashed edges) the theory of monotone systems cannot be straightforwardly applied. Next, we interpret this system as the positive feedback interconnection of two subsystems, respectively the z and s subsystem, having defined $z = [z_1, z_2]'$ and $s = [s_1, s_2, s_3]'$. In particular then:

$$
\begin{align*}
\dot{s}_1 &= -k_1 s_1 + k_2 s_2 + 9.2 \frac{u_5^5}{1+u_5^5} \\
\dot{s}_2 &= -(k_2 + k_3) s_2 + k_1 s_1 + k_4 s_3 \\
\dot{s}_3 &= -(k_4 + k_5) s_3 + k_3 s_2 \\
\dot{y}_s &= s_1 \\
\dot{z}_1 &= -z_1^3 + \frac{z_1^2}{1+z_1+z_2} \\
\dot{z}_2 &= -\frac{z_2^3}{1+z_1+z_2} + 0.5 \frac{0.2+0.001u_3^3}{1+0.001u_3^3} \\
\dot{y}_z &= z_1
\end{align*}
$$

(30)

with the interconnection rule $u_s = y_z$ and $u_z = y_z$. The s subsystem is a tridiagonal cooperative linear system, (asymptotically stable for any positive choice of the $k_i$'s) which is forced by a bounded signal $u_3^3/(1+u_3^3)$. Hence, boundedness of the s-trajectory trivially holds. As for the z subsystem we have the following inequality:

$$
\dot{z}_1 + 2 \dot{z}_2 \leq -z_1^3 - \frac{z_2^2}{1+z_1+z_2} + 1. \quad (31)
$$

Fig. 2. Sign pattern of Jacobian matrix, graphical representation

Hence, if $|z|$ is sufficiently large, (and therefore either $z_1$ or $z_2$ is large), the right-hand side of (31) is negative. Since, $z_1 + 2z_2$ is a radially unbounded function (with respect to the positive orthant) we may conclude boundedness of the z component of the solution for arbitrary initial conditions in the positive orthant as well. Counter-clockwise dynamics of the two subsystem is easily detected by making use of the theorems previously discussed. The s subsystem is in fact a tridiagonal cooperative system of relative degree 1, and the z subsystem is a planar system of relative degree 2 corresponding to a “predator-prey” sign-pattern. Hence, the s subsystem enjoys ccw dynamics with respect to arbitrary density functions, while the z subsystem is ccw only with respect to some density function. Moreover, since there are no solutions confined on the boundary of $\mathbb{R}_2^{2,0}$, both properties hold in a strict sense. We are now left to show that both systems admit well-defined and hyperbolic Input-Output characteristics. The s subsystem admits an input-output characteristic that can be computed analytically. It is in fact the cascade of a static nonlinearity with a third order asymptotically stable linear system. Explicit computation gives $y_s \simeq 87.5 \cdot \frac{u_5^5}{1+u_5^5}$. The z subsystem is globally asymptotically stable for each constant value of the input $u_z$. This can be easily shown by Poincaré-Bendixson criterion by noticing that the divergence is always negative. Moreover, the Jacobian has a sign-pattern which is asymptotically stable regardless of the specific values of its entries, see [17]. Despite this, analytical determination of the Input-Output characteristic is not easy due to the specific form of the nonlinearities. We evaluated it by numerically integrating the solution corresponding to a slowly varying monotone input signal, thus obtaining the shape in Figure 3. Hence, application of Theorem 2 implies that all solutions converge to equilibria, and their stability can be investigated looking at the intersections of the Input-Output characteristics of the individual subsystems. Strictly speaking, the conclusions of the Theorem only hold if assumption 3) is fulfilled. This can be checked straightforwardly. Simulations starting from a grid of initial conditions of the type $[0, 0, 0, z_1(0), 0]$ or $[1, 0, 0, z_1(0), 0]$ are shown in Figure 4. Solutions converging to different asymptotically stable equilibria (both labeled with an X) are plotted using different line styles (respectively solid and dashed). Notice, that only the $z_1$ and $s_1$ components of the state have been plotted, this is therefore not a phase-plane analysis (and characteristics are not nullclines), but just a projection on a bidimensional plane of solutions evolving in $\mathbb{R}^5$. This justifies the presence of intersections between trajectories. Nevertheless, it is apparent, comparing Fig. 3 and 4, that the simple characteristics plot carries a lot of information on the actual systems trajectories.

V. Conclusions

The paper extends and elaborates on the theory of systems with Counter-Clockwise dynamics, by making use of suitable density functions defined on the input-output plane and by showing how to use such notions in the analysis and prediction of multistable behaviour. In particular, a criterion which on the basis of Input-Output measurements performed at steady-state for individual subsystems is capable of fully characterizing the stability and convergence properties of their positive feedback interconnection, is derived, under the ass-
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References

APPENDIX

I. PRESERVATION OF CCW DYNAMICS UNDER LINEARIZATION

Before proving lemma II.6 it is useful to introduce a frequency domain characterization of ccw dynamics with respect to a density function \( \rho \).

**Proposition A.1:** For a SISO hyperbolic finite dimensional linear system:

\[
\dot{x} = Ax + Bu \\
y = Cx,
\]

with the pair \((A, B)\) completely reachable the following facts are equivalent:

1. the system has ccw Input-Output dynamics (with respect to \( \rho = 1 \))
2. the system has ccw Input-Output dynamics with respect to some density function \( \rho : \mathbb{R}^2 \to \mathbb{R}_{>0} \)
3. the frequency response \( G(j\omega) := C(j\omega I - A)^{-1}B \) satisfies:

\[
\text{Im}[G(j\omega)] \leq 0 \quad \forall \omega \geq 0
\]

**Proof:** Implication 1 \( \Rightarrow \) 2 is obvious. We look next at the implication 2 \( \Rightarrow \) 3. The proof is carried out by contradiction. Assume that there exists \( \omega > 0 \) such that \( \text{Im}[G(j\omega)] > 0 \). Let \( u(t) = \sin(\omega t) \). There exists an initial condition \( \xi \) such that \( y(t) = \psi(t, \xi, u(t)) = (G(j\omega)) \sin(\omega t + LG(j\omega)) \). Computing the area on the \((u, y)\) plane yields:

\[
\int_0^{2\pi/\omega} \dot{y}(t)u(t)dt < 0
\]

Moreover, since the curve parameterized by \( y(t) \) and \( u(t) \) is an ellipse (viz.never crosses itself ), the sign of the area does not depend upon the particular density function chosen \( (\rho = 1) \). Namely, for any \( \rho(u, y) > 0 \) we still get:

\[
\int_0^{2\pi/\omega} \dot{y}(t)u(t)\rho(\mu, y(t))d\mu dt < 0.
\]

As a consequence, exploiting periodicity of \( u \) and \( y \), taking liminf\(_s\) would yield:

\[
\liminf_{T \to -\infty} \int_0^T \dot{y}(t)u(t)\rho(\mu, y(t))d\mu dt = -\infty
\]

which violates ccw dynamics with respect to any possible choice of a positive density function. This completes the proof of the implication.

The last step consists in the proof of 3 \( \Rightarrow \) 1. Similar implications were proved in the companion paper [1] under the assumption of \( A \) being a Hurwitz matrix. Hereby Hurwitzianity is relaxed to hyperbolicity. On the other hand, we only need to show the inequality on bounded Input-Output pairs. Let us assume, without loss of generality, that the system be completely observable. The area in the \((u, y)\) plane is in fact a function of the output only and is not influenced by the unobservable state components. Let \( \xi \) be an arbitrary initial condition and \( u(\cdot), y(\cdot) = \psi(\cdot, \xi, u) \) be a bounded input-output pair. By complete reachability there exists a control \( u : [0, 1] \to \mathbb{R} \) capable of taking \( x(t) \) from \( 0 \) to \( \xi \) in 1 unit of time. This control only affects the area integral by a finite quantity, therefore we may, without loss of generality, consider \( u(t) = 0 \) and \( y(t) = 0 \) for all \( t \leq 0 \) and assume \( \xi = 0 \) as an initial condition. Since \( y(t) \) is bounded so is also \( x(t) \) (by complete observability). Assume \( |x(t)| \leq M \) for all \( t \geq 0 \). For any state \( |x| \leq M \) we may define a control \( u_x : [0, +\infty) \to \mathbb{R} \) steering the state to 0 (even asymptotically, for instance by applying the control obtained in closed-loop with a certain constant stabilizing feedback) as well as its derivative. By exponential convergence to 0 the family of such \( u_x \)'s gives a finite contribution to the area integral, moreover, the value of the integral can be bounded in terms of a constant \( K_M \) which only depends upon \( M \) (actually linearly with respect to \( M \), but we won’t need this additional property). Let \( u_T \) be defined as follows:

\[
u_T(t) = \begin{cases} 0 & t < 0 \\ u(t) & t \in [0, T] \\ u_x(T)(t - T) & t > T \end{cases}
\]
We can compute the area integral from time 0 to $T$ according to:
\[
\int_0^T \dot{y}(t)u(t)dt = \int_{-\infty}^{\infty} \dot{\psi}(t,0_x,u_T)u_T(t)dt
\]
\[
= \int_{-\infty}^{+\infty} \dot{\psi}(t,0_x,u_T)u_T(t)dt
\]
\[
= \int_{-\infty}^{+\infty} \dot{\psi}(t,-T,x(T),u_x(T))u_x(T)(-T)dt
\]
\[
\geq \int_{-\infty}^{+\infty} \dot{\psi}(t,0_x,u_T)u_T(t)dt - K_M
\]
(32)
Let $U_T(j\omega)$ and $Y_T(j\omega)$ be the Fourier transform of $u_T$ and $\psi(t,0_x,u_T)$ so that the following holds: $Y_T(j\omega) = G(j\omega)U_T(j\omega)$. Since the area integral are finite we may apply the Parseval Lemma in order to get, due to the assumption in 3:
\[
\frac{1}{2\pi} \int_{-\infty}^{+\infty} j\omega Y_T(j\omega)U_T(j\omega)d\omega = -\int_{0}^{\infty} \omega \text{Im}[G(j\omega)]|U_T(j\omega)|^2d\omega \geq 0.
\]
Exploiting the previous estimate in order to compute the lim inf in equation (32) yields:
\[
\liminf_{T \to +\infty} \int_0^T \dot{y}(t)u(t)dt \geq -K_M > -\infty
\]
which completes the proof of ccw dynamics. The proof of the proposition in therefore completed.

A. Proof of Lemma II.6

In order to conclude that a given linear system has ccw I-O dynamics it is enough to consider periodic sinusoidal input signals and check that the corresponding phase-shift be included in $[-\pi,0]$. Let $u_\mu(t) = u_e + \mu \sin(\omega t)$ be a family of periodic signals, with $\omega > 0$ an arbitrary frequency. By Theorem 6.1.1 in [9], for all sufficiently small $\mu$ there exists a unique periodic solutions $x_\mu(t)$, relative to the input $u_\mu$ and initial condition $x_\mu(0)$ so that $x_\mu(t) \to x_e$ in the uniform topology as $\mu \to 0$. Moreover $x_\mu$ is of class $C^2$ with respect to $t$ and $\mu$. Let $y_\mu(t) = \psi(x_\mu(t))$ be the corresponding periodic output trajectory. Clearly, due to the ccw dynamics assumption,
\[
\int_0^{2\pi/\omega} y_\mu(t)\int_{0}^{u_\mu(t)} \rho(\mu,y_\mu(t))d\mu dt \geq 0 \quad \forall \mu
\]
By Theorem 1 in [29], taking derivatives with respect to $\mu$ yields:
\[
\frac{\partial}{\partial \mu} x_\mu(t) = \frac{\partial}{\partial \mu} x(t,\mu_0,u_\mu) = x_L(t,\mu_0,\sin(\omega t))
\]
(33)
where $\xi_\mu' = \frac{\partial}{\partial \mu} \xi_\mu |_{\mu=0}$ and $x_L$ denotes the solution of the linearized system at the equilibrium $x_e$. By (33) it is trivially verified that $x_L(t,\xi_0',\sin(\omega t))$ is a periodic function with zero average. In order to verify the ccw assumption it is therefore enough to verify that:
\[
\int_0^{2\pi/\omega} y_L(t)\sin(\omega t)dt \geq 0
\]
(34)
By the chain rule $y_L(t) = \frac{\partial}{\partial \mu} y_\mu(t)|_{\mu=0}$, moreover, exchanging the order of derivatives, $\hat{y}_L(t) = \frac{\partial}{\partial \mu} \hat{y}_\mu(t)|_{\mu=0}$.

We can now compute the integral in (34) as follows:
\[
\int_0^{2\pi/\omega} y_\mu(t)\sin(\omega t)dt = \frac{\partial}{\partial \mu} \int_0^{2\pi/\omega} \hat{y}_\mu(t)\sin(\omega t)dt|_{\mu=0}
\]
\[
= \lim_{\mu \to 0} \int_0^{2\pi/\omega} \hat{y}_\mu(t)\sin(\omega t)dt\frac{\rho(\mu,y_\mu(t))d\mu dt}{\mu}
\]
Assume without loss of generality that $\rho(u_e,h(x_e)) = 1$; then, if $\rho$ is of class $C^0$, through tedious but straightforward calculations we have that
\[
\int_0^{2\pi/\omega} \hat{y}_\mu(t)\sin(\omega t)dt = \int_0^{\int_0^{\omega} \dot{y}_\mu(t)\sin(\omega t)\mu \rho(\nu,y_\mu(t))d\nu dt} \frac{\rho(\mu,y_\mu(t))d\mu dt}{\mu} = o(|\mu|)
\]
Therefore,
\[
\int_0^{2\pi/\omega} \hat{y}_\mu(t)\sin(\omega t)dt = \lim_{\mu \to 0} \int_0^{\int_0^{\omega} \dot{y}_\mu(t)\sin(\omega t)\mu \rho(\nu,y_\mu(t))d\nu dt} \frac{\rho(\mu,y_\mu(t))d\mu dt}{\mu} \geq 0
\]
which completes the proof of the Lemma.

B. Systems with quadratic dissipation rates

Nonlinear systems with quadratic dissipation rates enjoy stronger properties when linearized around an hyperbolic equilibrium. This is typically pursued in the passivity literature (see for instance [22], [23], [31]). In particular, strict ccw dynamics are preserved as well. In the following we provide a precise statement as well as a proof of this fact.

Lemma A.2: Let $x_e$ be an hyperbolic equilibrium, corresponding to the constant input $u_e$. Assume that the system has strictly ccw Input-Output dynamics with quadratic dissipation rates, viz.:
\[
\liminf_{T \to +\infty} \int_0^T \dot{y}(t)u(t) - \varepsilon |\dot{y}(t)|^2 dt > -\infty.
\]
(35)
for some $\varepsilon > 0$. Then the linearized system at $x_e,u_e$:
\[
\dot{x}_L = \frac{\partial f}{\partial x}|_{x=x_e,u=u_e} x + \frac{\partial f}{\partial u}|_{x=x_e,u=u_e} u
\]
(36)
has strictly ccw I-O dynamics. □

Proof: Let $u_\mu(t) = u_e + \mu \sin(\omega t)$ be a family of periodic signals, with $\omega > 0$ an arbitrary frequency.  

\[
\dot{x}_L = \frac{\partial f}{\partial x}|_{x=x_e,u=u_e} x + \frac{\partial f}{\partial u}|_{x=x_e,u=u_e} u
\]
(36)
has strictly ccw I-O dynamics. □
Following the same steps as in the proof of Lemma II.6 we may define for all sufficiently small \( \mu \) a unique periodic solution \( x_{\mu}(t) \), relative to the input \( u_\mu \) and initial condition \( \xi_\mu = x_\mu(0) \) so that \( x_{\mu}(t) \to x_e \) in the uniform topology as \( \mu \to 0 \). Let \( y_{\mu}(t) \) be the corresponding periodic output trajectory. Clearly, due to the strict ccw dynamics assumption,

\[
\int_0^{2\pi/\omega} \dot{y}_{\mu}(t)u_\mu(t) - \varepsilon|\dot{y}_{\mu}(t)|^2 \, dt \geq 0 \quad \forall \mu
\]

By Theorem 1 in [29], taking derivatives with respect to \( \mu \) yields:

\[
\frac{\partial}{\partial \mu} x_\mu(t) = \frac{\partial}{\partial \mu} x(t, \xi_\mu, u_\mu) = x_L(t, \xi'_0, \sin(\omega \cdot)) \quad (37)
\]

where \( \xi'_0 = \frac{\partial}{\partial \mu} \xi_\mu \bigg|_{\mu=0} \) and \( x_L \) denotes the solution of the linearized system at the equilibrium \( x_e \). By (33) it is trivially verified that \( x_L(t, \xi'_0, \sin(\omega \cdot)) \) is a periodic function. In order to verify the ccw assumption it is therefore enough to verify that:

\[
\int_0^{2\pi/\omega} \dot{y}_L(t) \sin(\omega t) - \varepsilon|\dot{y}_L(t)|^2 \, dt \geq 0 \quad (38)
\]

Recall that \( y_L(t) = \frac{\partial}{\partial \mu} y_\mu(t) \bigg|_{\mu=0} \) and \( \dot{y}_L(t) = \frac{\partial}{\partial \mu} \dot{y}_\mu(t) \bigg|_{\mu=0} \) which yields useful identity \( \dot{y}_L(t) = \lim_{\mu \to 0} \dot{y}_\mu(t)/\mu \). We can now compute the integral in (38) as follows:

\[
\int_0^{2\pi/\omega} \dot{y}_L(t) \sin(\omega t) - \varepsilon|\dot{y}_L(t)|^2 \, dt = \lim_{\mu \to 0} \int_0^{2\pi/\omega} \frac{\dot{y}_\mu(t)}{\mu} \sin(\omega t) - \varepsilon|\dot{y}_\mu|^2 \frac{dt}{\mu^2} = \lim_{\mu \to 0} \int_0^{2\pi/\omega} \frac{\dot{y}_\mu(t)(u_\mu(t) - u_e)}{\mu} - \varepsilon|\dot{y}_\mu|^2 \frac{dt}{\mu^2} = \lim_{\mu \to 0} \int_0^{2\pi/\omega} \frac{\dot{y}_\mu(t)u_\mu(t) - \varepsilon|\dot{y}_\mu|^2}{\mu^2} \, dt \geq 0. \quad (39)
\]

This completes the proof of the claim.