Remarks on the invalidation of biological models using monotone systems theory

David Angeli and Eduardo D. Sontag

***Abstract*— Cooperative systems, and more generally systems with sign-definite interactions between variables, are an important class of models in several domains of applications, and in particular in molecular biology. The goal of this paper is to present techniques for finding out what type of solutions are compatible with a given sign pattern of interactions among state/input variables, once the input behaviour is also known. By "type" of solutions we mean the sequence of upwards or downwards segments that variables can exhibit (essentially sign-patterns derivatives of variables) once input profiles are also specified.**

I. I/O Monotone Systems

We review the basic notions from [1]. (For concreteness, we make definitions for systems of ordinary differential equations, but similar definitions can be given for abstract dynamical systems, including in particular reaction-diffusion partial differential equations and delay-differential systems, see e.g. [2].) The basic setup is that of an input/output system in the sense of mathematical systems and control theory [3], that is, sets of equations

$$\dot{x} = f(x,u), \quad y = h(x) \tag{1}$$

in which states $x(t)$ evolve on some subset $X \subseteq \mathbb{R}^n$, and input and output values $u(t)$ and $y(t)$ belong to subsets $U \subseteq \mathbb{R}^m$ and $Y \subseteq \mathbb{R}^p$ respectively. The coordinates $x_1, \ldots, x_n$ of states typically represent concentrations of chemical species, such as proteins, mRNA, or metabolites. The input variables, which can be seen as controls, forcing functions, or external signals, act as stimuli. Output variables can be thought of as describing responses, such as movement, or as measurements provided by biological reporter devices like GFP that allow a partial read-out of the system state vector $(x_1, \ldots, x_n)$. The maps $f : X \times U \to \mathbb{R}^n$ and $h : X \to Y$ are taken to be continuously differentiable, in the sense that they may be extended as $\mathcal{C}^1$ functions to open subsets, and technical conditions on invariance of X are assumed, [1]. (Much less can be assumed for many results, so long as local existence and uniqueness of solutions is guaranteed.) An *input* is a signal $u : [0,\infty) \to U$ which is measurable and bounded on bounded intervals (in some of our results, we assume that $u(t)$ is differentiable on t). We write $\varphi(t, x_0, u)$ for the solution of the initial value problem $\dot{x}(t) = f(x(t), u(t))$ with $x(0) = x_0$, or just $x(t)$ if x_0 and u are clear from the context, and $y(t) = h(x(t))$. See [3] for more on i/o systems. For simplicity of exposition, we make the blanket assumption that solutions do not blow-up on finite time, so $x(t)$ (and $y(t)$) are defined for all $t \geq 0$. (In biological problems, almost always conservation laws and/or boundedness of vector fields insure this property. In any event, extensions to local semiflows are possible as well.)

Given three partial orders on X, U, Y (we use the same symbol $\preceq$ for all three orders), a monotone I/O system (MIOS), with respect to these partial orders, is a system (1) such that h is a monotone map (it preserves order) and: for all initial states x_1, x_2 for all inputs u_1, u_2, the following property holds: if

$$x_1 \preceq x_2 \quad \text{and} \quad u_1 \preceq u_2$$

(meaning that $u_1(t) \preceq u_2(t)$ for all $t \geq 0$), then

$$\varphi(t, x_1, u) \preceq \varphi(t, x_2, u_2)$$

for all $t \geq 0$. Here we consider partial orders induced by closed proper cones $K \subseteq \mathbb{R}^\ell$, in the sense that $x \preceq y$ iff $y - x \in K$. The cones K are assumed to have a nonempty interior and are pointed, i.e. $K \bigcap -K = \{0\}$. The most interesting particular case is that in which K is an *orthant* cone in $\mathbb{R}^n$, i.e. a set S_ε of the form $\{x \in \mathbb{R}^n \,|\, \varepsilon_i x_i \geq 0\}$, where $\varepsilon_i = \pm 1$ for each i. *Cooperative systems* are by definition systems that are monotone with respect to orthant cones. (Some authors use the terminology only for the special case of the standard order, $\varepsilon_i = 1$ for all i.)

When there are no inputs nor outputs, the definition of monotone systems reduces to the classical one of monotone dynamical systems studied by Hirsch, Smith, and others [4]. When there are no inputs, strongly monotone classical systems have especially nice dynamics. Not only is chaotic or other irregular behavior ruled out, but, in fact, almost all bounded trajectories converge to the set of steady states (Hirsch's generic convergence theorem [5], [6]).

Kamke conditions

A useful test for monotonicity with respect to orthant cones, which generalizes Kamke's condition from ordinary differential equations [4] to i/o systems, is as follows. Let us assume that all the partial derivatives $\frac{\partial f_i}{\partial x_j}(x,u)$ for $i \neq j$, $\frac{\partial f_i}{\partial u_j}(x,u)$ for all i,j, and $\frac{\partial h_i}{\partial x_j}(x)$ for all i,j (subscripts indicate components) do not change sign, i.e., they are either always ≥ 0 or always ≤ 0. We also assume that X is convex. We then associate a directed graph G to the given MIOS,

David Angeli is with the Dept. of Electrical and Electronic Engineering of Imperial College London, U.K., and with the Dip. Sistemi e Informatica of Università di Firenze, Italy. Email address: d.angeli@imperial.ac.uk

Eduardo Sontag is with the Dept. of Mathematics of Rutgers University, NJ, U.S.A. Email address: sontag@math.rutgers.edu. Work supported in part by NIH 1R01GM086881 and AFOSR FA9550-11-1-0247.

with $n+m+p$ nodes, and edges labeled "+" or "−" (or ± 1), whose labels are determined by the signs of the appropriate partial derivatives (ignoring diagonal elements of $\partial f/\partial x$). An undirected loop in G is a sequence of edges transversed in either direction, and the *parity* of a loop is defined by multiplication of signs along the loop. (See e.g. [7] for more details.) Then, it is easy to show that a system is monotone with respect to *some* orthant cones in $\mathbb{R}^n, \mathbb{R}^m, \mathbb{R}^p$ if and only if there are no negative loops in G.

Response from steady state

We will show that, for any monotone system, initial states that are steady states, and inputs that are non-decreasing in time with respect to the order structure in U, $u(t_1) \preceq u(t_2)$ for all $t_1 \leq t_2$, states are non-decreasing in time with respect to the order structure in X, $x(t_1) \preceq x(t_2)$ for all $t_1 \leq t_2$. Observe that, for the special case of orthant orders, this means that each coordinate of the state will either satisfy $x_i(t_1) \leq x_i(t_2)$ for all $t_1 \leq t_2$ or $x_i(t_1) \geq x_i(t_2)$ for all $t_1 \leq t_2$ ($i \in \{1, 2, \ldots, n\}$). Analogously, if inputs are non-increasing, that is, $u(t_2) \preceq u(t_1)$ for all $t_1 \leq t_2$, then, by reversing the orders in X and U, we obtain a new monotone system in which now $u(t)$ is non-decreasing, and therefore the same conclusions hold (with reversed orders).

We let $\varphi(t, x_0, v)$ denote the solution of $\dot{x} = f(x, u)$ at time $t > 0$ with initial condition $x(0) = x_0$ and input signal $v = v(t)$.

Theorem 1. Suppose that (1) is a monotone I/O system. Pick an input v that is non-decreasing in time with respect to the partial order in U, and an initial state x_0 that is a steady state with respect to $v_0 = v(0)$, that is, $f(x_0, v_0) = 0$. Then, $x(t) = \varphi(t, x_0, v)$ is non-decreasing with respect to the partial order in X. Also, the output $y(t) = h(x(t))$ is nondecreasing.

Proof. Since $v(t)$ is non-decreasing, we have that $v(t) \succeq v(0)$, so that, by comparison with the input that is identically equal to $v(0)$, we know that

$$\varphi(h, x_0, v) \succeq \varphi(h, x_0, v_0)$$

where by abuse of notation v_0 is the function that has the constant value v_0. We used the comparison theorem with respect to inputs, with the same initial state. The assumption that the system starts at a steady state gives that $\varphi(h, x_0, v_0) = x_0$. Therefore:

$$x(h) \succeq x(0) \qquad \text{for all } h \geq 0\,. \tag{2}$$

Next, we consider any two times $t \leq t+h$. We wish to show that $x(t) \preceq x(t+h)$. Using (2) and the comparison theorem with respect to initial states, with the same input, we have that:

$$x(t+h) = \varphi(t, x(h), v_h) \succeq \varphi(t, x(0), v_h)\,,$$

where v_h is the "tail" of v, defined by: $v_h(s) = v(s+h)$. On the other hand, since the function v is non-decreasing, it holds that $v_h \succeq v$, in the sense that the inputs are ordered: $v_h(t) \succeq v(t)$ for all $t \geq 0$. Therefore, using once again the comparison theorem with respect to inputs and with the same initial state, we have that

$$\varphi(t, x(0), v_h) \geq \varphi(t, x(0), v) = x(t)$$

and thus we proved that $x(t+h) \geq x(t)$. So x is a non-decreasing function. The conclusion for outputs $y(t) = h(x(t))$ follows by monotonicity of h. ∎

Single-input single-output systems

When only one output variable is of interest, much less than monotonicity of the entire system is required in order to guarantee a monotonic output. We first introduce some graph-theoretic definitions. Given any directed graph $(\mathcal{V}, \mathcal{E} \subset \mathcal{V} \times \mathcal{V})$, we define the *accessible* subgraph from a node $v \in \mathcal{V}$ to be

$$Acc(v) = (\mathcal{V}_v, \mathcal{E}_v)$$

defined as follows:

$$\mathcal{V}_v = \{w \in \mathcal{V} : \exists \text{ directed path from } v \text{ to } w\}$$

while $\mathcal{E}_v = \mathcal{E} \cap \mathcal{V}_v \times \mathcal{V}_v$. We define the *co-accessible* subgraph to a node $z \in \mathcal{V}$ to be:

$$coAcc(z) = (\mathcal{V}_z, \mathcal{E}_z)$$

where:

$$\mathcal{V}_z = \{w \in \mathcal{V} : \exists \text{ directed path from } w \text{ to } z\}$$

and $\mathcal{E}_z = \mathcal{E} \cap \mathcal{V}_z \times \mathcal{V}_z$.

Intuitively, given an input node v_i and an output node v_o in $\mathcal{V}$, in order to investigate monotonicity of the input-output response from the associated input signal to the corresponding output signal, it is enough to consider the graph:

$$\mathcal{G}_{i/o} := (\mathcal{V}_{i/o}, \mathcal{E}_{i/o}) = \text{Acc}(v_i) \cap \text{coAcc}(v_o).$$

The crucial features of this graph that may prevent monotonicity of the response is existence of two or more directed paths from v_i to v_o with inconsistent sign. Such paths can only exist if the graph $\mathcal{G}_{i/o}$ exhibits incoherent feedforward loops (IFFL's) and/or negative directed feedback loops. This condition may be verified for two nodes v_i and v_o even if the overall system is not monotone. For example, Fig. 1 shows a system that (a) is not monotone yet (b) has no IFFL's nor negative feedback loops. However, such a counterexample does not contradict our assertion, since we are interested in knowing how one input (affecting only one node) affects any given particular output node. Indeed, if all we ask is that input/output question, then the following is true. The key idea is to consider paths from the input node to the output node (these will include feedforward loops and closed loops in which a cycle occurs), and to reduce to the monotone subsystem whose states consist of those nodes that do not lie in any such path.

Theorem 2. Suppose that (1) is a monotone I/O system, with scalar inputs and outputs ($U \subseteq \mathbb{R}$ and $Y \subseteq \mathbb{R}$ with the usual orders), and that the parities of any two directed paths from

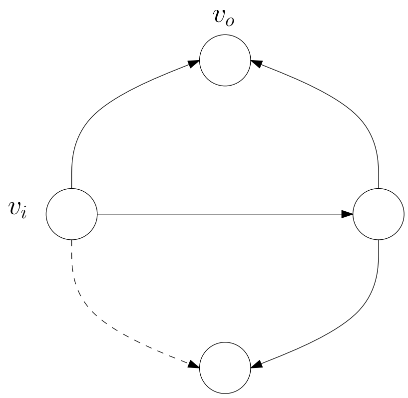

Fig. 1. The graph of a non-monotone system fulfilling I/O monotonicity conditions. The dashed edge is negative and all other edges are positive

the input node to the output node are the same. Then, if the system is initially at some equilibrium, the response to a monotonic input is monotonic.

II. Systems with sign-definite Jacobians

In this section, we consider again finite dimensional nonlinear control systems as in (1), but we now relax some of the monotonicity assumptions of the previous section. We take $f : X \times U \to \mathbb{R}^n$ to be a $\mathcal{C}^1$ function and $X \subseteq \mathbb{R}^n$ and $U \subseteq \mathbb{R}^m$ open subsets of Euclidean space. Our goal is to understand, given a certain input with a particular monotone behavior ($\text{sign}(\dot{u}(t))$ is constant in time), what are the possible shapes that solutions $x(t, x_0, u)$ can take, and in particular, what $\text{sign}(\dot{x}(t))$ may look like.

We denote by

$$\sigma(x) = \begin{cases} 1 & \text{if } x > 0 \\ -1 & \text{if } x < 0 \\ 0 & \text{if } x = 0 \end{cases}$$

the usual sign function. The analysis that follows is based on the following key technical assumption:

$$\sigma\left(\frac{\partial f_i}{\partial x_j}(x,u)\right) \text{ is constant } \forall\, i \neq j,\ \forall\, x \in X,\ \forall\, u \in U. \tag{3}$$

Let $\mathcal{V} := \{-1, 0, 1\}^{n+m}$, which we regard as the set of all possible sign-patterns of vectors $[\dot{x}', \dot{u}']' \in \mathbb{R}^{n+m}$. We define a matrix $J \in \{-1, 0, 1\}^{n\times(n+m)}$ according to:

$$\sigma\left(\begin{bmatrix} 0 & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \cdots & \frac{\partial f_1}{\partial x_n} & \frac{\partial f_1}{\partial u_1} & \cdots & \frac{\partial f_1}{\partial u_m} \\ \frac{\partial f_2}{\partial x_1} & 0 & \frac{\partial f_2}{\partial x_3} & \cdots & \frac{\partial f_2}{\partial x_n} & \frac{\partial f_2}{\partial u_2} & \cdots & \frac{\partial f_2}{\partial u_m} \\ \vdots & & \ddots & & \vdots & \vdots & & \vdots \\ \vdots & & & \ddots & \vdots & \vdots & & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_{n-1}} & 0 & \frac{\partial f_n}{\partial u_1} & \cdots & \frac{\partial f_n}{\partial u_m} \end{bmatrix}\right)$$

(σ is applied to each entry). Let

$$\mathcal{V}_0^2 := \left\{ (v_1, v_2) \in \mathcal{V}^2 \text{ s.t. } \sum_{i=1}^{n} |v_{1i} - v_{2i}| = 1 \right\}.$$

For each $(v_1, v_2) \in \mathcal{V}_0^2$, $i_{v_1,v_2} \in \{1, 2, \ldots, n\}$ is the (unique) integer for which $v_{1i} \neq v_{2i}$. Regarding $\mathcal{V}$ as a set of vertices in a directed graph, we denote by $\mathcal{E} \subset \mathcal{V}_0^2$ the set of edges for which

$$\begin{aligned} &\exists\, k \in \{1, \ldots, n+m\} \text{ s.t.} \\ &\quad J_{i_{v_1,v_2}k} v_{1k} (v_{2i_{v_1,v_2}} - v_{1i_{v_1,v_2}}) = 1. \end{aligned} \tag{4}$$

Note that in equation (4), we are placing a directed edge from v_1 to v_2 when these nodes differ by a single entry (the i-th one) and, among the input/states variables that affect $\dot{x}_i$ (with the exception of x_i itself), at least one has an influence on $\dot{x}_i$ which is equal in sign to that of the jump $v_{2i} - v_{1i}$). Our main result for this section is as follows:

Theorem 3. Let $I_1 < I_2$ be disjoint non-empty intervals of the real line such that $I = I_1 \cup I_2$ is also an interval. Let $x(t) : I \to X$ be a solution of (1) corresponding to the $\mathcal{C}^1$ input u of constant sign pattern $\sigma(\dot{u}(t))$. Assume that there exists v_1 and v_2 in $\mathcal{V}$ such that $\sigma([\dot{x}(t)', \dot{u}(t)']) = v_1$ for all $t \in I_1$ and $\sigma([\dot{x}(t)', \dot{u}(t)']) = v_2$ for all $t \in I_2$ and $|v_1 - v_2| = 1$. Then $(v_1, v_2) \in \mathcal{E}$.

Note that we are allowing either interval to consist of only one point.

Proof of Theorem 3. Consider the function

$$z(t) := \dot{x}_i(t) = f(x(t), u(t)).$$

Differentiating with respect to time we have by the chain rule:

$$\dot{z}(t) = \frac{\partial f}{\partial x}(x(t), u(t))\dot{x}(t) + \frac{\partial f}{\partial u}(x(t), u(t))\dot{u}(t)$$

Looking at the equation for the i-th component of z yields:

$$\begin{aligned} \dot{z}_i(t) &= \sum_j \frac{\partial f_i}{\partial x_j}(x(t), u(t)) z_j(t) + \sum_{j=1}^{m} \frac{\partial f_i}{\partial u_j}(x(t), u(t))\dot{u}_j(t) \\ &= a(t) z_i(t) + b(t) \end{aligned}$$

provided we define:

$$a(t) = \frac{\partial f_i}{\partial x_i}(x(t), u(t))$$

and:

$$b(t) = \sum_{j\neq i} \frac{\partial f_i}{\partial x_j}(x(t), u(t)) z_j(t) + \sum_{j=1}^{m} \frac{\partial f_i}{\partial u_j}(x(t), u(t))\dot{u}_j(t).$$

Let v_1 and v_2 be as in the statement of the theorem, and let $i = i_{v_1,v_2}$. There are four cases to consider:

1) $v_{1i} = 0$ and $v_{2i} = 1$
2) $v_{1i} = 0$ and $v_{2i} = -1$
3) $v_{1i} = -1$ and $v_{2i} = 0$
4) $v_{1i} = 1$ and $v_{2i} = 0$.

Case 1. We have $z_i(t) = 0$ for all $t \in I_1$ and $z_i(t) > 0$ for all $t \in I_2$. It follows that I_2 cannot be a one-point interval. Let $t_2 := \inf I_2$, and note that $z_i(t_2) = 0$. From the variation of parameters formula for the solution of $\dot{z}_i(t) = a(t)z_i(t) + b_i(t)$, it follows that if $z_i(t_2) = 0$ and $z_i(t) > 0$ for an open interval $[0, t_2 + \varepsilon)$, then there must exist some $\tau \in I_2$ such that $b(\tau) > 0$. Thus, at least one of the terms in the definition of $b(\tau)$ must be positive, which means that

$$J_{i_{v_1,v_2}k} v_{2k} = 1\,.$$

Note that this k is by definition not equal to i, so $v_{2k} = v_{1k}$ (because v_1 and v_2 differ only on their ith entry). Thus $J_{i_{v_1,v_2}k} v_{1k} = 1$. Moreover, in this case $v_{2i} - v_{1i} = 1 - 0 = 1$, so it follows that $J_{i_{v_1,v_2}k} v_{1k}(v_{2i_{v_1,v_2}} - v_{1i_{v_1,v_2}}) = 1$, as claimed.
Case 2. An analogous argument gives that there is some k such that $J_{i_{v_1,v_2}k} v_{1k} = J_{i_{v_1,v_2}k} v_{2k} = -1$, but now $v_{2i} - v_{1i} = -1 - 0 = -1$, so again $J_{i_{v_1,v_2}k} v_{1k}(v_{2i_{v_1,v_2}} - v_{1i_{v_1,v_2}}) = 1$.
Case 3. Now we argue with the final-time problem $\dot{z}_i(t) = a(t) z_i(t) + b_i(t)$, $z_i(t_1) = 0$, where $t_1 = \sup I_1$. We conclude that there is some k such that $J_{i_{v_1,v_2}k} v_{1k} = 1$, and since $v_{2i} - v_{1i} = 0 - (-1) = 1$, we have $J_{i_{v_1,v_2}k} v_{1k}(v_{2i_{v_1,v_2}} - v_{1i_{v_1,v_2}}) = 1$.
Case 4. Analogously, $J_{i_{v_1,v_2}k} v_{1k} = -1$, $v_{2i} - v_{1i} = 0 - 1 = -1$, so $J_{i_{v_1,v_2}k} v_{1k}(v_{2i_{v_1,v_2}} - v_{1i_{v_1,v_2}}) = 1$. ∎

The above theorem can be used to infer the potential shapes of solutions of nonlinear systems with sign-definite Jacobians, subject to piecewise monotone inputs. Notice that if the system is cooperative, this in some sense reduces to the previous result, although, for simplicity of derivation, only sign commutation of a single component of $\dot{x}$ at any given time is in fact considered.

Theorem 2 generalizes Theorem 1: if a system is monotone with respect to the standard order, i.e. with respect to the cone $K = S_\epsilon$, where $\varepsilon = (1, 1, \ldots, 1)$. Then, the off-diagonal elements of the sign Jacobian matrix J are non-negative. In that special case, it follows from Theorem 3 that the two subsets of nodes $\{0,1\}^{n+m}$ and $\{0,-1\}^{n+m}$ are forward-invariant in the graph with edges $\mathcal{E}$. Thus, in particular: (1) if the input is non-decreasing and if we start from a steady state (first n coordinates of edges are zero), then all reachable nodes have non-negative coordinates (that is to say, the solutions of the system are non-decreasing), and (2) if the input is non-increasing, then nodes are non-positive (solutions of the system are non-increasing).

A simple example

To illustrate the applicability of Theorem 3 we consider the bidimensional nonlinear system:

$$\begin{aligned} \dot{x}_1 &= u x_1 - k_1 x_1 x_2 \\ \dot{x}_2 &= -k_2 x_2 + k_3 x_1 x_2 \end{aligned} \tag{5}$$

with state space $X = (0, +\infty)^2$ and input taking values in $(0, +\infty)$ and k_1, k_2, k_3 being arbitrary positive coefficients. Notice that this can be interpreted as a model of predator-prey interactions with the reproduction rate of preys being an exogenous input u. Obviously the system is not cooperative due to the presence of a negative feedback loop. The J matrix in this case is given by:

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

Next we build the graph $(\mathcal{V}, \mathcal{E})$ with nodes:

$$\mathcal{V} = \{-1, 0, 1\}^3.$$

Let us focus on increasing inputs. This means we restrict our attention to nodes of the type $\{-1,0,1\}^2 \times \{1\}$ and for the sake of simplicity we may drop the $\dot{u}$ label in Fig. 2. This represents all the edges allowed by Theorem 3. Notice that

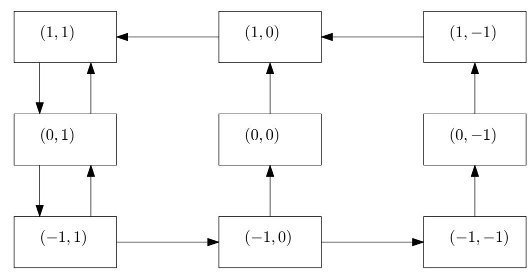

Fig. 2. Graph of allowed transitions for increasing inputs

commutations in the sign of $\dot{x}_2(t)$ (the predators) are only allowed in order to match the sign of $\dot{x}_1(t)$. This restricts the possible sign-patterns of $\dot{x}(t)$ which are compatible with a model of this kind even without assuming any knowledge of the specific values of the k_is (provided their sign is known apriori).

The previous example also suggests the possibility of introducing a reduced graph, which we define by considering a reduced set of nodes and a new set of edges. In particular, we may let: $\mathcal{G}_{red} = (\mathcal{V}_{red}, \mathcal{E}_{red})$, where $\mathcal{V}_{red} = \{1,-1\}^{n+m}$, $\mathcal{E}_{red} = \{(v_1, v_2) \in \mathcal{V}_{red}^2 :$ $\exists$ path of length 2 in $\mathcal{G}$ from v_1 to $v_2\}$. This graph represents, for a given and fixed sign pattern of the input variable, the set of all possible transitions between sets $\{x : f(x,u) \in \mathcal{O}\}$, where $\mathcal{O}$ denotes an arbitrary *closed* orthants and edges are only allowed between neighboring orthants (that is orthants sharing a face of maximal dimension). In particular, the orthant $\{x : f(x,u) \in \mathcal{O}\}$ where $\mathcal{O} = \text{diag}(v)[0, +\infty)^n$, and v is an arbitrary element of $\{1,-1\}^n$ is associated to the node v. It is straightforward to see that

$$\begin{aligned} \mathcal{E}_{red} \;\;=\;\; & \{(v_1, v_2) \in \mathcal{V}_{red}^2 :\ \exists\, k \in \{1, \ldots, n+m\} \text{ s.t.} \\ & J_{i_{v_1,v_2}k} v_{1k}(v_{2i_{v_1,v_2}} - v_{1i_{v_1,v_2}}) = 2\}. \end{aligned}$$

where with a slight abuse of notation i_{v_1,v_2} denotes the unique index i such that $|v_{1i} - v_{2i}| = 2$.

III. Identification of signed interactions

In the following we exploit the results of previous Sections, and in particular Theorem 3, in order to formulate and discuss an algorithm for identification of signed interactions based on available measured data. This is a systematic tool for hypotesis generation. The method assumes sign definite interactions between variables and allows, under such qualitative constraints, to find the family of minimal signed graphs which are compatible with given measured data. Our discussion in this section will be done very informally. A future paper will provide more precise formulations.

For the sake of simplicity all variables are assumed to be measured continuously so that no issue arises of what has been the intersample behaviour of individual variables and whether or not the adopted sampling time is sufficiently small to unambiguously detect changes of sign in the derivatives of the considered set of variables. Also we assume that at most one variable can switch at any given time (this assumption is reasonable only when there are no conservation laws involving exactly two variables).

The algorithm is particularly flexible as it allows to generate several plausible scenarios compatible with an initial hypotesis $\mathcal{H}_0$ which gathers all the apriori information available, namely all the interactions between variables which have been validated and invalidated by other means. In its basic formulation it assumes that all variables are known and available for measurement.

The following definitions are useful in order to precisely formulate the algorithm. Notice that we will identify a graphical object which is different from the graphs previously described.

Definition A signed graph $\mathcal{G}$ is a triple $\{\mathcal{V}, \mathcal{E}_+, \mathcal{E}_-\}$, in which $\mathcal{V}$ is a finite set of nodes (corresponding to the variables of the system), $\mathcal{E}_+ \subset \mathcal{V} \times \mathcal{V} \backslash \{(v,v) : v \in \mathcal{V}\}$ is the set of positive edges, each corresponding to directed excitatory influence of one variable to another, and $\mathcal{E}_- \subset \mathcal{V} \times \mathcal{V} \backslash \{(v,v) : v \in \mathcal{V}\}$ is the set of negative edges, corresponding to directed inhibitory influences.

Notice that variables may be states and inputs. In this respect it is convenient to partition $\mathcal{V}$ as $\mathcal{V}_s \cup \mathcal{V}_i$, with $\mathcal{V}_s \cap \mathcal{V}_i = \emptyset$ denoting the set of nodes corresponding to state variables and input variables respectively. The assumption of signed interactions means that $\mathcal{E}_+ \cap \mathcal{E}_- = \emptyset$. Notice also that we do not consider self-loops in our graphs (and, consequently, no assumption of signed self-interaction is made). We say that a graph is compatible with the observed data if all sign-switches of derivatives in the data are allowed by the sign-pattern of the adjacency matrix of $\mathcal{G}$ according to Theorem 3. Moreover, we say that a signed graph $\tilde{\mathcal{G}} = \{\mathcal{V}, \tilde{\mathcal{E}}_+, \tilde{\mathcal{E}}_-\}$ is an edge-subgraph of $\mathcal{G}$ if $\tilde{\mathcal{E}}_+ \subset \mathcal{E}_+$ and $\tilde{\mathcal{E}}_- \subset \mathcal{E}_-$. If at least one inclusion is strict we say that it is a proper edge-subgraph. We also say that $\mathcal{G}$ is an edge-supergraph of $\tilde{\mathcal{G}}$. An apriori hypotesis $\mathcal{H}$ is a signed graph with 2 types of signed edges $\{\mathcal{V}, \mathcal{E}^h_+, \mathcal{E}^h_-, \mathcal{F}^h_+, \mathcal{F}^h_-\}$ where $\mathcal{E}^h_+$ and $\mathcal{E}^h_-$ are respectively positive and negative edges which have already been validated (and are therefore known to exist in the graph of the system being identified), while $\mathcal{F}^h_+$ and $\mathcal{F}^h_-$ are forbidden positive and negative edges respectively.

Notice that $\mathcal{E}^h_+ \cap \mathcal{E}^h_- = \emptyset$, while the same is not necessarily true for $\mathcal{F}^h_+$ and $\mathcal{F}^h_-$. For instance, if a certain variable is known to be an input of the system, then all its incoming edges, both positive and negative should be listed as forbidden.

Definition A graph $\mathcal{G}$ is said to be a minimal graph compatible with data and with hypothesis $\mathcal{H}$ if no proper edge-subgraph of $\mathcal{G}$ exists that is both compatible with the data and an edge-supergraph of $\mathcal{H}$ with $\mathcal{F}^h_+ \cap \mathcal{E}_+ = \emptyset$ and $\mathcal{F}^h_- \cap \mathcal{E}_- = \emptyset$.

The first algorithm we discuss below allows to generate all minimal signed graphs compatible with the measured data and the given apriori hypothesis $\mathcal{H}$, (which could be empty, namely $\mathcal{H} = \{\mathcal{V}, \emptyset, \emptyset, \emptyset, \emptyset\}$). As more than one such graph may exist, depending on the data available, the algorithm creates a number of plausible scenarios by storing them in a tree, starting from the root node $\mathcal{H}$. The parent of each node is a proper edge-subgraph of all of its children. Measured data is scanned from initial to final time. Each time a sign switch is detected all leaves of the current tree are checked to see whether the switch is compatible with the graphs they represent. If so, nothing is done; otherwise, a single edge is added in order to restore compatibility of data with the graph. If more than one edge may be capable of restoring such compatibility multiple children are created for the considered parent node. If no such edge exists, (namely because the constraint $\mathcal{E}_+ \cap \mathcal{E}_- = \emptyset$ does not allow it), then that node is labeled as *Invalidated*.

In the following we denote by $\mathcal{L}(\mathcal{T})$ the set of leaves of a tree $\mathcal{T}$. Notice that, for the sake of simplicity, we assume that at each time t at most one variable may switch the sign of its derivative.

1) Let $\mathcal{H} = (\mathcal{V}, \mathcal{E}^h_+, \mathcal{E}^h_-)$ be the root of the tree $\mathcal{T}$;
2) Let $t_1, t_2, \dots t_N$ denote the time instants at which sign switches in state variable derivatives are detected;
3) For $i = 1 \dots N$
4) For $\mathcal{H} \in \mathcal{L}(\mathcal{T})$
5) If $\mathcal{H}$ is labeled 'Invalidated' or 'Redundant' do nothing, else:
6) If variable $v \in \mathcal{V}_s$ switches its derivative from positive to negative [from negative to positive] at time t_i then:
   - Check if there exists an edge in $\mathcal{E}_+$ from a node w with negative [positive] derivative (at t_i) to v or if there exists an edge in $\mathcal{E}_-$ from a node w with positive [negative] derivative (at t_i) to v;
   - If the check succeeds then do nothing. If the check fails then for all nodes u with positive derivative, such that (u,v) does not belong to $\mathcal{E}_+ \cup \mathcal{F}^h_-$, add the edge (u,v) to $\mathcal{E}_-$ and attach as a son to $\mathcal{H}$ the newly created graph;
   - Similarly, if the check fails, for all nodes u with negative derivative, such that (u,v) does not belong to $\mathcal{E}_- \cup \mathcal{F}^h_+$, add the edge (u,v) to $\mathcal{E}_+$ and attach as a son to $\mathcal{H}$ the newly created graph;
   - If no such nodes as in the previous two items exist, then label $\mathcal{H}$ as 'Invalidated';
7) End For $\mathcal{H}$;
8) Label all leaves of $\mathcal{T}$ that are proper edge-subgraph of other leaves as 'Redundant';
9) label as 'Redundant' all leaves except one of those which are equal to one another;
10) End For i;

The algorithm terminates with the set of non invalidated and non redundant leaves representing all minimal sign-definite graphs which are compatible with the initial hypothesis.

To illustrate the algorithms we apply it to synthetic data

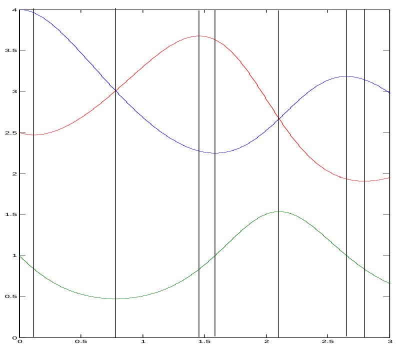

Fig. 3. Simulated species data

generated by numerically integrating the following differential equation:

$$\begin{aligned} \dot{x}_1 &= -x_1 + x_1 x_2 \\ \dot{x}_2 &= x_2 x_3 - x_1 x_2 \\ \dot{x}_3 &= x_3 - 1.2 x_2 x_3. \end{aligned} \tag{6}$$

This can be seen as a toy model of an ecosystem comprising 3 interacting species: Predators, Vegetarians and Vegetables, (x_1, x_2 and x_3 respectively). Clearly the algorithm does not assume knowledge of the 'nature' of the variable being measured and in fact the goal of the identification is precisely to find out the sign of interactions between such species, that is the role of each species in the ecosystem. The measured data is shown in Fig. 3, using 3 different colors for the 3 variables.

Notice that 7 sign switches of derivatives are detected in the finite time window considered and these are highlighted by vertical lines in the picture so as to emphasize the order in which variables switch their monotonicity. We start with the empty hypothesis comprising 3 nodes (labeled in the graph given in Figure 3 by colors: blue = predators, green = vegetarians, and red = vegetables), and no validated nor invalidated edges. The execution of the algorithm is shown in Fig. 4 Notice that the algorithm generates two minimal graphs compatible with the measured data. Two edges appear in both graphs and are therefore validated and should be present in any set of differential equations generating such monotonicity patterns. The remaining edge can be picked from any of the two scenarios. In fact the model used to generate the data is a supergraph of both scenarios and is given by their union. This, of course, need not always be the case. Extra data and experiments would be needed in order to refine the model. In fact, the outcome of the algorithm may be used in order to design further experiments targeting specific edges of the graph.

IV. Conclusion

This note studies the monotonicity in time of solutions for systems which preserve an orthant order and/or, more in general, that have a well-defined sign pattern of interaction between variables (that is each variable either enhances or inhibits (or leaves unchanged) the rate of variation of each other variable, and this consistently happens throughout state space).

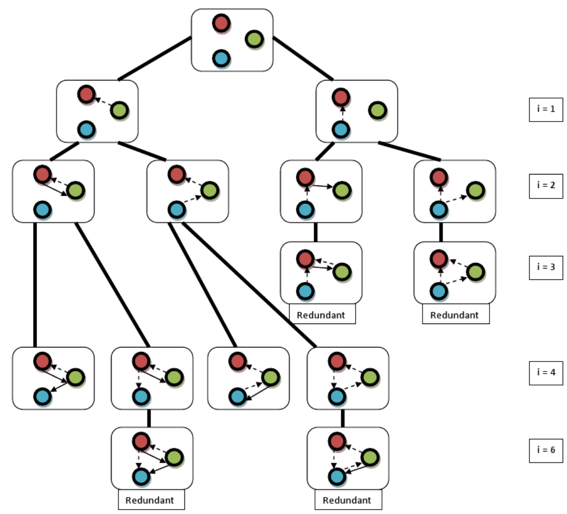

Fig. 4. Generation of minimal graphs compatible with available data. Dashed arrows indicate negative edges.

References

[1] D. Angeli and E.D. Sontag. Monotone control systems. *IEEE Trans. Automat. Control*, 48(10):1684–1698, 2003.

[2] G.A. Enciso and E.D. Sontag. Global attractivity, I/O monotone small-gain theorems, and biological delay systems. *Discrete Contin. Dyn. Syst.*, 14(3):549–578, 2006.

[3] E.D. Sontag. *Mathematical Control Theory. Deterministic Finite-Dimensional Systems*, volume 6 of *Texts in Applied Mathematics*. Springer-Verlag, New York, second edition, 1998.

[4] H. Smith. *Monotone dynamical systems: An introduction to the theory of competitive and cooperative systems, Mathematical Surveys and Monographs, vol. 41*. AMS, Providence, RI, 1995.

[5] M. Hirsch. Differential equations and convergence almost everywhere in strongly monotone flows. *Contemporary Mathematics*, 17:267–285, 1983.

[6] M. Hirsch. Systems of differential equations that are competitive or cooperative ii: Convergence almost everywhere. *SIAM J. Mathematical Analysis*, 16:423–439, 1985.

[7] D. Angeli and E.D. Sontag. Multi-stability in monotone input/output systems. *Systems Control Lett.*, 51(3-4):185–202, 2004.