

# A new necessary condition on interaction graphs for multistationarity

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## Abstract

We consider a dynamical system, described by a system of ordinary differential equations, and the associated interaction graphs, which are defined using the matrix of signs of the Jacobian matrix. After stating a few conjectures about the role of circuits in these graphs, we prove two new results relating them to the dynamic behaviour of the system: a sufficient condition for qualitative instability, and a necessary condition for the existence of several stationary states. These results are illustrated by examples of regulatory modules in two variables, such as those occurring in biological networks.

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## 1. Introduction

In this paper we study the qualitative properties of a dynamical system, described by a system of ordinary differential equations. For that purpose, we consider the interaction graphs attached to the system. These are defined using the signs of the entries of the Jacobian matrix. Several conjectures have been stated and/or proven in the past which relate circuits in these graphs to the behaviour of the corresponding dynamical system. We add here two new results. One is about the stability of a stationary state and the other is a new criterion for the existence of several stationary states.

Our interest in these results comes from biology: multistationarity in cellular networks can be viewed as a rationale for decision making and differentiation. This is explained in the next section, where we discuss how our problem originated from biological considerations. Then, after introducing some definitions, we formulate four conjectures relating circuits to the qualitative behaviour of a dynamical system. We discuss an example illustrating these conjectures and we summarize what is known about them.

The third section contains the statement of our main results. Theorem 1 gives a sufficient condition for a stationary point to be (strongly) unstable, and Theorem 2 gives a necessary condition for the existence of several nondegenerate stationary points. These theorems are proved in the Appendix. The case of two variables is discussed in detail.

In the fourth section we show with examples that the hypotheses of Theorem 2 cannot be weakened. Finally, we discuss in Section 5 how our results can be applied to a positive feedback system similar to those encountered in developmental Biology.

## 2. Some conjectures in nonlinear dynamics

### 2.1. Biological background

Epigenetic differences are those differences that are transmissible from cell to cell generation in the absence of any genetic difference. It has become clear for some time (Briggs and King, 1952; Wilmut et al., 1997) that with few exceptions all the cells of an organism contain all the genes of that organism. Thus, cell differentiation is essentially an epigenetic process.

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In a short but historical note, Delbrück (1949) mentioned (in other words) that epigenetic differences, including those involved in cell differentiation, can be understood in terms of a more general process, namely multistationarity. Multistationarity takes place when a system displays multiple steady states.

This urged us to identify the formal requirements of multistationarity and other nontrivial behaviour. We soon realized that the common point between all the biological systems that display multistationarity (e.g. Novick and Weiner, 1957; Cohn and Horibata, 1959; Monod and Jacob, 1961; Eisen et al., 1967; Kauffman, 1973) is the presence of a positive circuit in their underlying logic. In fact all these examples imply a switch from a “rest” state to an alternative latent state and thus point to the existence of a cellular memory based on a positive circuit. It was subsequently concluded (Thomas, 1981) that the presence of a positive circuit is not simply a convenient way to realize multistationarity, but is in fact a necessary condition for its occurrence. This conjecture was submitted to formal proofs in Plahte et al. (1995), Snoussi (1998), Gouzé (1998), Cinquin and Demongeot (2002) and Soulé (2003).

Of special relevance for the mechanisms of cell differentiation is the fact that a gene whose expression is under direct or indirect positive control of its own product can be switched on lastingly by a transient signal. This explains that during cell differentiation a gene can be switched on by the product of another gene and remains on after the disappearance of this product. On the other hand, in order to account for various cell types in terms of multiple steady states, one has to account for many steady states. As discussed in Kaufman and Thomas (1987) and Thomas and Richelle (1988), many regulatory interactions (and their composition) are sigmoid (or stepwise) in shape and a positive circuit thus usually results in no more than three steady states, two of which can be stable. However,  $m$  positive circuits can generate up to  $3^m$  steady states,  $2^m$  of which can be stable. Thus, eight genes under positive auto-control might suffice to generate  $2^8 = 256$  cell types. More generally, many steady states (and thus many potential cell types) can be generated by several positive circuits.

As briefly mentioned above, positive circuits are involved in cellular memory. For more recent examples, see, e.g. Acar et al. (2005) and Sha et al. (2003). Moreover, one can reason that whenever a set of neurons are connected into a positive circuit, this set will usually persist in a rest state, but any signal that can move it away from this state will lead it to the alternative complementary state of the circuit (Demongeot et al., 2000; Tonnelier et al., 1999). In other words, such a simple network can evocate a latent state that is kept as a memory. In the immune system as well, differentiation and memory can be understood in terms of positive circuits between the various types of cells involved (see Kaufman et al., 1985; Kaufman and Thomas, 1987; Segel, 1998; Yates et al., 2004).

Negative circuits also play a fundamental role in biology. That homeostasis (already recognized by Claude Bernard

as *elasticity*) operates, with or without oscillations, like a thermostat or a Watt regulator, has been understood for many years, and many authors (e.g. Szekely, 1965) have suggested an implication of what we now call *negative circuits* in these processes. A further step consisted of conjecturing that negative circuits are not only involved in homeostasis and periodicity, but are in fact a necessary condition of this type of behaviour (Thomas, 1981).

Although all biological processes are complex and involve many variables, essential qualitative features of these processes can usually be understood in terms of a small number of crucial variables. This view is strongly supported by the observation that extremely complex behaviour can arise from simple combinations of positive and negative circuits. In particular, we will deal with small modules (or “regulons”) whose consideration can be of interest in various domains. For example, it has become clear recently that such complex behaviours as deterministic chaos can take place in the presence of one positive and one negative circuit, and even in the presence of a single circuit, provided this circuit can be positive or negative depending on the values of relevant variables (Thomas, 1999).

## 2.2. Definitions

As explained in the previous section, the biological examples led us to propose several mathematical conjectures relating the behaviour of a dynamical system to the topology of its interaction graph. To state them precisely, we first need to introduce some terminology.

Given a positive integer  $n$ , we consider a differentiable map  $F: \mathbb{R}^n \rightarrow \mathbb{R}^n$ , i.e. a collection  $F = (f_1, \dots, f_n)$  of  $n$  differentiable maps  $f_i(x_1, \dots, x_n)$ ,  $1 \leq i \leq n$  (see 3.1 below). We are interested in the dynamical system

$$\frac{dx}{dt} = F(x), \quad (1)$$

where  $x = (x_1(t), \dots, x_n(t))$  is a trajectory in the  $n$ -dimensional Euclidean space.

The *interaction graph*  $G(x)$  of  $F$  at the point  $x \in \mathbb{R}^n$  is the finite oriented graph with  $\{1, \dots, n\}$  as set of vertices and such that there is a positive (resp. negative) arrow from  $j$  to  $i$  if and only if the partial derivative  $(\partial f_i / \partial x_j)(x)$  is positive (resp. negative). Each edge in  $G(x)$  is thus both oriented and endowed with a sign. The variable  $x$  is viewed as the *phase space location* of the graph  $G(x)$ .

A *circuit* in the graph  $G(x)$  is a sequence of distinct vertices  $i_1, i_2, \dots, i_k$  such that there is an edge from  $i_\alpha$  to  $i_{\alpha+1}$ ,  $1 \leq \alpha \leq k-1$ , and from  $i_k$  to  $i_1$ .

The *sign of a circuit* is the product of the signs of its edges.

A circuit is thus determined by a set of nonzero coefficients in the *Jacobian matrix*  $J(x) = ((\partial f_i / \partial x_j)(x))$  whose rows and columns are in cyclic permutation. Its sign is the sign of the product of these coefficients.

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