J. Math. Biol. (2011) 63:593–600
DOI 10.1007/s00285-010-0388-y

Mathematical Biology

Stable periodicity and negative circuits in differential systems

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Received: 5 July 2010 / Revised: 8 November 2010 / Published online: 1 December 2010

Abstract We provide a counter-example to a conjecture of René Thomas on the relationship between negative feedback circuits and stable periodicity in ordinary differential equation systems (Kaufman et al. in J Theor Biol 248:675–685, 2007). We also prove a weak version of this conjecture by using a theorem of Snoussi.

Keywords Feedback circuit · Regulatory network · Oscillation · Jacobian matrix · Interaction graph

Mathematics Subject Classification (2000) 34C10 · 92C42

1 Introduction

In the course of his studies on genetic regulatory networks, Thomas (1981) stated two general rules on dynamical systems. Informally, the first (resp. second) rule asserts that presence of a positive (resp. negative) circuit in the interaction graph of a dynamical system is a necessary condition for the presence of several stable states (resp. sustained oscillations). We refer the reader to Thomas (1981) and Kaufman et al. (2007) for the biological discussion.

The interaction graph of a dynamical system is often formally defined, globally or locally, from the Jacobian matrix of the system. To make this precise, consider a differential function $f : \mathbb{R}^n \to \mathbb{R}^n$, and the differential system

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x).$$

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In Soulé (2003) and Kaufman et al. (2007), the *local interaction graph* of the system evaluated at point $x \in \mathbb{R}^n$, that we denote by $Gf(x)$, is defined to be the signed directed graph with $\{1, \ldots, n\}$ as vertex-set, and with a positive (resp. negative) arc from j to i if $(\partial f_i/\partial x_j)(x)$ is positive (resp. negative) $(i, j = 1, \ldots, n)$. The *global interaction graph* of the system, that we denote by $G(f)$, is then defined to be the union of all the local interaction graphs: the vertex-set is $\{1, \ldots, n\}$, and there exists a positive (resp. negative) arc from j to i if there exists $x \in \mathbb{R}^n$ such that $(\partial f_i/\partial x_j)(x)$ is positive (resp. negative) ($G(f)$ can thus have both a positive and a negative arc from one vertex to another). In such signed directed graphs, a *positive* (resp. *negative*) *circuit* is an elementary directed cycle containing an even (resp. odd) number of negative arcs.

With these materials, the Thomas rules can be precisely stated as conjectures (Kaufman et al. 2007):

Conjecture 1 (*First Thomas' rule, global version*) If the system $\mathrm{d}x/\mathrm{d}t = f(x)$ has several stable states, then $G(f)$ has a positive circuit.

Conjecture $1'$ (*First Thomas' rule, local version*) If the system $\mathrm{d}x/\mathrm{d}t = f(x)$ has several stable states, then there exists $x \in \mathbb{R}^n$ such that $Gf(x)$ has a positive circuit.

Conjecture 2 (*Second Thomas' rule, global version*) If the system $\mathrm{d}x/\mathrm{d}t = f(x)$ has a stable periodic solution, then $G(f)$ has a negative circuit of length at least two.

Conjecture $2'$ (*Second Thomas' rule, local version*) If the system $\mathrm{d}x/\mathrm{d}t = f(x)$ has a stable periodic solution, then there exists $x \in \mathbb{R}^n$ such that $Gf(x)$ has a negative circuit of length at least two.

Note that since each local interaction graph $Gf(x)$ is a subgraph, generally strict, of the global interaction graph $G(f)$, the local versions of Thomas' rules are stronger than the global ones.

The proven results are the following. Conjectures 1 and 2 have been proved by Gouzé (1998) and Snoussi (1998) under additional assumptions, including the fact that $Gf(x)$ does not depend on x (see also Plahte et al. 1995; Cinquin and Demongeot 2002). Conjecture $1'$ has been latter proved by Soulé (2003). Besides, Boolean analogs of Conjecture $1'$ and 2 have been stated and proved by Remy et al. (2008), and extended to the non-Boolean discrete case in Richard and Comet (2007) and Richard (2010). Conjecture $2'$ has been recently explicitly stated in Kaufman et al. (2007), and a counter-example to a discrete analog of Conjecture $2'$ has been exhibited in Richard (2010).

The main result of this note is a counter-example to Conjecture $2'$, which is based on the discrete counter-example mentioned above. We also show that Conjecture 2 is an easy consequence of the work of Snoussi (1998). Finally, we state a conjecture that can be seen as a "semi-local" version of the second Thomas rule.[1]

[1] This semi-local version has been independently proposed by Soulé (personal communication).

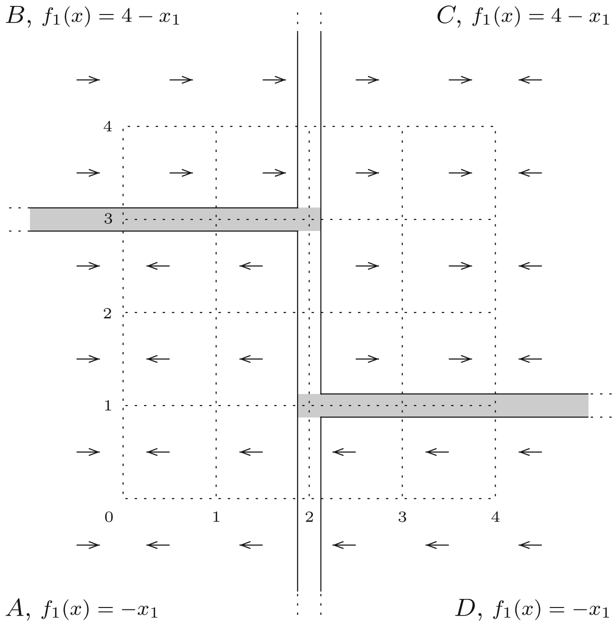

Fig. 1 A qualitative phase portrait of f_1 (the *arrows* represent the sign of $\mathrm{d}f_1/\mathrm{d}t$ and $\varepsilon = 1/8$). It is based on the fact that $f_1(x) = -x_1$ for x in $A =]-\infty, 2-\varepsilon] \times]-\infty, 3-\varepsilon]$ or $D = [2+\varepsilon, +\infty[\times]-\infty, 1-\varepsilon]$, and that $f_1(x) = 4 - x_1$ for x in $B =]-\infty, 2-\varepsilon] \times [3+\varepsilon, +\infty[$ or $C = [2+\varepsilon, +\infty[\times [1+\varepsilon, +\infty[$. The union of the two *grey* regions corresponds to the set Λ_1 considered in the text

2 Counter-example to Conjecture 2′

Let $\varepsilon < 1/2$ be a positive constant. For every integer a, let φ_a be any differential function from $\mathbb{R}$ to [0, 1] with the following property:

$$\varphi_a(x) = 1 \quad \text{if } x \geq a + \varepsilon; \qquad \varphi_a(x) = 0 \quad \text{if } x \leq a - \varepsilon. \tag{$*$}$$

Let $\overline{\varphi}_a : \mathbb{R} \to [0, 1]$ be defined by $\overline{\varphi}_a(x) = 1 - \varphi_a(x)$.

Consider the two-dimensional differential equation system $\mathrm{d}x/\mathrm{d}t = f(x)$ where $f : \mathbb{R}^2 \to \mathbb{R}^2$ is defined by

$$\begin{aligned} f_1(x_1, x_2) &= 4\varphi_3(x_2)\overline{\varphi}_2(x_1) + 4\varphi_1(x_2)\varphi_2(x_1) - x_1, \\ f_2(x_1, x_2) &= 4\overline{\varphi}_3(x_1)\varphi_2(x_2) + 4\overline{\varphi}_1(x_1)\overline{\varphi}_2(x_2) - x_2. \end{aligned}$$

A qualitative analysis of f is presented in Figs. 1, 2 and 3. A phase portrait of f is presented in Fig. 4.

We first prove that *for all* $x \in \mathbb{R}^n$, $Gf(x)$ *has no negative circuit of length at least two*. Indeed, if $(\partial f_1/\partial x_2)(x) \neq 0$, then x necessarily belongs to

$$\Lambda_1 =]-\infty, 2+\varepsilon[\times]3-\varepsilon, 3+\varepsilon[\ \cup\ ]2-\varepsilon, \infty[\times]1-\varepsilon, 1+\varepsilon[,$$

and if $(\partial f_2/\partial x_1)(x) \neq 0$ then x necessarily belongs to

$$\Lambda_2 =]3-\varepsilon, 3+\varepsilon[\times]2-\varepsilon, +\infty[\ \cup\ ]1-\varepsilon, 1+\varepsilon[\times]-\infty, 2+\varepsilon[;$$

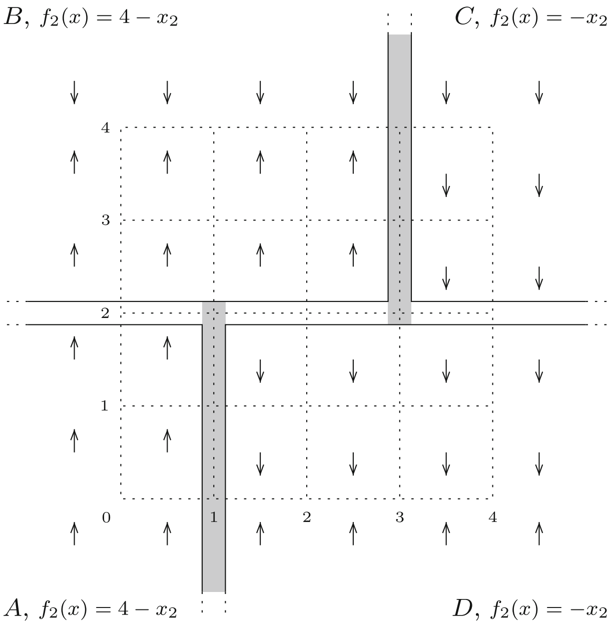

Fig. 2 A qualitative phase portrait of f_2 (the *arrows* represent the sign of $\mathrm{d}f_2/\mathrm{d}t$ and $\varepsilon = 1/8$). It is based on the fact that $f_2(x) = 4 - x_2$ for x in $A =]-\infty, 1-\varepsilon] \times]-\infty, 2-\varepsilon]$ or $B =]-\infty, 3-\varepsilon] \times [2+\varepsilon, +\infty[$, and that $f_2(x) = -x_2$ for x in $C = [3+\varepsilon, +\infty[\times [2+\varepsilon, +\infty[$ or $D = [1+\varepsilon, +\infty[\times]-\infty, 2-\varepsilon]$. The union of the two *grey* regions corresponds to the set Λ_2 considered in the text

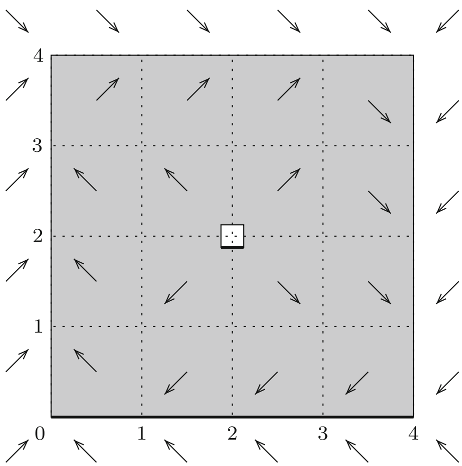

Fig. 3 The qualitative phase portrait of f resulting from the qualitative phase portraits of f_1 and f_2. The *grey* region corresponds to the set $\Omega = [0, 4]^2 \setminus]2-\varepsilon, 2+\varepsilon[^2$ considered in the text, and the two *bold* segments correspond to the segments $[0, 4] \times \{0\}$ and $[2-\varepsilon, 2+\varepsilon] \times \{2-\varepsilon\}$ considered in the text

see Figs. 1 and 2 for an illustration. Since $\Lambda_1 \cap \Lambda_2 = \emptyset$, we deduce that, for all $x \in \mathbb{R}^2$, $Gf(x)$ has no circuit of length at least two. So, in particular, $Gf(x)$ has no negative circuit of length at least two.

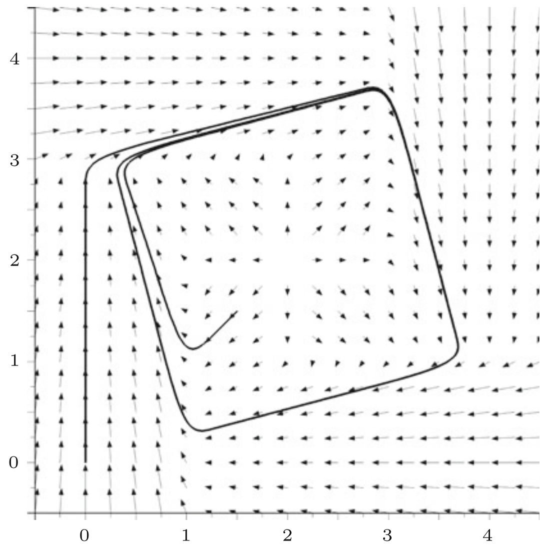

Fig. 4 A phase portrait of f with the trajectories starting at $(0, 0)$ and $(3/2, 3/2)$ [$\varepsilon = 1/4$, and φ_a is defined by $\varphi_a(x) = \lambda(x - a)$ where λ is a differentiable increasing function from $\mathbb{R}$ to $[0, 1]$ such that $\lambda(-\varepsilon) = 0$ and $\lambda(\varepsilon) = 1$]

It remains to prove that *the system* $\mathrm{d}x/\mathrm{d}t = f(x)$ *has a stable periodic solution*. One can check that there is no equilibrium point in the bounded region

$$\Omega = [0, 4]^2 \setminus]2 - \varepsilon, 2 + \varepsilon[^2,$$

and that all the solutions starting in Ω remain in Ω. Indeed, if x belongs to the segment $[0, 4] \times \{0\}$, then $f_2(x) = 4\bar{\varphi}_1(x_1) \geq 0$, and if x belongs to the segment $[2-\varepsilon, 2+\varepsilon] \times \{2-\varepsilon\}$ then $f_2(x) = \varepsilon - 2 \leq 0$. We deduce that if a solution starts in Ω, then it cannot leaves Ω by crossing one of these two segments. Reasoning similarly on the other segments at the boundary of Ω, we deduce that all the solutions starting in Ω remain in Ω; see Fig. 3 for an illustration. So following the Poincaré-Bendixon theorem (see e.g. Braun 1993, p. 433), there exists a periodic solution ψ of period $T > 0$ starting in Ω. Since it is clear that $(\partial f_i/\partial x_i)(x) < 0$ for all $x \in \Omega$, $i = 1, 2$, the well-known criterion

$$\int_0^T \frac{\partial f_1}{\partial x_1}(\psi(t)) + \frac{\partial f_2}{\partial x_2}(\psi(t))dt \; < \; 0$$

for the (orbital) asymptotic stability of the periodic solution ψ is satisfied (see e.g. Perko 2002, p. 216).

Remarks (1) When ε is small, the function φ_a is closed to the step function h_a defined by: $h_a(x) = 1$ if $x \geq a$; $h_a(x) = 0$ if $x < a$. Actually, by replacing φ_a by h_a in f, one obtain a piece-wise linear system that belongs to the class of piece-wise linear systems usually used to model gene networks (de Jong 2002). (2) There exists smooth functions with the property $(*)$. Indeed, let $\gamma : \mathbb{R} \to \mathbb{R}$ be defined by: $\gamma(x) = \exp(-1/(1-x^2))$ if $|x| < 1$, and $\gamma(x) = 0$ otherwise. Then, the function φ defined by

$\varphi(x) = (1/c)\int_{-\infty}^{x} \gamma(s)ds$ with $c = \int_{-\infty}^{+\infty} \gamma(s)ds$ is a function from $\mathbb{R}$ to [0, 1], which is smooth since γ is, and which has the following property: $\varphi(x) = 0$ if $x \leq -1$, and $\varphi(x) = 1$ if $x \geq 1$. Thus, one can easily defined, from φ, a smooth function satisfying $(*)$ for each a and each ε.

3 Proof of Conjecture 2

The proof needs few additional definitions. Let G be a signed directed graph with V as vertex set. A directed path is positive (resp. negative) if it has an even (resp. odd) number of negative arcs. A *strongly connected component* of G is a maximal subset C of V such that for all distinct vertices $i, j \in C$, there exists a directed path from i to j. The graph G is *strongly connected* if V is a strongly connected component.

Let us say that f has the property $\mathcal{H}$ if $Gf(x)$ does not depend on x, or equivalently, if

$$\partial f_i/\partial x_j > 0 \quad \text{or} \quad \partial f_i/\partial x_j = 0 \quad \text{or} \quad \partial f_i/\partial x_j < 0, \quad i, j = 1, \ldots, n. \qquad (\mathcal{H})$$

The proof of Conjecture 2 is based on the following theorem of Snoussi:

Snoussi's theorem (1998) If the system $\mathrm{d}x/\mathrm{d}t = f(x)$ has a stable periodic solution, if f has the property $\mathcal{H}$, and if $G(f)$ is strongly connected, then $G(f)$ has a negative circuit of length at least two.

Remarks (1) It is easy to see that the arguments used in Snoussi's proof are sufficient to establish the theorem under the following weaker assumption $\mathcal{H}'$:

$$\partial f_i/\partial x_j \geq 0 \quad \text{or} \quad \partial f_i/\partial x_j \leq 0, \quad i, j = 1, \ldots, n, \quad i \neq j. \qquad (\mathcal{H}')$$

(2) Gouzé (1998) proved that if the system $\mathrm{d}x/\mathrm{d}t = f(x)$ has a stable periodic solution and if f has the property $\mathcal{H}$, then $G(f)$ has a negative semi-circuit of length at least two (*i.e.* an undirected cycle of length at least two with an odd number of negative arcs). The theorem of Snoussi can be deduced from the one of Gouzé by using the following basic graph property: if an interaction graph is strongly connected and contains a negative semi-circuit of length at least two, then it contains a negative circuit of length at least two. A way to prove this property consists in considering a "miss-oriented" arc $j \to i$ of the negative semi-circuit and a directed path P from i to j: if $j \to i$ and P have opposite signs, then they form together a negative circuit; otherwise, by replacing $j \to i$ by P in the negative semi-circuit, one obtains another negative semi-circuit with less "miss-oriented" arcs, and the process can be iterated until obtaining a negative circuit.

Lemma *If the system* $\mathrm{d}x/\mathrm{d}t = f(x)$ *has a stable periodic solution, and if* $G(f)$ *is strongly connected, then* $G(f)$ *has a negative circuit of length at least two.*

Proof If f has the property $\mathcal{H}'$, then the lemma is given by Snoussi's theorem and the first remark. Otherwise, there exists $\alpha, \beta \in \mathbb{R}^n$ and $i \neq j$ such that $(\partial f_i/\partial x_j)(\alpha) < 0 < (\partial f_i/\partial x_j)(\beta)$. So $G(f)$ has both a positive and a negative arc from j to i. Since

$G(f)$ is strongly connected, there exists an elementary directed path from i to j. If this path is positive (resp. negative), then it forms, together with the negative (resp. positive) arc from j to i, a negative circuit of length at least two. □

We are now in position to prove Conjecture 2. We proceed by contradiction. Consider the smallest n for which a counter-example exists, that is, the smallest n for which there exists $f : \mathbb{R}^n \to \mathbb{R}^n$ such that: (1) $\mathrm{d}x/\mathrm{d}t = f(x)$ has a stable periodic solution $\psi = (\psi_1, \ldots, \psi_n) : \mathbb{R}_{\geq 0} \to \mathbb{R}^n$; and (2) $G(f)$ has no negative circuit of length at least two.

Suppose first that one of the components of ψ is constant. We only treat the case where $\psi_n = \text{cst} = c$, the other cases being similar. Let $\tilde{f} : \mathbb{R}^{n-1} \to \mathbb{R}^{n-1}$ be defined by

$$\tilde{f}_i(x_1, \ldots, x_{n-1}) = f_i(x_1, \ldots, x_{n-1}, c) \qquad (i = 1, \ldots, n-1).$$

Then, $\tilde{\psi} = (\psi_1, \ldots, \psi_{n-1}) : \mathbb{R}_{\geq 0} \to \mathbb{R}^{n-1}$ is a stable periodic solution of $\mathrm{d}x/\mathrm{d}t = \tilde{f}(x)$ (which has the same period as ψ). Furthermore, since $G(\tilde{f})$ is a subgraph of $G(f)$, $G(\tilde{f})$ has no negative circuit of length at least two. So $\tilde{f}$ is a counter-example of dimension $n-1$, a contradiction.

Now, suppose that $\psi_i \neq \text{cst}$ for $i = 1, \ldots, n$, and consider a strongly connected component C of $G(f)$ that has no input arc, *i.e.* such that there is no arc from a vertex $i \notin C$ to a vertex $j \in C$ (such a component always exists). Without loss of generality, suppose that $C = \{1, \ldots, m\}$. According to the lemma, $G(f)$ is not strongly connected, so $m < n$. Furthermore, since C has no input arc, we deduce that, for $i = 1, \ldots, m$, $f_i(x)$ does not depend on $x_{m+1}, \ldots, x_n$. So there exists $\bar{f} : \mathbb{R}^m \to \mathbb{R}^m$ such that, for all $x \in \mathbb{R}^n$,

$$\bar{f}_i(x_1, \ldots, x_m) = f_i(x_1, \ldots, x_m, x_{m+1}, \ldots, x_n) \qquad (i = 1, \ldots, m).$$

Then, $\bar{\psi} = (\psi_1, \ldots, \psi_m) : \mathbb{R}_{\geq 0} \to \mathbb{R}^m$ is a stable periodic solution of $\mathrm{d}x/\mathrm{d}t = \bar{f}(x)$ (the period is not zero since the components of $\bar{\psi}$ are not constants). Furthermore, since $G(\bar{f})$ is a subgraph of $G(f)$, $G(\bar{f})$ has no negative circuit of length at least two. We deduce that $\bar{f}$ is a counter-example of dimension $m < n$, a contradiction. This completes the proof of Conjecture 2.

4 A semi-local version of the second Thomas rule

We have disproved the local version of the second Thomas rule, and proved the global one. It would be now interesting to study the following semi-local version of the second Thomas rule, which is weaker than the local version, and stronger than the global one.

Conjecture (*Second Thomas' rule, semi-local version*) If the system $\mathrm{d}x/\mathrm{d}t = f(x)$ has a stable periodic solution with orbit Γ, then

$$\bigcup_{x \in \Gamma} Gf(x)$$

has a negative circuit of length at least two.

(Here, if G and G' are two directed signed graph on V with A and A' as arc set, then $G \cup G'$ is the signed directed graph on V with $A \cup A'$ as arc set.)

Remark Discrete analogs of this conjecture have been stated and proved in Remy et al. (2008) and Richard (2010).

Acknowledgments Many thanks to Bruno Soubeyran and René Thomas for constructive discussions and encouragements.

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