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# Periodic solutions of piecewise affine gene network models: the case of a negative feedback loop

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**Abstract:** In this paper the existence and unicity of a stable periodic orbit is proven, for a class of piecewise affine differential equations in dimension 3 or more, provided their interaction structure is a negative feedback loop. It is also shown that the same systems converge toward a unique stable equilibrium point in dimension 2. This extends a theorem of Snoussi, which showed the existence of these orbits only. The considered class of equations is usually studied as a model of gene regulatory networks. It is not assumed that all decay rates are identical, which is biologically irrelevant, but has been done in the vast majority of previous studies. Our work relies on classical results about fixed points of monotone, concave operators acting on positive variables. Moreover, the used techniques are very likely to apply in more general contexts, opening directions for future work.

**Key-words:**   periodic solutions, piecewise-linear, monotone operators

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# Solutions périodiques de modèles affines par morceaux de réseaux génétiques : le cas d'une boucle négative de retroaction

**Résumé :** Dans ce rapport l'existence et l'unicité d'une orbite périodique stable est démontrée, pour une classe d'équations différentielles affines par morceaux en dimension 3 et plus, pour les systèmes dont la structure d'interaction est une boucle négative. Il est également démontré que ces mêmes systèmes convergent vers un unique équilibre stable en dimension 2. Ceci étend un résultat dû à Snoussi, qui assurait l'existence seule de ces solutions. La classe d'équations considérée est couramment utilisée comme modèle de réseaux de régulation génétique. Les taux de dégradations ne sont pas supposés égaux entre eux, hypothèse biologiquement injustifiée, mais effectuée dans la plupart des travaux sur le sujet. Ce travail s'appuie sur des théorèmes classiques de point fixe d'opérateurs monotones et concaves, avec variables positives. De plus, les techniques développées sont très certainement applicables à des situations plus générales, ouvrant une voie pour de futures recherches.

**Mots-clés :** solutions périodiques, linéaire par morceaux, opérateurs monotones

# 1 Preliminaries

## 1.1 Previous works

Among recent biological concepts, *gene regulatory networks* is a particularly intriguing one. Coarsely said, it refers to a set of genes coding for proteins being able to activate or inhibit the expression of other genes within the same set. Since such systems are likely to involve large numbers of genes, and since moreover gene expression is known to be a non-linear mechanism, mathematical models are, though a required tool, facing a major challenge. This fact has impelled a large amount of work, giving birth to numerous models, see [2] for a review. Among different types of models, a special class of piecewise linear differential equations have been proposed in the early 1970's [5]. This class has the advantage of being mathematically much more tractable than more classical, smooth non-linear equations, nonetheless offering a comparable variety of behaviours.

Since its introduction, the class of piecewise-linear models has thus been studied in various fashions. Periodic trajectories, or limit cycles, of these systems have been especially investigated. The first results concerned a particular case, characterized by the equality of all decay rates of the system. Under this assumption, trajectories are straight lines in regions where the system is affine, and the whole analysis becomes much simpler. Notably, an explicit Poincaré map is possibly derived, which is a fractional linear map. It is then possible to reduce the problem of existence and stability of periodic orbits to an eigenanalysis. This method was introduced in [6, 7], and subsequently improved by different authors [12, 8, 9].

To our knowledge, only one study did not require this uniform decay rates assumption, but concerned on the other hand systems whose interaction structure consists in a single, negative loop [14]. Biological examples, such as the *repressilator* [4] make this type of interaction structure relevant. For such systems, the existence, but not unicity, of a stable limit cycle in dimension $\geqslant 3$, and of a stable focus in dimension 2 is proven in [14]. This proof relies on Brouwer's fixed point theorem, and is not entirely self contained.

Our main result is a complete proof of the existence and unicity of the mentioned attractors in feedback loop systems. Moreover, the mathematical tools involved to prove this result seem to have been ignored in the context of piecewise linear gene network models, and offer a very promising framework.

More precisely, the result on which we mainly rely is a fixed point theorem for monotone, concave operators, where monotonicity and concavity are defined with respect to a partial order. There exists actually a well-developed corpus about operators satisfying such properties, especially for systems with positive variables. These results have the advantage of being generic, and the hypotheses on which they rely are on the other hand naturally satisfied in the context of piecewise affine models of gene networks. In order to give a more precise foretaste of the rest of this paper let us state now the main result. To make it understandable, let us just say that $\mathcal{C}$ is a periodic sequence of regions, crossed by the trajectories of any piecewise affine model of gene networks consisting in a negative feedback loop. Also, $\mathcal{Z}^1$ is a particular subset of one region, or 'zone', which is a well defined Poincaré section, and $\mathbf{T}$ is a first return map on $\mathcal{Z}^1$.

**Theorem 2.** *Let* $\mathbf{T} : \mathcal{Z}^1 \to \mathcal{Z}^1$ *be the Poincaré map of* $\mathcal{C}$.

- *If $n = 2$, then $\forall x \in \mathcal{Z}^1$, $\mathbf{T}^m x \to 0$ when $m \to \infty$.*

- *If $n > 2$, then there exists a unique nonzero fixed point $q = \mathbf{T}q$.*
  *Moreover, $q \in \mathring{\mathcal{Z}}^1$ and for every $x \in \mathcal{Z}^1 \setminus \{0\}$, $\mathbf{T}^m x \to q$ as $m \to \infty$.*

A rapid overview of the tools and references we rely on is given in section 1.2. Then, the class of piecewise affine models we focus on is presented in section 2. Some general observations about monotonicity and concavity for this class of systems are made in section 3. These remarks lead to focus on negative feedback loop systems in section 4, where the main results are stated and proven.

## 1.2 Useful mathematical results

The main result of this paper strongly rely on one theorem, that we recall here. It is a fixed point theorem of monotone, concave operators. Both monotonicity and concavity shall be understood with respect to some partial order, see below for definitions and notations. Operators with both these properties have lead to various results on existence and unicity of fixed points. Among early studies, Krasnosel'skii has provided

important results [11]. Here, we use a more recent presentation of such results, due to Smith [13], whose formulation is well adapted to our purpose and context. Namely, we use theorem 2.2 of [13].

Before stating the latter, let us introduce some notations (which are similar to those in [13]). We denote $x < y$ and $x \leqslant y$ if these inequalities hold for each coordinate (resp. entry) of vectors (resp. matrices) $x$ and $y$. Then, we denote $x \lneqq y$ if $x \leqslant y$ and $x \neq y$. For $x \leqslant y$, $[x, y] = \{z \mid x \leqslant z \leqslant y\}$, and $(x, y) = \{z \mid x < z < y\}$. For any set $A$, $\mathring{A}$ denotes the interior of $A$, and $c\ell(A)$ its closure. Now, we can state the following,

**Theorem 1.** *Let $p \in \mathring{\mathbf{R}}_+^n$, and $T : [0, p] \to [0, p]$ continuous, $C^1$ in $(0, p)$.*
*Suppose $DT(0) = \lim_{\substack{x \to 0 \\ x > 0}} DT(x)$ exists. Assume:*

> *(M)      $DT(x) > 0$ if $x > 0$, $x < p$.*

> *(C)      $DT(y) \lneqq DT(x)$ if $0 < x < y < p$.*

*Assume also $Tp < p$.*
*Suppose that $T0 = 0$, and define $\lambda = \rho(DT(0))$, the spectral radius of $DT(0)$. Then,*

> $\lambda \leqslant 1 \implies \forall x \in [0, p]$, $T^n x \to 0$ when $n \to \infty$.

> $\lambda > 1 \implies$ *There exists a unique nonzero fixed point $q = Tq$. Moreover, $q \in (0, p)$ and for every $x \in [0, p] \setminus \{0\}$, $T^n x \to q$ as $n \to \infty$.*

The case $T0 \neq 0$ leads to either a unique fixed point, or to diverging orbits. However, this case will not appear in our context, and thus it is not detailed in the theorem above.

One may remark now that in the case when $T$ is twice differentiable, the concavity condition $(C)$ admits a simple sufficient condition. The map $T_i : [0, p] \to \mathbf{R}_+$ denotes the $i$th coordinate function of $T : [0, p] \to [0, p]$.

**Proposition 1.** *Suppose that for all $i, j, k \in \{1 \cdots n\}$, and for all $0 < x < p$,*

$$\frac{\partial^2 T_i}{\partial x_k \partial x_j}(x) \leqslant 0,$$

*and for all $i, j$ there exists a $k$ such that the inequality is strict.*
*Then $T$ satisfies condition $(C)$ of theorem 1.*

Actually, it is clear that under this condition each term $\frac{\partial T_i}{\partial x_j}$ of $DT$ is a decreasing function of each coordinate $x_k$. It is moreover strictly decreasing in at least one of these coordinates, and $(C)$ thus follows. Observe by the way that the notion of concavity (w.r.t a partial order) we deal with here is weakened by the fact that it concerns only ordered pairs $(x, y)$ of variables.

Remarkably, theorem 1 relies on Perron-Frobenius theorem, which will be used at some point in the proof of our main result. It usually says that any matrix with positive entries admits a positive, simple eigenvalue, associated to a positive eigenvector. Here, we will only need the following corollary: if $A$ is a real $n \times n$ matrix such that $A > 0$, then $A$ admits a positive real eigenvalue.

## 2   Piecewise affine models

### 2.1   Formulation

The general form of the piecewise affine models we consider here may be written as:

$$\frac{dx}{dt} = \kappa(x) - \Gamma x \tag{1}$$

The variables $(x_1 \ldots x_n)$ represent concentrations in proteins or mRNA produced from $n$ interacting genes. Since gene transcriptional regulation is widely supposed to follow a steep sigmoid law, it has been suggested

that idealized, discontinuous switches may be used instead to model these complex systems [5]. Accordingly, $\mathsf{s}^+(\cdot\,,\theta) : \mathbf{R} \to \{0,1\}$ denote the increasing step function, or Heaviside function:

$$\left\{ \begin{array}{rcll} \mathsf{s}^+(x,\theta) & = & 0 & \text{if } x < \theta, \\ \mathsf{s}^+(x,\theta) & = & 1 & \text{if } x \geqslant \theta, \end{array} \right.$$

which represent an effect of activation. Also, $\mathsf{s}^-(x,\theta) = 1 - \mathsf{s}^+(x,\theta)$, is its decreasing version, and represents inhibition.

Then, $\kappa : \mathbf{R}_+^n \to \mathbf{R}_+^n$ is a piecewise constant production term that can be expressed in terms of step functions $\mathsf{s}^\pm(x_i,\theta_i)$. $\Gamma \in \mathbf{R}_+^{n \times n}$ is a diagonal matrix whose diagonal entries $\Gamma_{ii} = \gamma_i$, are degradation rates of variables in the system.

Since each variable $x_i$ is a concentration (of mRNA or of protein), it ranges in some interval of non-negative values denoted $[0, \mathsf{max}_i]$. When this concentration reaches a threshold value, some other gene in the network, say gene number $j$, is suddenly produced with a different production rate : the value of $\kappa_j$ changes. For each $i \in \{1 \cdots n\}$ there is thus a finite set of threshold values, which serve as parameter of step functions :

$$\Theta_i = \{\theta_i^1, \ldots, \theta_i^{q_i-1}\}, \tag{2}$$

where the thresholds are ordered: $0 < \theta_i^1 < \cdots < \theta_i^{q_i-1} < \mathsf{max}_i$. The extreme values 0 and $\mathsf{max}_i$ are not thresholds, since they bound the values of $x_i$, and thus may not be crossed. However, a conventional notation will be : $\theta_i^0 = 0$, and $\theta_i^{q_i} = \mathsf{max}_i$.

Now, at a time $t$ such that $x_i(t) \in \Theta_i$, there is some $j \in \{1 \cdots n\}$ such that $\kappa_j(x(t^+)) \neq \kappa_j(x(t^-))$. It follows that each axis of the state space will be usefully partitioned into open segments between thresholds. Since the extreme values will not be crossed by the flow (see later), the first and last segments include one of their endpoints :

$$\mathcal{D}_i \in \left\{ [\theta_i^0, \theta_i^1), \ (\theta_i^{q_i-1}, \theta_i^{q_i}] \right\} \cup \left\{ (\theta_i^j, \theta_i^{j+1}) \,|\, j \in \{1 \cdots q_i - 2\} \right\} \cup \Theta_i \tag{3}$$

Each product $\mathcal{D} = \prod_{i=1}^n \mathcal{D}_i$ defines a rectangular *domain*, whose dimension is the number of $\mathcal{D}_i$ that are not singletons. When $\dim \mathcal{D} = n$, one usually says that it is a *regulatory domain*, or *regular domain*, and those domain with lower dimension are called *switching domains* [3]. We use the notation $\mathscr{D}$ to represent the set of all domains of the form above. Then, $\mathscr{D}_r$ will denote the set of all regulatory domains, and $\mathscr{D}_s$ the set of all switching domains.

A convenient way to represent regular domains makes use of a discrete map, whose range we write as:

$$\mathcal{A} = \prod_{i=1}^n \{0 \cdots q_i - 1\}. \tag{4}$$

The map in question is then defined as $\mathsf{d} : \mathscr{D}_r \to \mathcal{A}$, and sends each regular domain to the superscript of its "lower-left" corner: $\mathsf{d} \left( \prod_i (\theta_i^{a_i-1}, \theta_i^{a_i}) \right) = (a_1 - 1 \ldots a_n - 1)$. In the following, we will often identify regular domains and their image in $\mathcal{A}$, talking for example about some 'domain $a$'.

The dynamics on regular domains, called here *regular dynamics* can be defined quite simply, due to the simple expression of the flow in each $\mathcal{D} \in \mathscr{D}_r$. On sets of $\mathscr{D}_s$ on the other hand, the flow is in general not uniquely defined. It is anyway possible to define solutions in a rigorous way, yielding what will be mentioned as the *singular dynamics*, at the price of considering set-valued solutions. The latter's definition rests on Filippov's theory of differential equations with a discontinuous right-hand side, and its formulation in the particular case of equations (1) can be found in [1, 10], among others. Since we will only encounter systems for which the Filippov solutions lead to single valued trajectories, we shall only describe the regular dynamics with some detail.

## 2.2 Regular dynamics

Regulatory domains are of particular importance. They form the main part of state space, and the dynamics on them can be expressed quite simply. Actually, on such a domain $\mathcal{D}$, the production rate $\kappa$ is constant, and thus equation (1) is affine. Its solution is explicitly known, for each coordinate $i$ :

$$\varphi_i(x,t) = x_i(t) = \frac{\kappa_i}{\gamma_i} - e^{-\gamma_i t} \left( x_i - \frac{\kappa_i}{\gamma_i} \right), \tag{5}$$

and is valid for all $t \in \mathbf{R}_+$ such that $x(t) \in \mathcal{D}$. It follows immediately that

$$\phi(\mathcal{D}) = (\phi_1 \cdots \phi_n) = \left( \frac{\kappa_1}{\gamma_1} \cdots \frac{\kappa_n}{\gamma_n} \right)$$

is an attractive equilibrium point for the flow (5). Hence, if it lies inside $\mathcal{D}$, it is an actual equilibrium of system (1). Otherwise, the flow will reach the boundary $\partial \mathcal{D}$ in finite time, unless $\phi(\mathcal{D})$ lies exactly on the boundary of $\mathcal{D}$. However this situation is clearly not generic, and we assume in the rest of this paper it never occurs. At the time when the flow reaches $\partial \mathcal{D}$ thus, the value of $\kappa$ will change, and that of $\phi$ accordingly. The point $\phi(\mathcal{D})$ is often called *focal point* of the domain $\mathcal{D}$. Then, the continuous flow can be reduced to a discrete-time dynamical system, with a state space supported by the boundaries of boxes in $\mathcal{D}_r$.

Hence, the state space of this discrete-time system is part of $\mathcal{D}_s$, which may seem problematic at first sight. In fact, it is actually not always possible to define discrete-time trajectories on domains of $\mathcal{D}_s$ having dimension $n-2$ or less. On any $n-1$ domain $\mathcal{D}$, on the other hand, such a definition may always be properly provided, in terms of the flow lines in the two regular domains separated by $\mathcal{D}$. If these flow lines both point towards, or away from $\mathcal{D}$ (which is expressed formally using the flow coordinate which is normal to $\mathcal{D}$), the latter is called respectively *black wall* or *white wall*. Otherwise, *i.e.* when flow lines both cross $\mathcal{D}$ in the same direction, one usually refers to $\mathcal{D}$ as a *transparent wall*. In the two first cases, the Filippov theory is required, providing set-valued trajectories on the walls, the so-called sliding modes [10]. On transparent walls, trajectories are simply defined by continuity, from the flow lines on both sides. We shall encounter only this third kind of wall in the rest of this paper.

Note that if $\mathcal{D} \in \mathcal{D}_r$ is represented by $a \in \mathcal{A}$, *i.e.* $\mathsf{d}(\mathcal{D}) = a$, one shall most often denote by $\phi(a)$, or $\phi^a$, the focal point associated to this domain.

Once the flow (5) is given in a box $\mathcal{D}_a$, it is easy to compute the time and position at which it intersects the boundary of $\mathcal{D}_a$, if ever. The possibility for each facet to be encountered by the flow depends uniquely on the position of the focal point : $\{x \,|\, x_i = \theta_i^{a_i-1}\}$ (resp. $\{x \,|\, x_i = \theta_i^{a_i}\}$) can be crossed if and only if $\phi_i < \theta_i^{a_i-1}$ (resp. $\phi_i > \theta_i^{a_i}$). According to this observation, we denote $I_{out}^+(a) = \{i \in \{1 \cdots n\} | \phi_i > \theta_i^{a_i}\}$, and $I_{out}^-(a) = \{i \in \{1 \cdots n\} | \phi_i < \theta_i^{a_i-1}\}$.

Then, $I_{out}(a) = I_{out}^+(a) \cup I_{out}^-(a)$ is the set of escaping directions of $\mathcal{D}_a$.

Also, it will be practical to point out the lower and upper thresholds bounding a box, thanks to the pairs of functions $\theta_i^{\pm} : \mathcal{A} \to \Theta_i$, $\theta_i^-(a) = \theta_i^{a_i-1}$ and $\theta_i^+(a) = \theta_i^{a_i}$. These functions will clearly only be useful notations, and bring no further information about the system.

When it is unambiguous, we will omit the dependence on $a$ in the sequel.

Now, in each direction $i \in I_{out}$ the time at which $x(t)$ encounters the corresponding hyperplane, for $x \in \mathcal{D}_a$, can easily be shown to be:

$$\tau_i(x) = \frac{-1}{\gamma_i} \ln \left( \min \left\{ \frac{\phi_i - \theta_i^-(a)}{\phi_i - x_i}, \frac{\phi_i - \theta_i^+(a)}{\phi_i - x_i} \right\} \right). \tag{6}$$

Taking the minimum $\tau(x) = \min_{i \in I_{out}} \tau_i(x)$, and reinjecting it in equation (5), we get the exiting point of $\mathcal{D}_a$ when starting at $x$. Since this process is intended to be repeated along trajectories, $x$ will generally lie on the boundary of the current box, except for the initial condition, which may however be chosen on a facet without loss of generality. We then get a *transition map* $\mathcal{T}^a : \partial \mathcal{D}_a \to \partial \mathcal{D}_a$ :

$$\begin{aligned} \mathcal{T}^a x &= \varphi(x, \tau(x)) \\ &= \phi + \alpha(x)(x - \phi). \end{aligned} \tag{7}$$

where $\alpha(x) = \exp(-\tau(x)\Gamma)$. The latter depends on $a$, as seen from (6).

Now, the initial system (1) may been reduced to a discrete time dynamical system, as mentioned earlier. It consists in iterates of a global map $\mathcal{T}$ on a domain $\mathrm{Dom}_{\mathcal{T}}$. As already mentioned, $\mathrm{Dom}_{\mathcal{T}}$ must be contained in the set of $n-1$ domains of $\mathcal{D}_s$. Since $\mathcal{T}$ has to be iterated on this domain, all points which reach some $n-2$ dimensional (or less) domain after applying $\mathcal{T}$ a finite number of times, must be excluded from $\mathrm{Dom}_{\mathcal{T}}$. Furthermore, whereas $\mathcal{T}$ is readily defined on transparent walls, black and white walls are much less obvious to deal with. We thus suppose from now on that $\mathrm{Dom}_{\mathcal{T}}$ entirely consists of transparent walls. A more detailed discussion about the topology of this domain can be found in [9]. A simple criterion to ensure that

all walls are transparent is the absence of auto-regulation, in the sense that no production term $\kappa_i$ depends on $x_i$.

At each point of such a domain, it is possible to consistently apply a unique local map $\mathcal{T}^a$. Actually, each wall is either on the boundary of the whole domain $\bigcup_a \mathcal{D}_a$, and thus of a single regular domain $\mathcal{D}_a$, or can be written as an intersection $\partial \mathcal{D}_a \cap \partial \mathcal{D}_b$ of two regular domain boundaries. It is clear that on transparent walls there is always exactly one of the two domains, say $\mathcal{D}_a$, such that $\mathcal{T}^a$ is not the identity. Applying $\mathcal{T}^a$ is then consistent with the orientation of the flow lines. Yet, we only care here with forward trajectories, since $\mathcal{T}^{-1}$ is not properly defined on the full domain $\mathrm{Dom}\,_\mathcal{T}$.

Suppose now that there is a wall $W \subset \mathrm{Dom}\,_\mathcal{T}$, and a sequence $a^1 \ldots a^\ell$ of regular domains such that $(\mathcal{T}^{a^\ell} \circ \mathcal{T}^{a^{\ell-1}} \cdots \circ \mathcal{T}^{a^1})(W) \cap W \neq \varnothing$. Now, it is tempting to study the dynamics of this iterated map on $W$. In particular, any fixed point of this map determines a periodic trajectory of the continuous time system (1).

# 3    Regions of fixed monotonicity and concavity

In order to apply theorem 1 to an iterate of the transition map, as defined in previous section, it is necessary to check whether it is monotone and concave, in the sense of properties $(M)$ and $(C)$. In this section it is shown that these conditions cannot be satisfied by the transition map on a whole wall, and that some refinement should be done. To this aim, one should compute the jacobian of a composite map, of the form: $D(\mathcal{T}^{a^\ell} \circ \mathcal{T}^{a^{\ell-1}} \cdots \circ \mathcal{T}^{a^1})$. This requires the computation of an arbitrary $D\mathcal{T}^{a^i}$.

Let $W$ be an arbitrary wall. One has seen in previous section that $\mathcal{T} = \mathcal{T}^a$, for some uniquely defined $a$. Let moreover $x \in W$ such that there exists a unique $s \in I_{out}(a)$ such that $\tau(x) = \tau_s(x)$, and denote $W' \subset \{x \mid x_s = \theta_s\}$ the wall such that $\mathcal{T}x \in W'$. Then there exists an open neighbourhood of $x$ in which the following holds:

$$\mathcal{T}_i x = \phi_i^a + (x_i - \phi_i^a)\,\alpha_i(x), \tag{8}$$

where $\mathcal{T}_i$ is the $i$th coordinate function of $\mathcal{T}$. To abbreviate computations, we have denoted $\alpha_i$ the $i$th diagonal entry of the diagonal matrix $\alpha(x)$ defined in previous section:

$$\alpha_i(x) = \left(\frac{\phi_s^a - \theta_s}{\phi_s^a - x_s}\right)^{\frac{\gamma_i}{\gamma_s}}. \tag{9}$$

Then it is rather straightforward to compute the partial derivatives at a point $x$:

$$\frac{\partial \mathcal{T}_i}{\partial x_j} = \begin{cases} (\alpha_s(x))^{\frac{\gamma_i}{\gamma_s}} & \text{if } i = j \\ -\dfrac{\gamma_i}{\gamma_s} \dfrac{\phi_i^a - x_i}{\phi_s^a - x_s} (\alpha_s(x))^{\frac{\gamma_i}{\gamma_s}} & \text{if } j = s \\ 0 & \text{otherwise.} \end{cases} \tag{10}$$

It appears from (10) that the partial derivative are of constant sign if, and only if, $\mathrm{sign}\,(\phi_i^a - x_i)$ is fixed. Actually, all degradation rates $\gamma_i$ are positive, and $\alpha_s(x) = \exp(-\gamma_s \tau(x)) \in (0,1)$ since $\tau(x)$ is non-negative.

Now make two observations on the sign pattern of $\phi^a - x$ in general. The first one concerns its invariance with respect to time evolution:

**Proposition 2.** *From the expression (5), one can observe that the quantities* $\mathrm{sign}\,(\phi_i^a - x_i)$ *are preserved by the flow, in the sense that* $\mathrm{sign}\,(\phi_i^a - x_i) = \mathrm{sign}\,(\phi_i^a - \varphi_i(x,t))$ *for any* $t \geqslant 0$.
*In particular, since the wall $W$ chosen at the beginning of this section is included in a hyperplane of the form* $\{x \mid x_j = \theta_j\}$, *the above observation yields* $\mathrm{sign}\,(\phi_j^a - \mathcal{T}_j x) = \mathrm{sign}\,(\phi_j^a - \theta_j)$.
*Similarly, for any $x$ which escapes via the wall $W' \subset \{x \mid x_s = \theta_s\}$, one has* $\mathrm{sign}\,(\phi_s^a - x_s) = \mathrm{sign}\,(\phi_s^a - \theta_s)$.

A second fact concerns the influence of the different coordinates on $\mathrm{sign}\,(\phi^a - x)$.

**Proposition 3.** *For any escaping direction $i \in I_{out}(a)$, one has either $x_i < \theta_i^+(a) < \phi_i^a$, or $\phi_i^a < \theta_i^-(a) < x_i$, and in both cases $\mathrm{sign}\,(\phi_i^a - x_i)$ is constant in the whole closure $\mathrm{cl}(\mathcal{D}_a)$ of the domain. If $\theta_i \in \{\theta_i^-(a), \theta_i^+(a)\}$ is the escaping threshold, this sign equals $\mathrm{sign}\,(\phi_i^a - \theta_i)$.*

*For the non escaping directions on the other hand,* $\operatorname{sign}(\phi_i^a - x_i)$ *is not constant on* $W$*, since* $\theta_i^-(a) < \phi_i^a < \theta_i^+(a)$*.*

Thus, condition $(M)$ cannot be valid on the whole wall $W$, unless all directions are escaping.

Since a differential of the form $D(\mathfrak{T}^{a^\ell} \circ \mathfrak{T}^{a^{\ell-1}} \cdots \circ \mathfrak{T}^{a^1})$ is a product of differentials of local maps $D(\mathfrak{T}^{a^i})$, and since the latter may only be positive in a region where the vector $\phi^{a^i} - x$ has a fixed sign pattern, it seems relevant to restrict the study to such regions.

Now, condition $(C)$ concerns the variations of the terms in (10). As shown by proposition 1, the second-order derivatives are informative in this case. They can be expressed as:

$$\frac{\partial^2 \mathfrak{T}_i}{\partial x_m \partial x_j} = \begin{cases} \dfrac{\gamma_i}{\gamma_s} \dfrac{(\alpha_s(x))^{\frac{\gamma_i}{\gamma_s}}}{\phi_s - x_s} & \text{if } i = j, m = s \quad \text{or } j = s, m = i \\ \dfrac{\gamma_i}{\gamma_s} \left(1 + \dfrac{\gamma_i}{\gamma_s}\right) \dfrac{\phi_i^a - x_i}{(\phi_s^a - x_s)^2} (\alpha_s(x))^{\frac{\gamma_i}{\gamma_s}} & \text{if } m = j = s \\ 0 & \text{otherwise.} \end{cases} \tag{11}$$

Here again, these derivatives are of fixed sign only if $\phi^a - x$ has a fixed sign pattern. Hence, both first order and second order derivatives are of constant sign in the same regions. One is thus naturally led to consider rectangular regions partitioning the wall $W^i$, defined by the sign of $\phi^a - x$, or in other words by the position (in terms of the partial order) of points with respect to the focal point.

It will be shown in the following sections that in the special case of negative feedback loop systems, only one such region contains the long-term dynamics, on each wall of a periodic sequence of domains in state space. Before proving this, let us discuss a slightly more general case than feedback loop systems. Our hope here is that this discussion give some intuition of the basic facts that will serve afterwards. It also suggests that tools from positive operators theory might be efficient in a broader context than the sole feedback loop systems.

Namely, suppose given a periodic sequence of domains $a^1, \ldots a^\ell, a^{\ell+1} = a^1$, such that there exists a unique escaping direction for each box $a^i$. This case is actually the simplest one when studying periodic orbits, since if there are several escaping directions for one box in the sequence, then some trajectories escape the cycle at this box. The set of points remaining in the periodic sequence $a^1 \ldots a^\ell$ is not easily defined in general, though under the uniform decay rates assumption it may be expressed by a list of affine inequalities [8, 9].

Then, each wall reached by successive iterates of the transition map has to be partitioned into $2^{n-2}$ regions in general. Actually, on such a wall points have $n - 1$ coordinates which are not constant: in one direction it equals a threshold value. Among these $n - 1$, one exactly is the escaping direction $s_{i-1}$ of the previous box, $a^{i-1}$. Thus according to proposition 2, the following is fixed

$$\operatorname{sign}(\phi_{s_{i-1}}^{a^i} - x_{s_{i-1}}) = \operatorname{sign}(\phi_{s_{i-1}}^{a^i} - \theta_{s_{i-1}}^m),$$

for some $m$, and any point $x$ on a trajectory crossing the considered sequence of domains.

Thus if one assumes $s_i \neq s_{i-1}$, then $n - 2$ directions remain for which two signs are possible. At each wall, the images of these $2^{n-2}$ region may intersect several regions among the $2^{n-2}$ partitioning the next wall. Hence, one may refine the partition of the latter, and iterating this process, obtain a partition of a wall into regions such that all partial derivatives of iterates, of the form $\frac{\partial \mathfrak{T}_i^k}{\partial x_j}$, for $k \in \{1 \cdots \ell\}$ are of fixed sign, and the second order derivatives as well. This process would lead to consider a high number of regions in general, each of which may satisfy the hypotheses of 1. This seems far from trivial in the most general case, but would certainly be fruitful in some more particular cases.

Hence, let us look for such special cases of equations (1). For two successive boxes $a^{i-1}$ and $a^i$, one has, as seen from (8):

$$\phi_j^{a^i} - \mathfrak{T}_j x = \phi_j^{a^i} - \phi_j^{a^{i-1}} + (\phi_j^{a^{i-1}} - x_j)\alpha_j(x), \tag{12}$$

and if the focal points are 'aligned', in the sense that $\phi_j^{a^i} = \phi_j^{a^{i-1}}$, the sign of the quantity $\phi_j - x_j$ remains unchanged after applying $\mathfrak{T}$. Actually one as seen already that $\alpha_s(x) \in (0, 1)$, and applying $\mathfrak{T}$ implies that

the focal point must be replaced by that of the following box. This geometric condition should thus avoid us to refine the partitions of successive walls, as mentioned in the above discussion, since it imposes that these regions do not overlap from one wall to the following.

It may be stated more formally. Recall that $a^i$ refers to the $i$th crossed box, and that $s_i$ is its unique escaping direction. Assume a strong version of the previous alignment of focal points:

$$\forall i \in \{1 \cdots \ell\}, \, \forall j \in \{1 \cdots n\} \setminus \{s_{i+1}\}, \quad \phi_j^{a^i} = \phi_j^{a^{i+1}}. \tag{13}$$

This alignment assumption will allow us to use theorem 1 in the region where the long-term dynamics take place. Furthermore, it will be shown that the geometric property (13) can also be obtained as a consequence of further assumptions on the interaction structure of the system: if the latter consists in a single negative feedback loop, it follows that there exists a periodic sequence of boxes satisfying (13), as we will see in the next section.

# 4 Negative feedback loop systems

## 4.1 Preliminary definitions

In this section, we focus on systems of the form:

$$\begin{cases} \dfrac{dx_1}{dt} & = \; \kappa_1^0 + \kappa_1^1 \, \mathsf{s}^-(x_n, \theta_n^1) - \gamma_1 x_1 \\[2mm] \dfrac{dx_i}{dt} & = \; \kappa_i^0 + \kappa_i^1 \, \mathsf{s}^+(x_{i-1}, \theta_{i-1}^1) - \gamma_i x_i, \qquad i = 2 \ldots n. \end{cases} \tag{14}$$

In such systems, each variable $x_i$ activates the production of the next variable, $x_{i+1}$, except $x_n$ which inhibits $x_1$. Hence, their interaction structure is that of a negative feedback loop. Up to a translation, they are of the form dealt with by Snoussi in [14]. In the case $n = 3$ one finds the well-known *repressilator* [4]. Remark now that any production term $\kappa_i$ is independent on the variable $x_i$, and thus all walls must be transparent. Without introducing unnecessary formalism, let us only say that we call *interaction graph*, IG is an oriented, labeled graph, whose vertices represent variables of the system, and edges represent interactions between them. For example, $x_i \longrightarrow^- x_j$ if an increase of $x_i$ may lead to a decrease of $\kappa_j$ at least at some point $x$ in state space. Then, a negative loop is a cycle in IG with an odd number of negative edges. It is easily shown that any system whose interaction graph consists in a single negative loop (involving all variables) is equivalent to (14), up to a symmetry in state space.

The particular form of (14) implies that there is only one threshold $\theta_i^1$ in each direction $i$, and $\theta_i^0$, $\theta_i^2$ represent the bounds of the range of $x_i$, in accordance with (2).

In the following we always assume that

$$\forall i \in \{1 \cdots n\} \qquad \kappa_i^0 + \kappa_i^1 > \gamma_i \, \theta_i^1 \quad \text{and} \quad \kappa_i^0 < \gamma_i \, \theta_i^1 \tag{15}$$

This implies that higher values of focal points are above thresholds, and lower values are below thresholds. Otherwise, all trajectories would converge to a unique fixed point, see [14] lemma 1.

Before entering into more detail, let us operate a few simplifying operations. First, we chose to set $w_j = x_j - \theta_j^1$. Then,

$$\dot{w}_j = \kappa_j^0 + \kappa_j^1 \mathsf{h}^\pm(w_{j-1}, 0) - \gamma_j \theta_j^1 - \gamma_j w_j,$$

and thus all threshold values are zero. Accordingly, all regular domains are now identified with (bounded rectangular regions of) the $2^n$ orthants of $\mathbf{R}^n$. They are mapped as explained in section 2.1, onto the discrete set $\mathcal{A} = \{0, 1\}^n$. The corresponding discrete mapping $\mathsf{d} : \mathscr{D}_r \to \mathcal{A}$ sends negative coordinates to 0, and positive ones to 1.

The bounds of the whole domain are now denoted

$$\theta_i^- = \theta_i^0 - \theta_i^1 = -\theta_i^1 \quad \text{and} \qquad \theta_i^+ = \theta_i^2 - \theta_i^1.$$

Observe that variables may now be negative, and do represent concentrations only up to a translation.
The new dynamical system behaves identically to (14), once thresholds have been set to zero, and the
following renamings have been done:

$$\kappa_i^0 \leftarrow \kappa_i^0 - \gamma_i \theta_i^1, \qquad \text{and} \qquad \phi_i \leftarrow \phi_i - \theta_i^1.$$

Then, for each $i \in \{1 \cdots n\}$, the focal point coordinate $\phi_i$ may only take two values. We abbreviate them as
follows:

$$\phi_i^- = \frac{\kappa_i^0}{\gamma_i} \qquad \text{and} \qquad \phi_i^+ = \frac{\kappa_i^0 + \kappa_i^1}{\gamma_i}. \tag{16}$$

One shall also note $\kappa_i^\pm = \gamma_i \, \phi_i^\pm$.
Remark that $\phi_i^-$ is negative and $\phi_i^+$ positive (and similarly for $\kappa_i^\pm$). From this observation, one deduces that
the focal points are entirely determined by the sign of their coordinates. In other words, the coordinates of
any focal point are known exactly from the regular domain it belongs to. More precisely, if a focal points
belongs to a domain $a \in \mathcal{A}$, the sign of $\phi_i$ is $2a_i - 1 \in \{\pm 1\}$, for each $i \in \{1 \cdots n\}$.

Now it is time to describe the dynamics of (14). In brief, we now focus on systems of the form below,
into which any system (14) can be transformed:

$$\begin{cases} \dfrac{dx_1}{dt} &= \kappa_1^- + (\kappa_1^+ - \kappa_1^-)\,\mathsf{s}^-(x_n, 0) - \gamma_1 x_1 \\ \dfrac{dx_i}{dt} &= \kappa_i^- + (\kappa_i^+ - \kappa_i^-)\,\mathsf{s}^+(x_{i-1}, 0) - \gamma_i x_i, \qquad i = 2 \ldots n. \end{cases} \tag{17}$$

A first, coarse-grained description can be achieved in terms of discrete transitions between qualitative
states in $\mathcal{A}$. This can be conveniently explained with the aid of the *state transition graph*, or simply *transition
graph*, whose vertices are elements of $\mathcal{A}$, and edges $(a, b)$ exist if and only if there exists some continuous
trajectory crossing successively the corresponding regular domains in state space, $\mathcal{D}_a$ and $\mathcal{D}_b$. This graph
will be denoted $\mathsf{TG}$.
It is easily deduced from the properties presented in section 2.2 that $\mathsf{TG}$ is entirely determined by the position
of focal points. More precisely, $(a, b) \in \mathcal{E}$ if and only if $b = a = \phi(a)$, or

$$b \in \{a + \mathbf{e}_i \,|\, i \text{ such that } a_i = 0 \text{ and } \phi_i(a) > 0\} \cup \{a - \mathbf{e}_i \,|\, i \text{ such that } a_i = 1 \text{ and } \phi_i(a) < 0\}.$$

Observe that $a$ and $b$ may differ at one coordinate at most, since $\mathsf{TG}$ represents the regular dynamics only.
From (17) and (15), one can deduce the presence of the following cycle of length $2n$ in $\mathsf{TG}$:

$$\mathcal{C} = \begin{array}{ccccccccc} 1\cdots 11 & \longrightarrow & 01\cdots 1 & \longrightarrow & \cdots & \longrightarrow & 0\cdots 011 & \longrightarrow & 0\cdots 01 \\ \uparrow & & & & & & & & \downarrow \\ 1\cdots 10 & \longleftarrow & \cdots & \longleftarrow & 110\cdots 0 & \longleftarrow & 10\cdots 0 & \longleftarrow & 00\cdots 0 \end{array}$$

It can be shown that there is no fixed state in $\mathsf{TG}$, and that $\mathcal{C}$ is the only cycle without escaping edge. Then,
we denote

$$\begin{array}{c|c|c|c|c|c|c|c|c} a^1 & a^2 & a^3 & \ldots & a^n & a^{n+1} & \ldots & a^{2n-1} & a^{2n} \\ \hline 1\cdots 11 & 01\cdots 1 & 001\cdots 1 & \ldots & 0\cdots 01 & 0\cdots 0 & \ldots & 1\cdots 100 & 1\cdots 10 \end{array} \tag{18}$$

Furthermore, let us write $\phi^i = \phi(a^i)$, the focal point of domain $a^i$, and $W^i$ the wall between boxes $a^i$ and
$a^{i+1}$, *i.e.* it verifies $c\ell(W^i) = c\ell(\mathcal{D}_{a^i}) \cap c\ell(\mathcal{D}_{a^{i+1}})$.
In the following, the superscript in $a^i$ must be understood periodically, so that for instance $a^{2n+1}$ will mean
$a^1$. It appears that each pair of successive states $a^i$, $a^{i+1}$ in this cycle differ only at one coordinate, which
we denote $s_i$. If moreover we denote $s_i^\pm$ where $\pm$ is the sign of $a_{s_i}^{i+1} - a_{s_i}^i$, which is also the sign of $\phi_{s_i}^i$, one
obtains

$$\begin{array}{c|ccccc} i & 1 & \cdots & n & n+1 & \cdots & 2n \\ \hline s_i^\pm & 1^- & \cdots & n^- & 1^+ & \cdots & n^+ \end{array} \tag{19}$$

Hence $s_i$ is the only escaping direction of box $a^i$, a fact that can also be written as $I_{out}(a^i) = \{s_i\}$. As
seen in section 2.2, this implies that all trajectories in a domain $a^i$ leave it in finite time, via the wall
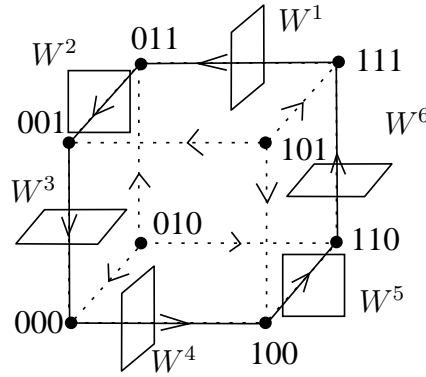
Figure 1: *The transition graph of a feedback loop system of the form (17) with three variables. The cycle $\mathcal{C}$ is represented with plain lines, and the walls $W^i$ have been schematically depicted as well.*

$W^i \subset \{x \,|\, x_{s_i} = 0\}$, and enter domain $a^{i+1}$. It follows that no trajectory can escape the cycle, *i.e.* $\mathcal{C}$ is an invariant region. This cycle is represented on figure 1 for $n = 3$.

A rapid inspection shows that the walls can be described in a quite explicit manner:

$$W^i = \begin{cases} \displaystyle\prod_{j<s_i} [\theta_j^-, 0) \times \{0\} \times \prod_{j>s_i} (0, \theta_j^+] & \text{for } i \in \{1 \cdots n\}, \\ \displaystyle\prod_{j<s_i} (0, \theta_j^+] \times \{0\} \times \prod_{j>s_i} [\theta_j^-, 0) & \text{for } i \in \{n+1 \cdots 2n\}. \end{cases} \tag{20}$$

From the remark under equation (16) it is not difficult to deduce that each pair of focal points $\phi^i$, $\phi^{i+1}$ differ only at coordinate $s_{i+1}$. Actually, they verify $\phi^i \in \mathcal{D}_{a^{i+1}}$, and one has seen that $a^{i+1}$ and $a^{i+2}$ only differ at coordinate $s_{i+1}$. Hence, the cycle $\mathcal{C}$ satisfies the alignment condition (13) seen in previous section. We can state it with our current notations:

$$\forall i \in \{1 \cdots 2n\}, \, \forall j \in \{1 \cdots n\} \setminus \{s_{i+1}\}, \quad \phi_j^i = \phi_j^{i+1}. \tag{21}$$

Remark also that by construction one has for the remaining coordinate:

$$\forall i \in \{1 \cdots 2n\}, \quad \phi_{s_{i+1}}^i = -\phi_{s_{i+1}}^{i+1}. \tag{22}$$

Since our aim is to study limit cycles arising from (14), with the help of theorem 1, it seems natural to consider the following map:

$$\mathcal{T}^{a^1} \mathcal{T}^{a^{2n}} \mathcal{T}^{a^{2n-1}} \cdots \mathcal{T}^{a^2} : W^1 \longrightarrow W^1$$

Although each $\mathcal{T}^a$ is defined on the whole boundary of $\mathcal{D}_a$, see (7), one considers here the restrictions to walls $W^{i-1}$ only, which we write explicitly:

$$\mathcal{T}^{a^i} : \begin{array}{ccc} W^{i-1} & \longrightarrow & W^i \\ x & \longmapsto & \left( \phi_j^i + (x_j - \phi_j^i)\alpha_j(x) \right)_{j=1\ldots n}, \end{array} \tag{23}$$

where, as in (9),

$$\alpha_j(x) = \alpha_j(x_{s_i}) = \left( \frac{\phi_{s_i}^i}{\phi_{s_i}^i - x_{s_i}} \right)^{\frac{\gamma_j}{\gamma_{s_i}}}.$$

Remark here that the expression of $\alpha_j$ depends on the number $i$ of the region under consideration. However, this region will always be clear from the context, and we thus leave this dependence hidden, avoiding notations such as $\alpha_j^i(x)$.

## 4.2 Restriction of domains

### 4.2.1 Projection and extension to the closure of walls

To fit the hypotheses of theorem 1, one must consider a closed domain of the form $[0,p]$, $p \in \mathbf{R}_+^n$, with nonempty interior, and since the walls are $n-1$ dimensional, their interior is empty.

Therefore, one may first project $W^1$ to $\mathbf{R}^{n-1}$, and drop out the first coordinate, which is zero. Similarly, there is no loss in suppressing the $s_i$th coordinate of points in $W^i$, since it equals zero by construction.

Second, each $\mathcal{T}^{a^i}$ has an extension to the closure $cl(W^{i-1})$, defined by continuity of the expression (23). To compose these extensions, one has to check that each of them maps $cl(W^{i-1})$ to $cl(W^i)$. Since the walls themselves are correctly mapped, and are products of one singleton $\{0\}$ and of segments of the form $(0, \theta_j^+]$ or $[\theta_j^-, 0)$, it suffices to check that the points of $cl(W^{i-1})$ having at least one coordinate equal to 0 are mapped to $cl(W^i)$.

So, let $x \in cl(W^{i-1})$ such that $x_j = 0$. Since $cl(W^{i-1}) \subset \{x \,|\, x_{s_{i-1}} = 0\}$ it is relevant to consider only $j \neq s_{i-1}$. Then, $\mathcal{T}^{a^i} x \in cl(W^i)$ if, and only if, each coordinate $\mathcal{T}_k^{a^i} x$ belongs to the projection in direction $k$ of $cl(W^i)$, which is either $[0, \theta_k^+]$ or $[\theta_k^-, 0]$. Let us call this segment $\mathcal{I}_k$ to simplify the exposition. The explicit formula given in (23) shows that the coordinate map $\mathcal{T}_j^{a^i}$ depends only on variables $x_j$ and $x_{s_i}$. Hence, if $j \neq s_i$, one only has to check whether $\mathcal{T}_j^{a^i} x \in \mathcal{I}_j$, while if $j = s_i$ all coordinates must be checked. These two cases give

- If $j \neq s_i$, $\mathcal{T}_j^{a^i} x = (1 - \alpha_j(x)) \phi_j^i$. From the inequalities between $x_j$, $\phi_j^i$ and $\theta_j = 0$, it is easily checked that $\alpha_j(x) \in (0, 1]$. Moreover, for $j \notin \{s_i\} = I_{out}(a^i)$, $\phi_j^i$ is in $\mathcal{I}_j \setminus \{0\}$. Then, $\mathcal{T}_j^{a^i} x \in \mathcal{I}_j$ follows easily.

- If $j = s_i$, remark first that $x \in cl(W^{i-1}) \cap cl(W^i)$. Then $\mathcal{T}_{s_i}^{a^i} x = 0 \in \mathcal{I}_j$. Moreover, for any $k \in \{1 \cdots n\}$, $\alpha_{s_k}(x) = 1$, so that $\mathcal{T}_k^{a^i} x = x_k$, that is to say $x$ is a fixed point.

It follows that in any case, $\mathcal{T}^{a^i} x \in cl(W^i)$, as awaited, and we consider now that the maps $\mathcal{T}^{a^i}$ are defined on the closure of walls.

Finally, proposition 2 implies that the image $\mathcal{T}^{a^i}\left(cl(W^{i-1})\right)$ is always contained in the subset of $cl(W^i)$ whose points satisfy

$$\text{sign}\,(\phi_{s_{i-1}}^i - x_{s_{i-1}}) = \text{sign}\,(\phi_{s_{i-1}}^i). \tag{24}$$

This restriction is illustrated on figure 2. Since our interest is in the iterates of those maps, we should restrict them to such subsets.

In summary, three simplifications can be done:

- The $s_i$th coordinate of $x \in W^i$ can be suppressed without loss of information

- The transition maps can be defined on the closure of walls.

- Only the points verifying (24) can be reached by $\mathcal{T}^{a^i}$.

The notation $\widetilde{W}^i$ will be used to denote the domains obtained after these three simplifications. More explicitly $\widetilde{W}^i$ is obtained from (20) by suppressing the $\{0\}$ term, using closed intervals, and replacing moreover $[\theta_{s_{i-1}}^-, 0]$ by $[\phi_{s_{i-1}}^-, 0]$, or $[0, \theta_{s_{i-1}}^+]$ by $[0, \phi_{s_{i-1}}^+]$. For example:

$$W^1 = \{0\} \times \prod_{i=2}^n (0, \theta_i^+], \quad \text{so that} \quad \widetilde{W}^1 = \prod_{i=2}^{n-1} [0, \theta_i^+] \times [0, \phi_n^+].$$

Each $\widetilde{W}^i$ is a rectangular region in $\mathbf{R}^{n-1}$ with nonempty interior, still called wall in the sequel, and the preceding discussion shows that each map $\mathcal{T}^{a^i}$ induces a well defined map

$$\widetilde{\mathcal{T}}^{a^i} : \widetilde{W}^{i-1} \to \widetilde{W}^i.$$

Remark that although points in $\widetilde{W}^{i-1}$ do not have a $s_{i-1}$th coordinate, $\widetilde{\mathcal{T}}_{s_{i-1}}^{a^i}$ is defined using expression (23), with $x_{s_{i-1}} = 0$. Let us write it explicitly for later purpose:

$$\widetilde{\mathcal{T}}_{s_{i-1}}^{a^i} x = \left(1 - \alpha_{s_{i-1}}(x)\right) \phi_{s_{i-1}}^i \tag{25}$$
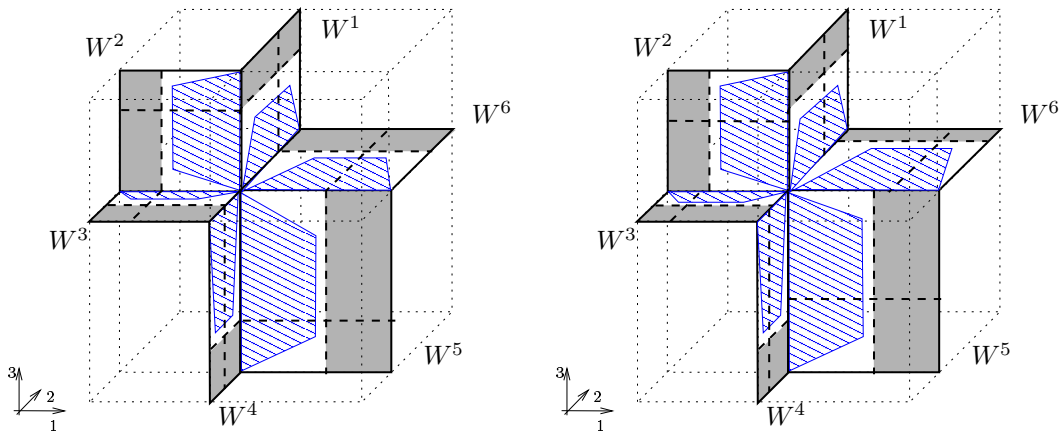
Figure 2: *The same walls as in figure 1, this time in phase space. Dotted lines represent thresholds. The dashed lines on a wall $W^i$ represent lines where $x_j = \phi^i_j$. The alignment condition (21) is fulfilled on the left, and not on the right hand side. The right-hand side figure is thus only presented as a counterexample to (21). The blue region on each such wall represents the image $\mathcal{T}^{a^i}\left(W^{i-1}\right)$. They are shown as polyhedras for ease of observation, but they have in general a piecewise smooth boundary, and not a piecewise linear one (unless all decay rates are equal). The shaded regions are not reachable, as an illustration of eq. (24).*

Now, we define a map

$$\mathbf{T} = \widetilde{\mathcal{T}}^{a^1}\widetilde{\mathcal{T}}^{a^{2n}}\widetilde{\mathcal{T}}^{a^{2n-1}}\cdots\widetilde{\mathcal{T}}^{a^2} : \widetilde{W}^1 \longrightarrow \widetilde{W}^1 \tag{26}$$

Our aim will be to check the hypotheses of theorem 1 for this map $\mathbf{T}$.

### 4.2.2 Partition of walls

Let us now consider how $\widetilde{W}^i$ may be partitioned according to the sign pattern of $\phi^i - x$. Following (24), the coordinate $s_{i-1}$ of this sign is fixed by construction. As for the coordinate $s_i$, it has been suppressed from $\widetilde{W}^i$ by construction. On the other hand, proposition 3 implies that this sign is not constant for any other coordinate $j$. Then, denoting

$$J_i = \{1\cdots n\} \setminus \{s_{i-1}, s_i\},$$

it follows that the above mentioned regions may be described using sign vectors in the finite set $\Sigma_i = \{\pm 1\}^{J_i}$. Vectors in $\Sigma_i$ will then have their coordinates indexed by $J_i$, which will prove more convenient than indexing them by $\{1\cdots n-2\}$. For any sign pattern $\sigma \in \Sigma_i$, let us define a corresponding 'zone'

$$\mathcal{Z}^i(\sigma) = \{x \in \widetilde{W}^i \,|\, \forall j \in J_i,\ \mathrm{sign}\,(\phi^i_j - x_j) = \sigma_j\}.$$

Now, from the translation of all thresholds to zero, the origin of $\mathbf{R}^{n-1}$ belongs to every wall $\widetilde{W}^i$. Moreover, no focal point have a coordinate equal to zero. Hence, on each wall $\widetilde{W}^i$, there is a unique zone containing the origin on its boundary, and the corresponding sign vector in $\Sigma_i$ is

$$\sigma^i = \left(\mathrm{sign}\,(\phi^i_j)\right)_{j \in J_i} \tag{27}$$

We will see now that these particular zones, having the origin on their boundary, in fact attract all trajectories of the system, and then remain invariant. As they will be the only zones we consider eventually, we simply denote:

$$\mathcal{Z}^i = \mathcal{Z}^i(\sigma^i).$$

Remark that the definition of these zones and equation (20) allow for a more explicit formulation:

$$
\mathcal{Z}^i = \begin{cases}
\displaystyle\prod_{j<s_i}[\phi_j^-,\,0] \times \prod_{j>s_i}[0,\,\phi_j^+] & \text{for } i \in \{1\cdots n\}, \\[2em]
\displaystyle\prod_{j<s_i}[0,\,\phi_j^+] \times \prod_{j>s_i}[\phi_j^-,\,0] & \text{for } i \in \{n+1\cdots 2n\}.
\end{cases}
\tag{28}
$$

### 4.2.3  Attractive and invariant regions

**Proposition 4.** *The zone $\mathcal{Z}^1$ is attractive for the dynamics induced by* $\mathbf{T}$:

$$
\mathbf{T}\left(\widetilde{W}^1\right) \subset \mathcal{Z}^1.
$$

*Proof.* From (18) and (19) it follows that $\mathrm{sign}(\phi_1) = (-1, 1\cdots 1) \in \{\pm 1\}^n$. Then, $s_1 = 1$ and $s_0 \simeq s_{2n} = n$ implies $J_1 = \{2\cdots n-1\}$. Then, $\sigma^1 = (1\cdots 1) \in \{\pm 1\}^{J_1}$, and

$$
\begin{aligned}
\mathcal{Z}^1 &= \{x \in \widetilde{W}^1 \,|\, \forall j \in J_1,\ x_j < \phi_j^1\} \\
&= \prod_{j=2}^{n}[0,\,\phi_j^+], \qquad \text{since } \phi_j^1 = \phi_j^+ \text{ for } j \in J_1.
\end{aligned}
$$

Let $x^1 \in \widetilde{W}^1$. In the following we denote $x^i = \widetilde{\mathcal{T}}^{a^i} x^{i-1}$ for $i \geqslant 2$, so that $\mathbf{T}x^1 = x^{2n+1}$. Clearly, $x^i \in \widetilde{W}^i$ for all $i$.

Now, for each $i \in \{1\cdots 2n\}$, the alignment condition (21) and the expression (23) of $\mathcal{T}^{a^i}$ imply the following conservation of signs:

$$
\forall i \in \{1\cdots 2n\},\, \forall j \neq s_{i+1}, \quad \mathrm{sign}(\phi_j^i - x_j^i) = \mathrm{sign}(\phi_j^{i+1} - x_j^{i+1}).
$$

In particular for the $n$ last domains of the cycle $\mathcal{C}$, remarking from table (19) that $s_{n+i} = i$, the above has the following consequence:

$$
\forall i \in \{1\cdots n\},\, \forall j < i+1, \quad \mathrm{sign}(\phi_j^{n+i} - x_j^{n+i}) = \mathrm{sign}(\phi_j^{n+i+1} - x_j^{n+i+1}).
$$

This equality can be propagated, in the sense that

$$
\begin{aligned}
\mathrm{sign}(\phi_1^{n+1} - x_1^{n+1}) &= \mathrm{sign}(\phi_1^{n+2} - x_1^{n+2}) = \ldots = \mathrm{sign}(\phi_1^{2n} - x_1^{2n}) = \mathrm{sign}(\phi_1^1 - x_1^{2n+1}), \\
\mathrm{sign}(\phi_2^{n+2} - x_2^{n+2}) &= \mathrm{sign}(\phi_2^{n+3} - x_2^{n+3}) = \ldots = \mathrm{sign}(\phi_2^{2n} - x_2^{2n}) = \mathrm{sign}(\phi_2^1 - x_2^{2n+1}), \\
&\vdots \\
\mathrm{sign}(\phi_{n-1}^{2n-1} - x_{n-1}^{2n-1}) &= \mathrm{sign}(\phi_{n-1}^{2n} - x_{n-1}^{2n}) = \mathrm{sign}(\phi_{n-1}^1 - x_{n-1}^{2n+1}) \\
\mathrm{sign}(\phi_n^{2n} - x_n^{2n}) &= \mathrm{sign}(\phi_n^1 - x_n^{2n+1})
\end{aligned}
$$

Now, since $x^{n+i} \in \widetilde{W}^{n+i}$, and since (24) is satisfied on $\widetilde{W}^{n+i}$ by definition, one obtains

$$
\mathrm{sign}(\phi_i^{n+i+1} - x_i^{n+i+1}) = \mathrm{sign}(\phi_i^{n+i+1}), \qquad i \in \{1\cdots n\}.
\tag{29}
$$

Combining this with the previous list of equalities gives

$$
\mathrm{sign}(\phi_i^1 - x_i^{2n+1}) = \mathrm{sign}(\phi_i^1), \qquad i \in \{1\cdots n\},
$$

which exactly means $x^{2n+1} = \mathbf{T}x^1 \in \mathcal{Z}^1$, as expected. □

One may now consider the restriction of $\mathbf{T}$ to $\mathcal{Z}^1$. Actually, the previous proposition implies that chosing any initial condition $x^1 \in \widetilde{W}^1$, the trajectory $\{\mathbf{T}^m x \,|\, m \in \mathbf{N}\}$ is contained in $\mathcal{Z}^1$, except maybe for $x^1$. So, there is no loss of generality in chosing initial conditions in this invariant subset only.

We can also verify that, on each wall all trajectories of system (17) are eventually contained in the region $\mathcal{Z}^i$. This fact is a consequence of proposition 4 and the following:
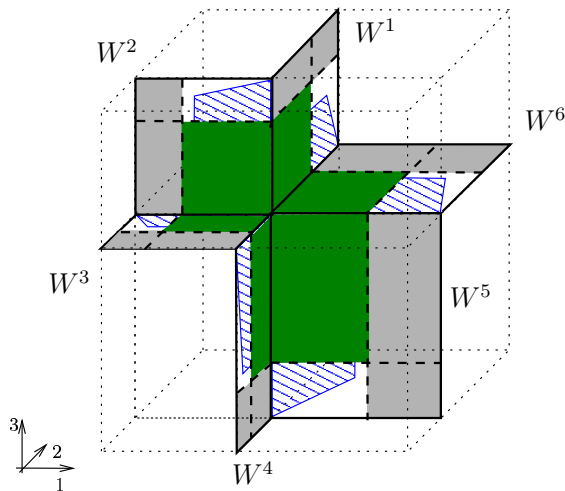
Figure 3: *The same walls as in figure 2. Now, the invariant region $\bigcup_i \mathcal{Z}^i$ has been shaded in dark green. The reader may check on the figure that trajectories originating on any wall eventually fall into this region.*

**Proposition 5.** *For all $i \in \{1 \cdots 2n\}$,   $\widetilde{\mathcal{T}}^{a^i}\left(\mathcal{Z}^{i-1}\right) \subset \mathcal{Z}^i$.*

*Proof.* Let $x \in \mathcal{Z}^i$, which by definition is equivalent to

$$\forall j \in \{1 \cdots n\} \setminus \{s_{i-1}\}, \qquad \text{sign}\left(\phi_j^i - x_j\right) = \text{sign}\left(\phi_j^i\right). \tag{30}$$

First, observe that in dimension $n = 2$, $J_i = \varnothing$ by definition and thus $\mathcal{Z}_i(\sigma^i) = \widetilde{W}^i$. There is nothing to prove in this case, and one thus assumes $n \geqslant 3$ in the rest of the proof.
From the alignment condition (21) one gets,

$$\forall j \neq s_i, \qquad \phi_j^i - \widetilde{\mathcal{T}}_j^{a^i} x = \left(\phi_j^{i-1} - x_j\right) \alpha_j(x).$$

Since $\alpha_j(x) > 0$, using (30) leads to

$$\forall j \in \{1 \cdots n\} \setminus \{s_{i-1}, s_i\}, \qquad \text{sign}\left(\phi_j^i - \widetilde{\mathcal{T}}_j^{a^i} x\right) = \text{sign}\left(\phi_j^{i-1}\right) = \text{sign}\left(\phi_j^i\right).$$

From (24) it is immediate that

$$\text{sign}\left(\phi_{s_{i-1}}^i - \widetilde{\mathcal{T}}_{s_{i-1}}^{a^i} x\right) = \text{sign}\left(\phi_{s_{i-1}}^{i-1}\right) = \text{sign}\left(\phi_{s_{i-1}}^i\right),$$

which terminates the proof.                                                                                   $\square$

This proposition allows us to consider only the restrictions:

$$\widetilde{\mathcal{T}}^{a^i} : \mathcal{Z}^{i-1} \to \mathcal{Z}^i$$

in the following. Figure 3 shows the domains $\mathcal{Z}^i$ on a 3 dimensional example.

## 4.3   Main result

The main result of this paper will essentially consist in applying theorem 1 to feedback loop systems of the form (14), or equivalently (17). Among the hypotheses to be checked, the concavity condition $(C)$ will be verified with the aid of the following lemma.

**Lemma 1.** *Let $p, q, r \in \mathring{\mathbf{R}}_+^n$. Let also $T : [0, p] \to [0, q]$ and $M : [0, q] \to [0, r]$ be twice differentiable mappings satisfying condition $(M)$ of theorem 1. Suppose that any of the second order derivatives of $T$ and $M$ are non-positive, and that at least one of them is negative, for both mappings.*
*Then, their composite $MT : [0, p] \to [0, r]$ satisfies $(M)$ and $(C)$.*

*Proof.* The result is obtained from the chain rule. Let $x \in [0, p]$. Then $Tx \in [0, q]$ and

$$D\left(MT\right)(x) = DM\left(Tx\right)DT(x).$$

From this expression it is clear that the composite $MT$ satisfies $(M)$ if both $T$ and $M$ do. Now, given given any $x < y$ in $[0, p]$, condition $(M)$ on $M$ implies $Tx < Ty$, by monotonicity of each coordinate function $T_i$, $M_i$.
Then the nonpositivity of second order derivatives gives $DM(Ty) \lesssim DM(Tx)$. Then using both conditions $(M)$ and $(C)$ on $T$, and condition $(M)$ on $M$, the chain rule expression leads to

$$D\left(MT\right)(y) = DM\left(Ty\right)DT(y) \lesssim DM\left(Ty\right)DT(x) \lesssim DM\left(Tx\right)DT(x) = D\left(MT\right)(x).$$

$\square$

We are now in good position to state our main result.

**Theorem 2.** *Consider the map $\mathbf{T} : \mathcal{Z}^1 \to \mathcal{Z}^1$ defined in the previous section.*

- *If $n = 2$, then $\forall x \in \mathcal{Z}^1$, $\mathbf{T}^m x \to 0$ when $m \to \infty$.*

- *If $n > 2$, then there exists a unique nonzero fixed point $q = \mathbf{T}q$. Moreover, $q \in \mathring{\mathcal{Z}}^1$ and for every $x \in \mathcal{Z}^1 \setminus \{0\}$, $\mathbf{T}^m x \to q$ as $m \to \infty$.*

*Proof.* The proof consists in checking the hypotheses of theorem 1, which then yields precisely the above proposition.
First, the upper corner of $\mathcal{Z}^1$ is the point $(\phi_2^+ \dots \phi_n^+)$, which belongs to $\mathring{\mathbf{R}}_+^{n-1}$. Second, it is clear from the expression (23) that each $\widetilde{\mathcal{T}}^{a^i}$ is $C^1$. Hence, $\mathbf{T}$ is $C^1$ one the whole rectangle $\mathcal{Z}_1$. It follows in particular that $D\mathbf{T}(0)$ is well defined.
Since the proof is a little lengthy, it will be structured in three parts.

**Preliminary change of variables.**
Before checking the hypotheses of theorem 1, it will prove convenient to apply a local transformation $\rho^i : \mathcal{Z}^i \to \mathcal{P}^i$ at each wall, such that $\mathcal{P}^i \subset \mathbf{R}_+^{n-1}$. This will allow us to deal with non-negative variables only.
According to (27), $\sigma_j^i$ denotes the sign of $\phi_j^i$, for $j \in J_i$. From (30), $\phi_j^i$ and $x_j^i$ have the same sign, for $x^i \in \mathcal{Z}^i$. We also note $\sigma_j^i$ the sign of $\phi_j^i$ when $j \in \{s_{i-1}, s_i\}$. Then, simply define the $j$th coordinate of this transformation as

$$\rho_j^i(x) = \sigma_j^i \, x_j. \tag{31}$$

In other words, $\rho^i$ is just a multiplication by a diagonal matrix, whose $j$th entry is $\sigma_j^i \in \{\pm 1\}$. This implies that $\rho^i$ is invertible, and equals its inverse. Hence we also denote $\rho^i$ this inverse: $\rho^i : \mathcal{P}^i \to \mathcal{Z}^i$. One may also formulate $\mathcal{P}^i$ explicitly:

$$\mathcal{P}^i = \prod_{j \neq s_i} \left[0, |\phi_j^i|\right]. \tag{32}$$

It is tempting now to define maps $\mathcal{M}^{(i)}$, by the condition that the following diagram commutes, for any $i \in \{1 \cdots 2n\}$:

$$
\begin{array}{ccc}
\mathcal{Z}^{i-1} & \xrightarrow{\mathcal{T}^{a^i}} & \mathcal{Z}^i \\
\downarrow{\scriptstyle \rho^{i-1}} & & \downarrow{\scriptstyle \rho^i} \\
\mathcal{P}^{i-1} & \xrightarrow{\mathcal{M}^{(i)}} & \mathcal{P}^i
\end{array}
\tag{33}
$$

With the previous remark on $\rho^i$ this may also be written as $\mathcal{M}^{(i)} = \rho^i \, \mathcal{T}^{a^i} \rho^{i-1}$. Composing the diagrams above for successive $i$, and since $\rho^1 = \rho^{2n} = id$, one gets $\mathcal{P}^1 = \mathcal{Z}^1$, and

$$\mathbf{T} = \mathcal{M}^{(1)} \mathcal{M}^{(2n)} \mathcal{M}^{(2n-1)} \cdots \mathcal{M}^{(2)} \tag{34}$$

For any $x^1 \in \mathcal{P}^1 = [0, p]$ we write $x^i = \widetilde{\mathcal{M}}^{(i)} x^{i-1}$, $i \geqslant 2$. From proposition 5, one gets $x^i \in \mathcal{Z}^i$.
Each $\mathcal{M}^{(i)}$ can be expressed coordinate-wise:

$$\mathcal{M}_j^{(i)} x = \sigma_j^i \phi_j^i + \sigma_j^i \left( \sigma_j^{i-1} x_j - \phi_j^i \right) \left( \frac{\phi_{s_i}^i}{\phi_{s_i}^i - \sigma_{s_i}^{i-1} x_{s_i}} \right)^{\frac{\gamma_j}{\gamma_{s_i}}} \qquad j \neq s_i.$$

From their definition, the $\sigma_j^i$s clearly satisfy the alignment condition (21): $\sigma_j^i = \sigma_j^{i-1}$ for $j \neq s_i$. It also comes from (22) that: $\sigma_{s_i}^i = -\sigma_{s_i}^{i-1}$. Hence, one also has:

$$\mathcal{M}_j^{(i)} x = |\phi_j^i| + \left( x_j - |\phi_j^i| \right) \alpha_j \left( \sigma_{s_i}^{i-1} x_{s_i} \right) \qquad j \neq s_i, \tag{35}$$

where

$$\alpha_j \left( \sigma_{s_i}^{i-1} x_{s_i} \right) = \left( \frac{\phi_{s_i}^i}{\phi_{s_i}^i - \sigma_{s_i}^{i-1} x_{s_i}} \right)^{\frac{\gamma_j}{\gamma_{s_i}}} = \left( \frac{|\phi_{s_i}^i|}{|\phi_{s_i}^i| + x_{s_i}} \right)^{\frac{\gamma_j}{\gamma_{s_i}}}$$

**Monotonicity and concavity.**
One computes now:

$$\frac{\partial \mathcal{M}_j^{(i)}}{\partial x_k}(x) = \begin{cases} \alpha_j \left( \sigma_{s_i}^{i-1} x_{s_i} \right) & \text{if } j = k \\[2mm] \dfrac{\gamma_j}{\gamma_{s_i}} \dfrac{|\phi_j^i| - x_j}{|\phi_{s_i}^i| + x_{s_i}} \alpha_j \left( \sigma_{s_i}^{i-1} x_{s_i} \right) & \text{if } k = s_i \\[2mm] 0 & \text{otherwise.} \end{cases} \tag{36}$$

and

$$\frac{\partial^2 \mathcal{M}_j^{(i)}}{\partial x_m \partial x_k}(x) = \begin{cases} -\dfrac{\gamma_j}{\gamma_{s_i}} \dfrac{\alpha_j \left( \sigma_{s_i}^{i-1} x_{s_i} \right)}{|\phi_{s_i}^i| + x_{s_i}} & \begin{array}{l} \text{if } j = k, \, m = s_i \\ \text{or } k = s_i, \, m = j \end{array} \\[3mm] -\dfrac{\gamma_j}{\gamma_{s_i}} \left( 1 + \dfrac{\gamma_j}{\gamma_{s_i}} \right) \dfrac{|\phi_j^i| - x_j}{(|\phi_{s_i}^i| + x_{s_i})^2} \alpha_j \left( \sigma_{s_i}^{i-1} x_{s_i} \right) & \text{if } m = k = s_i \\[3mm] 0 & \text{otherwise.} \end{cases} \tag{37}$$

One sees that $\mathcal{M}^{(i)}$ is very similar to $\mathcal{T}^{a^i}$, so that equations above are strongly reminiscent of (10) and (11). Let us evaluate the sign of these quantities. From $x \in \mathcal{P}^{i-1}$ and (32) it follows that $|\phi_j^i| - x_j \geqslant 0$. It is clear also that $|\phi_{s_i}^i| + x_{s_i} > 0$. It follows that, for all maps $\mathcal{M}^{(i)}$, the nonzero terms of the jacobian are positive, while the nonzero derivatives of order 2 are negative, at any point $x \in \mathcal{P}^{i-1}$.
Applied to (34), the chain rule gives

$$D\mathbf{T}(x^1) = D\mathcal{M}^{(1)}(x^{2n}) D\mathcal{M}^{(2n)}(x^{2n-1}) \cdots D\mathcal{M}^{(2)}(x^1). \tag{38}$$

Moreover, it seems from (36) that the jacobians in the product above are the sum of a diagonal matrix and a matrix whose column number $s_i$ contains the only nonzero elements.
Some care must be taken though, due to the particular indexing of matrices. Actually, from (36) the diagonal entries of $D\mathcal{M}^{(i)}$ are at first sight $D\mathcal{M}_{jj}^{(i)} = \alpha_j \left( \sigma_{s_i}^{i-1} x_{s_i}^{i-1} \right)$. However, the row subscripts of $D\mathcal{M}^{(i)}$ belong to $\{1 \cdots n\} \setminus \{s_i\}$, while the columns are indexed by $\{1 \cdots n\} \setminus \{s_{i-1}\}$. This implies that neither $D\mathcal{M}_{s_i, s_i}^{(i)}$ nor $D\mathcal{M}_{s_{i-1}, s_{i-1}}^{(i)}$ are defined. The exact shape of nonzero entries in $D\mathcal{M}^{(i)}$ depends on the order in which $s_{i-1}$ and $s_i$ are sorted. In our case, table (19) shows that either $s_i = s_{i-1} + 1$, or $s_i = 1$ and $s_{i-1} = n$, the latter occurring for $i \in \{1, n+1\}$.

Let us represent the subscripts of nonzero entries in both cases. First, if $i \notin \{1, n+1\}$, both $D\mathcal{M}^{(i)}$ and $D\mathcal{M}^{(n+i)}$ have the following shape:

$$
\begin{matrix}
 & & & \overset{\overset{\displaystyle s_{i-1}}{\downarrow}}{} & & \\
\end{matrix}
$$

$$
\begin{bmatrix}
(1,1) & & & (1, s_i) & & \\
 & \ddots & & \vdots & & \\
 & & (s_{i-1}-1, s_{i-1}-1) & (s_{i-1}-1, s_i) & & \\
 & & & (s_{i-1}, s_i) & & \\
 & & & (s_i+1, s_i) & (s_i+1, s_i+1) & \\
 & & & \vdots & & \ddots & \\
 & & & (n, s_i) & & & (n,n)
\end{bmatrix}
\tag{39}
$$

Now, if $i \in \{1, n+1\}$ which implies that row 1 and column $n$ are removed:

$$
D\mathcal{M}^{(i)} \equiv
\begin{bmatrix}
(2,1) & (2,2) & & \\
\vdots & & \ddots & \\
\vdots & & & (n-1, n-1) \\
(n,1) & 0 & \cdots & 0
\end{bmatrix}
\tag{40}
$$

Since $s_{i-1}$ ranges over $\{1 \cdots n-1\}$ when $i$ or $n+i$ varies in $\{2 \cdots n\}$, it is not hard to deduce from (39) that both products:

$$
\Pi^2 = D\mathcal{M}^{(2n)}(x^{2n-1}) \cdots D\mathcal{M}^{(n+2)}(x^{n+1}) \qquad \text{and} \qquad \Pi^1 = \mathcal{M}^{(n)}(x^{n-1}) \cdots D\mathcal{M}^{(2)}(x^1)
$$

have no zero entries, and are thus positive. Then, from (40) one deduces that

$$
D\mathbf{T}(x^1) = D\mathcal{M}^{(1)}(x^{2n}) \, \Pi^2 \, D\mathcal{M}^{(n+1)}(x^n) \, \Pi^1
$$

is positive as well. Hence we have just shown $(M)$:

$$
\forall x^1 \in \mathcal{P}^1, \quad D\mathbf{T}(x^1) > 0.
$$

As for concavity, it follows from the negative terms in (37) and lemma 1 that

$$
D\left(\mathcal{M}^{(i+1)}\mathcal{M}^{(i)}\right)(x^{i-1}) \lesssim D\left(\mathcal{M}^{(i+1)}\mathcal{M}^{(i)}\right)(y^{i-1}).
$$

Then a simple induction shows that $D\mathbf{T}$, as expressed in (38), satisfies condition $(C)$:

$$
\forall x^1, y^1 \in \mathcal{P}^1, \ 0 < x^1 < y^1, \quad D\mathbf{T}(y^1) \lesssim D\mathbf{T}(x^1).
$$

**Behaviour at the upper corner and the origin.**
Before studying the origin, let us show that $\mathbf{T}p < p$, as required by theorem 1. Here, $p = (\phi_2^+ \ldots \phi_n^+)$ is the upper corner of $\mathcal{Z}^1$, *i.e.* $\mathcal{Z}^1 = [0, p]$. Now, let us consider the last maps composing $\mathbf{T}$, as in the proof of proposition 4. Namely, one deduces from (25) that:

$$
\forall x \in \widetilde{W}^{n+i-1}, \qquad \widetilde{\mathcal{J}}_{i-1}^{a^{n+i}} x = (1 - \alpha_{i-1}(x)) \, \phi_{i-1}^{n+i},
$$

As usual, one identifies $a^{2n+1}$ and $a^1$. Then for $i \in \{2 \cdots n+1\}$, $\alpha_{i-1}(x) \in (0, 1]$ gives:

$$
\widetilde{\mathcal{J}}_{i-1}^{a^{n+i}} x = (1 - \alpha_{i-1}(x)) \, \phi_{i-1}^+ < \phi_{i-1}^+.
$$

Now, from equation (29) in the proof of proposition 4, one knows that $\text{sign}\,(\phi_{s_{i-1}}^{n+i} - x_{s_{i-1}})$ is conserved through the last steps of the cycle, so that

$$
\forall i \in \{2 \cdots n\}, \forall x \in \widetilde{W}^{n+i-1}, \qquad \left(\widetilde{\mathcal{J}}^{a^1} \widetilde{\mathcal{J}}^{a^{2n}} \cdots \widetilde{\mathcal{J}}^{a^{n+2}}\right)_i x < \phi_i^+
$$

Since in particular

$$
\widetilde{\mathcal{J}}^{a^{n+1}} \widetilde{\mathcal{J}}^{a^n} \cdots \widetilde{\mathcal{J}}^{a^2} p \in \widetilde{W}^{n+1},
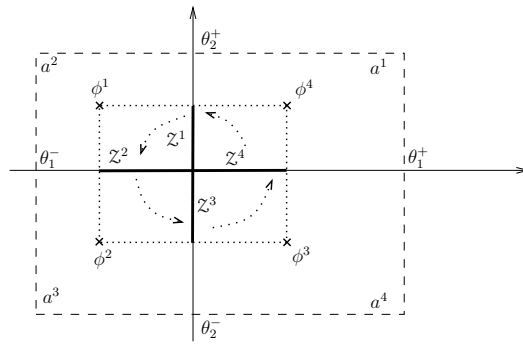$$

*Figure 4: The state space of a feedback loop with only two variables, schematically. The notations are those explained in the text.*

it follows that $\mathbf{T}p < p$.

To terminate the proof, it remains to check whether the spectral radius of $D\mathbf{T}(0)$ is greater than 1 or not. First, remark that $\mathbf{T}(0) = 0$ implies that each $D\mathcal{M}^{(i)}$ has to be evaluated at 0 in expression (38). Then from the expression of $\alpha_j$ in (36), for $i \in \{2 \cdots n\}$ the diagonal terms of each $D\mathcal{M}^{(i)}(0)$ equal 1, except at $(i-1, i-1)$. Here, it is given by the second line in (36), just as the rest of column $i-1$. The latter is given by:

$$\forall i \in \{2 \cdots n\} \qquad D\mathcal{M}^{(i)}_{j,\,i-1}(0) = \frac{\gamma_j \,|\phi^i_j|}{\gamma_i \,|\phi^i_i|} = \left| \frac{\kappa^i_j}{\kappa^i_i} \right|,$$

with the notation $\kappa^i_j = \kappa_j(a^i)$.

If the case $n = 2$, matrices $D\mathcal{M}^{(i)}(0)$ are in fact scalars of the form above. From equations (14) and (17) one obtains

$$\kappa^1_2 = \kappa^4_2 = \kappa^+_2, \quad \kappa^4_1 = \kappa^3_1 = \kappa^+_1, \quad \kappa^3_2 = \kappa^2_2 = \kappa^-_2, \quad \text{and} \quad \kappa^1_1 = \kappa^2_1 = \kappa^-_1.$$

See figure 4 for the state space of two dimensional feedback loops. Then, (38) gives

$$D\mathbf{T}(0) = \left| \frac{\kappa^1_2}{\kappa^1_1} \frac{\kappa^4_1}{\kappa^4_2} \frac{\kappa^3_2}{\kappa^3_1} \frac{\kappa^2_1}{\kappa^2_2} \right| = 1.$$

Suppose now that $n \geqslant 3$. Before going further, let us remark the following fact: if a matrix $A$ is such that $A - Id > 0$, then the spectral radius $\rho(A) > 1$. This is a direct consequence of Perron-Frobenius theorem. Actually, $\rho(A)$ is the maximal eigenvalue of $A$, or the maximal root of its characteristic polynomial, which we denote $\pi_A(X)$. One clearly has $\pi_{A-Id}(X) = \pi_A(X - 1)$, so that the roots of $\pi_{A-Id}$ are exactly those of $\pi_A$ minus one. Applying Perron-Frobenius theorem to the positive matrix $A - Id$ implies $\rho(A) > 1$.

Hence to terminate the proof, it suffices to show that $D\mathbf{T}(0) - Id > 0$, or equivalently that the diagonal terms of $D\mathbf{T}(0)$ are strictly greater than 1, since we have shown $(M)$ already. We use (38), from which it is possible to derive the general term of $D\mathbf{T}$.

The subscripts in (39) and (40) are those to be used in equation (36). To compute (38) on the other hand, it is more relevant to use the actual row and column numbers, as represented in (39) over the nonzero column, which is numbered $s_{i-1}$. Hence in the expressions below, $D\mathcal{M}^{(i)}_{jk}$ refers to the entry $j, k$ of matrix $D\mathcal{M}^{(i)}(0)$, which is not necessarily $\dfrac{\partial \mathcal{M}^{(i)}_j}{\partial x_k}(0)$. A simple induction shows that

$$\left( D\mathbf{T}(x^1) \right)_{ij} = \sum_{k_1, \dots k_{2n-1} = 1}^{n-1} D\mathcal{M}^{(1)}_{ik_1} D\mathcal{M}^{(2n)}_{k_1 k_2} \cdots D\mathcal{M}^{(2)}_{k_{2n-1} j}$$

In particular, the diagonal terms can be conveniently denoted using the following abbreviation. Define the integer vector $\mathbf{k} = (k_1 \dots k_{2n-1}) \in \{1 \cdots n-1\}^{2n-1}$, and denote

$$p^i_{\mathbf{k}} = D\mathcal{M}^{(1)}_{ik_1} D\mathcal{M}^{(2n)}_{k_1 k_2} \cdots D\mathcal{M}^{(2)}_{k_{2n-1} i}.$$

Note that the general form of terms in products above is the following:

$$DM^{(j)}_{k_{2n+1-j}k_{2n+2-j}} \qquad\qquad j \in \{3 \cdots 2n\}.$$

Then, $\left(D\mathbf{T}(x^1)\right)_{ii}$ equals the sum of products $p^i_{\mathbf{k}}$ when $\mathbf{k}$ varies in the whole set $\{1 \cdots n-1\}^{2n-1}$.

Now, since each matrix $DM^{(i)}(0)$ is composed of zeros and positive terms, it follows that each nonzero product $p^i_{\mathbf{k}}$ is positive. Hence, if for all $i$ there is one $\mathbf{k}$ such that $p^i_{\mathbf{k}} = 1$, and at least one other nonzero $p^i_{\mathbf{k}}$, the proof will be finished.

To help intuition let us detail the shape of $DM^{(i)}(0)$ and $DM^{(n+i)}(0)$ for $n \geqslant i > 1$, thanks to (39) and (40):

$$
\begin{matrix}
& & & \overset{\displaystyle i-1}{\downarrow} & & \\
\end{matrix}
$$

$$
\begin{bmatrix}
1 & & & |\kappa^i_1/\kappa^i_i| & & \\
 & \ddots & & \vdots & & \\
 & & 1 & |\kappa^i_{i-2}/\kappa^i_i| & & \\
 & & & |\kappa^i_{i-1}/\kappa^i_i| & & \\
 & & & |\kappa^i_{i+1}/\kappa^i_i| & 1 & \\
 & & & \vdots & & \ddots \\
 & & & |\kappa^i_n/\kappa^i_i| & & 1
\end{bmatrix}
\tag{41}
$$

For $i \in \{1, n+1\}$:

$$
DM^{(i)} \equiv
\begin{bmatrix}
|\kappa^i_2/\kappa^i_1| & 1 & & \\
\vdots & & \ddots & \\
\vdots & & & 1 \\
|\kappa^i_n/\kappa^i_1| & 0 & \cdots & 0
\end{bmatrix}
\tag{42}
$$

Now, we claim that $p^i_{\mathbf{k}} = 1$, for $1 < i \leqslant n-1$, and

$$\mathbf{k} = (1 \cdots 1, i \cdots i, 1 \cdots 1, i \cdots i) \tag{43}$$

where $k_j = i$ for $n+1-i \leqslant j \leqslant n$, and $2n+1-i \leqslant j \leqslant 2n-1$, and $k_j = 1$ otherwise. Actually, one has on the one hand:

$$DM^{(1)}_{i,k_1} = DM^{(1)}_{i,1} = \left|\frac{\kappa^1_{i+1}}{\kappa^1_1}\right| \qquad \text{and} \qquad DM^{(n+1)}_{k_n,k_{n+1}} = DM^{(n+1)}_{i,1} = \left|\frac{\kappa^{n+1}_{i+1}}{\kappa^{n+1}_1}\right|$$

and on the other hand

$$DM^{(n+i+1)}_{k_{n-i},k_{n+1-i}} = DM^{(n+i+1)}_{1,i} = \left|\frac{\kappa^{n+i+1}_1}{\kappa^{n+i+1}_{i+1}}\right| \qquad \text{and} \qquad DM^{(i+1)}_{k_{2n-i},k_{2n+1-i}} = DM^{(i+1)}_{1,i} = \left|\frac{\kappa^{i+1}_1}{\kappa^{i+1}_{i+1}}\right|.$$

Moreover, for any $j \in \{2n+1-i \cdots 2n-1\} \cup \{n+1-i \cdots n\}$, it appears that $DM^{(j)}_{i,i} = 1$, since $i \neq s_j - 1$, and similarly, for $j \in \{1 \cdots n-i\} \cup \{n+1 \cdots 2n-i\}$ one has $DM^{(j)}_{1,1} = 1$. As a consequence, for $\mathbf{k}$ as in (43),

$$
\begin{aligned}
p^i_{\mathbf{k}} &= DM^{(1)}_{i,1} \, DM^{(n+i+1)}_{1,i} \, DM^{(n+1)}_{i,1} \, DM^{(i+1)}_{1,i} \\
&= \left|\frac{\kappa^1_{i+1}}{\kappa^1_1} \frac{\kappa^{n+i+1}_1}{\kappa^{n+i+1}_{i+1}} \frac{\kappa^{n+1}_{i+1}}{\kappa^{n+1}_1} \frac{\kappa^{i+1}_1}{\kappa^{i+1}_{i+1}}\right|
\end{aligned}
\tag{44}
$$

Now we refer to the table (18) of successive boxes, and recall that $\phi^i$ belongs to the domain $a^{i+1}$. Then it is rather straightforward to check that

$$\mathrm{sign}\left(\phi^{n+i}\right) = -\mathrm{sign}\left(\phi^i\right)$$

for any $i \in \{1 \cdots n\}$. It follows immediately that $\text{sign}\,(\kappa^{n+i}) = -\text{sign}\,(\kappa^i)$ as well. From this and the fact that any production term $\kappa^i_j$ is fully determined by its sign, it follows that

$$\frac{\kappa^{i+1}_1\,\kappa^{n+i+1}_1}{\kappa^1_1\,\kappa^{n+1}_1} = 1 \qquad \text{and} \qquad \frac{\kappa^1_{i+1}\,\kappa^{n+1}_{i+1}}{\kappa^{i+1}_{i+1}\,\kappa^{n+i+1}_{i+1}} = 1,$$

whence $p^i_{\mathbf{k}} = 1$.

Recall that the previous holds only for $i > 1$. Now, let $\mathbf{k} = (1 \cdots 1)$. Then,

$$DM^{(1)}_{1,k_1} = DM^{(1)}_{1,1} = \left|\frac{\kappa^1_2}{\kappa^1_1}\right| \qquad \text{and} \qquad DM^{(n+1)}_{k_n,k_{n+1}} = DM^{(n+1)}_{1,1} = \left|\frac{\kappa^{n+1}_2}{\kappa^{n+1}_1}\right|$$

while

$$DM^{(n+2)}_{k_{n-1},k_n} = DM^{(n+2)}_{1,1} = \left|\frac{\kappa^{n+2}_1}{\kappa^{n+2}_2}\right| \qquad \text{and} \qquad DM^{(2)}_{k_{2n-1},1} = DM^{(2)}_{1,1} = \left|\frac{\kappa^2_1}{\kappa^2_2}\right|.$$

Moreover for any other $j$, $DM^{(j)}_{1,1} = 1$, and thus

$$\begin{aligned} p^1_{\mathbf{k}} &= \left|\frac{\kappa^1_2}{\kappa^1_1}\frac{\kappa^{n+2}_1}{\kappa^{n+2}_2}\frac{\kappa^{n+1}_2}{\kappa^{n+1}_1}\frac{\kappa^2_1}{\kappa^2_2}\right| \\ &= 1, \qquad\qquad\qquad \text{for the same reason as in (44).} \end{aligned}$$

Thus, we have found, for each $i \in \{1 \cdots n{-}1\}$, a $\mathbf{k}$ such that $p^i_{\mathbf{k}} = 1$. Now, for any $i > 1$, let $\mathbf{k} = (1 \cdots 1, i \cdots i)$, where $k_j = i$ for $2n + 1 - i \leqslant j \leqslant 2n - 1$. This leads to

$$p^i_{\mathbf{k}} = DM^{(1)}_{i,1}DM^{(2n)}_{1,1}\cdots DM^{(i+1)}_{1,i}DM^{(i)}_{i,i}\cdots DM^{(2)}_{1,i},$$

and from (41) and (42) one checks readily that the above is positive: the entry $(1,1)$ is actually never zero in the first terms, the $i$th column of $DM^{(i+1)}$ is nonzero, and the diagonal terms of the last terms in the product are positive as well.

For $i = 1$, a positive $p^1_{\mathbf{k}}$ is found for instance with $\mathbf{k} = (2 \cdots 2)$. Actually, $(2,2)$ entries are never zero in (41), and moreover $DM^{(1)}_{1,2}$ and $DM^{(2)}_{2,1}$ are also positive. $\square$

## 5   Conclusion

The main result of this paper is theorem 2, which is a direct application of a theorem of Smith [13], here referred to as theorem 1. It is in fact very similar to the main theorem of Snoussi [14], since the latter states existence of a limit cycle where theorem 2 states existence and unicity, for the class of negative feedback loop systems of the form (17). The improvement is entirely obtained from the use of theorem 1. This use is made possible by the natural occurrence of monotone, concave transformations in the context of piecewise affine gene network models of the form (1). In general, these transformations only appear on particular regions in phase space, as shown in section 3. Also, they are monotone and concave only up to a symmetry (or say with respect to the order induced by orthants which are not necessarily positive), which depends on the region on which they are defined. For negative feedback loop systems however, it is shown in section 4.2 that after a finite number of steps, all trajectories belong to one region, where the first-return dynamics is monotone and concave. It seems promising then, to study systems of a more general from than a negative feedback loop, using the same tools as in the present paper. For such systems, one should not concentrate on a single monotone concave transformation, but on several of them, and take into account the possible transitions between their domains of definition.

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