About block-parallel Boolean networks: a position paper

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Abstract

In automata networks, it is well known that the way entities update their states over time has a major impact on their dynamics. In particular, depending on the chosen update schedule, the underlying dynamical systems may exhibit more or less asymptotic dynamical behaviours such as fixed points or limit cycles. Since such mathematical models have been used in the framework of biological networks modelling, the question of choosing appropriate update schedules has arisen soon. In this note, focusing on Boolean networks, our aim is to emphasise that the adequate way of thinking regulations and genetic expression over time is certainly not to consider a wall segregating synchronicity from asynchronicity because they actually complement rather well. In particular, we highlight that specific update schedules, namely block-parallel update schedules, whose intrinsic features are still not known from a theoretical point of view, admit realistic and pertinent properties in the context of biological modelling and deserve certainly more attention from the community.

Keywords: Discrete dynamical systems Automata networks Threshold Boolean networks Block-parallel updating schedules.

1 Introduction

Automata networks (ANs) are discrete dynamical systems, introduced in 1943 by McCulloch and Pitts [26], widely used to model genetic control networks and more generally biological networks since the end of the 1970's and the seminal works of Kauffman [23, 24, 25] and Thomas [44, 45, 46]. In this context of molecular systems biology, the ANs considered are finite, *i.e.*, they are composed of a finite number of nodes (or automata) that interact with each other over a discrete time.

As soon as they have been used as models of genetic regulation networks, the way that nodes had to be updated over time was discussed. Indeed, when Kauffman introduced them at the end of the 1960's by scheduling nodes

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in parallel (certainly due to mathematical usabilities), biological arguments were highlighted notably by Thomas arguing that parallelism was not likely because of the impossibility for genetic expressions to occur simultaneously. Of course, the links between parallelism and simultaneity could be discussed further in the context of modelling but this is not the purpose of this note. So, other ways of updating ANs were introduced that are located at the other end of the spectrum, based on the concept of asynchronicity such as the asynchronous method of Thomas et al. [32, 44, 47], and random sequential ANs [9, 15, 22, 39]. This created a strong separation between the synchronous and sequential ways of considering ANs, to such an extent that the schedules mixing together synchronicity and asynchronicity were set aside for decades in the context of modelling. Fortunately, it was not the case in mathematics and computer science, as shown in the works of Robert [35, 36, 37] on block-sequential update schedules, that were used in [27] in the framework of the modelling of the floral morphogenesis of the plant *Arabidopsis thaliana* and began to be studied in depth from the second half of the 2000's [5, 10, 14].

In this note, following a natural computing approach that consists in using the well known biologically-inspired computational model of ANs, and studying instances of them to model real biological phenomena, our wish is to highlight that the update schedules studied until now (all belonging to the family of block-sequential update schedules), even if they are interesting theoretically, are far from being sufficient to capture specific biological intricacies. In particular, biological timers (classically called "Zeitgebers" in biology and medicine) and clocks that can be of genetic or physiological nature/origin [21, 20] need other ways of thinking updatings to be modelled. Here, our very aim is to put the emphasis on block-parallel update schedules, introduced initially in [41] and never studied *per se* until now, by giving insights essentially, and to highlight that they have interesting theoretical properties because of their intrinsic complexity, and pertinent features from a modelling point of view since they allow to model biological timers.

Section 2 recalls the basics related to ANs, and some of the seminal results obtained in the past. In Section 3, block-parallel update schedules are presented together with some of their very basic properties. Through two examples coming from distinct areas of biology, Section 4 underlines the ability of block-parallel modes to model biological timers. Finally, open questions are given in Section 5.

2   Preliminary

This section presents the classical notions and definitions used and widely studied in the literature related to Boolean networks. Of course, all of these can be easily generalised for other alphabets and multi-valued automata

networks. Moreover, for the sake of simplicity without losing generality, we reduce the set of Boolean networks considered to threshold Boolean networks.

Threshold Boolean networks Let $V = \{1, ..., n\}$ a set of nodes (often called automata in the literature). A *configuration* on V is a one-to-one function $x : V \to \mathbb{B} = \{0, 1\}$ so that a Boolean value is associated with each node of V. In other terms, a configuration $x = (x_1, x_2, ..., x_n)$ is a Boolean vector of dimension n, where any of the $x_i \in \mathbb{B}$ is the *state* of node i in configuration x. The discrete evolution of the local state of node i is defined as a *local transition function*

$$f_i : \left\{ \begin{array}{ccc} \mathbb{B}^n & \to & \mathbb{B} \\ x & \mapsto & H(\sum_{j=1}^n w_{i,j} \cdot x_j(t) - \theta_i) \end{array} \right. ,$$

where W is the *interaction matrix*, *i.e.*, the real-valued square matrix of order n such that coefficient $w_{i,j}$ is the weight of the influence that node j has on node i, Θ is the *activation vector*, *i.e.*, the real-valued vector of dimension n such that θ_i is the activation threshold of node i, and H is the Heaviside step function such that $H(x) = 0$ if $x < 0$, and 1 otherwise. Consequently, $f = (f_i)_{i \in \{1, ..., n\}}$ is such that

$$f : \left\{ \begin{array}{ccc} \mathbb{B}^n & \to & \mathbb{B}^n \\ x & \mapsto & H(W \cdot x - \Theta) \end{array} \right. ,$$

and defines the threshold Boolean network.

Interaction graphs Let f be a threshold Boolean network. From its interaction matrix W, we can derive the *interaction graph* $G(f) = (V, I)$, with $I \subseteq V \times \mathbb{R} \times V$, where $(i, w_{j,i}, j) \in I$ if $w_{j,i} \neq 0$. When $w_{j,i} > 0$ (resp. $w_{j,i} < 0$, $w_{j,i} = 0$), node i tends to activate (resp. tends to inhibit, has no influence on) node j. We generally speak of positive or negative influences. Figure 1 depicts a threshold Boolean network composed of 3 nodes whose interaction graph is a cycle of size 3. Notice that this network is more precisely a canonical *positive cycle* [12, 30, 42, 46], which means a cycle composed of an even number of negative influences (not to be confused with a *negative cycle* which would be composed of an odd number of negative influences).

Update schedules In any configuration of a network, one or several punctual events may take place. Here, we consider events that consist in the update of at least one node state. Supposing that the network is currently in configuration $x \in \mathbb{B}^n$, node $i \in V$ is *scheduled* if its state switches from x_i to $f_i(x)$. Remark that, possibly, $f_i(x) = x_i$ so that the update of i is

$$f: \quad W = \begin{pmatrix} 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix} \quad \Theta = \begin{pmatrix} +\varepsilon \\ +\varepsilon \\ +\varepsilon \end{pmatrix} \quad \bigg| \quad G(f):$$
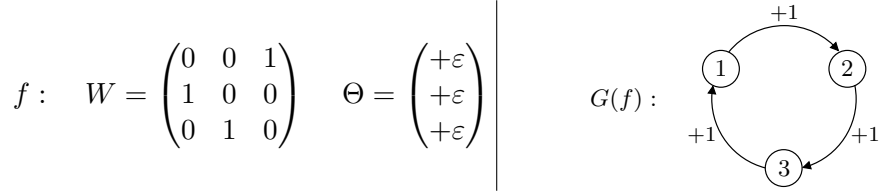

Figure 1: (left) Definition of a network f with its interaction matrix W and its threshold vector Θ; (right) its associated interaction graph $G(f)$.

not effective in x. In any case, this local event that we call a *transition* yields a global network configuration change (possibly not effective) which is described by the *i-update function* $F_i : \mathbb{B}^n \to \mathbb{B}^n$ such that

$$\forall x \in \mathbb{B}^n, \ F_i(x) = (x_1, \ldots x_{i-1}, f_i(x), x_{i+1}, \ldots, x_n).$$

This transition is said to be atomic because it involves only one automaton. We also consider non-atomic transitions that correspond to the synchronous update of several nodes. In the general case, the *B-update function*[1] $F_B : \mathbb{B}^n \to \mathbb{B}^n$ describes the network configuration change that results in the update of all the nodes of the subset (or block) B of V such that

$$\forall x \in \mathbb{B}^n, \ \forall i \in V, \ F_B(x)_i = \begin{cases} f_i(x) & \text{if } i \in B \\ x_i & \text{otherwise} \end{cases}.$$

An *update schedule* δ of a network whose set of nodes is V is defined by an ordered (finite or infinite) sequence $(B_i)_{i \in \{0,\ldots,t-1\}}$ of t non-empty subsets of nodes. We write $\delta = (B_i)_{i \in \{0,\ldots,t-1\}}$ or just $\delta = (B_0, B_1, \ldots, B_{t-1})$. Under an update schedule δ, starting in configuration $x \in \mathbb{B}^n$, a network takes sequentially the configurations $x^0 = F_{B_0}(x)$, $x^1 = F_{B_1} \circ F_{B_0}(x)$, ..., $x^{t-1} = F_{B_{t-1}} \circ \ldots \circ F_{B_0}(x)$.

Periodic update schedules of arbitrary period $p \in \mathbb{N}$ are infinite periodic sequences $(B_0, B_1, \ldots, B_{p-1}, B_0, B_1, \ldots, B_{p-1}, \ldots)$. For the sake of simplicity, they are rather defined by finite ordered lists $(B_i)_{i \in \mathbb{N}/p\mathbb{N}}$ of size p: $\delta = (B_0, B_1, \ldots, B_{p-1})$. When $\bigcup_{i=0}^{p-1} B_i = V$, such update schedules are called *fair update schedules* and are strong ergodic update schedules, the latter being defined as: there exists $m \in \mathbb{N}$ such that every node is updated in the time interval $[\![k; k + m]\!]$, $\forall k \in \mathbb{N}$. *Global transition functions* $F[\delta] : \mathbb{B}^n \to \mathbb{B}^n$ related to such periodic update schedules are defined as

$$\forall x \in \mathbb{B}^n, \ F[\delta](x) = F_{B_{p-1}} \circ \ldots \circ F_{B_1} \circ F_{B_0}(x).$$

Such very update schedule has never been studied in depth, certainly because of their inherent generality and underlying complexity. Remark nevertheless that they have been mentioned in [19].

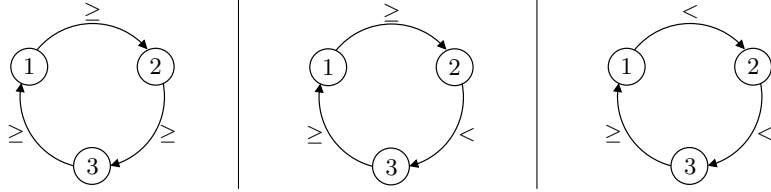[1] $\forall i \in V$, F_i obviously equals $F_{\{i\}}$.

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Figure 2: Update graphs of the network f defined in Figure 1: (left) Parallel update graph $\mathscr{U}_{(\{1,2,3\})}(f)$; (centre) Block-sequential update graph $\mathscr{U}_{(\{1,2\},\{3\})}(f)$; (right) Sequential update graph $\mathscr{U}_{(\{1\},\{2\},\{3\})}(f)$.

Well known instances of periodic update schedules are *block-sequential ones* [10, 14, 18, 19, 37, 38]. Their particularity lies in that their periodic sequence of updates involves exactly once each automaton of the network. Formally, a block-sequential update schedule of a network of node set V is an ordered partition P of V. With our notations, it can be defined as a finite sequence $(B_i)_{i \in \mathbb{N}/p\mathbb{N}}$ such that $V = \bigsqcup_{i \in \mathbb{N}/p\mathbb{N}} B_i$. It can also be defined as a function $\delta : V \to \mathbb{N}/p\mathbb{N}$. The *parallel update schedule* is the unique block-sequential update schedule of period $p = 1$ ($\forall i \in V,\ \delta(i) = 1$). It updates all the nodes of the network at each time step, simultaneously. The $n!$ *sequential update schedules* [29, 31] are block-sequential update schedules with period equal to the size of the network ($p = n$). They update only one node of the network at a time ($\forall i \in \mathbb{N}/p\mathbb{N},\ |B_i| = 1$). For the sake of clarity, when a network is subjected to a block-sequential schedule $\delta = (B_i)_{i \in \mathbb{N}/p\mathbb{N}}$, the nodes inside a subset of P are updated simultaneously and the subsets are iterated sequentially at each time step, from B_0 to B_{p-1}.

A non-classical way (but quite useful for proofs related to robustness of update schedules) to represent a block-sequential update schedule is the update graph introduced by Aracena et al. in [1, 2, 4, 5, 6]. On the basis of f a threshold Boolean network and the unlabelled version of its interaction graph $G'(f) = (V, I')$, where $I' = \{(i, j) \mid (i, w_{j,i}, j) \in I\}_{i,j \in V}$, a labelled graph $(G'(f), \mathrm{lab})$ is defined, with $\mathrm{lab} : I' \to \{<, \geq\}$. Given a block-sequential update schedule δ (seen as a function $\delta : V \to \mathbb{N}/p\mathbb{N}$), $U_\delta(f) = (G'(f), \mathrm{lab})$ is the update graph associated with δ if:

$$\forall (i, j) \in I',\ \mathrm{lab}(i, j) = \begin{cases} \geq & \text{if } \delta(i) \geq \delta(j) \\ < & \text{if } \delta(i) < \delta(j) \end{cases}.$$

An illustration of the concept of update graphs is given in Figure 2. From this update graph, Aracena et al. obtained the following very interesting result that gives strong insights on the role of block-sequential update schedules on the possible dynamical behaviours of a network.

Theorem 1 (Aracena et al. [5]). *Let f be a Boolean network. Let δ_1 and δ_2 be two block-sequential update schedules. If $U_{\delta_1}(f) = U_{\delta_2}(f)$ then $F[\delta_1] = F[\delta_2]$.*

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Transition graphs Given a network f and a block-sequential update schedule δ, the related *transition graph* is $\mathscr{G}_\delta(f) = (\mathbb{B}^n, T_\delta)$, whose nodes are network configurations and arcs are network transitions such that $T_\delta \subseteq \mathbb{B}^n \times \mathbb{B}^n$. Formally, if $\delta = (B_i)_{i \in \mathbb{N}/p\mathbb{N}}$,

$$\mathscr{G}_\delta(f) = (\mathbb{B}^n, T_\delta) \text{ where } T_\delta = \{(x, F[\delta](x)) \mid x \in \mathbb{B}^n\}.$$

A transition graph $\mathscr{G}_\delta(f)$ represents the dynamics over time of network f associated with update schedule δ (see Figure 3). From this graph, given a configuration $x \in \mathbb{B}^n$, the *trajectory* of x is the path (*i.e.*, the transition sequence) that starts in x. Since the number of configurations is finite and $F[\delta]$ is a deterministic one-to-one function mapping $\mathbb{B}^n$ to itself, the trajectory of x necessary ends up in a cycle of configurations, called an attractor. In this framework, an *attractor* can be either a *fixed point* of $F[\delta]$ (*i.e.*, a stable configuration that repeats endlessly), or a *limit cycle* of $F[\delta]$ (*i.e.*, a sequence of recurrent configurations that repeats endlessly). Remark that, from a more applied point of view, a transition graph could be restricted to specific strict subsets of V depending on the observability of the node states from which it could be relevant to compute and/or extract the related restricted attractors. Moreover, notice also that a transition graph can be extended by integrating all the intermediary visited configurations resulted from the application of $F_{B_i}, \forall B_i \in (B_i)_{i \in \mathbb{N}/p\mathbb{N}}$. It is then called a *complete transition graph*.

Let us recall now seminal and general theoretical results on *(i)* the computable features and *(ii)* the relations between the static (syntactic) and dynamical (semantic) properties of networks.

Theorem 2 (Goles and Martinez [17]). *The computational model of Boolean networks is Turing-complete.*

Theorem 3 (Goles and Martinez [17]). *Let f be a Boolean network, π the parallel update schedule and δ an arbitrary update schedule. If $x \in \mathbb{B}^n$ is a fixed point of $F[\pi]$, then x is a fixed point of $F[\delta]$.*

Notice that the reciprocal of Theorem 3 is not true. A simple illustration of this consists in considering the positive cycle presented in Figure 1 that admits two fixed points, 000 and 111, when scheduled block-sequentially, and that admits the four following fixed points 000, 010, 101, and 111 when scheduled according to $\delta = (\{2, 3\}, \{1, 3\}, \{1, 2\})$.

Theorem 4 (Robert [37, 38]). *Let f be a Boolean network associated with a directed acyclic interaction graph. Whatever the update schedule δ, $F[\delta]$ admits a unique attractor that is a stable configuration.*

The following theorem gives a strong global relation between interaction graphs and the existence of multi-stationarity of the underlying dynamical systems. It originally comes from a conjecture of Thomas presented
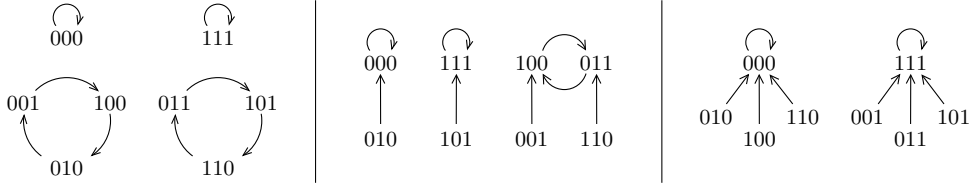
Figure 3: Periodic dynamics of the network f defined in Figure 1: (left) Parallel graph transition $\mathscr{G}_{(\{1,2,3\})}(f)$; (centre) Block-sequential graph transition $\mathscr{G}_{(\{1,2\},\{3\})}(f)$; (right) Sequential graph transition $\mathscr{G}_{(\{1\},\{2\},\{3\})}(f)$.

in [46], was proven in the context of block-sequential update schedules by Aracena [3] and then in the context of Thomas' asynchronous representation in [33, 34] before it was proven generally for any kind of update schedule by Noual and Sené in [30, 42].

Theorem 5. *Let f be a Boolean network and $G(f)$ its associated interaction graph. Whatever the update schedule δ, if $F[\delta]$ admits several stable configurations then $G(f)$ contains a positive cycle.*

3   Block-parallel threshold Boolean networks

In the previous section, we have emphasised that fair update schedules are very interesting from a theoretical point of view. Indeed, given a network f and its interaction graph $G(f) = (V, I)$, they can make emerge peculiar asymptotic dynamics, such as stable configurations that are not fixed points of the parallel global transition function $F[(V)]$. However, on the one hand, such an intrinsic mathematical richness seems to be too much important from a more applied point of view directed toward the qualitative modelling of genetic regulation networks. Conversely, on the other hand, block-sequential update schedules are not sufficiently rich to model specific observed biological abilities. In particular, there exist some examples of genetic regulation networks in which a specific subnetwork plays a role of "Zeitgeber" (*i.e.*, a timer) having its own clock. For instance, in Drosophila, this subnetwork consists in a small set of genes like TIME and PER [16, 21, 40] exhibiting as its unique attractor a limit cycle with its proper free-run period. This subnetwork influences other groups of genes, each of them having their own biological functionalities. Such a time command cannot be modelled by the classically studied block-sequential update schedules, simply because they prevent from having update repetitions of nodes in a same period of updates. Nevertheless, it can be modelled by another family of fair update schedules that we call block-parallel update schedules which are the topic of this note.
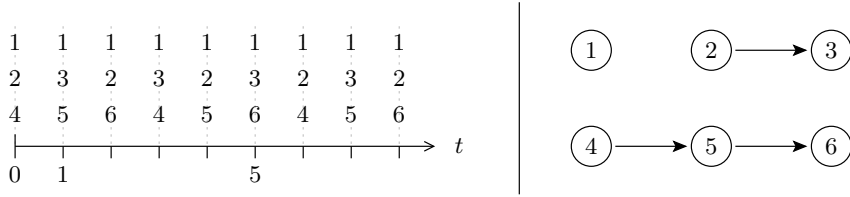
Figure 4: (left) Time diagram of the updates and (right) partial order graph of the anteriorities defined from the block-parallel update schedule $\delta = \{(1), (2, 3), (4, 5, 6)\}$.

Where a network f scheduled block-sequentially evolves so that the nodes are updated simultaneously inside a block and the blocks themselves are iterated sequentially, a network scheduled block-parallelly evolves conversely. The blocks are iterated simultaneously and the nodes inside them are updated sequentially. In other terms, where a block-sequential update schedule is defined by an ordered partition of V (*i.e.*, a finite sequence of non-empty and disjoint subsets of V recovering V), a block-parallel update schedule is defined by a set of non-empty and disjoint finite sub-sequences S_i of V whose union of elements recovers V. Thus, a block-parallel update schedule can be formally defined as $\delta = \{S_i\}_{i \in \{0, ..., |\delta|-1\}}$, such that $1 \leq |\delta| \leq |V|$. Remark that if $|\delta| = 1$ (resp. $|\delta| = |V|$), δ is a sequential (resp. the parallel) update schedule. Furthermore, notice that this definition satisfies the assumptions of a fair update schedule. Indeed, there exists a rewriting of any block-parallel update schedule into a finite sequence of subsets of V, complying with the dynamical properties of the underlying network. For instance, consider an arbitrary network of size 6 with $V = \{1, ..., 6\}$ and the following block-parallel update schedule: $\{(1), (2, 3), (4, 5, 6)\}$. The updatings along time of node states follow Figure 4(left), which corresponds exactly to the following finite sequence of subsets of V:

$$(\{1, 2, 4\}, \{1, 3, 5\}, \{1, 2, 6\}, \{1, 3, 4\}, \{1, 2, 5\}, \{1, 3, 6\}).$$

A block-parallel update schedule can also be represented by a graph $\delta \equiv (V, A)$ that is simply the partial order graph associated with the partial order of the anteriorities defined by δ (see Figure 4(right)).

Remark that block-parallel and block-sequential update schedules are distinct families of fair update schedules having a non-empty intersection made only of the block-sequential update schedules whose subsets have the same cardinality. Moreover, the union of these two families does not coincide with fair update schedules. Consider for instance a network f of 3 elements and $\delta = \{(0, 1), (1, 2), (0, 1, 2)\}$ that is not a block-parallel one since the sub-sequences are not disjoint. Its rewriting as a sequence of subsets is $(\{0, 1\}, \{1, 2\}, \{0, 1, 2\}, \{0, 1, 2\}, \{0, 1\}, \{1, 2\})$ which does not correspond to

$$f: \quad W = \begin{pmatrix} 1 & -2 & -2 & -2 & 0 \\ -2 & 1 & -2 & -2 & 0 \\ -2 & -2 & 1 & -2 & 0 \\ 0 & 0 & 0 & 1 & -2 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \quad \Theta = \begin{pmatrix} -\varepsilon \\ -\varepsilon \\ -\varepsilon \\ -\varepsilon \\ \varepsilon \end{pmatrix}$$
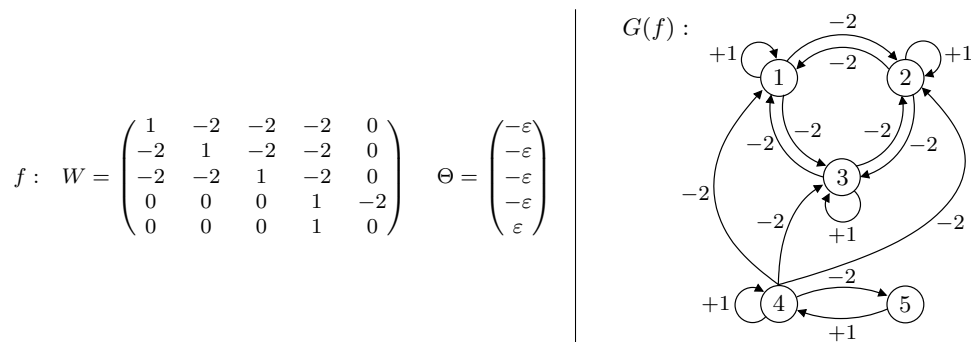
Figure 5: (left) Definition of the genetic network controlling the plant growth f with its interaction matrix W and its threshold vector Θ; (right) its associated interaction graph $G(f)$.

a block-sequential update schedule. However, it respects the definition of a fair update schedule.

4 Applications to biology

Now the block-parallel update schedules have been introduced, let us highlight their relevance in the qualitative modelling of biological regulation networks. We present two applications, the first one in genetics and the second one in physiology.

4.1 Genetic control of plant growth

The first example of a timer is the biological clock ruling the plant growth. A very schematic view of the functioning of the genetic control of the plant growth is to consider two components evolving independently. The first one can be modelled as a sub-network made of three genes that correspond to the localised expressions of the protein auxin (one of the plant growth regulators). The first gene AUXa corresponds to the apical localisation, the others correspond to the axillary bud localisations, AUXℓ for the left bud and AUXr for the right bud. The second one can be modelled as a sub-network localised in the cotyledon and composed of two genes: CCA (Circadian Clock Associated gene) and TOC (Timing Of CAB expression gene).

The dynamics of the plant growth is governed by the threshold Boolean network f where AUX$a \equiv 1$, AUX$\ell \equiv 2$, AUX$r \equiv 3$, CCA $\equiv 4$ and TOC $\equiv 5$, defined in Figure 5 which is derived from [8, 43]. Now, the idea is to focus only on the most realistic initial conditions for computing the dynamical behaviour. These conditions have to integrate the following biological observations:

- In the first component, the apical auxin is the first expressed during the plant growth. The other left and right bud auxins start at state 0 because the axillary buds are still not existing.

- In the second component, CCA is induced by photosynthesis (it starts at state 1) and activates secondarily TOC [8].

As a consequence, the most realistic initial configuration is $100\,10$. Let us consider now the update schedule. First of all, concerning the timer component, whatever the local update schedule, its dynamics remains the same. So, for the sake of simplicity, we have chosen that CCA and TOC evolve simultaneously. Now, concerning the auxin component, the messages transmitted from $\text{AUX}a$ to $\text{AUX}\ell$ corresponds to the diffusion along the stem of the auxin expressed by the gene $\text{AUX}a$. The same process can be observed between $\text{AUX}\ell$ and $\text{AUX}r$. As a consequence, a natural local update schedule for this component is the sequential one $(\{\text{AUX}a\}, \{\text{AUX}\ell\}, \{\text{AUX}r\})$. To sum up, a realistic global update schedule of f is the following block-parallel one:

$$\delta = \{(1, 2, 3), (4), (5)\} \iff \delta = (\{1, 4, 5\}, \{2, 4, 5\}, \{3, 4, 5\}),$$

whose partial order graph is

$$\boxed{1} \longrightarrow \boxed{2} \longrightarrow \boxed{3} \qquad \boxed{4} \qquad \boxed{5}.$$

Exploiting all the knowledge given above about the networks, its interaction graph and block-parallel update schedule, the trajectory of the initial configuration is given in Figure 6(left). It leads to a limit cycle of period 4 (resp. of period 12 if we consider it in the complete transition graph as it is the case in Figure 6 (left)) starting in $01\,000$, whose internal structure made of every intermediary configuration comes from the combination of the three fixed points of the auxin component and of the limit cycle of period 4 of the timer component. Notice also that the sequential growth of the three parts of the plant is correctly induced, in a uniform way. This regular scheme of growth could correspond to the quasi-perfect growth of *Araucaria araucana* which consists in the succession of triplets made of a central and two lateral stems, as illustrated in Figure 6(right).

4.2 Cardio-respiratory regulation

The second example of a timer is the biological clock ruling the cardio-respiratory regulation. As for the plant growth, the functioning of the physiological process of this regulation can be described by two components. The first one corresponds to the central vegetative system and plays the role of a timer. It comprises inspiratory (I) and expiratory (E) neurons. The second component is peripheral. It comprises the sino-atrial node ruling the heart activity (S) and the baroreceptor located at the exit the left ventricle (B).

$100\,10 \to 000\,11 \to 000\,01$

$\to \mathbf{010\,00} \to \mathbf{010\,10} \to \mathbf{010\,11}$

$\to \mathbf{000\,01} \to \mathbf{100\,00} \to \mathbf{100\,10}$

$\to \mathbf{100\,11} \to \mathbf{000\,01} \to \mathbf{001\,00}$

$\to \mathbf{001\,10} \to \mathbf{001\,11} \to \mathbf{000\,01}$

$\to 010\,00$

Figure 6: (left) Trajectory of configuration $100\,10$ of network modelling the genetic control of plant growth governed by the biological timer made of CCA and TOC; (right) Example of the growth of *Araucaria araucana* made by the succession the triplets corresponding to an apical and two lateral stems.

The dynamics of the cardio-respiratory regulation is governed by the network g where $E \equiv 1$, $I \equiv 2$, $B \equiv 3$, and $S \equiv 4$, defined in Figure 7 and derived from [7, 11, 13, 28]. Here also, let us consider the realistic initial condition $00\,00$ that corresponds to the end of an expiration just before the activity start of inspiratory neurons, and to low levels of the sino-atrial and baroreceptor activities.

The local updating schedule of the timer is similar to that of a plant growth. That of the second component comes from the information transmission from S to B thanks to the blood flow. It is consequently sequential and defined by $(\{S\}, \{B\})$. To sum up, the realistic global update schedule of g is the following block-parallel one:

$$\delta = \{(1), (2), (4, 3)\} \iff \delta = (\{1, 2, 4\}, \{1, 2, 3\}).$$

The trajectory of initial realistic configuration $00\,00$ is

$00\,00 \to 01\,00 \to 11\,00 \to 10\,01 \to \mathbf{00\,11} \to \mathbf{01\,11} \to \mathbf{11\,01} \to \mathbf{10\,01} \to 00\,11.$

It suggests that the cardio-respiratory network presents a limit-cycle of period 2 (resp. of period 4 if we consider it in the complete transition graph as it is the case above with black and gray bold configurations) decomposed into two phases as in the real biological functioning. It is composed of the succession of the activity periods of the two families of central neurons (E and I) that are both inactive and then active, and that can hence trigger the two intermediary inspiratory and expiratory phases. For the peripheral activity, we can observe a constant sino-atrial activity inducing an important cardiac activity at the end of the expiration and during the inspiration that is reduced after the inspiration and during the expiration. Such an observation could refer to the idea of a qualitative model for the well known phenomenon called cardiac sinusal arrhythmia.

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$$g: \quad W = \begin{pmatrix} 0 & 2 & 0 & -1 \\ -2 & 1 & 1 & 0 \\ 0 & -1 & 0 & 1 \\ 1 & 0 & -1 & 2 \end{pmatrix} \quad \Theta = \begin{pmatrix} \varepsilon \\ -\varepsilon \\ \varepsilon \\ \varepsilon \end{pmatrix}$$
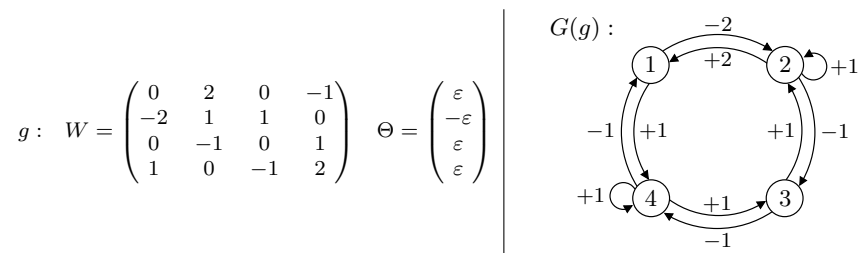
Figure 7: (left) Definition of the physiologic network g controlling the cardio-respiratory regulation with its interaction matrix W and its threshold vector Θ; (right) its associated interaction graph $G(g)$.

A relevant characteristics of the network g is that the reduction of the influence of the sino-atrial node on itself, by changing $w_{4,4} = 2$ to $w_{4,4} = 1$ suffices to retrieve the normal cardiac functioning with no sinus arrhythmia. Indeed, in this case, the trajectory of $00\,00$ becomes:

$$00\,00 \to 01\,00 \to \mathbf{11\,00} \to 10\,01 \to \mathbf{00\,11} \to 01\,10 \to 11\,00.$$

However, this trajectory highlights a phase shifting of the cardiac activity with respect to the firing of respiratory neurons of the vegetative system, which does not comply with the biological assumptions. As a consequence, a refining of the model seems to be required, which paves the way for further modelling studies.

5   Conclusion and open problems/questions

This position paper aimed at putting the focus on block-parallel schedules and highlighting especially their ability to model autonomous timers that govern the dynamics of impacted sub-networks, for underlining their pertinence from a biological modelling point of view with respect to "Zeitgebers" (timers). Beyond the modelling interest, these modes seem also to have very interesting theoretical properties that deserve without any doubt to be studied in depth from mathematical and theoretical computer science points of view, as it has been the case for block-sequential update schedules. Eventually, in order to illustrate our purpose, let us present open problems/questions which, if addressed, could lead to relevant advances in both theoretical and applied frameworks:

- In [18], the authors showed that any block-sequential isolated positive or negative cycle can be simulated by a smaller parallel cycle of same sign. So, a natural question is to understand if a similar property holds for block-parallel and another schedule that the parallel one. Indeed, it is easy to see that the repetition of at least one node updating is a lock here and that consequently, generally speaking, a block-parallel cycle

cannot be simulated by a smaller parallel cycle. As a consequence, the open question is: as the parallel is the canonical block-sequential update schedule for Boolean cycles, does there exist a canonical block-parallel update schedule?

- In [12], by basing themselves on the result of [18], the authors proved all the combinatorial transient and asymptotic properties of parallel Boolean cycles. If a positive answer is found to the previous open question leading to the definition of a canonical block-parallel update schedules, it will be crucial to lead a similar combinatorial study to obtain a perfect knowledge of cycles in this context since the latter remain important in this framework in terms of dynamical complexity.

- As presented in the note, in [2, 4, 5], the authors introduced block-sequential update graphs. This graph is of real interest since it allows to know efficiently if a network associated with two block-sequential update schedules admits an equivalent dynamics (see Theorem 1). In order to prove similar equivalence properties in the context of block-parallel update schedules, it seems that it would be of great interest to develop the concept of block-parallel update graphs. Can such a concept be found? If yes, given a network f and a block-parallel update schedule δ, is it as easy to define/construct as for block-sequential update schedules?

- Concerning the attractors of block-parallel models with timers of real biological networks, are the *complete limit cycles* (*i.e.*, the limit cycles including intermediary configurations) always made of an alternation of the attractors projected on the nodes of the peripheral sub-networks provoked by the period of the limit cycle(s) of the timer(s)? Even if it seems to be efficient, does nature tend to classically use such timers/processes to make biological networks able to oscillate between attraction basins and thus create functional rhythms? To answer to these questions, a statistical study in depth of well known networks modelling biological rhythms will be necessary.

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