

On the preservation of limit cycles in Boolean networks under different updating schemes

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Abstract

Boolean networks under different deterministic updating schemes are analyzed. It is direct to show that fixed points are invariant against changes in the updating scheme, nevertheless, it is still an open problem to fully understand what happens to the limit cycles. In this paper, a theorem is presented which gives a sufficient condition for a Boolean network not to share the same limit cycle under different updating modes. We show that the hypotheses of the theorem are sharp, in the sense that if any of these hypotheses do not hold, then shared limit cycles may appear. We find that the connectivity of the network is an important factor as well as the Boolean functions in each node, in particular the *XOR* functions.

Introduction

Boolean networks were introduced by S. Kauffman (Kauffman, 1969) and R. Thomas (Thomas, 1973) as a mathematical model of gene regulatory networks. It has been used to model, for example, the floral morphogenesis of *Arabidopsis thaliana* (Mendoza and Alvarez-Buylla, 1998), the fission yeast cell cycle (Davidich and Bornholdt, 2008; Goles et al., 2013), and the budding yeast cell cycle (Li et al., 2004; Goles et al., 2013). Formally, let $\mathbf{x} = \{x_1, \dots, x_n\}$ be a finite set with $x_i \in \{0, 1\}$ for $i = 1, \dots, n$. Let $N = (G, F, \pi)$ be a Boolean network, where $G = (V, E)$ is a digraph; V being the set of n nodes and E the set of edges. F is a Boolean function, $F : \{0, 1\}^n \rightarrow \{0, 1\}^n$ composed of n local functions $f_i : \{0, 1\}^n \rightarrow \{0, 1\}$. Each local function f_i depends only on the variables belonging to the neighborhood $V^-(i) = \{j \in V | (j, i) \in E\}$. The indegree of vertex i is $|V^-(i)|$, and π is an arbitrary order to update the nodes $\pi : \{1, \dots, n\} \rightarrow \{1, \dots, n\}$. For example, the parallel or synchronous updating mode (or scheme) has $\pi(i) = 1$ (every node is updated at the same time), whereas, for the sequential one, π is a permutation. A combination of the parallel and the sequential updating mode is the block-sequential where the set of nodes, for a given sequence, is partitioned into blocks. The nodes in a same block are updated in parallel, but blocks follow each other sequentially. Overall, there are an exponential number of updates. In fact,

if the network has n nodes, the number of updates is given by Demongeot et al. (2008):

$$T_n = \sum_{k=0}^{n-1} \binom{n}{k} T_k, \quad T_0 = 1.$$

Without loss of generality, $f_i(\mathbf{x}) = f_i(x_1, \dots, x_n)$ will be used sometimes, although it should be clear to the reader that the local function really depends only on the variables in the neighborhood. Since the updating schemes are repeated periodically and the hypercube is a finite set, the dynamics of the network converges to attractors which are fixed points, i.e vectors such that $x_i = f_i(\mathbf{x})$ for any i , or limit cycles, defined by $x_i^{t+p} = x_i^t$ for $i = \{1, \dots, n\}$, where $p > 1$ is the period. In this paper we will consider limit cycles that have *non-constant* values (a constant node does not change its value during the limit cycle) within it¹.

One of the first to compare updating modes was F. Robert (Robert, 1986) for the parallel and sequential update. More recently, the robustness of such networks related to changes in the updating modes have been studied in Goles and Salinas (2008), where the authors prove that networks with monotonic loops² can not share limit cycles between the parallel and the sequential update. Furthermore, a first step to understand the different updates was done in Elena (2009); numerical experiments, under small threshold networks ($n = 3$) were carried out in order to exhibit the different dynamics for every updating mode. Also, theoretical tools were developed in order to classify dynamics under different updating modes as well as to build efficient algorithms (Aracena et al., 2009; Montalva, 2011). In Goles and Noual (2012) a theoretical study of the dynamics of disjunctive networks under all updating schedules was presented. In Ruz and Goles (2013), results from reverse engineering synthesizing threshold Boolean networks with predefined limit cycles, showed that shared limit cycles, of length two, from parallel to sequential updates, were obtained for networks with indegree 3 and indegree 5.

¹If there is a constant node, one may consider a new network, smaller than the original one, with non-constant nodes.

²A loop is a self connected node.

In this work, we characterize a class of Boolean network such that, two different updating modes (or a class of them) do not share non-constant limit cycles. We will see that connectivity plays an important role in this problem, in fact, if the digraph admits nodes of indegree 3, then we may find networks such that, for a specific Boolean function, the parallel and sequential updates (among others) share non-constant limit cycles (see Fig. 1). Therefore, we restrict

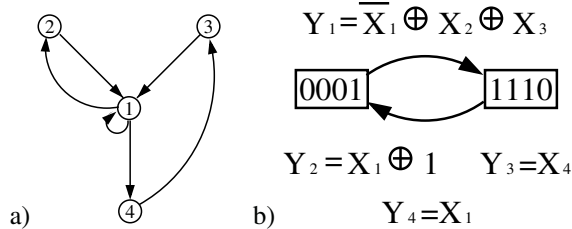


Figure 1: a) Strongly connected digraph G with $|V^-(1)| = 3$. b) Limit cycle shared by $N_1 = (G, F, \pi_1)$ and $N_2 = (G, F, \pi_2)$ where $\pi_1 = \emptyset$ is the parallel updating mode, $\pi_2 = (2)(3)(4)(1)$ and $F = (Y_1, \dots, Y_4)$.

our study to digraphs of indegree at most 2. In this context, we have 16 two-input Boolean functions. It is easy to see that 14 of these functions are *canalizing* (Fogelman et al., 1982) in, at least, one input (i.e., when this input is fixed in a Boolean value a , $f(a, x) = f(a, \bar{x})$). We will prove that for the majority of the canalizing functions, one may find different updating schemes such that they share non-constant limit cycles; the exception will be the case when the function is *positive canalizing*³ in its own input. In this case, the sequential and the parallel updates do not share non-constant limit cycles, which is a particular case of the result proved in Goles and Salinas (2008). Further, if the local function is *non-canalizing* (i.e., the XOR ($x \oplus y = 1 \Leftrightarrow x \neq y$) or the *EQUIVALENCE* ($f(x, y) = 1 \Leftrightarrow x = y$)), we prove that, for any network of indegree at most 2 and a huge family of updating modes, the networks do not share non-constant limit cycles. In addition, for the particular case of the parallel and sequential updates, when the digraph is strongly connected we have the same result. We point out that the XOR and EQUIVALENCE functions are not monotone in any variable. It was remarked in Kauffman (1969); Walker and Gelfand (1979); Fogelman et al. (1982); Noual et al. (2012) that these kind of networks admits very long limit cycles, also, their dynamics are very sensitive to the variation of the updating mode.

³A function $f : \{0, 1\}^n \rightarrow \{0, 1\}$ is *positive canalizing* on input i if for every Boolean vector x , $f(x_1, \dots, x_{i-1}, 0, x_{i+1}, \dots, x_n) \leq f(x_1, \dots, x_{i-1}, 1, x_{i+1}, \dots, x_n)$.

Unshared limit cycles in Boolean networks

The main result of this section is Theorem 1 that shows a sufficient condition such that a Boolean network can not share limit cycles when it is updated by different updating modes. After, we will deduce a particular case for unshared limit cycles between the parallel and any other updating mode. Next, we will show that the hypotheses of the Theorem 1 are sharp (if we change any of them, shared limit cycles may appear). Finally, we will also show that such sufficient condition is not a necessary one.

In order to prove the main result we will assume that the indegree is ≤ 2 , since shared cycles may appear when the indegree is ≥ 3 . On the other hand, we define appropriate partitions of the different updating modes.

Let G be a digraph and S_n the set of all update schedules over V . For $i \in V$ such that $V^-(i) = \{u, v\}$, we define the following partition of S_n :

$$\begin{aligned} P_1(i) &= \{s \in S_n : s(u) < s(i) \leq s(v)\} \\ P_2(i) &= \{s \in S_n : s(v) < s(i) \leq s(u)\} \\ P_3(i) &= \{s \in S_n : s(i) > s(u) \wedge s(i) > s(v)\} \\ P_4(i) &= \{s \in S_n : s(i) \leq s(u) \wedge s(i) \leq s(v)\} \end{aligned}$$

and the XOR family $\mathcal{F} \equiv \{x_u \oplus x_v, x_u \oplus x_v \oplus 1, x_u, x_u \oplus 1\}$, where $x \oplus y = 1 \Leftrightarrow x \neq y$.

If $i \in V$ is such that $V^-(i) = \{u\}$, we define the following partition of S_n :

$$\begin{aligned} P_1(i) &= P_2(i) = \emptyset \\ P_3(i) &= \{s \in S_n : s(i) > s(u)\} \\ P_4(i) &= \{s \in S_n : s(i) \leq s(u)\} \end{aligned}$$

In this case, the family is reduced to $\mathcal{F} \equiv \{x_u, \bar{x}_u\}$.

Theorem 1 (Unshared limit cycles). *Let G be a digraph such that $1 \leq |V^-(i)| \leq 2, \forall i \in V$ and consider a Boolean network $N_1 = (G, F, \pi_1)$ that admits a limit cycle C . If every $f_i \in \mathcal{F}$, then, for any updating mode $\pi_2 \neq \pi_1$ verifying that:*

$$\begin{aligned} \text{Update condition: } & \exists i \in \{1, \dots, n\}, \pi_1 \in P_4(i) \\ & \text{and } \pi_2 \in P_1(i) \cup P_2(i) \cup P_3(i), \end{aligned}$$

the dynamics associated to the updates π_1 and π_2 do not share the same limit cycle C .

Proof. Let $N_1 = (G, F, \pi_1)$ be a Boolean network of n nodes such that $1 \leq |V^-(i)| \leq 2, \forall i \in V$ and that admits a non-constant limit cycle C associated to the updating mode π_1 . Moreover, suppose that $f_i \in \mathcal{F}, \forall i \in \{1, \dots, n\}$.

First, note that for this kind of functions:

$$\forall i \in \{1, \dots, n\}, \forall x \in \{0, 1\}, f_i(0, x) \neq f_i(1, x) \quad (1)$$

We denote by $x_j^{\pi_1}(t)$ and $x_j^{\pi_2}(t)$ the state of node j at time t for the updating modes π_1 and π_2 respectively.

Let $\pi_2 \neq \pi_1$ be a given updating mode verifying (1) for some $i \in V$ such that $V^-(i) = \{u, v\}$ and suppose on the contrary that $N_2 = (G, F, \pi_2)$ has the same non-constant limit cycle C of N_1 , i.e:

$$\forall j \in \{1, \dots, n\}, \forall x^{\pi_2} \in \{0, 1\}^n \cap C : x_j^{\pi_2}(t) = x_j^{\pi_1}(t) \quad (2)$$

For i as above, we have that $\pi_1 \in P_4(i)$ and the following three cases are possible:

Case 1: $\pi_2 \in P_1(i)$. Then the updates are computed by

$$\begin{aligned} x_i^{\pi_1}(t+1) &= f_i(x_u^{\pi_1}(t), x_v^{\pi_1}(t)) \\ x_i^{\pi_2}(t+1) &= f_i(x_u^{\pi_2}(t+1), x_v^{\pi_2}(t)) \end{aligned} \quad (3)$$

$$\begin{aligned} &\stackrel{\text{by (2)}}{=} f_i(x_u^{\pi_1}(t+1), x_v^{\pi_1}(t)) \end{aligned} \quad (4)$$

Because the variables in C are non-constant, $x_u^{\pi_1}(t) \neq x_u^{\pi_1}(t+1)$. Hence, we can assume w.l.o.g. that $x_u^{\pi_1}(t) = 0$ and $x_u^{\pi_1}(t+1) = 1$. Replacing these values in (3) and (4) we have that:

$$x_i^{\pi_1}(t+1) = f_i(0, x_v^{\pi_1}(t)) \text{ and,}$$

$$x_i^{\pi_2}(t+1) = f_i(1, x_v^{\pi_1}(t))$$

Thus, due to (1) we have that $x_i^{\pi_1}(t+1) \neq x_i^{\pi_2}(t+1)$ which contradicts (2).

Case 2: $\pi_2 \in P_2(i)$. This is similar to Case 1 but considering the calculations over v .

Case 3: $\pi_2 \in P_3(i)$. Then the updates are computed by

$$x_i^{\pi_1}(t+1) = f_i(x_u^{\pi_1}(t), x_v^{\pi_1}(t)) \text{ and,}$$

$$\begin{aligned} x_i^{\pi_2}(t+1) &= f_i(x_u^{\pi_2}(t+1), x_v^{\pi_2}(t+1)) \stackrel{\text{by (2)}}{=} \\ f_i(x_u^{\pi_1}(t+1), x_v^{\pi_1}(t+1)) &= x_i^{\pi_1}(t+2) \stackrel{\text{by (2)}}{=} x_i^{\pi_2}(t+2) = \dots \end{aligned}$$

This means that the state of vertex i must never change within C , which contradicts the assumption that each variable in the limit cycle is non-constant.

Finally, note that if $V^-(i) = \{u\}$, then the analysis of the case $\pi_2 \in P_3(i)$ is similar to Case 3. \square

Corollary 1. *Let G be a strongly connected digraph such that $|V^-(i)| \leq 2, \forall i \in V$ and consider the Boolean network $N_1 = (G, F, \varphi)$ associated to the parallel updating mode, φ ,*

that admits a limit cycle C . If every $f_i \in \mathcal{F}$, then, for any updating mode $\pi \neq \varphi$, the Boolean network $N_2 = (G, F, \pi)$ does not share the same limit cycle C .

Proof. Let $N_1 = (G, F, \varphi)$ be a Boolean network of n nodes that admits a non-constant limit cycle C associated to the parallel updating mode φ . Suppose also that G is strongly connected with $|V^-(i)| \leq 2, \forall i \in V$. The latter implies that:

$$1 \leq |V^-(i)| \leq 2, \forall i \in V \quad (5)$$

φ is the parallel updating mode $\Leftrightarrow \forall j \in V, \varphi \in P_4(j)$ (6)

Moreover, suppose that $f_i \in \mathcal{F}, \forall i \in \{1, \dots, n\}$.

Let us prove the sufficient condition. Let $\pi \neq \varphi$ be an updating mode. By (6), we have that $\pi \in P_1(i) \cup P_2(i) \cup P_3(i)$, for some $i \in V$ such that $V^-(i) = \{u, v\}$. This, together with (5) and the assumptions made at the beginning gives us the hypotheses of Theorem 1, with $\pi_1 = \varphi$ and $\pi_2 = \pi$, which guarantees that C is not a limit cycle of $N_2 = (G, F, \pi)$.

Finally, note that the above analysis is similar when $V^-(i) = \{u\}$. \square

Corollary 2. *If C is a limit cycle associated to the parallel updating mode of a Boolean network such that its digraph is a circuit, then, C is not shared by any other updating mode.*

Proof. A circuit is a strongly connected digraph such that, $\forall i \in \{1, \dots, n\}; |V^-(i)| = 1$ and $f_i \in \mathcal{F} \equiv \{x_u, \overline{x_u}\}$, where $u \in V^-(i)$. Thus, by Corollary 1, C is not shared by any other updating mode. \square

Remark. In particular, we have that the parallel and the sequential updating modes do not share non-constant limit cycles.

Now, we will show the sharpness of the hypotheses of Theorem 1.

Case 1: Not all the local functions are in \mathcal{F} . In Fig.2a) we exhibit a strongly connected digraph G with $|V^-(i)| \leq 2, \forall i \in V$ where the network $N_1 = (G, F, \pi_1)$ admits a limit cycle C showed in Fig.2b) for the parallel update schedule $\pi_1 = \varphi$ and the global function $F = (Y_1, \dots, Y_4)$ defined in Fig.2b) as well. However, although there exists $N_2 = (G, F, \pi_2)$ with $\pi_2 = (2)(1, 3, 4)$ such that $\pi_1 \in P_4(1)$ and $\pi_2 \in P_1(1)$ as in the update condition of Theorem 1, C is shared anyway for both dynamics, because in this case, the local function $Y_1 = X_2 \wedge X_3$ is not a *XOR* function. Similarly, we arrive to the same conclusion if we consider $Y_1 = X_2 \vee X_3$ and, in general, given that every local function $f(x, y)$ (different to a *XOR* function) is a combination of \wedge and \vee , we can construct other examples, as the above one, but for f .

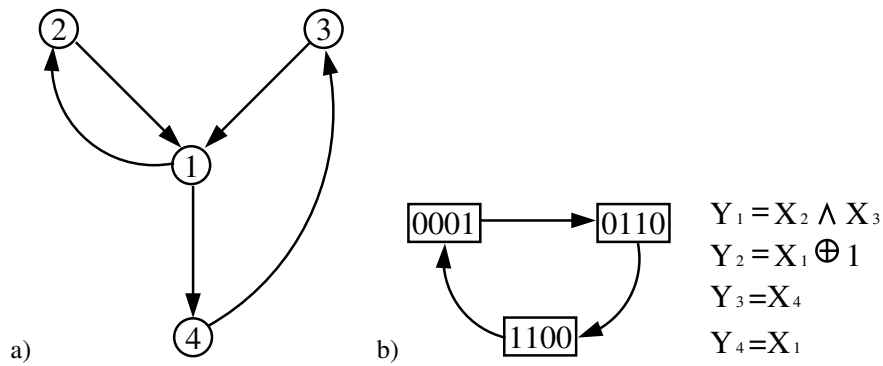


Figure 2: Example for Case 1. Note that $Y_1 = X_2 \wedge X_3$ is the only hypothesis that does not match with Theorem 1.

Case 2: The update condition of Theorem 1 does not hold. First, we consider the same strongly connected digraph G of Fig.2a). The network $N_1 = (G, F, \pi_1)$ admits a limit cycle C showed in Fig.3 for $\pi_1 = (2)(1, 3)(4)$ and the global function $F = (Y_1, \dots, Y_4)$ where all its components, that depend of two variables, are *XOR* functions. However, $N_2 = (G, F, \pi_2)$ with $\pi_2 = (3)(1, 2)(4)$ also shares C , because in this case, π_1 and π_2 do not verify the update condition of Theorem 1. We remark that it is also possible to show an example for each case not included in the above condition.

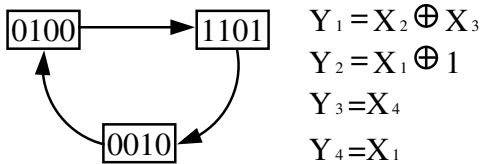


Figure 3: Example for Case 2. Note that $\pi_1 = (2)(1, 3)(4)$ and $\pi_2 = (3)(1, 2)(4)$ do not verify the update condition of Theorem 1.

Case 3: Accepting constant limit cycles. Consider the strongly connected digraph G showed in Fig.4a). Note that $|V^-(i)| \leq 2, \forall i \in V$. On the other hand, consider the limit cycle C showed in Fig.4b) admitted by $N_1 = (G, F, \pi_1 = \varphi)$ where its first component is constant and equal to one. Also, on this same figure, $F = (Y_1, Y_2, Y_3)$ is defined with all its components being *XOR* functions. So, it is easy to check that $N_2 = (G, F, \pi_2)$ with $\pi_2 = (2, 3)(1)$ is such that $\varphi \in P_4(1)$ and $\pi_2 \in P_3(1)$ as in the update condition of Theorem 1, but, N_2 also shares C .

Case 4: The sufficient condition of Theorem 1 is not a necessary condition. The sufficient condition of Theorem 1 for unshared limit cycles (i.e., to have *XOR* functions in all the nodes with indegree equal to two) is not a necessary

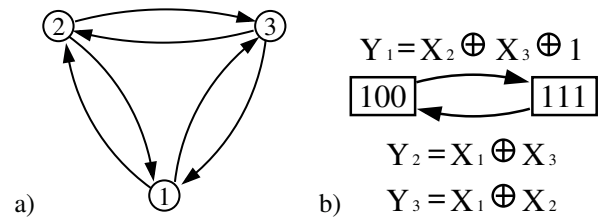


Figure 4: Example for Case 3. This constant limit cycle is the only hypothesis that does not match with Theorem 1.

condition. Consider the digraph of Fig.5a), the limit cycle C and $F = (Y_1, Y_2, Y_3)$ of Fig.5b) verifying $|V^-(i)| \leq 2, \forall i \in V$. The network $N = (G, F, \varphi)$ admits C as a limit cycle which is not shared by any other updating mode, in spite of the fact that $Y_3 = X_1 \wedge X_2$ is not a *XOR* function.

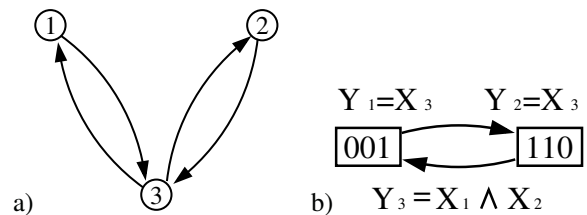


Figure 5: Example showing that the sufficient condition of Theorem 1 for unshared limit cycles is not a necessary condition.

Simulations

In order to see how common it is to find Boolean networks (BN) that share the same limit cycles for different updating schemes (or modes), we conducted an exhaustive study for $n = 3$ updating all the BN (graph + local functions) with

indegree at most 2, which yields 46656 BN, under all the deterministic updating schemes, i.e., $T_3 = 13$. This requires order of 10^6 calculations approximately. Whereas to carry out the same analysis for $n = 4$, requires much more computational power (at least order of 10^9 calculations), therefore we computed only for $n = 3$. Also, for $n = 3$ we are able to obtain a vast spectrum of BN necessary to study our theorem.

The 46656 BN can be divided into: 1728 XOR type (i.e., the functions over all its nodes are XOR or XOR \oplus 1) and 44928 non XOR type. Also, from the 46656 BN, 33023 BN have at least one updating mode that produces at least one limit cycle (that can be either constant or non-constant). The remaining 13633 BN have only fixed points for any updating mode.

The 33023 BN can be divided into 1647 that are XOR type and 31376 non XOR type. They can also be divided in 15443 BN that have at least one updating mode that produces at least one non-constant limit cycle, the remaining 17580 BN never have non-constant limit cycles.

From the 15443 BN, 1275 are XOR type, and the remaining 14168 are non XOR type.

From the 1275 BN, 1227 share at least one non-constant limit cycle. From the 14168 BN, 10208 share at least one non-constant limit cycle.

Finally, we conclude that $1227 + 10208 = 11435$, which represent approximately 25% of the total, is the amount of BN that, regardless if they are XOR or non XOR type, share at least one non-constant limit cycle.

A summary of these results are shown in Fig. 6.

Conclusion

In this paper we have characterized digraphs of low connectivity (indegree ≤ 2) and local Boolean functions (XOR or EQUIVALENCE) such that a relevant (actually, an exponential number) set of different updating modes do not share non constant limit cycles. Furthermore, the updating modes that can be compared according to the hypotheses of Theorem 1, conform a set that, in the restricted case of strong connectivity (Corollary 1), includes the particular cases of the parallel and serial updates studied in Goles and Salinas (2008) for Boolean networks with monotonic loops. In this context, taking into account our results and the ones obtained in Goles and Salinas (2008), we conclude that unshared limit cycles between the parallel and sequential updating modes occur in at least two situations: when the loops, if they exist, are positive canalizing or when all the local functions are in the XOR family \mathcal{F} .

Finally, the results presented in this paper using XOR functions, confirm their importance in the dynamical behavior of Boolean networks, a fact that was recently highlighted in Noual et al. (2012). In addition, our results use sharp hypotheses in the sense that we can exhibit counterexamples in every case where any of these hypotheses do not hold.

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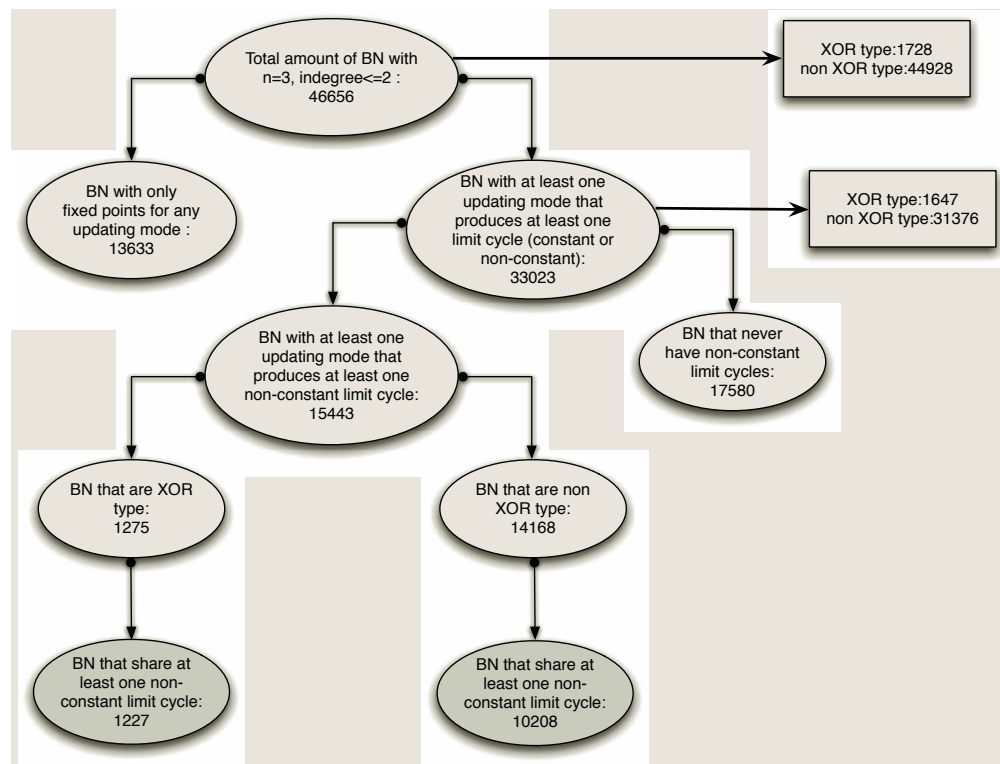


Figure 6: Summary of the results obtained by simulations that show the amount of Boolean networks (BN) that share at least one non-constant limit cycles for different updating modes.

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