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Variable-Depth Simulation of Most Permissive Boolean Networks

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Abstract. In systems biology, Boolean networks (BNs) aim at modeling the qualitative dynamics of quantitative biological systems. Contrary to their (a)synchronous interpretations, the Most Permissive (MP) interpretation guarantees capturing all the trajectories of any quantitative system compatible with the BN, without additional parameters. Notably, the MP mode has the ability to capture transitions related to the heterogeneity of time scales and concentration scales in the abstracted quantitative system and which are not captured by asynchronous modes. So far, the analysis of MPBNs has focused on Boolean dynamical properties, such as the existence of particular trajectories or attractors. This paper addresses the sampling of trajectories from MPBNs in order to quantify the propensities of attractors reachable from a given initial BN configuration. The computation of MP transitions from a configuration is performed by iteratively discovering possible state changes. The number of iterations is referred to as the permissive depth, where the first depth corresponds to the asynchronous transitions. This permissive depth reflects the potential concentration and time scales heterogeneity along the abstracted quantitative process. The simulation of MPBNs is illustrated on several models from the literature, on which the depth parametrization can help to assess the robustness of predictions on attractor propensities changes triggered by model perturbations.

1 Introduction

Boolean networks (BNs) have been employed to model the temporal evolution of gene expression and protein activities in biological systems [5,15,16,7]. A BN is composed of a finite set of components having two states, either 0 (false) or 1 (true). The BN then specifies in which contexts the components can change state, such as “component 3 can switch to state 1 if and only if component 1 is in state 0 and component 2 is in state 1; in all other contexts, component 3 can only switch to 0”. These rules can be given as one Boolean function per component, associating each possible configuration (which associates each component to a state) to a Boolean value: in our example, the function of component 3 is $f_3 : \{0,1\}^2 \rightarrow \{0,1\}$ with $f_3(x) = \neg x_1 \land x_2$, where $\neg$ and $\land$ denote the logical negation and conjunction, respectively.
The execution of a BN relies on a given update mode which specifies how are computed the evolution of the states of components. In the systems biology literature, two main update modes are widely employed: the synchronous (or parallel) and fully-asynchronous. In synchronous, each component is updated simultaneously: the configuration \( x = (x_1, x_2, x_3) \) evolves in one step to \( (f_1(x), f_2(x), f_3(x)) \). In fully-asynchronous, only one component can be updated at a time, possibly leading to non-deterministic transitions: the configuration \( x \) can evolve either to \( (f_1(x), x_2, x_3) \), \( (x_1, f_2(x), x_3) \), or \( (x_1, x_2, f_3(x)) \). Whatever the chosen update mode, as there is a finite number of configurations, an execution eventually reaches a set of limit configurations which will be visited infinitely often. These sets of configurations are called attractors: each execution eventually reaches and stays within one attractor. Attractors are prominent dynamical features when modeling biological processes: they represent stable behaviors and are usually associated to cellular phenotypes.

Computing the attractors reachable from a given initial configuration is at the core of many studies of biological processes with BNs [1,2,11,6,7]. These studies typically involve comparing the effect of a network mutation (forcing some components to have fixed value) on the sets of reachable attractors and their propensities. This later notion is often related to the number of paths leading from the initial configuration to each attractor: under some mutations, the same set of attractors may still be reachable, but the proportion of trajectories leading to them may substantially differ. This motivated the development of simulation algorithms for BNs in order to sample trajectories and quantify the propensities to reach attractors. These methods replace the non-determinism of asynchronous transitions by a probabilistic choice [6,14].

Whenever employed as qualitative models of quantitative systems, dynamics of BNs aim at giving a coarse-grained view of system dynamics without requiring numerous quantitative parameters. However, the Boolean (a)synchronous modes are not correct abstractions of quantitative dynamics [8]: they lead at the same time to predict spurious transitions and, importantly, preclude transitions which are actually possible when considering delays for instance. Let us illustrate this with the following BN, denoted (A) in the rest of the text:

\[
f_1(x) = 1 \quad f_2(x) = x_1 \quad f_3(x) = (\neg x_1 \land x_2) \lor x_3 \quad (A)
\]

From the initial configuration where all components are 0, we write 000, there is only one possible transition: the activation of 1, leading to the configuration 100. Then, again, only one transition is possible, activating 2, thus leading to 110. There, the execution will stay infinitely on this configuration: no other state changes are possible: from 000 it is impossible to eventually activate 3, and \{110\} is the only reachable attractor. However, it is known that this system can actually activate 3 for a range of kinetics, as observed experimentally [13], and easily captured with quantitative models [4,12]. Indeed, consider that 1 has actually several activation levels: one intermediate \( \frac{1}{2} \) which is sufficient to activate 2 but not enough sufficient to inhibit 3: when in \( \frac{1}{2}00 \), 2 can be activated, going to \( \frac{1}{2}10 \), and then 3 can change state, going to \( \frac{1}{2}11 \). When 1 becomes fully active
Variable-Depth Simulation of Most Permissive Boolean Networks 3

(111), 3 will self-maintain its activation. Thus, a correct Boolean analysis of the BN $f$ above should conclude that from 000, two attractors are reachable: \{110\}, when 1 goes rapidly to its maximum level, and \{111\} when 3 had time to activate before the full activation of 1. This example shows the limit of (a)synchronous interpretations of BNs when used as abstraction of quantitative systems: they enforce that the Boolean 0 matches with the quantitative 0, and the Boolean 1 matches with the quantitative non-zero ($>0$), making impossible to capture transitions happening at different activation levels or different time scales.

The Most Permissive (MP) update mode of BNs [8,9] is a recently-introduced execution paradigm which enables capturing dynamics precluded by the asynchronous ones. The main idea behind the MP update mode is to systematically consider a potential delay when a component changes state, and consider any additional transitions that could occur if the changing component is in an intermediate state. It can be modeled as additional dynamic states “increase” ($\nearrow$) and “decrease” ($\searrow$): when a component can be activated, it will first go through the “increase” state where it can be interpreted as either 0 or 1 by the other components, until eventually reaching the Boolean 1 state. With the previous example, starting from 000, the first component is put as increasing, thus going to the MP configuration $\nearrow\nearrow00$. In this configuration, 2 can be activated because $\nearrow$ can be interpreted as 1, leading to $\nearrow\nearrow0$. Then, 3 can be activated, as it can interpret the dynamic state of 1 as the Boolean 0, and 2 as the Boolean 1. This model the fact that the component 1 is not high enough for inhibiting 3, while 2 is high enough to activate it. Thus, in this example, there is a trajectory from 000 to 111, i.e., a configuration where all the components are active. As 111 is a fixed point of $f$, the MP analysis would thus conclude that two attractors are reachable from 000: \{110\} and \{111\}.

The MP update mode brings a formal abstraction property to BN dynamics with respect to quantitative models, without requiring additional parameters: essentially, MPBNs capture any behavior that is achievable by any quantitative model being compatible with the logic of the BN. This include, for instance, models which result from introducing quantitative parameters, such as transition speed and interaction thresholds. We give here a brief informal overview of the property (see [8] for details): let us consider multivalued networks (MNs) of dimension $n$ where components can have values in $M = \{0, \ldots, m\}$ for some $m \in \mathbb{N}_{>0}$. A MN can be considered as map from multivalued configurations to the derivative of the value of the components, i.e., of the form $F : M^n \rightarrow \{-1, 0, 1\}$. A multivalued configuration $z \in M^n$ can be binarized by associating components with value 0 to the Boolean state 0, components with value $m$ to the Boolean state 1, and other components to any Boolean state. A MN $F$ is a refinement of a BN $f$ whenever for any multivalued configuration $z$ and for each component $i$, if component $i$ increases (resp. decreases), i.e., $F_i(z) > 0$ (resp. $F_i(z) < 0$), there exists a binarization of this configuration such that $f_i$ is evaluated to 1 (resp. to 0). Then, for any pair of Boolean configurations $x$ and $y$, if there exists a trajectory from $m \cdot x$ to $m \cdot y$ in the asynchronous dynamics of the MN, there necessarily exists a trajectory from $x$ to $y$ in the MP dynamics of the BN.
Moreover, to any transition computed according the MP update mode, there is refinement of the BN which realizes it. One of the major consequences of the abstraction property is that if a configuration is not reachable from another with the MP update mode, then no quantitative models being compatible with the BN can produce the trajectory. In addition, the MP mode has a lower computational complexity for computing reachability and attractor properties, enabling formal analysis of genome-scale BNs [8,10].

However, the simulation of MPBNs, i.e., the sampling of transitions following the MP update mode, has not been addressed so far. Thus, besides computing Boolean properties, such as the existence or absence of reachable attractors, there is no algorithm nor tools to approach the effect of a mutation on the propensities to reach attractors, as we mentioned above with asynchronous BNs.

In this paper, we present a first algorithm for sampling trajectories of BNs with the MP update mode, subject to additional simulation parameters for assigning probabilities to the transitions. The MP transitions enabled from a single configuration are computed iteratively, and we refer to the number of times this iteration is performed as the depth of the MP computation. At depth 1, the transitions match with the asynchronous update mode, but further depths bring additional behaviors. These iterations capture possibly different time scales: while component 1 is changing (depth 1), 2 can change (depth 2); then while 2 is changing, 3 can change (depth 3), etc. In our simulation algorithm, the probability of a transition can be affected by its depth and the number of components it changes simultaneously. Thus, similarly to [6,14] with the fully-asynchronous mode, our sampling of trajectories can be assimilated to a random walk in the MP dynamics, where the probability of transitions can be tuned with the simulation parameters. As we will show on case studies, the MP interpretation can lead to drastic changes in the predicted probabilities of reachable attractors, enabling assessing the robustness of prediction to the heterogeneity of time scales and concentration scales in the quantitative system captured by the discrete MP dynamics. Nevertheless, the simulation parameters and derived transition probabilities are empirical and cannot be formally related to a putative abstracted system.

2 Background

2.1 Boolean networks and dynamics

A **Boolean network** (BN) of dimension \( n \) is a function \( f : \mathbb{B}^n \to \mathbb{B}^n \), with \( \mathbb{B} = \{0,1\} \). For each \( i \in \{1, \ldots, n\} \), \( f_i : \mathbb{B}^n \to \mathbb{B} \) is the **local function** of component \( i \). The Boolean vectors \( x \in \mathbb{B}^n \) are the **configurations** of \( f \), where for each \( i \in \{1, \ldots, n\} \), \( x_i \) is the state of \( i \). Given two configurations \( x, y \in \mathbb{B}^n \), the components having a different state are noted \( \Delta(x,y) = \{ i \in \{1, \ldots, n\} \mid x_i \neq y_i \} \).

The **influence graph** \( G(f) \) of a BN \( f \) is a signed digraph whose nodes are the components and edges mark the dependencies between them in the local functions: for all \( i, j \in \{1, \ldots, n\} \), there is an edge \( i \xrightarrow{s} j \) in \( G(f) \) with \( s \in \).
\{ -1, +1 \} if and only if there exists a configuration $x \in \mathbb{B}^n$ with $x_i = 0$ such that $s = f_j(x_1, \ldots, x_{i-1}, 1, x_{i+1}, \ldots, x_n) - f_j(x)$: the sole increasing of component $i$ causes $f_j$ to increase ($s = +1$) or decrease ($s = -1$). Note there may exist $i$ and $j$ so that both $i \xrightarrow{+1} j$ and $i \xrightarrow{-1} j$ are in $G(f)$, for instance with $f_j(x) = x_i \text{xor} \ x_k$.

A BN $f$ is locally monotone whenever there is no $i, j \in \{1, \ldots, n\}$ such that both $i \xrightarrow{+1} j$ and $i \xrightarrow{-1} j$ are in $G(f)$, i.e., each of its local function is unate. Computing $G(f)$ is a DP-complete problem (both in NP and coNP) [3]. For the example BN $f$ of Eq.(A), $G(f) = \{1 \xrightarrow{+1} 2, 1 \xrightarrow{-1} 3, 2 \xrightarrow{+1} 3, 3 \xrightarrow{-1} 3\}$: it is locally monotone.

An update mode $\mu$ of $f$ specifies a binary transition relation between configurations $\rightarrow_\mu \subseteq \mathbb{B}^n \times \mathbb{B}^n$. Classical update modes include the synchronous (or parallel) update mode where $x \rightarrow_s y$ iff $x \neq y$ and $y = f(x)$; the fully-asynchronous update mode where $x \rightarrow_a y$ iff $x$ and $y$ differ on only one component $i$ and $y_i = f_i(x)$; and the (general) asynchronous update mode where $x \rightarrow_g y$ iff $x \neq y$ and for each component $i \in \Delta(x, y)$, $y_i = f_i(x)$.

Given an update mode $\mu$, a configuration $y \in \mathbb{B}^n$ is reachable from a configuration $x \in \mathbb{B}^n$, noted $x \rightarrow_\mu y$, if and only if either $x = y$ or there exists a sequence of transitions $x \rightarrow_\mu \cdots \rightarrow_\mu y$. A non-empty set of configurations $A \subseteq \mathbb{B}^n$ is an attractor if and only if for each pair of configurations $x, y \in A$, $y$ is reachable from $x$, and there is no configuration $z \in \mathbb{B}^n \setminus A$ that is reachable by a configuration in $A$. Remark that attractors are the bottom strongly connected components of the digraph $(\mathbb{B}^n, \rightarrow_\mu)$. Whenever $A$ is a singleton configuration $\{x\}$, it is said to be a fixed point of the dynamics. Otherwise, $A$ is a cyclic attractor. In the case of (a)synchronous and MP update modes, the fixed points of the dynamics match exactly with the fixed points of $f$, i.e., the configurations $x \in \mathbb{B}^n$ such that $f(x) = x$. Finally, the strong basin of an attractor $A$ is the set of configurations that can reach $A$ and no other distinct attractor.

Fig. 1 shows the transitions computed with the above defined update modes with the BN $f$ defined as follows:

\[
\begin{align*}
f_1(x) &= x_1 \land \neg x_3 & f_2(x) &= x_1 & f_3(x) &= \neg x_1
\end{align*}
\]

This model has two attractors, being fixed points 001 and 110. With the syn-

![Fig. 1. Transitions of the BN (B) from the configuration 111 with different modes](image-url)
chronous mode, only 001 is reachable from 111, whereas both are reachable with the asynchronous modes.

2.2 Sub-hypercubes and closures

The MP update mode and the algorithm presented in this paper gravitate around the notion of sub-hypercube of $\mathbb{B}^n$ and their partial closure by $f$.

A Boolean sub-hypercube of dimension $n$ is specified by a vector in $\{0, 1, *\}^n$, where components having value $*$ are said free, otherwise they are fixed. The number of free components in a sub-hypercube $h \in \{0, 1, *\}^n$ is denoted by $\text{rank}(h) = |\{i \in \{1, \ldots, n\} \mid h_i = *\}|$. A sub-hypercube $h$ has $2^{\text{rank}(h)}$ vertices, denoted by $c(h) = \{x \in \mathbb{B}^n \mid \forall i \in \{1, \ldots, n\}, h_i \in \mathbb{B} \Rightarrow x_i = h_i\}$. A sub-hypercube $h' \in \{0, 1, *\}^n$ is smaller than a sub-hypercube $h \in \{0, 1, *\}^n$ whenever for each $i \in \{1, \ldots, n\}$ fixed in $h$ ($h_i \in \mathbb{B}$), it is fixed to the value in $h'$ ($h'_i = h_i$). Then, remark that $c(h') \subseteq c(h)$.

A sub-hypercube $h$ is closed by a BN $f$ if the result of $f$ applied to any of its vertices is one of its vertices: $\forall x \in c(h), f(x) \in c(h)$; it is also known as a trap space. Given components $K \subseteq \{1, \ldots, n\}$, $h$ is $K$-closed by $f$ whenever, for each component $i \in K$, either $i$ is free in $h$, or $f_i$ applied on any vertices of $h$ results in the fixed value $h_i$. In other words, for all configurations in the $K$-closed sub-hypercube $h$, the next states of the components $i \in K$ are in $h$:

$$\forall x \in c(h), \forall i \in K, h_i \neq * \Rightarrow f_i(x) = h_i.$$  

Let us consider the BN $f$ defined in (B). The sub-hypercube $h = 0 \ast \ast$ is closed by $f$, where $c(0 \ast \ast) = \{000, 010, 001, 011\}$. This trap space indicates that component 1 can never get activated once deactivated. The sub-hypercube $h = 0 \ast 1$ is $\{1, 2\}$-closed by $f$ as $f_1(001) = f_1(011) = 0$. Sub-hypercubes $1 \ast 0$ and $\ast \ast 0$ are also $\{1, 2\}$-closed by $f$, where $1 \ast 0$ is smaller than $\ast \ast 0$. In contrast, $1 \ast 1$ is not $\{1, 2\}$-closed by $f$.

2.3 The Most Permissive update mode

Whenever a component changes state, e.g., increases from its minimal value 0 to its maximal value 1, the MP mode captures any behavior that could arise in the course of this change. For example, it may be that at some point, the component becomes high enough to activate one of its targets, whereas it remains not high enough to activate another one (because it has not reached its maximal value yet). These dynamic states can be captured by sub-hypercubes, where the changing components are free: they can be read both as 0 or 1.

Formally, the MP update mode can be defined as follows. Given a set of components $K \subseteq \{1, \ldots, n\}$, let us denote by $h^{(x,K)}$ the smallest sub-hypercube of dimension $n$ that contains $x$ and that is $K$-closed by $f$. There is an MP transition from $x$ to $y$ whenever (a) $y$ is a vertex of $h^{(x,K)}$, and (b) the new state of all the components in $K$ can be computed from $h^{(x,K)}$:

$$\forall x, y \in \mathbb{B}^n, \quad x \rightarrow_{\text{MP}} y \iff \exists K \subseteq \{1, \ldots, n\} : y \in c(h^{(x,K)}) \land \forall i \in K, \exists z \in c(h^{(x,K)}) : y_i = f_i(z).$$  

(2)
The abstraction properties and complexity results are detailed in [8]. One can remark that the transition and reachability relations are identical: $y$ is reachable from $x$ if and only if $x \rightarrow_{\text{MP}} y$.

As this formalism serves as the cornerstone for the simulation algorithm, let us illustrate it by using the BN (A). Fig. 2 depicts the smallest sub-hypercubes with respect to a configuration $x$ and a set $K$. Bold configurations belong to $h^{(x,K)}$ and those satisfying reachability condition (b) are boxed. The left side focuses on the initial configuration 001 and shows an iterative computation of $h^{(001,K)}$ from $K = \emptyset$ to $K = \{1, 2, 3\}$. As component 1 can flip in configuration 001, one obtains $h^{(001,\{1\})} = \ast 01$. If component 1 is active, component 2 can flip, leading to $h^{(001,\{1,2\})} = \ast \ast 1$. For all configurations $z \in c(h^{(001,\{1,2\})})$, component 3 stays active: $f_3(z) = 1$. Hence, one obtains $h^{(001,\{1,2,3\})} = \ast \ast 1$.

Here, some reachable configurations from $x$ can be deduced. For instance, transitions 001 $\rightarrow_{\text{MP}}$ 101 and 001 $\rightarrow_{\text{MP}}$ 111 exist because reachability properties (a) and (b) are verified. However, 000 and 011 do not verify properties (a) and (b) respectively. Multiple sub-hypercubes may be required to capture all the MP transitions. This is illustrated in Fig. 2 on the right side with the configuration 011. The sub-hypercube $h^{(011,\{1,2,3\})}$ does not capture the transition to 001 because property (b) is not satisfied, while $h^{(011,\{2,3\})}$ does.
3 Simulation algorithm

3.1 Main principle

In its basic formal definition (2), the MP update mode defines the possible next configurations by considering all the subsets of components \( K \subseteq \{1, \ldots, n\} \) and compute the associated sub-hypercube \( h^{(x,K)}_i \), that is the smallest \( K \)-closed sub-hypercube containing \( x \). However, part of these subsets may be redundant. Let \( H \) be the components free in \( h^{(x,K)}_i \) (3). By the minimality of \( h^{(x,K)}_i \), it means that for each component \( i \in H \), there exists a configuration \( y \in c(h^{(x,K)}_i) \) such that \( f_i(y) \neq x_i \). The set \( H \) can then be split in two: the components \( J \) for which their local function can be evaluated both to 0 and 1 from the configurations \( \bar{h}^{(x,K)}_i \), and the components \( L \) for which their local function is always evaluated to \( \neg x_i \) from any of the configurations of \( h^{(x,K)}_i \):

\[
H = \left\{ i \in K \mid h^{(x,K)}_i = * \right\}, \tag{3}
\]
\[
J = \left\{ i \in H \mid \exists y, z \in c(h^{(x,K)}_i) : f_i(y) = 0 \land f_i(z) = 1 \right\}, \tag{4}
\]
\[
L = \left\{ i \in H \mid \forall y \in c(h^{(x,K)}_i) : f_i(y) \neq x_i \right\}. \tag{5}
\]

We have \( H = J \cup L \) and \( J \cap L = \emptyset \). Then, remark that in (2), for a fixed \( x \) and \( K \), there exists an MP transition \( x \rightarrow_{MP} y \) if and only if \( L \subseteq \Delta(x,y) \subseteq H \). Indeed, for each component \( i \in \{1, \ldots, n\} \), if \( y_i \neq x_i \) then necessarily \( i \in H \). Moreover, if \( i \in L \), the second condition of (2) imposes that \( y_i = \neg x_i \).

Whenever \( L = \emptyset \), it results that for any strict subset \( K' \subsetneq K \), the transitions generated from the sub-hypercube \( h^{(x,K')} \) form a (strict) subset of transitions generated from \( h^{(x,K)} \); the set of free components is a (strict) subset of \( H \). Therefore, it is useless to explore any subset of \( K \).

Whenever \( L \neq \emptyset \), by the \( K \)-closeness property of \( h^{(x,K)}_i \), changing the state of a component \( i \in L \) would be irreversible while updating only components in \( K \). Let us illustrate it by using the previous example without the \( \forall x_3 \) part: \( f(x) = (1, x_1, \neg x_1 \land x_2) \). With the initial configuration \( x = 001 \), one can obtain the sub-hypercube \( h^{(001,\{1,2,3\})} = *** \), \( L = \{1\} \) and \( J = \{2,3\} \). \( L = \{1\} \) means that component 1 cannot return to its initial state when it has begun to flip. Moreover, by the definition of MP transitions, all the components in \( L \) are modified. Therefore, whenever \( L \) is not empty, one should consider all the sub-hypercubes \( h^{(x,K')} \) with \( (H \setminus L) \subseteq K' \subseteq H \), to account for all these potential dependencies. Let us consider \( K' = H \setminus L = \{2,3\} \) in the previous example. One can obtain \( h^{(001,\{2,3\})} = 00* \) and \( L = \{3\} \), which allows discovering a new transition: \( 001 \rightarrow_{MP} 000 \).

This approach leads us to compute a set of sub-hypercubes \( h^{(x,K)}_i \) from subsets \( K \) of \( \{1, \ldots, n\} \), and where each of them can be characterized by a triplet \( (x,H,L) \) to which we refer to as a space. Each space \( (x,H,L) \) characterizes a set of MP transitions from \( x \) where the state of all the components in \( L \) is flipped, as well as any subset of components in \( H \setminus L \): the transitions \( x \rightarrow_{MP} y \) with \( L \subseteq \Delta(x,y) \subseteq H \). In our algorithm, the set of transitions generated by a space
is never enumerated explicitly, as it is exponential in $|H \setminus L|$. Instead, we count the number of transitions changing $m$ components, from $m = |L|$ (or 1 whenever $L$ is empty) to $|H|$, i.e., the binomial coefficient $\binom{|H \setminus L|}{m - |L|}$.

Overall, the sampling of the configuration following $x$ can be summarized with the following steps:

1. compute a set of spaces $S = \{(x, H^1, L^1), \ldots, (x, H^q, L^q)\}$, corresponding to the sub-hypercubes $\{h^{(x,K^1)}, \ldots, h^{(x,K^q)}\}$: starting with $K^1 = \{1, \ldots, n\}$, we consider the sub-hypercubes closed along $K^1 \setminus \ell$ with each $\ell \subseteq L^1$, and recursively (thus whenever $L^1 = \emptyset$, $q = 1$).
2. for each space, count the number of transitions it can generate per number of changing components;
3. generate one random number to select the space $(x, H, L)$ and the number $m$ of components to flip;
4. randomly select $m - |L|$ components in $H \setminus L$, let us denote by $C$ these chosen components;
5. flip the state of the components in $L \cup C$.

The size of sets $H$ and $L$ is at most $n$. However, the number of spaces $q$ can be exponential with $n$ in the worst case.

Now, let us focus on the computation of $h^{(x,K)}$, the smallest sub-hypercube containing $x$ and $K$-closed by $f$. The main principle is to start from the sub-hypercube of rank 0 with $x$ as the sole vertex, and iteratively free components to fulfill the $K$-closure property. To do so, we collect the set of components (among $K$) which can flip of state from at least one vertex of the sub-hypercube: for each $i \in K$, if there exists a vertex $y$ of the sub-hypercube such that $f_i(y) \neq x_i$, then $i$ must be free to verify the closeness property. This process is then repeated until the $K$-closeness property is verified, which in the worst case may require $n$ iterations. It appears that the transitions generated by the asynchronous update mode match with the components marked as free in the first iteration only: the components $i \in \{1, \ldots, n\}$ such that $f_i(x) \neq x_i$. Thus, the additional transitions brought by the MP update mode are discovered in the later iterations only. This highlights the concept of permissive depth we introduce in this paper: the number of iterations in the computation of $h^{(x,K)}$ required to discover an MP transition. A depth of 1 corresponds to the asynchronous transitions, while a depth of $n$ corresponds to the full MP dynamics. The simulation algorithm we propose in this paper allows controlling the depth of MP transitions, for instance by following a probabilistic distribution.

### 3.2 Algorithm

Listings 1 and 2 detail the steps for computing the reachable spaces and sampling the next configurations from them, as sketched in the previous section. In the description of the algorithms, we assumed fixed (1) a BN $f$ of dimension $n$; (2) a function $\text{depth}$ to determine the depth threshold for computing the sub-hypercubes (it has to be an integer between 1 and $n$). For instance, it can be
Listing 1. Computation of reachable spaces with the MP update mode

def can_flip(x: configuration, i: index, H: index set, v: bool):
    # assumes f is locally monotone
    if v == 1:
        z = min_configuration(x, i, H)
    else:
        z = max_configuration(x, i, H)
    return f[i](z) != v

def spread(x: configuration, K: index set, d: depth):
    # returns subset of K that can flip within the given depth
    H = {}
    repeat d times:
        H = H ∪ {i for i in K if can_flip(x, i, H, x[i])}
        K = K \ H
    return H

def irreversible(x: configuration, H: index set):
    # returns subset of H that cannot flip back
    return {i for i in H if not can_flip(x, i, H, 1-x[i])}

def reachable_spaces(x: configuration):
    d = depth()
    S = []  # map of index set → (index set, index set)
    K = {1, ..., n}
    Q = {K}
    while Q is not empty:
        K = Q.pop()
        H = spread(x, K, d)  # H is subset of K
        L = irreversible(x, H) if d > 1 else {}  # L is subset of H
        for each M non-empty subset of L:
            J = K \ M
            if J not in S and J not in Q:
                Q.push(J)
        S[K] = (H, L)
    return S

a constant, or a sampling from a discrete distribution; (3) a weighting vector $W \in \mathbb{R}^n_0; W_m$ is the sampling of a transition modifying the state of $m$ components simultaneously. A uniform random walk along MP transitions is thus obtained with $W = 1_n$ and $d = n$.

The spread function computes the $K$-closure of the sub-hypercube starting from the configuration $x$ and stops after $d$ iterations, $d$ being a given depth. Determining whether the component $i$ can change state requires determining the existence of a vertex $z$ of the sub-hypercube such that $f_i(z) \neq x_i$. This is an
**Listing 2.** Sampling of the next configurations with the MP update mode

```python
def sample_next_configuration(x: configuration):
    S = reachable_spaces(x)
    if |S| = 0: return x  # fixed point
    # compute apparent rate of transitions
    R = 0(len(S), n)  # len(S)*n zero-filled matrix
    for i = 1 to len(S):
        if |L| > 0:
            R[i, |L|] = |L| * W[|L|]
        for j = 1 to |H \ L|:
            R[i, |L|+j] = binom(|H \ L|, j) * W[|L|+j]
    r = U[0, sum(R)]  # uniform sampling between 0 and sum(R) excluded
    s, m = where(cumsum(R) > r)  # s = space, m = nb of components to flip
    H, L = S[s]
    C = L \ random.sample(H \ L, m - |L|)
    y = copy(x)
    y[C] = 1 - y[C]
    return y
```

instance of the classical Boolean satisfiability (SAT) problem, which, in general, is NP-complete.

The given algorithm makes the assumption that the BN $f$ is locally monotone. In that case, given a sub-hypercube $h$, one can build in linear time from the influence graph $G(f)$ a configuration $x^\text{min} \in c(h)$ so that $f_i(x^\text{min}) = \min\{f_i(x) \mid x \in c(h)\}$: the idea is that for each component $j$ free in $h$, if $j$ has a positive (monotone) influence on $i$ (i.e., $j \xrightarrow{+1} i \in G(f)$), then $x^\text{min}_j = 0$; if it has a negative influence on $i$, then $x^\text{min}_j = 1$. If $j$ has no influence on $i$, its state in $x^\text{min}$ can be arbitrary. A similar reasoning can be applied to compute a configuration $x^\text{max} \in c(h)$ so that $f_i(x^\text{max}) = \max\{f_i(x) \mid x \in c(h)\}$. Then, one can decide in linear time whether $i$ can change state in $x$ in the scope of the sub-hypercube $h$: if $x_i$ is 1, then $f_i(x^\text{min})$ must be 0, and if $x_i$ is 0, then $f_i(x^\text{max})$ must be 1. Without this assumption, the `can_flip` function should be replaced with a call to a SAT solver.

### 3.3 Correctness, complexity, and parametrization

The sampling of the next configuration is driven by two parameters: a distribution over permissive depth, and a weight $W \in \mathbb{R}_{\geq 0}$ for transitions depending on the number of components they flip. These parameters can affect the generated dynamics and the complexity of the sampling.

**General case: full MP dynamics.** Let us assume that the depth function can always return $n$ (either it is a constant function returning $n$, or the returned values follow a discrete distribution where the probability of drawing $n$ is not
0), and that \( W \in \mathbb{R}_{>0}^n \). Then, any MP transition has a non-zero probability to be sampled.

Given a space \((x, H, L)\), as computed by \texttt{reachable\_spaces} and characterized by a configuration \(x\), a set \(H \subseteq \{1, \ldots, n\}\) of free components, and a subset \(L \subseteq H\) of irreversible components, let us denote by \(\text{tr}(x, H, L)\) the set of candidate next configurations considered by \texttt{sample\_next\_configuration}:

\[
\text{tr}(x, H, L) = \{ y \in \mathbb{B}^n \mid L \subseteq \Delta(x, y) \subseteq H \}.
\]

We prove that the set of transitions the algorithm can generate from the computed spaces is equal to the full MP dynamics, except self-loops (Lemma 1), and that spaces generate disjoint sets of transitions (Lemma 2).

**Lemma 1.** Given a BN \( f \) of dimension \(n\) and one of its configuration \(x \in \mathbb{B}^n\), and denoting by \(S\) the set of spaces returned by \texttt{reachable\_spaces}(\(x\)) function,

\[
\bigcup_{(x, H, L) \in S} \text{tr}(x, H, L) = \{ y \mid x \rightarrow_{\text{MP}} y, x \neq y \}.
\]

**Lemma 2.** Given a BN \( f \) of dimension \(n\) and one of its configuration \(x \in \mathbb{B}^n\), and denoting by \(S\) the set of spaces returned by \texttt{reachable\_spaces}(\(x\)), for any distinct pair of spaces \((x, H, L)\), \((x', H', L') \in S\), \(\text{tr}(x, H, L) \cap \text{tr}(x', H', L') = \emptyset\).

Proofs are given in Appendix A.

**Worst-case complexity.** Assuming locally-monotone BNs, \texttt{can\_flip} is performed in linear time (we assume the influence graph \(G(f)\) is given); \texttt{spread} makes in the worst case \(n^2\) call to \texttt{can\_flip}, resulting in a cubic time in \(n\); whereas \texttt{irreversible} is quadratic in \(n\). Function \texttt{reachable\_spaces} can then generate an exponential number of spaces. The sampling is then linear with respect to the number of spaces generated, and linear with respect to \(n\). In the non-monotone case, \texttt{can\_flip} is an NP-complete problem which currently can be solved in exponential time and space with SAT solvers.

**Unitary depth: asynchronous and fully-asynchronous dynamics** Let us consider the case whenever \texttt{depth} function always returns 1. The algorithm computes only one space \((x, H, L = \emptyset)\) with \(H\) being the set of components \(i\) such that \(f_i(x) \neq x\), and can generate any transition to \(y \neq x\) where \(\Delta(x, y) \subseteq H\). This corresponds exactly to the (general) asynchronous dynamics \(\rightarrow_{g}\) assuming \(W \in \mathbb{R}_{>0}^n\). Moreover, as only one space is computed, the complexity drops to being linear in \(n\), without any assumption on the local-monotony of \(f\).

Finally, whenever \(W_1 > 0\) and for all \(m \in \{2, \ldots, n\}\), \(W_m = 0\), only transitions modifying one component are generated, matching exactly with the fully-asynchronous dynamics \(\rightarrow_{a}\) with equiprobable transitions, and with complexity similar to the previous restriction.
### Listing 3. Algorithms for sampling a reachable attractor with the MP update mode

```python
def sample_reachable_attractor(x: configuration):
    stop = False
    while not stop:
        x = sample_next_configuration(x)
        every k iterations:  # no need to verify at each step
            if in_attractor(x):
                stop = True
        A = reachable_attractors(x)
        return A[1]  # A contains only one element

def filter_reachable_attractors(A: sub-hypercube list, x: configuration):
    H = spread(x, {1,...,n}, n)
    return [a for a in A if a ⪯ x/H]  # a is smaller than the sub-hypercube formed by x and H

def sample_reachable_attractor_bis(x: configuration):
    A = reachable_attractors(x)  # list of attractors
    while len(A) > 1:
        x = sample_next_configuration(x)
        every k iterations:  # no need to verify at each step
            A = filter_reachable_attractors(A, x)
    return A[1]  # A contains only one element
```

### 3.4 Sampling reachable attractors

The simulation of BNs is typically employed to assess the probability of reaching the different attractors. Because determining whether a configuration belongs to a cyclic attractor is a PSPACE-complete problem with (a)synchronous update modes [8], most simulation algorithms are parametrized with a maximum number of steps to sample, without guarantee that an attractor has been reached.

In the case of the MP update mode, the attractors turn out to be exactly the smallest closed sub-hypercubes (minimal trap spaces) of f, which can be computed at a much lower cost, albeit still relying on SAT solving [8]. Thus, instead of fixing an arbitrary number of simulation steps, one can verify during the simulation whether the current configuration belongs to an attractor, and stop the sampling in that case. (sample_reachable_attractor of Listing 3).

In practice, the number of attractors reachable from a fixed initial configuration is usually small, and can be efficiently enumerated with the MP update mode, for instance using the mpbn tool [8]. In that case, the MP simulations can be employed to estimate the probability of reaching the different attractors depending on the depth and weight parameters. We then proceed as follows. Before simulating, we first compute the full set of attractors reachable from the initial configuration x. This set is then progressively refined during the simulation by removing attractors which are no longer included in \( h(x,\{1,...,n\}) \). The simulation

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1 https://github.com/bnediction/mpbn
can then stop as soon as only one attractor can be reached, i.e., the current configuration is in the strong basin of an attractor (sample_reachable_attractor_bis of Listing 3).

These two schemes assume that the full MP dynamics is sampled, or that the attractors of the sampled dynamics match with the MP attractors as follows: each MP attractor is a superset of one and only one attractor of the sampled dynamics, and each attractor of the sampled dynamics is a subset of one and only one MP attractor. This is always the case for BNs having no cyclic attractors.

4 Evaluation

Using a prototype written in Python\(^2\), we demonstrate the applicability of MP simulation on several Boolean models from the literature comprising about thirty components. After an illustration on toy examples, we study the effect of the parametrization on the assessment of the robustness of mutations impacting the propensities of reachable attractors in those models.

Our MP simulation algorithm has two parameters: the permissive depth and the weight of transitions \(W\) depending on the number of binary state changes. For the permissive depth, we will consider the constant \(n\) (full MP dynamics), constant 1 (asynchronous dynamics), and random sampling from a discrete exponentially decreasing distribution: depth \(d\) has probability \(1/(2^d.M)\) with \(M = \sum_{i=1}^{n} 1/2^i\) the normalization factor. As depth \(n\) has a non-zero probability, this parametrization also enables the full MP dynamics, although largely prioritize transitions from low permissive depths. Regarding \(W\), we will consider the uniform weight \(1/n\) (random walk), and one-change only \(1_{n-1}\).

4.1 Toy examples

Let us first consider the bi-stable example (A) from the configuration \(000\). This BN has two fixed points: \(110\) and \(111\). As explained in Sect. 1, the (a)synchronous dynamics from \(000\) predicts only one trajectory: \(000 \rightarrow g 100 \rightarrow g 110\). Thus, only one attractor is reachable (100% propensity). The MP dynamics uncovers another reachable attractor (111), as depicted in Fig. 3(left). Considering all the transitions, the MP simulation would conclude that the reachability of these two attractors are equiprobable: from the 4 initial transitions, 2 lead to the strong basin of \(110\) and two to the strong basin of \(111\). Whenever the depth is a random variable with an exponentially decreasing distribution, reaching 111 requires drawing a depth of 3 (probability of 1/7), leading to reaching 111 with probability 1/14, and 110 with probability 13/14. This indicates the sensitivity of the reachability of 111 to the permissive depth, and thus to the time scales of the underlying quantitative model.

Let us now consider the example (B) where the two attractors reachable with the asynchronous mode (Fig. 1(c)) are identical to ones reachable with MP

\(^2\) https://github.com/bnediction/mpbn-sim
Fig. 3. MP transitions of BN (A) from configuration 000 (left) and of BN (B) from configuration 111 (right). Plain transitions have permissive depth 1, dashed depth 2, and dotted depth 3.

mode (Fig. 3(right)). In fully-asynchronous mode, they have an equal propensity, however in the (general) asynchronous mode, 001 propensity is twice the one of 110. Whereas the MP dynamics uncover additional trajectories and reachable configurations, in this particular example, the propensities of attractors is the same as with the general asynchronous case.

An important aspect of MP dynamics is that it is transitive: any state reachable in a sequence of transitions is reachable in one transition. Thus, the size of the (reachable) strong basins of attractors can contribute significantly to their propensities. In the above two examples, the propensities of the attractors in MP uniform random walk is entirely determined by the size of their basins.

It should be also stressed that the parameters for determining the transition probabilities are usually arbitrary. Thus, analyzing the impact of parameters on the probability of reaching the different attractors by a random walk in the MP dynamics may only give an empirical insight on the Boolean dynamics, and cannot be formally transferred to an associated quantitative model.

4.2 Models from literature with different mutation conditions

From the literature, we selected BNs modeling cell fate decision processes: the reduced cell death receptor model [1] with 14 components; the tumor invasion model [2] with 32 components; and the bladder model [11] with 35 components. These models have been designed with the fully-asynchronous update mode, and have been evaluated with respect to their ability to predict the changes of the attractors propensities subject to different mutation conditions (modeled by forcing some components to some state). For each model, we performed 10,000 simulations from the relevant initial configurations and for several mutation conditions, with different simulation parameters. With our prototype, the computational cost of the permissive depth is substantial, the simulations being between 3 times to 50 times slower than with depth 1 only, depending on
### Fig. 4.
Estimated propensities of reachable attractors from a unique configuration of the tumor invasion model in two mutation conditions (no mutation; p53 forced to 0), and different simulation parameters.

| Model Configuration | Wild Type | p53 LoF |
|---------------------|-----------|---------|
| Depth = 1, $W = 10^n$ | 97.5% 2.5% | 60.9% 39.1% |
| Depth = 1, $W = 1^n$ | 96.7% 3.3% | 87.3% 12.7% |
| Depth $\sim n\exp(n)$, $W = 1^n$ | 79.7% 20.3% | 86.2% 13.8% |
| Depth = 1, $W = 1^{0.1n-1}$ | 76.0% 24.0% | 50.7% 49.3% |

The number of reachable spaces computed at each simulation step. However, no particular optimization has been implemented.

Fig. 4 gives an example of the estimated propensities of attractors reachable from a unique initial configuration of the tumor invasion model with different mutation conditions and parameters. On the one hand, we can observe that the permissive depth can change drastically the proportions of reachable attractors: there are much more paths to the Metastasis attractor when considering potential time scale heterogeneity. The difference can be reduced by still considering the full MP dynamics, but giving exponentially decreasing probability to transitions with high permissive depth (computing transitions at depth at least $D$ is done with probability $\sum_{d=D}^{n} (2^d \cdot \sum_{i=1}^{n} 2^{-i})^{-1}$, with $n$ the number of nodes in the model, 32 in this case). On the other hand, the qualitative effect of the p53 mutation is similar whenever analyzed only with the asynchronous simulations (permissive depth = 1), or in the most permissive cases: the propensity of the Metastasis attractor is larger in the mutant.

From a global analysis on the 3 models\(^3\), we observe that the absolute value of the propensities of the reachable attractors changes substantially when considering MP dynamics, in particular with depth fixed to $n$ and uniform transition rates. Variable depth enables reducing the difference with the asynchronous dynamics while giving access to the full MP dynamics. Regarding the effect of mutations, it appears that, in most cases, the propensities of reachable attractors are affected in qualitatively the same direction, with various MP simulation parameters. This may indicate that these perturbations should be robust to heterogeneous time scales in the quantitative models captured by the BN abstraction. On the contrary, perturbations having a different qualitative effect on attractor propensities when considering permissive depth may be sensitive to

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\(^3\) See [https://doi.org/10.5281/zenodo.6725844](https://doi.org/10.5281/zenodo.6725844) for supplementary information
the variety of time scales of the actual system, which could not be captured with usual (a)synchronous modes.

5 Discussion

The simulation of (asynchronous) BNs is a usual task in systems biology applications for assessing the effect of genetic perturbations on the propensities of the different cellular phenotypes. However, it is known that the asynchronous dynamics of BNs can preclude behaviors observed in quantitative systems, which may lead to substantial biases for the aforementioned analysis. On the contrary, the MP update mode ensures the completeness of the Boolean dynamics.

In this paper, we provide a first algorithm to sample trajectories from MP dynamics. The additional transitions predicted by MP come from iterative computations of possible state changes for each component, and where the first iteration corresponds to the asynchronous updates. By parameterizing the depth of this computation, we obtain a generalization of transition sampling from BNs with MP, (general) asynchronous, and fully-asynchronous dynamics. The main bottleneck of the provided algorithm is its potential exponential blow-up when considering all reachable spaces. Further work will address its efficient implementations and approximations.

As illustrated on different models from the literature, the simulation with the MP mode can largely affect predictions, both in terms of reachable attractors, and in terms of their propensities. Because of the transitive properties of MP dynamics (there is a direct transition to any reachable configuration), the attractors having a large (reachable) strong basin will dominate an equiprobable random walk of MP dynamics. Variable-depth simulation can then give more weight to transition with low permissive depth and sooth the effect of the size of the basins while still capturing the full MP dynamics.

It should be noted that, as with usual simulations of asynchronous BNs [6,14], the estimated attractor propensities are purely empirical and do not relate formally to the actual propensities in the modeled quantitative system. Due to its abstraction level, a BN is intrinsically non-deterministic. Assigning probabilities to transitions is a very strong assumption which, in this context, cannot be justified with any modeling or physical principle. At this level of abstraction, the behavior of the modeled system is not a Markov process and cannot be approximated by a Markov process (would the coefficient be fitted on data, for instance).

From a modeling perspective, our algorithm could be extended to have the permissive depth being different among components, enabling to fine-tune the time scale of their updates: the slower components should allow the more permissive depth. This would bring further control over the transitions added by the MP mode, while capturing trajectories precluded by the asynchronous mode.

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A Proofs

A.1 Proof of Lemma 1

Consider any \((x, H, L) \in S\). Let \(h \in \{0, 1, *\}^n\) be the sub-hypercube where dimensions in \(H\) are free, and otherwise fixed as in \(x\): for each \(i \in \{1, \ldots, n\}\), if \(i \in H\), then \(h_i = *\), otherwise, \(h_i = x_i\). In such a configuration \(y\), for each \(i \in H\), there exists a configuration \(z \in \mathcal{c}(h)\) such that \(f_i(z) = y_i\); indeed, if \(y_i = x_i\), then \(i \notin L\). Thus, \(x \to_{\text{MP}} y\) by instantiating Eq. (2) with \(K = H\).

Conversely, let us assume that there exists \(K \subseteq \{1, \ldots, n\}\) leading to \(x \to_{\text{MP}} y\), and let \(H^0\) be the set of free components in \(h^{(x,K)}\) (note that \(\Delta(x, y) \subseteq H^0\)). Let \((x, H^1, L^1)\) be the first space computed by our algorithm (i.e., from \(K = \{1, \ldots, n\}\)). By construction, \(H^1\) is the set of free components in \(h^{(x,\{1,\ldots,n\})}\), thus \(H^0 \subseteq H^1\). Two cases arise: either \(L^1 \subseteq \Delta(x, y)\) and then the transition to \(y\) is generated from this first space, or there exists at least one component \(i \in L^1\) whereas \(x_i = y_i\). Recall that a component \(i\) can be in \(L^1\) only if from each vertex \(z\) of the sub-hypercube \(f_i(z) \neq x_i\). Thus \(K\) is necessarily a strict subset of \(H^1\), excluding at least the component \(i\). Therefore, \(H^0 \subseteq K \subseteq H^1 \setminus \{i \in L^1 \mid x_i = y_i\} = H^2\), and by construction, \((x, H^2, L^2) \in S\) with \(L^2 \subseteq \Delta(x, y)\).

A.2 Proof of Lemma 2

The set of spaces computed by \texttt{reachable_spaces} can be inductively characterized by a map \(S^l\) for some \(l \in \mathbb{N}\) from sets of components \(K\) to their associated sub-hypercube \(h^{(x,K)}\) characterized by \((H, L)\), as defined below (\(x\) being fixed it is omitted):

\[
S^0 = \{\{1, \ldots, n\} \mapsto (H^0, L^0)\} \\
S^{k+1} = S^k \cup \{K \setminus M \mapsto (H', L') \mid K \mapsto (H, L) \in S^k, \emptyset \subsetneq M \subsetneq L\} \\
\text{(8)}
\]

Recall that \(\forall K \mapsto (H, L) \in S^k, L \subseteq H \subseteq K\), and \(\text{tr}(x, H, L) = \{y \in \mathbb{B}^n \mid L \subseteq \Delta(x, y) \subseteq H\}\).

We prove that for any \(k \in \mathbb{N}\), \(\forall K \mapsto (H, L), K' \mapsto (H', L') \in S^k, K \neq K'\),

\[
\text{tr}(x, H, L) \cap \text{tr}(x, H', L') = \emptyset .
\]

Let us first consider the cases whenever \(L \subsetneq H'\) or \(L' \subsetneq H\); by \texttt{tr} definition, \(\text{tr}(x, H, L) \cap \text{tr}(x, H', L') = \emptyset\). Indeed, in the first case, remark that \(\forall y \in \text{tr}(x, H, L), L \setminus H' \subseteq \Delta(x, y)\) while \(\forall y' \in \text{tr}(x, H', L'), (L \setminus H') \cap \Delta(x, y') = \emptyset,\) thus \(y \neq y'\). The second case is a symmetry.

We establish the following propositions:

- (P1) Any component \(i \in \{1, \ldots, n\}\) such that there exists \(K \mapsto (H, L)\) with \(i \in L\) verifies \(f_i(x) = \neg x_i\). Thus, \(\forall K' \mapsto (H', L'), i \in K' \Rightarrow i \in H'\).
- (P2) By definition of \(S^k\), \(K \mapsto (H, L) \in S^k \Rightarrow \forall i \in \{1, \ldots, n\} \setminus K\) there exists \(K' \mapsto (H', L') \in S^{k-1}\) with \(i \in L'\). Thus by P1, \(f_i(x) = \neg x_i\).
(P3) By sub-hypercube $K$-closeness definition and minimality,
\[
\forall K \mapsto (H, L), K' \mapsto (H', L') \in S^k, K' \subseteq K \implies K' \cap L \subseteq L' \subseteq H'.
\]

(P4) for any $K \neq \{1, \ldots, n\}$, $K \mapsto (H, L) \in S^k \setminus S^{k-1} \implies \exists K' \mapsto (H', L') \in S^{k-1}$ with $K \subseteq K'$ and $K' \setminus K \subseteq L' \subseteq H'$ (by P2).

Consider any $K \mapsto (H, L), K' \mapsto (H', L') \in S^k, K \neq K'$, such that both $L \subseteq H'$ and $L' \subseteq H'$. By P4, there exists $K'' \mapsto (H'', L'') \in S^{k-1}$ with $(K \cup K') \subseteq K''$ and such that there exists $i \in L''$ where $i \notin K$ (note: it always work with $K'' = \{1, \ldots, n\}$). If $i \in K'$, then $i \in L'$ (by P3), thus $L' \not\subseteq H$, a contradiction. Thus, $i \notin K'$. By induction using P2 and P4, we obtain that $K' \subseteq K'$. By symmetry (apply the same reasoning by swapping $K$ and $K'$), $K = K'$.

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