ON STABILITY AND CONTROLLABILITY OF CONJUNCTIVE BOOLEAN NETWORKS

BY

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THESIS

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ABSTRACT

A Boolean network (BN) is a finite state discrete time dynamical system. At each step, each variable takes a value from a binary set. The value update rule for each variable is a local function which depends only on a selected subset of variables. BNs have been used in modeling gene regulatory networks. We focus in this thesis on a special class of BNs, termed as *conjunctive Boolean networks* (CBNs). A BN is *conjunctive* if the associated value update rule is comprised of only AND operations.

It is known that any trajectory of a finite dynamical system will enter a periodic orbit. Periodic orbits of a CBN are now completely understood. We first characterize in this thesis all periodic orbits of a CBN. In particular, we establish a bijection between the set of periodic orbits and the set of binary necklaces of a certain length. We further investigate the stability of a periodic orbit. Specifically, we perturb a state in the periodic orbit by changing the value of a single entry of the state. The trajectory, with the perturbed state being the initial condition, will enter another (possibly the same) periodic orbit in finite time steps. We then provide a complete characterization of all such transitions from one periodic orbit to another. In particular, we construct a digraph, with the vertices being the periodic orbits, and the (directed) edges representing the transitions among the orbits. We call such a digraph the stability structure of the CBN.

We then investigate the *orbit-controllability* and *state-controllability* of a CBN. We ask the question of how one can steer a CBN to enter any periodic orbit or to reach any final state, from any initial state. Suppose that there is a selected subset of variables whose values can be controlled for some finite time steps, while other variables still follow the value update rule during all time. We establish in the thesis a necessary and sufficient condition for this subset such that the trajectory, with any initial condition, will enter any desired periodic orbit or reach any final state. We also provide algorithms specifying the methods of manipulating the values of these variables to realize these control goals.

To my grandmother, Jing Li, for her love and support.

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CONTENTS

LIST OF ABBREVIATIONS

BN(s)	Boolean Network(s)
CBN(s)	Conjunctive Boolean Network(s)
DAG	Directed Acyclic Graph
DNA	Deoxyribonucleic Acid
mRNA	Messenger RNA
RNA	Ribonucleic Acid

Chapter 1

INTRODUCTION

1.1 Motivation

One of the central foci of today's genomic research is to study the regulation of gene expressions, i.e., the underlying mechanism used by a cell to execute and control the production of gene products (protein or RNA) [1]. Questions about how to model such a mechanism become more and more relevant and have been studied to some extent. In particular, we note here two different approaches for modeling the interactions among genes in a regulatory network—one is called the "dynamic-system" method and the other is called the "Boolean" method [2]. Specifically, the dynamic-system method uses ordinary differential equations to describe the rates of change of the concentrations of gene products. Yet, the associated differential equations are often quite complex and do not admit explicit solutions. For large-sized gene networks, computer simulation of the evolution of the dynamics usually takes a significant amount of time. The Boolean method, on the other hand, leads to some loss of accuracy due to simplifying the expression status of a gene to a Boolean variable. Such a simplification, however, makes it possible to analyze and simulate the interactions among genes, and hence finds several natural applications (see, for example, λ-bacteriophage circuitry [3]). Our focus in this thesis will be on the Boolean method.

Since the expression process of a gene involves participation of proteins, which are products of some other genes, genes interact with each other through their products [4]. These interactions can then be naturally described by certain types of Boolean functions whose inputs are the previous values of the genes and the outputs are their updated values. Boolean variables, usually labeled as "1" or "0", combined with Boolean functions, comprise a Boolean network (BN), which is a discrete-time dynamical system with a finite state space (finite dynamical system). BNs were originally introduced in [5, 6], later generalized in [7], and have been extensively used in systems biology and (mathematical) computational biology [8–13].

There have been extensive studies of various classes of Boolean functions which are particularly suited to the logical expression of gene regulation [14, 15]. Evidence has been provided in [16] that biochemical networks are "close to monotone". Roughly speaking, a BN is monotonic if its Boolean function has the property that the output value of the function for each variable is non-decreasing if the number of "1"s in the inputs increases. Monotonic BNs have been studied both theoretically [17–20] and in applications [21, 22]. For example, BNs whose Boolean functions are monomials [23–26] are monotonic. For other types of monotonic BNs, we refer the reader to [27–30] and the references therein. Also, there have been studies of BNs with other types of Boolean functions: The work [31] considers the dynamics of systems where the Boolean functions are comprised of semilattice operators, i.e., operators that are commutative, associative, and idempotent. BNs whose Boolean functions are comprised only of XOR operations were investigated in [32], and those whose Boolean functions are comprised of AND and NOT operations were studied in [33, 34]. We also refer to [35–38] for research on BNs whose Boolean functions are randomly generated, known as random Boolean networks, and to [39–41] for research on BNs whose Boolean functions are chosen from a set of functions with probabilities assigned to each function, known as probabilistic Boolean networks.

A special type of monotonic Boolean function, of particular interest to us, is the so-called nested canalyzing function. This class of function was introduced in [42], and was often used to model genetic networks [43, 44]. Roughly speaking, a canalyzing function is one where if an input of the function holds a certain value, called the "canalyzing value", then the output value of the function is uniquely determined regardless of the other values of the inputs [45]. The majority of Boolean functions that appear in the literature on BNs are nested canalyzing functions. Among the nested canalyzing functions, there are two simple but important classes: The first class comprises functions of only AND operations, with "0" being the canalyzing value, while the second class comprises functions of OR operations, with "1" being the canalyzing value. The corresponding BNs are said to be *conjunctive* [26] (resp. *disjunctive*) [26, 46]. Note that there is a natural isomorphism between the class of conjunctive Boolean networks (CBNs) and the class of disjunctive Boolean networks: indeed, if f (resp. g) is a function on n

Boolean variables $x_1, \dots, x_n$, comprising only AND (resp. OR) operations, then

$$f(x_1, \dots, x_n) = \neg g(\neg x_1, \dots, \neg x_n),$$

where "$\neg$" is the negation operator, i.e., $\neg 0 = 1$ and $\neg 1 = 0$. It thus suffices to consider only CBNs. We note here that a conjunctive/disjunctive BN is monotonic.

CBNs constitute an appealing model in systems biology, especially in the study of gene regulation, and have drawn special attention most recently [26, 47–52]. A gene is a portion of the DNA, and in the expression process of a gene, the DNA is first transcribed to mRNA, which is then translated to one or several proteins, called the product of that gene. Since proteins can influence the transcription and translation stages, genes interact with each other through their products. In a CBN, the status of each gene is either "on" or "off", indicating whether it is expressed or not, and is represented by the Boolean variable "1" or "0". Now, consider the situation where the expression process of a gene involves the participation of several proteins, and these proteins can be produced by a selected subset of genes in the network during the previous time step. Then, this gene is expressed if and only if all the genes in the selected subset were expressed in the previous time step. Therefore, the dynamics of a CBN capture a certain aspect of the interactions among the genes while entailing a tractable analysis. We further refer to Fig. 1.1 (originally from [53] and reproduced here) for the validity of CBNs in modeling the process of gene expressions.

1.2 Problem Description and Contribution

We consider in this thesis the stability and controllability issues on CBNs.

1.2.1 Stability

Since a BN is a finite dynamical system, for any initial condition, the trajectory generated by the system will enter a periodic orbit (also known as a limit cycle) in finite time steps (see, for example, [23]). A question that comes up naturally is how the dynamical system behaves if a "perturbation" occurs in a state of a periodic orbit—meaning that one (and only one) of the variables fails to follow the

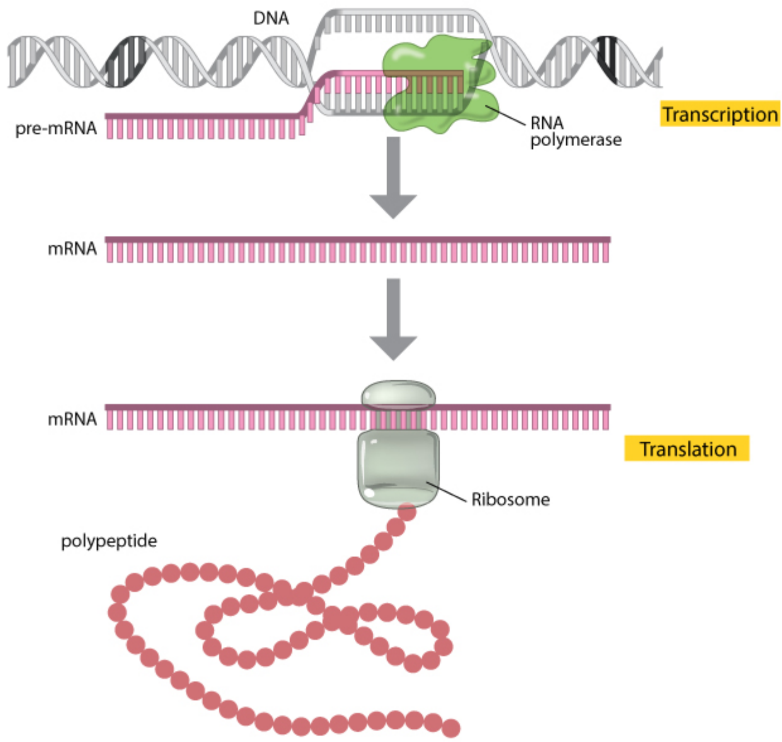

Figure 1.1: This figure, originally from [53], illustrates the expression process of a gene. It can be seen that the transcription stage requires the participation of RNA polymerase, which is essentially a protein. The translation stage involves ribosome, which contains ribosomal proteins. These proteins are all products of some other genes at the previous time steps. Thus, the gene in the figure can be expressed (holding "1") if and only if all other related genes were expressed (holding "1") previously.

update rule for the next time step (a precise definition is given in Section 3.2.2). The trajectory, with the perturbed state as its initial condition, will then enter another periodic orbit (possibly return to the original orbit). One of the questions addressed in this work is thus characterization of all possible transitions among the periodic orbits upon the occurrence of a perturbation. We find this question important because from a biological perspective, we know that most genes are regulated under certain rules. But, in rare cases, the genes may break the rules. Such an occurrence will lead to an unusual expression of a gene or a mutation, which could cause serious diseases.

A complete characterization of these transitions among the periodic orbits is given in Theorem 2, which captures the stability structure of a CBN. The analysis of Theorem 2 relies on a representation of periodic orbits, which identifies the orbits with the so-called binary necklaces (a definition is given in Section 2.2). In particular, we show that there is a bijection between the set of periodic orbits and the set of binary necklaces of a certain length. To establish this bijection, we introduce in Section 3.1 a new approach for analyzing the system behavior of a CBN: Roughly speaking, we decompose the original BN into several components. For each of the components, there corresponds an induced dynamics. We then relate in Theorem 1 the original dynamic to these induced dynamics and establish several necessary and sufficient conditions for a state to be in a periodic orbit. This new approach may be of independent interest as it can be applied to other types of BNs as well.

1.2.2 Controllability

We also address in the thesis the controllability problems of a CBN. Assuming that there is a subset of variables whose values are determined by external inputs (the controls), we ask and answer two questions. First, how can one steer the system from any initial state to any desired periodic orbit? If this is possible, we say that the system is *orbit-controllable* and the subset of variables whose values are determined by external inputs (the controls) is termed the *orbit-controlling set*. Second, how can one make the system *state-controllable*, meaning that the trajectory generated by the control system can be driven into any desired final state (not necessarily a state in a periodic orbit), starting from any initial condition? When the system is state-controllable, the subset of variables is termed the *state-controlling set*. Note that state-controllability is a stronger notion than orbit-controllability, and hence it is more restrictive for a subset to be a state-controlling set than to be an orbit-controlling set. The control problems posed here find their applications in gene regulation, where the objective is to control the expressions of a selected subset of genes so as to steer a bio-system to reach a desired final state (or a periodic orbit) [54–61], and hence to look for criteria for the selection so that the system is controllable.

Reachability and observability for general BNs have been addressed to some extent [62–71]. For example, [69] used a semi-tensor product approach to establish necessary and sufficient conditions for a given final state to be reachable from a given initial state; [70] also addressed the reachability question, but via the Perron−Frobenius theory; [71] studied the controllability (as well as observability) of a Boolean network by looking at the algebraic variety of a certain ideal generated by certain polynomials defined over the finite field $\mathbb{F}_2 = \{0, 1\}$. Most recently, [52] provided a polynomial-time algorithm for solving the minimal observability problem in CBNs. To address the controllability questions, we adopt in this thesis a graphical approach which, to the best of our knowledge, is different from all the other existing methods, thus providing a new perspective. We provide necessary and sufficient conditions for a subset of variables to be an orbit-controlling set (Theorem 3) and a state-controlling set (Theorem 4). Furthermore, explicit control laws for steering the system to a desired periodic orbit (Algorithm 1) or desired final state (Algorithm 2) are also provided. While the ultimate goal is to find an orbit- or state-controlling set with minimal cardinality, the condition we establish in this thesis helps reduce the size of such a set significantly.

1.3 Organizations

This thesis is based on the results of two journal papers [47, 50], with some of the results also appearing in two recent conference papers [48,49]. The rest of the thesis is organized as follows. In Chapter 2, we first provide some basic definitions and notations for directed graphs and the binary necklace. We then introduce the class of conjunctive Boolean networks in precise terms. Some preliminary results on such networks are also given. In Chapter 3, we introduce the new graph decomposition approach as mentioned above, and use that approach to characterize all possible transitions among periodic orbits. Moreover, we associate with each transition a positive real number, termed as transition weight, which can be understood as the likelihood of the occurrence of the transition. In Chapter 4, we raise a two-part controllability question that is answered fully in the chapter and introduce important related concepts. We then establish necessary and sufficient conditions for a CBN to be orbit-controllable (Theorem 3) and state-controllable (Theorem 4). The control procedures are also provided in Algorithms 1 and 2. Chapter 5 summarizes the results on stability and controllability of CBNs and points out future research directions. The thesis ends with an Appendix which contains analyses that are used to support a technical result.

Chapter 2

PRELIMINARIES

2.1 Directed Graph

We introduce here some notations associated with a directed graph (or simply digraph). Let $D = (V, E)$ be a directed graph, with V the set of nodes (vertices) and E the set of edges. We denote by v_iv_j an edge from v_i to v_j in D. We say that v_i is an *in-neighbor* of v_j and v_j is an *out-neighbor* of v_i. The sets of in-neighbors and out-neighbors of node v_i are denoted by $\mathcal{N}_{\text{in}}(v_i)$ and $\mathcal{N}_{\text{out}}(v_i)$, respectively. We write, on occasion, $\mathcal{N}_{\text{in}}(v_i; D)$ (resp. $\mathcal{N}_{\text{out}}(v_i; D)$) to indicate that the in-neighbors (resp. out-neighbors) of v_i are taken within the digraph D. The *in-degree* and *out-degree* of node v_i are defined to be $|\mathcal{N}_{\text{in}}(v_i)|$ and $|\mathcal{N}_{\text{out}}(v_i)|$, respectively. We call v_iv_j an *out-edge* of v_i and an *in-edge* of v_j. We denote by $\mathcal{E}_{\text{in}}(v_i)$ (resp. $\mathcal{E}_{\text{out}}(v_i)$) the set of in-edges (resp. out-edges) of node v_i.

Given a node v_i of V and a nonnegative integer k, we define a subset $\mathcal{N}^k_{\text{out}}(v_i)$ by induction: For $k = 0$, let $\mathcal{N}^0_{\text{out}}(v_i) := \{v_i\}$; for $k \geq 1$, we define

$$\mathcal{N}^k_{\text{out}}(v_i) := \cup_{v_j \in \mathcal{N}^{k-1}_{\text{out}}(v_i)} \mathcal{N}_{\text{out}}(v_j). \tag{2.1}$$

Note that if $\mathcal{N}^{k-1}_{\text{out}}(v_i) = \varnothing$, then $\mathcal{N}^k_{\text{out}}(v_i) = \varnothing$. Similarly, we define $\mathcal{N}^k_{\text{out}}(v_i)$ by replacing $\mathcal{N}_{\text{in}}$ with $\mathcal{N}_{\text{out}}$ in (2.1).

Let v_i and v_j be two nodes of D. A *walk* from v_i to v_j, denoted by w_{ij}, is a sequence $v_{i_0}v_{i_2}\cdots v_{i_m}$ (with $v_{i_0} = v_i$ and $v_{i_m} = v_j$) in which $v_{i_k}v_{i_{k+1}}$ is an edge of D for all $k \in \{0, 1, \ldots, m-1\}$. A walk is said to be a *path*, denoted by p_{ij}, if all the nodes in the walk are pairwise distinct. We use P_{ij} to denote the set of all paths from v_i to v_j. A *closed walk* is a walk w_{ij} such that the starting vertex and ending vertex are the same, i.e., $v_i = v_j$. A walk is said to be a *cycle* if there is no repetition of nodes in the walk other than the repetition of the starting- and ending-node. The *length* of a path/cycle/walk is defined to be the number of edges in that path/cycle/walk. The length of a walk w is denoted by $l(w)$, and the length of a path p is denoted by $l(p)$.

A *strongly connected graph* is a directed graph such that for any two nodes v_i and v_j in the graph, there is a path from v_i to v_j. A *cycle digraph* is a directed graph that consists of a single cycle. A *directed acyclic graph* (DAG) is a directed graph containing no cycles. In a directed acyclic graph, a node with no in-neighbors (and hence no in-edges) is called a *source node*. We note that in a DAG, any walk must also be a path. For any digraph $D = (V, E)$, a *subgraph* of $D = (V, E)$ is a digraph whose node set and edge set are subsets of V and E, respectively.

2.2 Binary Necklace

A **binary necklace** of length p is an equivalence class of p-character strings over the binary set $\mathbb{F}_2 = \{0, 1\}$, taking all rotations (circular shifts) as equivalent. For example, in the case of $n = 4$, there are six different binary necklaces, as illustrated in Fig. 2.1. A *necklace with fixed density* is a necklace in which the number of zeros (and hence, ones) is fixed. The **order** of a necklace is the cardinality of the corresponding equivalence class, and it is always a divisor of p. An *aperiodic necklace* (see, for example, [72]) is a necklace of order p, i.e., no two distinct rotations of a necklace from such a class are equal. Thus, an aperiodic necklace cannot be partitioned into more than one sub-string with the same alphabet pattern. For example, a necklace of 1010 (row 2, column 1 in Fig. 2.1) can be partitioned into two substrings 10 and 10 which have the same alphabet pattern, and thus is not aperiodic. A necklace of 1000 (row 1, column 2 in Fig. 2.1) cannot be partitioned into more than one sub-string with the same alphabet pattern, and is aperiodic.

2.3 Conjunctive Boolean Network (CBN)

Let $\mathbb{F}_2 = \{0, 1\}$ be the finite field with two elements. The two elements “0” and “1” can, for example, represent the “off” status and “on” status of a gene, respectively. We call a function g on n variables a *Boolean function* if it is of the form $g : \mathbb{F}_2^n \to \mathbb{F}_2$. The so-called *Boolean network* (BN) on n Boolean variables $x_1(t), \dots, x_n(t)$ is a discrete-time dynamical system, whose update rule can be

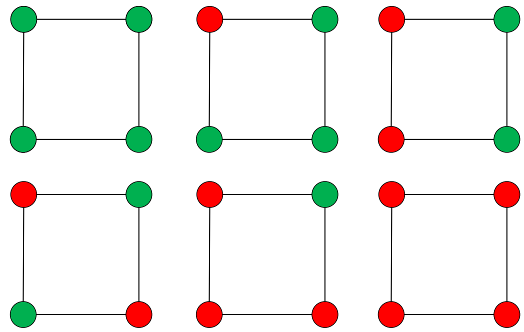

Figure 2.1: All binary necklaces of length 4. If the bead is plotted in red (resp. green), then it holds value "1" (resp, "0").

described by a set of Boolean functions $f_1, \ldots, f_n$:

$$x_i(t+1) = f_i(x_1(t), \ldots, x_n(t)), \ \forall i = 1, \ldots, n.$$

For convenience, we let $x(t) := (x_1(t), \ldots, x_n(t)) \in \mathbb{F}_2^n$ be the state of the BN at time t. We further let

$$f := (f_1, \ldots, f_n) : x(t) \mapsto x(t+1).$$

We refer to f as the **value update rule** associated with the BN. Note that following this value update rule, all Boolean variables update their values synchronously (in parallel) at each time step. We refer to [4, 46, 73] for results on BNs with asynchronous (sequential) updating schemes.

Since a BN is a finite dynamical system, it is well known that for any initial condition $x(0) \in \mathbb{F}_2$, the trajectory $x(0), x(1), \ldots$ will enter a *periodic orbit* in a finite amount time. More precisely, there exists a time $t_0 \geq 0$ and an integer number $p \geq 1$ such that $x(t_0 + p) = x(t_0)$. Moreover, if $x(t_0 + q) \neq x(t_0)$ for any $q = 1, \ldots, p-1$, then the sequence $\{x(t_0), \ldots, x(t_0+p-1)\}$, taking rotations as equivalent, is said to be a **periodic orbit**, and we call p its **period**. If the period of a periodic orbit is one, i.e., $x(t_0) = x(t_0 + k)$ for any $k \geq 1$, then the state $x(t_0)$ is said to be a **fixed point**. We refer the reader to [74, 75] for studies on the number of fixed points of a BN.

We consider, in this thesis, a special class of BNs, termed *conjunctive Boolean networks* (CBNs). Roughly speaking, a BN is conjunctive if each Boolean function f_i is an AND operation on a selected subset of the n variables. We provide below a precise definition:

Definition 1 (Conjunctive Boolean network [26])**.** *A Boolean network (BN)* $f = (f_1, \ldots, f_n)$ *is* **conjunctive** *if each Boolean function* f_i*, for all* $i = 1, \ldots, n$*, can be expressed as follows:*

$$f_i(x_1, \ldots, x_n) = \prod_{j=1}^{n} x_j^{\epsilon_{ji}} \tag{2.2}$$

with $\epsilon_{ji} \in \{0, 1\}$ *for all* $j = 1, \ldots, n$*.*

Note that states $(0, \ldots, 0)$ and $(1, \ldots, 1)$ are always fixed points for CBNs. If we let $I_i := \{j \mid \epsilon_{ji} = 1\}$, then f_i is nothing but an AND operator on the variables x_j, for $j \in I_i$.

We can associate with each CBN a unique directed graph, termed *dependency graph*, whose definition is given below:

Definition 2 (Dependency graph [26])**.** *Let* $f = (f_1, \ldots, f_n)$ *be the value update rule associated with a CBN. The associated* **dependency graph** *is a directed graph* $D = (V, E)$ *of* n *vertices. An edge from* v_i *to* v_j*, denoted by* $v_i v_j$*, exists in* E *if* $\epsilon_{ij} = 1$*.*

Remark 1. *A CBN uniquely determines its dependency graph. Conversely, given a digraph* D*, there is a unique CBN whose dependency graph is* D*.*

In the majority of this thesis, we assume that the dependency graph D is strongly connected (this assumption will be relaxed in Section 4.3). We now present some preliminary results on the network and the associated digraph.

First, note that if a digraph $D = (V, E)$ is strongly connected, then it can be written as the union of its cycles ([76]): Let $D_1 = (V_1, E_1), \ldots, D_N = (V_N, E_N)$, with $V_i \subset V$ and $E_i \subset E$, be the cycles of D. Then,

$$D = \left(\cup_{i=1}^{N} V_i, \cup_{i=1}^{N} E_i\right).$$

Said in another way, each vertex of D is contained in at least one cycle of D. Now, let n_i be the length of D_i. Then, we have the following fact for the possible periods of the CBN:

Lemma 1. *A positive integer* p *is the period of a periodic orbit of a CBN if and only if* p *divides the length of each cycle.*

Remark 2. *Note that if the greatest common divisor of the cycle lengths is one, then the period p of a periodic orbit $\{x(t_0), \ldots, x(t_0+p-1)\}$ has to be one, and hence $x(t_0)$ is a fixed point of the CBN.*

We refer to [26, 77] for proofs of Lemma 1. We further have the following fact:

Lemma 2. *A state $x \in \mathbb{F}_2^n$ is a fixed point of a CBN if and only if all the x_i's hold the same value.*

Proof. It should be clear that if all the x_i's hold the same value, then x is a fixed point. We now show that the converse is also true. The proof is done by contradiction: assume that there are two vertices v_i and v_j such that $x_i = 0$ and $x_j = 1$. Since the dependency graph D is strongly connected, there is a walk w_{ij} from v_i to v_j. Let $l(w_{ij}) = q$, and label the vertices along the walk as follows:

$$w_{ij} = v_{k_0} v_{k_1} \ldots v_{k_q}$$

with $v_{k_0} = v_i$ and $v_{k_q} = v_j$. Now, suppose that $x_{k_0}(t_0) = 0$; then, from (2.2), we have $x_{k_1}(t_0+1) = 0$, and $x_{k_2}(t_0+2) = 0, \ldots, x_{k_q}(t_0+q) = 0$. On the other hand, since x is a fixed point, $x_{k_q}(t_0+q) = x_{k_q}(t_0) = 1$, which is a contradiction. ■

Chapter 3

STABILITY STRUCTURES

3.1 Irreducible Components of Strongly Connected Graphs

Let $D = (V, E)$ be the dependency graph associated with a CBN. Assume that D is strongly connected, and recall that $D_1, \ldots, D_N$ are cycles of D, and $n_1, \ldots, n_N$ are their lengths. Now, let p^* be the greatest common divisor of n_i, for $i = 1, \ldots, N$:

$$p^* := \gcd\{n_1, n_2, ..., n_N\}.$$

This is also known as the *loop number* of D [23]. The digraph D is said to be **irreducible** if $p^* = 1$. If the digraph D is not irreducible, then we show in this section that there is a decomposition of D into p^* components each of which is irreducible. This section is thus organized as follows: In Subsection 3.1.1, we partition the vertex set V in a particular way into p^* subsets. Following this partition, we then construct, in Subsection 3.1.2, p^* digraphs, as we call the irreducible components of D, whose vertex sets are the p^* partitioned subsets. We show in Proposition 2 that each irreducible component is indeed irreducible, and moreover, strongly connected. Then, in Subsection 3.1.3, we define a CBN, as we call an induced dynamics, on each irreducible component. We further establish the relationships between the original dynamics and the p^* induced dynamics.

3.1.1 Vertex set partition

Following Lemma 1, we introduce a partition of the vertex set V. Roughly speaking, the partition is defined such that the vertices in a partitioned subset are connected by walks whose lengths are multiples of a common divisor of the cycle lengths. We now define the partition in precise terms. To proceed, we first have some definitions and notations. Let v_i, v_j be any two vertices in V, and w_{ij} be a walk from v_i to v_j. We denote by $l(w_{ij})$ the length of w_{ij}.

Definition 3. *Let p divide the lengths of cycles of the dependency graph D. We say that a vertex v_i is* **related to** *another vertex v_j (or simply write $v_i \sim_p v_j$) if there exists a walk w_{ij} from v_i to v_j such that p divides $l(w_{ij})$.*

We note here that the relation introduced in Definition 3 is in fact an equivalence relation. Specifically, we have the following fact:

Lemma 3. *The relation $\sim_p$ is an equivalence relation, i.e., for any $v_i, v_j, v_r \in V$, the following three properties hold:*

1. *Reflexivity: $v_i \sim_p v_i$.*
2. *Symmetry: $v_j \sim_p v_i$ if and only if $v_i \sim_p v_j$.*
3. *Transitivity: if $v_i \sim_p v_j$ and $v_j \sim_p v_r$, then $v_i \sim_p v_r$.*

Proof. We establish below the reflexivity, symmetry and transitivity of the relation "$\sim_p$".

1. Reflexivity. Since D is strongly connected, for any $v_i \in V$, v_i belongs to a cycle. Furthermore, p divides the length of the cycle. We thus have $v_i \sim_p v_i$.

2. Symmetry. Suppose that $v_i \sim_p v_j$; then, there exists a walk w_{ij} such that p divides $l(w_{ij})$. Since the graph is strongly connected, there exists a walk w_{ji} from v_j to v_i. By concatenating w_{ij} with w_{ji}, we obtain a closed walk w_{ii} from v_i to itself. It is known that any closed walk can be decomposed into cycles. This, in particular, implies that p divides $l(w_{ii})$. Since p divides $l(w_{ij})$, p divides $l(w_{ji})$, and hence $v_j \sim_p v_i$.

3. Transitivity. Suppose that $v_i \sim_p v_j$ and $v_j \sim_p v_k$; then, there exist walks w_{ij} and w_{jk} such that p divides both $l(w_{ij})$ and $l(w_{jk})$. By concatenating w_{ij} with w_{jk}, we obtain a walk w_{ik} from v_i to v_k. Moreover, p divides $l(w_{ik})$, and hence $v_i \sim_p v_k$. ■

With the preliminaries above, we construct a subset of V as follows: First, we choose an arbitrary vertex v_i as a base vertex; then, we define

$$[v_i]_p := \{v_j \in V \mid v_j \sim_p v_i\}. \tag{3.1}$$

Note that from Lemma 3, the subset $[v_i]_p$, for any $v_i \in V$, is an equivalence class of v_i. We further establish the following result:

Proposition 1. *The following two properties hold:*

1. *If $v_i \sim_p v_j$, then $[v_i]_p = [v_j]_p$. If $v_i \not\sim_p v_j$, then $[v_i]_p \cap [v_j]_p = \varnothing$.*

2. *Let $v_0 \in V$, and choose vertices $v_1, \dots, v_{p-1}$ such that*

$$v_1 \in \mathcal{N}_{\text{out}}(v_0), \dots, v_{p-1} \in \mathcal{N}_{\text{out}}(v_{p-2}).$$

Then, the subsets $[v_0]_p, \dots, [v_{p-1}]_p$ form a partition of V:

$$V = \sqcup_{i=0}^{p-1} [v_i]_p. \tag{3.2}$$

We provide in Fig. 3.1 an example of such a partition of V.

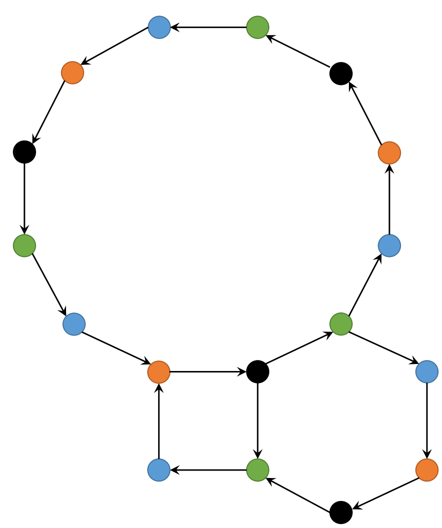

Figure 3.1: The digraph in the figure has three cycles, whose lengths are 4, 8, and 12, respectively. Let $p = 4$ be a common divisor of the cycle lengths. Then, the associated partition yields 4 disjoint subsets, with the vertices of the same color belonging to the same subset.

The remainder of this subsection is devoted to the proof of Proposition 1. The first item of the proposition directly follows from the fact that each $[v_i]_p$, for any $v_i \in V$, is an equivalence class of v_i. We now prove the second item of the proposition. To proceed, first note that in (3.1), if $v_j \in [v_i]_p$, then there is a walk w_{ji} from v_j to v_i with $l(w_{ji})$ a multiple of p. We now show that if w_{ji} is a walk from v_j to v_i, then $l(w_{ji})$ has to be a multiple of p.

Lemma 4. *Let $v_i \sim_p v_j$, and w_{ij} be an arbitrary walk from v_i to v_j. Then, $l(w_{ij})$ is a multiple of p.*

Proof. Since $v_i \sim_p v_j$, there exists a walk w_{ij} such that $l(w_{ij}) = k_1 p$ for some $k_1 \in \mathbb{Z}^+$. Suppose there is a different walk w'_{ij} which connects v_i to v_j. We need to prove that $l(w'_{ij})$ is a multiple of p. By Lemma 3 (reflexivity), we have $v_j \sim_p v_i$. Therefore, there exists a walk w_{ji} whose length $l(w_{ji}) = k_2 p$. Concatenating w'_{ij} and w_{ji}, we get a closed walk w'_{ii}. It is known that in strongly connected graphs, any closed walk can be decomposed into cycles. Since p divides the lengths of all cycles, we have that p divides $l(w'_{ii})$. Now we have that p divides both $l(w_{ji})$ and $l(w'_{ii})$. Thus, p also divides $l(w'_{ii}) - l(w_{ji}) = l(w'_{ij})$. ■

With Lemma 4 at hand, we are now in a position to complete the proof of Proposition 1:

Proof. We prove here item 2 of Proposition 1. We first show that the subsets $[v_i]_p$ for $i = 1, \ldots, p$, are pairwise disjoint, and then show that their union is V.

Choose a pair (i, j) with $0 \le i < j \le p - 1$. Then, it should be clear that there is a walk w_{ij} from v_i to v_j with $l(w_{ij}) = j - i < p$. So, by Lemma 4, $v_i \not\sim_p v_j$, and hence $[v_i]_p \cap [v_j]_p = \varnothing$.

It now suffices to show that $V = \cup_{i=0}^{p-1} [v_i]_p$. Picking an arbitrary vertex v_r, we show that $v_r \in [v_i]_p$ for some $i = 0, \ldots, p - 1$. Since the digraph D is strongly connected, there is a walk w_{r0} from v_r to v_0. We then write $l(w_{r0}) = kp + q$, with $0 \le q \le p - 1$. If $q = 0$, then $v_r \in [v_0]_p$. We thus assume that $q \ne 0$. Now, let $w_{0,p-q}$ be a walk from v_0 to v_{p-q} with $l(w_{0,p-q}) = p - q$. Then, by concatenating w_{r0} with $w_{0,p-q}$, we obtain a walk $w_{r,p-q}$ from v_r to v_{p-q} with $l(w_{r,p-q}) = (k+1)p$. Thus, $v_r \in [v_{p-q}]_p$. ■

3.1.2 Irreducible components

Let $D = (V, E)$ be a strongly connected digraph, and p^* be its loop number. For a vertex $v \in V$, we simply write $[v_0]$ instead of $[v_0]_p$ if $p = p^*$. We now decompose the digraph D into p^* components:

Definition 4 (Irreducible components)**.** *Let $D = (V, E)$ be a strongly connected digraph, and p^* be its loop number. Choose a vertex v_0 of D, and let $v_1 \in \mathcal{N}_{\mathrm{out}}(v_0), \ldots, v_{p^*-1} \in \mathcal{N}_{\mathrm{out}}(v_{p^*-2})$. The subsets $[v_0], \ldots, [v_{p^*-1}]$ then form a partition of V. The* **irreducible components** *of D are digraphs*

$$G_0 = (U_0, F_0),\ \ldots,\ G_{p^*-1} = (U_{p^*-1}, F_{p^*-1}),$$

with their vertex sets U_k's given by

$$U_k := [v_k], \quad \forall k = 0, \dots, p^* - 1.$$

The edge set F_k of G_k is determined as follows: Let u_i and u_j be two vertices of G_k. Then, $u_i u_j$ is an edge of G_k if there is a walk w_{ij} from u_i to u_j in D with $l(w_{ij}) = p^*$.

As we will see in Proposition 2, each irreducible component of D is indeed irreducible.

Remark 3. *The walk w_{ij} in the definition above is either a path or a cycle (which is the case if $u_i = u_j$) because otherwise there will be a cycle of D properly contained in w_{ij} which contradicts the fact that $l(w_{ij}) = p^*$ divides all the cycle lengths. If w_{ij} is a cycle, then the edge $u_i u_j$ is a self-loop.*

We provide an example in Fig. 3.2 in which we show the irreducible components of the digraph shown in Fig. 3.1.

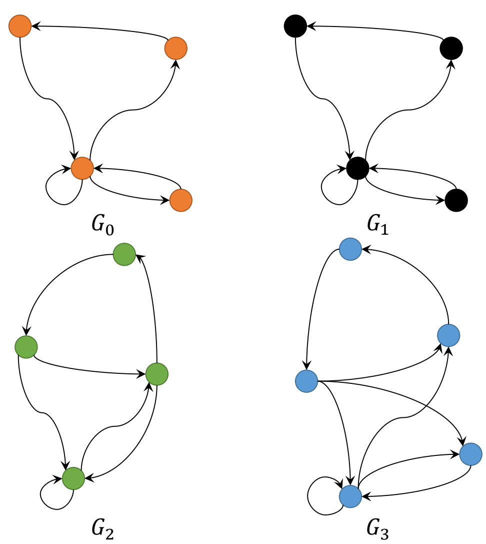

Figure 3.2: Irreducible components of the digraph shown in Fig. 3.1.

We now establish some properties associated with the irreducible components. We first have the following result:

Proposition 2. *Each G_k, for $k = 0, \dots, p^* - 1$, is strongly connected and irreducible.*

To establish the proposition, we need the following lemma:

Lemma 5. *If there is a cycle of length n_i in the digraph D, then there is a cycle of length n_i/p^* in any one of its irreducible components.*

Proof. Let $D_i = (V_i, E_i)$ be a cycle of length n_i in D. Note that p^* divides $|V_i|$. By Definition 4, each irreducible component $G_k = (U_k, F_k)$ contains n_i/p^* vertices of D_i. For ease of notation, we let $m := n_i/p^*$. Let

$$V_i \cap U_k = \{u_1, \ldots, u_m\}.$$

We can further assume that there exist walks $w_{i,i+1}$, for $i = 1, \ldots, m$, from u_i to u_{i+1} in D with $l(w_{i,i+1}) = p^*$ (if $i = m$, we identify $u_{m+1} = u_1$). It then follows from Definition 4 that $u_1u_2, \ldots, u_mu_1$ are edges of G_k. Thus, the vertices $u_1, \ldots, u_m$, together with the edges $u_1u_2, \ldots, u_mu_1$, form a cycle in G_k, whose length is n_i/p^*. ■

Remark 4. *We note here that the converse of Lemma 5 does not hold, i.e., even if there is a cycle of length m in each irreducible component G_k, the original digraph D does not necessarily have a cycle of length mp^*. A counterexample is provided in the Appendix.*

With Lemma 5 at hand, we now prove Proposition 2:

Proof of Proposition 2. We first prove that each G_k is strongly connected. Let u_i and u_j be two vertices of U_k. We show that there exists a walk in G_k from u_i to u_j. Since $u_i \in [u_j]$, from (3.1), there is a walk w_{ij} in D with $l(w_{ij}) = rp^*$ for some positive integer r. For a later purpose, we label the vertices, along the walk, as

$$w_{ij} = v_0v_1 \ldots v_{rp^*},$$

with $v_0 = u_i$ and $v_{rp^*} = u_j$. It then follows from Definition 4 that $v_0, v_{p^*}, \ldots, v_{rp^*}$ are vertices of G_k. Moreover, $v_0v_{p^*}, \ldots, v_{(r-1)p^*}v_{rp^*}$ are edges of G_k. So, there is a walk $v_0v_{p^*} \ldots v_{rp^*}$ from v_0 to v_{rp^*} in G_k.

We next show that G_k is irreducible. Let $D_i = (V_i, E_i)$ be a cycle in G_k, with n_i the length of D_i. Then, from Lemma 5, there is a cycle in each G_k whose length is n_i/p^*. We thus conclude that the loop number of each G_k is at most

$$\gcd\{n_1/p^*, \ldots, n_N/p^*\} = 1,$$

and hence each G_k is irreducible. ■

Given a subset V' of V and a nonnegative integer p, we define a subset $\mathcal{N}_{\text{in}}^{p}(V')$ by induction: For $p = 0$, let $\mathcal{N}_{\text{in}}^{0}(V') := V'$; for $p \geq 1$, we define

$$\mathcal{N}_{\text{in}}^{p}(V') := \cup_{v_j \in \mathcal{N}_{\text{in}}^{p-1}(V')} \mathcal{N}_{\text{in}}(v_j). \tag{3.3}$$

Similarly, we define $\mathcal{N}_{\text{out}}^{p}(V')$ by replacing $\mathcal{N}_{\text{in}}$ with $\mathcal{N}_{\text{out}}$ in (3.3). With the notations above, we have the following result about the relationships between the vertex sets of the irreducible components:

Proposition 3. *For $k \geq 0$, we have*

$$\begin{cases} \mathcal{N}_{\text{out}}^{k}(U_0) = U_{(k \bmod p^*)}, \\ \mathcal{N}_{\text{in}}^{k}(U_0) = U_{(-k \bmod p^*)}. \end{cases}$$

Proof. We prove here only the first relation $\mathcal{N}_{\text{out}}^{k}(U_0) = U_{(k \bmod p^*)}$; the other relation can be established in a similar way. It suffices to show that for any $k = 0, \ldots, p^* - 1$, we have $\mathcal{N}_{\text{out}}(U_k) = U_{(k+1 \bmod p^*)}$. There are two cases:

Case I: $0 \leq k \leq p^* - 2$. We first show that $\mathcal{N}_{\text{out}}(U_k) \subseteq U_{(k+1 \bmod p^*)}$. Let $u \in U_k = [v_k]$, and $u' \in \mathcal{N}_{\text{out}}(u)$. Since D is strongly connected, there is a walk w' from u' to v_k. Moreover, from Lemma 4, $l(w') \equiv p^* - 1 \bmod p^*$. To see this, note that by concatenating the edge uu' with w', we obtain a walk w from u to v_k. Since $u \sim_{p^*} v_k$,

$$l(w) = l(w') + 1 \equiv 0 \bmod p^*.$$

Now, using the fact that v_{k+1} is the out-neighbor of v_k, we obtain a walk w^* from u' to v_{k+1} by concatenating w' with the edge $v_k v_{k+1}$. Since $l(w^*)$ is a multiple of p^*, $u' \in [v_{k+1}] = U_{k+1}$. We now show that $\mathcal{N}_{\text{out}}(U_k) \supseteq U_{(k+1 \bmod p^*)}$. Let $u' \in U_{k+1}$, and w' be a walk from u' to v_k. Then, by the same argument, $l(w') \equiv p^* - 1 \bmod p^*$. Now, let $u \in \mathcal{N}_{\text{in}}(u')$. Then, by concatenating the edge uu' with w', we obtain a walk w from u to v_k. Moreover, $l(w)$ is a multiple of p^*, and hence $u \in [v_k]$, which implies that $u' \in \mathcal{N}_{\text{out}}(u) \subseteq \mathcal{N}_{\text{out}}(U_k)$.

Case II: $k = p^* - 1$. Let $v_{p^*} \in \mathcal{N}_{\text{out}}(v_{p^*-1})$. It should be clear that $[v_{p^*}] = [v_0]$. On the other hand, we can apply the arguments above, and obtain that $\mathcal{N}_{\text{out}}(U_{p^*-1}) = [v_{p^*}]$. So, $\mathcal{N}_{\text{out}}(U_{p^*-1}) = U_0$. ■

In the end of this subsection, we introduce a special class of digraphs as follows:

Definition 5. *A digraph D is a* **rose** *if all the cycles of D satisfy the following two conditions:*

1. *They have the same length.*
2. *They share at least one common vertex of D.*

We provide in Fig. 3.3 an example of a rose. We now have the following result:

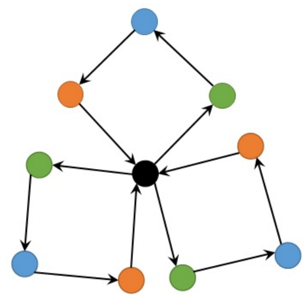

Figure 3.3: A rose with three cycles of length 4. The vertex in black is a common vertex of all cycles.

Proposition 4. *Let $G_k = (U_k, F_k)$, for $k = 0, \dots, p^* - 1$, be irreducible components of D. Then, the following hold:*

1. *D is a rose if and only if there is at least one $k \in \{0, \dots, p^* - 1\}$ such that $|U_k| = 1$.*
2. *D is a cycle digraph if and only if $|U_k| = 1$, for all $k = 0, \dots, p^* - 1$.*

Proof. We prove the two items separately.

1. Proof of item 1.

The "if" part. We first prove that if there is at least one $k = 0, \dots, p^* - 1$ such that $|U_k| = 1$, then D is a rose. The proof is carried out by contradiction.

Suppose that the cycles in D do not have the same length. Then, there exists at least one cycle whose length is greater than p^*. Without loss of generality, we assume that the length of D_1 is rp^*, for $r \geq 2$. Label the vertices in D_1 as $v_0, \dots, v_{rp^*-1}$. We then define subsets $[v_0], \dots, [v_{p^*-1}]$. From the second item of Proposition 1, these subsets form a partition of V. Now, consider the vertices $v_{p^*}, \dots, v_{2p^*-1}$ in D_1. Within D_1 (and hence D), there is a path from v_k to v_{k+p^*} for all $k = 0, \dots, p^* - 1$. So, we have that $v_{p^*} \in [v_0], \dots, v_{2p^*-1} \in [v_{p^*-1}]$. In other words, $|U_k| = |[v_k]| \geq 2$ for all k, which contradicts the assumption that $|U_k| = 1$ for at least one k.

We thus assume that all cycles have the same length, yet do not share a common vertex. Note that in this case, the greatest common divisor p^* is the length of any cycle of D. Since there is at least one k such that $|U_k| = 1$, we can assume, without loss of generality, that $|U_0| = 1$, and let $U_0 = \{v_0\}$. Since v_0 is not shared by all cycles, there is a cycle D_i of D such that v_i is not in D_i. Label the vertices of D_i as $v'_0, \ldots, v'_{p^*-1}$. Appealing again to the second item of Proposition 1, we have that the subsets $[v'_0], \ldots, [v'_{p^*-1}]$ form a partition of V. Hence, there is some k such that $v_0 \in [v'_k]$. Since v_0 is not in D_i and v'_k is a vertex of D_i, $v_0 \neq v'_k$. But then, $|U_0| = |[v_0]| = |[v'_k]| \geq 2$, which is a contradiction.

The "only if" part. We now prove that if D is a rose, then there is at least one $k \in \{0, \ldots, p^* - 1\}$ such that $|U_k| = 1$. Without loss of generality, we let v_0 be a common vertex shared by the cycles of D. We now show that $|[v_0]| = 1$. Suppose not, then there is a vertex v_i such that $v_i \neq v_0$ and $v_i \in [v_0]$. Since D is strongly connected, v_i is contained in a cycle D_j of D. Since v_0 is a common vertex, v_0 is also contained in D_j. So, within the cycle D_i, there is a path from v_0 to v_i. Moreover, the length of the path must be greater than 0, yet less than the length of D_i, which is p^*. On the other hand, since $v_i \sim_{p^*} v_0$, from Lemma 4, the length of any walk from v_0 to v_i has to be a multiple of p^*, which is a contradiction.

2. Proof of item 2.

If $D = (V, E)$ is a cycle digraph where the cycle has length p^*, then by the construction of the irreducible components, there are p^* of them, each of which contains only one vertex. Now, suppose that $|U_k| = 1$ for all $k = 0, \ldots, p^* - 1$; we show that D is a cycle digraph where the cycle has length p^*. Let vertices $v_0, \ldots, v_{p^*-1}$ be such that $U_k = \{v_k\}$ for all $k = 0, \ldots, p^* - 1$. Since $U_0, \ldots, U_{p^*-1}$ form a partition of V, we have that the vertex set of D is given by $\{v_0, \ldots, v_{p^*-1}\}$. Since the number of vertices of D is p^*, the length of any cycle of D is no greater than p^*. Furthermore, if the loop number of D is p^*, then each cycle of D has to be a Hamiltonian cycle (i.e., a cycle that passes all the vertices of D). But this happens if and only if D itself is a cycle digraph. ∎

3.1.3 Induced dynamics

Let $f = (f_1, \ldots, f_n)$ be a CBN, and D be the dependency graph. Let $G_0, \ldots, G_{p^*-1}$ be the irreducible components of D. Now, for each $k = 0, \ldots, p^* - 1$, we can define a CBN as follows:

Definition 6 (Induced dynamics)**.** *An* **induced dynamics** *on G_k is a CBN whose dependency graph is G_k.*

We can express the induced dynamics on G_k explicitly as follows: Let $U_k = \{u_1, \ldots, u_m\}$, and $(y_1, \ldots, y_m)$ be the state of the network. Let $g_k = (g_{k_1}, \ldots, g_{k_m})$ be the associated value update rule. Then,

$$g_{k_i}(y_1, \ldots, y_m) = \prod_{u_j \in U_k} y_j^{\epsilon_{ji}},$$

where $\epsilon_{ji} = 1$ if u_j is an in-neighbor of u_i and $\epsilon_{ji} = 0$ otherwise.

We now relate the original dynamics f on D to the induced dynamics on the irreducible components. We first introduce some notations. Let V' be a subset of V. We define $f_{V'}$ to be the restriction of f to V'. For a positive integer p, we let f^p be the map defined by applying the map f p times. Given a state $x \in \mathbb{F}_2^n$ and a subset V' of V, we let $x_{V'}$ be the restriction of x to V'. We now establish the main result of this section as follows:

Theorem 1. *Let $G_k = (U_k, F_k)$ be an irreducible component of D. Then, the following hold:*

1. *Let g_k be the induced dynamics on G_k. Then,*

$$g_k(x_{U_k}) = f_{U_k}^{p^*}(x), \quad \forall x \in \mathbb{F}_2^n.$$

2. *Suppose that $x(t_0)$ is in a periodic orbit. Then,*

$$x_{U_{(k+1 \bmod p^*)}}(t_0 + 1) = x_{U_k}(t_0). \tag{3.4}$$

We note here that if $x(t_0)$ is in a periodic orbit, then for each $k = 0, \ldots, p^* - 1$, the entries of $x_{U_k}(t_0)$ hold the same value. This indeed follows from the first item of Theorem 1:

Corollary 1. *Let $D = (V, E)$ be the dependency graph of a CBN, and $G_k = (U_k, F_k)$, for $k = 0, \dots, p^* - 1$, be its irreducible components. A state $x \in \mathbb{F}_2^n$ is in a periodic orbit of the CBN if and only if for each $k = 0, \dots, p^* - 1$, the entries of x_{U_k} hold the same value.*

Proof. Let $x \in \mathbb{F}_2^n$ be a state. If for each $k = 0, \dots, p^* - 1$, the entries of x_{U_k} hold the same value, then from the first item of Theorem 1,

$$f_{U_k}^{p^*}(x) = g_k(x_{U_k}) = x_{U_k},$$

and hence $f^{p^*}(x) = x$. Conversely, if x is in a periodic orbit of period p, then

$$x_{U_k} = f_{U_k}^{p}(x) = f_{U_k}^{p^*}(x) = g_k(x_{U_k}).$$

The first equality holds because $x = f^p(x)$. The second equality holds because p divides p^* (from Lemma 1). The third equality follows from the first item of Theorem 1. So, x_{U_k} is a fixed point of the induced dynamic on G_k. From Lemma 2, we conclude that the entries of x_{U_k} hold the same value. ∎

So, if $x(t_0)$ is in a periodic orbit, then from the second item of Theorem 1 and Corollary 1, the entries of $x_{U_k}(t_0)$ hold the same value, and moreover, this value will be passed onto the entries of $x_{U_{(k+1 \bmod p^*)}}$ at the next time step. We also illustrate this fact in Fig. 3.4.

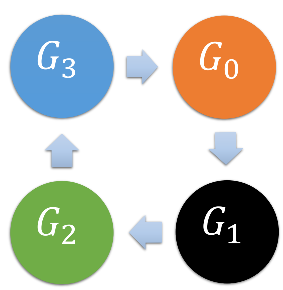

Figure 3.4: In this figure, $G_0, \dots, G_3$ are irreducible components of the digraph shown in Fig. 3.1. If $x(t_0)$ is in a periodic orbit, then the vertices of each G_k, for $k = 0, \dots, 3$, hold the same value $y_k(t_0)$. Moreover, the value $y_k(t_0)$ will be passed to the vertices of $G_{(k+1) \bmod 4}$ at time step $(t_0 + 1)$.

The remainder of this section is devoted to the proof of Theorem 1. For a vertex v_i of D and a positive integer p, we define a subset $\mathcal{N}_{\text{in}}^{p}(v_i)$ of V via induction:

For $p = 1$, $\mathcal{N}^1_{\text{in}}(v_i)$ is simply the in-neighbor of v_i. For $p \geq 1$, we define

$$\mathcal{N}^p_{\text{in}}(v_i) := \cup_{v_j \in \mathcal{N}^{p-1}_{\text{in}}(v_i)} \mathcal{N}_{\text{in}}(v_j).$$

In particular, if $p = p^*$ and v_i is a vertex of G_k, then from Definition 4, $\mathcal{N}^p_{\text{in}}(v_i)$ is the set of in-neighbors of v_i in G_k. We further note the following fact:

Lemma 6. *For any positive integer p, we have*

$$f^p_i(x) = \prod_{v_j \in \mathcal{N}^p_{\text{in}}(v_i)} x_j. \tag{3.5}$$

Proof. We prove the lemma by induction on p. For $p = 1$, $f_i(x) = \prod_{v_j \in \mathcal{N}_{\text{in}}(v_i)} x_j$, which directly follows from Definition 1. Now, we assume that (3.5) holds for $p - 1$, and prove for p. By the induction hypothesis, we have that

$$x_i(t + p) = \prod_{v_j \in \mathcal{N}^{p-1}_{\text{in}}(v_i)} x_j(t + 1).$$

From the value update rule, we have that

$$x_j(t + 1) = \prod_{v_k \in \mathcal{N}_{\text{in}}(v_j)} x_k(t).$$

So,

$$x_i(t + p) = \prod_{v_j \in \mathcal{N}^{p-1}_{\text{in}}(v_i)} \prod_{v_k \in \mathcal{N}_{\text{in}}(v_j)} x_k(t).$$

Using the fact that

$$\mathcal{N}^p_{\text{in}}(v_i) = \cup_{v_j \in \mathcal{N}^{p-1}_{\text{in}}(v_i)} \mathcal{N}_{\text{in}}(v_j),$$

we conclude that (3.5) holds for p. ∎

We now prove Theorem 1:

Proof of Theorem 1. The first item of Theorem 1 directly follows from Lemma 6. We prove here the second item. From the proof of Proposition 3,

$$U_{(k+1 \bmod p^*)} = \mathcal{N}_{\text{out}}(U_k).$$

So, by the value update rule, the value of $x_{U_{(k+1 \bmod p^*)}}(t_0+1)$ depends only on $x_{U_k}(t_0)$. Since $x(t_0)$ is in a periodic orbit, from Corollary 1, the entries of $x_{U_k}(t_0)$ hold the same value, which then implies that (3.4) holds. ■

3.2 Stability of Periodic Orbits

3.2.1 Labeling periodic orbits

In this subsection, we find and label all the periodic orbits of a CBN. Let $D = (V, E)$ be the associated dependency graph, and p^* be its loop number. Recall that a binary necklace of length p^* is an equivalence class of p^*-character strings over $\mathbb{F}_2$, taking rotations as equivalent. The order of a necklace is the cardinality of the equivalence class.

We now show that each periodic orbit can be uniquely identified with a binary necklace of length p^*: Let $\{x(t_0), \dots, x(t_0+p-1)\}$ be a periodic orbit of period p. Let $G_k = (U_k, F_k)$, for $k = 0, \dots, p^*-1$, be the irreducible components of D. From Corollary 1, for each $k = 0, \dots, p^*-1$, the entries of $x_{U_k}(t_0)$ hold the same value. We label these values as $y_0(t_0), \dots, y_{p^*-1}(t_0)$, with $y_k(t_0)$ being the value of the entries of $x_{U_k}(t_0)$. From the second item of Theorem 1, we have that

$$y_k(t_0+q) = y_{(k-q \bmod p^*)}(t_0)$$

for all $k = 0, \dots, p^*-1$ and for all $q \geq 0$. This then implies that the periodic orbit $\{x(t_0), \dots, x(t_0+p-1)\}$ can be represented by a binary necklace $y_0(t_0)\dots y_{p^*-1}(t_0)$ whose order is p. Conversely, given a binary necklace $y_0 \dots y_{p^*-1}$ of order p, we can construct a periodic orbit of period p as follows: Define a state $x \in \mathbb{F}_2^n$ such that the entries of x_{U_k} hold the value y_k for all $k = 0, \dots, p^*-1$. Appealing again to Corollary 1 and the second item of Theorem 1, we have that $\{x, f(x), \dots, f^{p-1}(x)\}$ is a periodic orbit of period p. The arguments above thus imply the following fact:

Proposition 5. *There is a bijection between the set of periodic orbits and the set of binary necklaces of length p^*. Moreover, such a bijection maps a periodic orbit of period p to a necklace of order p.*

Remark 5. *From the proposition, if two dependency graphs share the same loop number, then the associated CBNs have the same number of periodic orbits.*

For the remainder of this thesis, we let S denote the set of periodic orbits. Each periodic orbit $s \in S$ can be identified with a binary necklace $s = y_0 \dots y_{p^*-1}$. To proceed, we introduce some definitions and notations. Let $\sigma(s)$ be the number of "1"s in the string $s = y_0 \dots y_{p^*-1}$. We then partition the set S into (p^*+1) subsets $S_0, \dots, S_{p^*+1}$:

$$S_d := \{s \in S \mid \sigma(s) = d\}.$$

Recall that the so-called Euler's totient function $\phi(k)$ counts the total number of integers in the range $[1, k]$ that are relatively prime to k. We now present some known results about counting the number of periodic orbits in S.

Lemma 7. *The following two relations hold:*

1. *For a divisor* p *of* p^**, we let* $p = \prod_{i=1}^{r} p_i^{k_i}$ *be its prime factorization. Then, the number of periodic orbits of period* p *is given by*

$$\frac{1}{p} \sum_{i_1=0}^{1} \cdots \sum_{i_r=0}^{1} \left((-1)^{\sum_{j=1}^{r} i_j} \prod_{j=1}^{r} 2^{p_j^{k_j - i_j}} \right).$$

2. *For a number* $d = 0, \dots, p^*$*, we have*

$$|S_d| = \frac{1}{p^*} \sum_{k \mid \gcd(p^*-d, d)} \phi(k) \left(\frac{(p^*/k)!}{((p^*-d)/k)!(d/k)!} \right).$$

We refer to [26] for a proof of item 1, and [78, 79] for proofs of item 2. We note here that item 1 of Lemma 7 is equivalent to Moreau's necklace-counting formula [80], which computes the number of binary aperiodic necklaces:

$$M_k(p) = \frac{1}{p} \sum_{j \mid p} \mu(j) 2^{p/j},$$

where μ is the Möbius function.[1]

[1]For any positive integer j, $\mu(j) = 1$ if j is a square-free positive integer (an integer which is divisible by no perfect square other than 1) with an even number of prime factors; $\mu(j) = -1$ if j is a square-free positive integer with an odd number of prime factors; $\mu(j) = 0$ if j has a squared prime factor.

3.2.2 Stability structure

We investigate in this subsection the stability of each periodic orbit of a CBN. The motivation for this work comes from the fact that the actual process of gene expression is highly complicated. Though CBNs provide a good model to determine whether a gene can be expressed or not, there are still exceptions and unknown mechanisms that could possibly affect the expression process. We thus want to explore how the system behaves when one gene is not expressed although all necessary proteins are present, or it is expressed even in lack of some necessary proteins.

Let $x(t_0)$ be a state in a periodic orbit s. We say that a *perturbation* occurs at $(t_0 + 1)$ if there is one (and only one) $i \in \{1, \dots, n\}$ such that $x_i(t_0 + 1) = \neg f_i(x(t_0))$. As a consequence, $x(t_0 + 1)$ may not be in the periodic orbit s anymore. However, after finite time steps, the system, with $x(t_0 + 1)$ as its initial condition, will enter a periodic orbit, denoted by s', which may or may not be the same as s. Our goal in this subsection is to characterize all these transition pairs (s, s').

To proceed, we first introduce some definitions and notation. Given a state $x \in \mathbb{F}_2^n$, we let $\mathcal{I}(x) \subset \mathbb{F}_2^n$ be defined as follows: a state x' is in $\mathcal{I}(x)$ if and only if x' differs from x by only one entry, i.e., there is an $i \in \{1, \dots, n\}$ such that $x'_i \neq x_i$ and $x'_j = x_j$ for all $j \neq i$. Note that if $x = x(t_0)$ for $x(t_0)$ a state in a periodic orbit, then $\mathcal{I}(x)$ is the set of states upon the condition that a perturbation occurs at $(t_0 + 1)$. We now have the following definition:

Definition 7 (Successor)**.** *Let s and s' be two periodic orbits. Let $x \in \mathbb{F}_2^n$ be a state in s, and $x' \in \mathcal{I}(x)$. If the trajectory of the dynamics, with x' the initial condition, enters into s' (in finite time steps), then we say that s' is a successor of s.*

This then naturally leads to the following definition:

Definition 8 (Stability structure)**.** *The* **stability structure** *of a CBN is a digraph $H = (S, A)$, with the vertex set being the set of periodic orbits. The edge set of H is defined as follows: Let s_i and s_j be in S. Then, $s_i s_j$ is an edge of H if s_j is a successor of s_i. Furthermore, an edge $s_i s_j$ of H is a* **down-edge** *(resp. an* **up-edge***) if $\sigma(s_i) > \sigma(s_j)$ (resp, $\sigma(s_i) < \sigma(s_j)$).*

Our goal here is to determine the edge set A of H. To proceed, we first introduce a *partial order* on the set of binary necklaces of length p^*: Let $s = y_0 \dots y_{p^*-1}$

and $s' = y'_0 \dots y'_{p^*-1}$ be two binary necklaces. We say that s is **greater than** s', or simply write $s \succ s'$, if we can obtain s by replacing at least one "0" in s' with "1". For example, if $s = 11100$ and $s' = 11000$, then we can obtain s by replacing the third bit "0" in s' with "1", and thus $s \succ s'$. If, instead, $s = 11010$, then there is no way to obtain s by replacing some "0" in s' with "1", and thus s and s' are not comparable.

With the definitions and notation above, we state the main result of this section as follows:

Theorem 2. *Let D be the dependency graph associated with a CBN, and $H = (S, A)$ be the stability structure. Let s_i and s_j be two vertices of H. Then, there is an edge from s_i to s_j if and only if one of the following three conditions is satisfied:*

1. *Down-edges: $s_i \succ s_j$ and $\sigma(s_i) - \sigma(s_j) = 1$.*
2. *Up-edges: $s_i \prec s_j$, $\sigma(s_j) - \sigma(s_i) = 1$, and D has to be a rose.*
3. *Self-loops: $s_i = s_j$, $s_i \neq 1 \dots 1$, and D is not a cycle digraph.*

We state here a fact as a corollary to Theorem 2:

Corollary 2. *Let D_1 and D_2 be two dependency graphs associated with two CBNs, having the same loop number p^*. Let H_1 and H_2 be the corresponding stability structures. Then, $H_1 = H_2$ if one of the following three conditions hold:*

1. *Neither D_1 nor D_2 is a rose.*
2. *Both D_1 and D_2 are roses, but not cycle digraphs.*
3. *Both D_1 and D_2 are cycle digraphs (and hence $D_1 = D_2$).*

We omit the proof of the corollary as it directly follows from Theorem 2. We provide an example in Fig. 3.5 for the case when the loop number $p^* = 4$.

The remainder of this subsection is devoted to the proof of Theorem 2.

Let $s = y_0 \dots y_{p^*-1}$ be a periodic orbit, and x be a state in s. Let $x' \in \mathcal{I}(x)$, with $x'_1 \neq x_1$. Let $G_k = (U_k, F_k)$, for $k = 0, \dots, p^* - 1$, be irreducible components of D. Then, from Corollary 1, we can assume without loss of generality that

$$x_{U_k} = y_k \mathbf{1}, \quad \forall k = 0, \dots, p^* - 1,$$

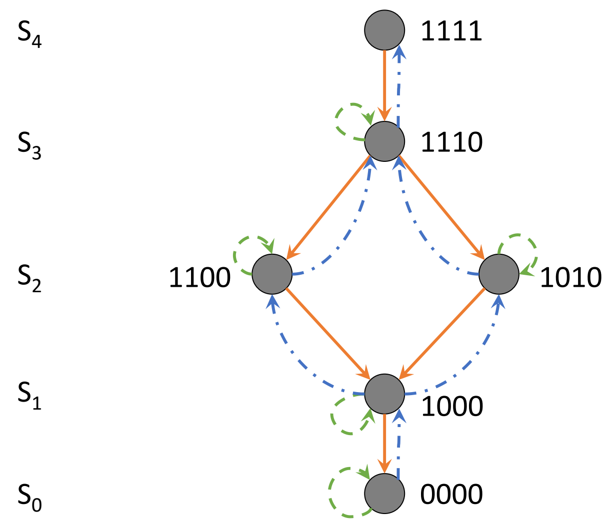

Figure 3.5: The stability structure H for a dependency graph D with the loop number $p^* = 4$. Each edge in H represents a possible transition of the periodic orbit after a single perturbation. The up-edges exist only for the cases when D is a rose, and the self-loops exist only for the cases when D is not a cycle digraph.

where $\mathbf{1}$ is a vector of all ones with an appropriate dimension. We may further assume that x_1 is an entry of x_{U_0}. So, $x_1 = y_0$ and $x'_1 = \neg y_0$ (negating the value of y_0). With these preliminaries, we establish the following result:

Proposition 6. *Let s, x and x' be defined as above. Suppose that the trajectory, with x' the initial condition, enters the periodic orbit s'. Then, there are two cases:*

1. *If $|U_0| = 1$, then $s' = (\neg y_0)y_1 \dots y_{p^*-1}$.*
2. *If $|U_0| > 1$, then $s' = 0y_1 \dots y_{p^*-1}$.*

Proof. For the case $|U_0| = 1$, we note from Corollary 1 that the state x' is already in the periodic orbit s'. We now prove for the case $|U_0| > 1$.

First, note that the vector x'_{U_0}, obtained by restricting x' to U_0, must contain an entry of value 0. This holds because if $y_0 = 0$, then from Corollary 1, all the entries of x_{U_0} hold value 0. Since x'_{U_0} is derived by negating the value of x_1, there are $(|U_0| - 1)$ zeros in x'_{U_0}. If $y_0 = 1$, then by construction, $x'_1 = 0$, which is contained in x'_{U_0}.

Next, consider the induced dynamics on G_0: First, from the value update rule and the first item of Theorem 1, if $x'_{U_0}(0)$ contains an entry of value 0, then so does $x'_{U_0}(tp^*)$ for all $t \geq 0$. Second, since G_0 is irreducible, a periodic orbit of the induced dynamics has to be a fixed point. Combining these two facts, we know that there is a time $t_0 \geq 0$ such that $x'_{U_0}(tp^*) = \mathbf{0}$ for all $t \geq t_0$.

Now, for each $k = 1, \ldots, p^* - 1$, we appeal again to the first item of Theorem 1 and obtain

$$x'_{U_k}(tp^*) = f^{tp^*}_{U_k}(x'_{U_k}(0)) = g^t_k(x'_{U_k}(0)) = x'_{U_k}(0).$$

The last equality holds because by construction of x', we have that $x'_{U_k}(0) = y_k\mathbf{1}$ which is a fixed point of the induced dynamics on G_k. The relation above holds for all $t \geq 0$.

Combining the arguments above, we conclude that for any $t \geq t_0$, we have

$$x'_{U_k}(tp^*) = \begin{cases} 0 & \text{if } k = 0 \\ y_k\mathbf{1} & \text{otherwise.} \end{cases}$$

Thus, $s' = 0y_1 \ldots y_{p^*-1}$. ■

With Proposition 6, we prove Theorem 2:

Proof of Theorem 2. Let $s_i = y_0 \ldots y_{p^*-1}$ and $s_j = y'_0 \ldots y'_{p^*-1}$. There are three cases to consider:

Case 1: $\sigma(s_i) > \sigma(s_j)$. If s_is_j is an edge of H, then from the proof of Proposition 6, we must have $y_0 = 1$, $y'_0 = 0$, and $y_i = y'_i$ for all $i = 1, \ldots, p^* - 1$ (after appropriate rotations of the strings). In other words, we have $s_i \succ s_j$ and $\sigma(s_i) - \sigma(s_j) = 1$. Conversely, if the condition in the first item of the theorem is satisfied, then we can always write $s_i = 1y_1 \ldots y_{p^*-1}$ and $s_j = 0y_1 \ldots y_{p^*-1}$. Let x be a state in s_i, with $x_{U_0} = \mathbf{1}$ and $x_{U_k} = y_k\mathbf{1}$ for all $k = 1, \ldots, p^* - 1$. Then, by negating the value of an entry of x_{U_1}, we obtain a state x'. Moreover, from Proposition 6, the trajectory, with x' the initial condition, will enter s_j in finite time steps, and hence s_j is a successor of s_i.

Case 2: $\sigma(s_i) < \sigma(s_j)$. If s_is_j is an edge of H, then from Proposition 6, we must have $s_i \prec s_j$ and $\sigma(s_j) - \sigma(s_i) = 1$, and moreover there exists at least one k such that $|U_k| = 1$. Then, from the first item of Proposition 4, D has to be a rose. Conversely, if the condition in the second item of the theorem is satisfied, then again, by the first item of Proposition 4, there is a k such that $|U_k| = 1$. Without loss of generality, we assume that $k = 0$, and write $s_i = 0y_1 \ldots y_{p^*-1}$ and $s_j = 1y_1 \ldots y_{p^*-1}$. Let x be a state in s_i with $x_{U_0} = 0$ (note that x_{U_0} is a scalar in this case). By negating the value of x_{U_0}, we obtain a new state x'. Then, from

Proposition 6, the trajectory, with x' the initial condition, will enter the periodic orbit s_j. Thus, s_j is a successor of s_i.

Case 3: $\sigma(s_i) = \sigma(s_j)$. If $s_i s_j$ is an edge of H, then from Proposition 6, we must have that (i) $s_i = s_j$; (ii) there exists at least one $k = 0, \ldots, p^* - 1$ such that $y_k = 0$ and $|U_k| > 1$. Combining the condition (ii) and the second item of Proposition 4, we know that D cannot be a cycle digraph and $s_i \neq 1 \ldots 1$. Conversely, if the condition in the third item of the theorem is satisfied, then there is a k such that $|U_k| > 1$. Without loss of generality, we assume that $k = 0$, and hence s_i can be written as $0y_1 \ldots y_{p^*-1}$. Since $s_i \neq 1 \ldots 1$, we can find a state x in the periodic orbit s_i such that $x_{U_0} = \mathbf{0}$. Now, by negating the value of an entry of x_{U_0}, we obtain a new state x'. Then, from Proposition 6, the trajectory, with x' the initial condition, will enter the periodic orbit $0y_1 \ldots y_{p^*-1}$, which is s_i itself. ■

3.2.3 Transition weights

In this subsection, we introduce and compute the transition weight for each edge of the stability structure H. First, recall that the set $\mathcal{I}(x)$ comprises the states that differ from x by only one entry. It should be clear that $|\mathcal{I}(x)| = n$ for all $x \in \mathbb{F}_2^n$. Now, let $s_i = \{x(t_0), \ldots, x(t_0 + p - 1)\}$ be a periodic orbit, and s_j be a successor of s_i. We define $\mu(s_i, s_j)$ to be the total number of pairs (x, x'), for $x \in s_i$ and $x' \in \mathcal{I}(x)$, such that the trajectory of the CBN, with x' the initial condition, enters into s_j. We then have the following definition:

Definition 9 (Transition weight)**.** *Let s_i be a periodic orbit of period p, and s_j be its successor. Then, the transition weight $P(s_i, s_j)$ on the edge $s_i s_j$ of the stability structure H is*

$$P(s_i, s_j) := \frac{\mu(s_i, s_j)}{np}.$$

We note here that by the definition, $\sum_{s_j} P(s_i, s_j) = 1$, where the summation is over the successors of s_i. Thus, each $P(s_i, s_j)$ can be understood as the probability of the transition from s_i to s_j upon the condition that the pair (x, x') is uniformly chosen from the set $\{(x, x') \mid x \in s_i, x' \in \mathcal{I}(x)\}$.

For the remainder of this subsection, we evaluate the transition weight $P(s_i, s_j)$. To proceed, first note that by the arguments in the beginning of Subsection 3.2.1, we can identify the two periodic orbits s_i and s_j with two binary necklaces: $s_i =$

$y_0 \dots y_{p^*-1}$ and $s_j = y'_0 \dots y'_{p^*-1}$. From Theorem 2, we know that one of the following three conditions holds:

1. $s_i \succ s_j$ and $\sigma(s_i) - \sigma(s_j) = 1$.
2. $s_i = s_j$, $\sigma(s_i) \neq p^*$ and D is not a cycle digraph.
3. $s_i \prec s_j$, $\sigma(s_j) - \sigma(s_i) = 1$ and D is a rose.

We thus introduce the following number for a pair of necklaces: Let s, s' be two necklaces of equal length p^*, with $s \succ s'$ and $\sigma(s) - \sigma(s') = 1$. We define $\gamma(s, s')$ to be the number of ways to obtain s' from s by replacing a "1" in s with a "0". We note here that from its definition, $\gamma(s, s')$ can also be viewed as the number of ways to obtain s from s' by replacing a "0" in s' with a "1". For example, consider the case where $p^* = 4$, and $s = 1110$, $s' = 1100$. Then, there are two ways to obtain s' from s: One way is to replace the first "1" in s with "0". The other way is to replace the third "1" with "0". So, in this case, $\gamma(s, s') = 2$. We also refer to Fig. 3.6 for other values of $\gamma(s, s')$ under the case $p^* = 4$. We further note that $\sum_{s'} \gamma(s, s') = \sigma(s)$, where the summation is over the successors of s other than itself.

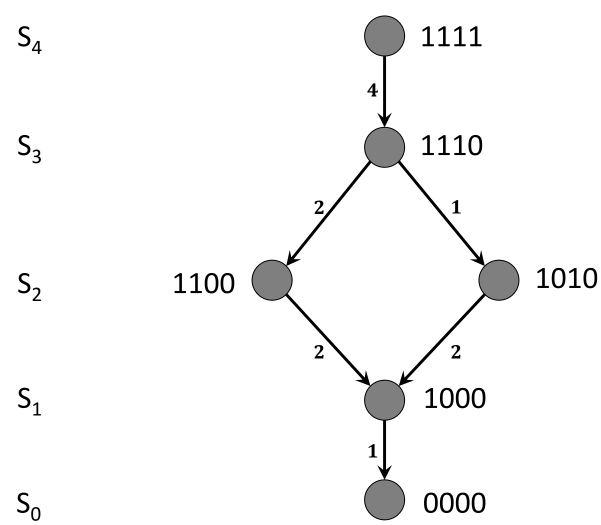

Figure 3.6: The values of γ's for a dependency graph D with the loop number $p^* = 4$. The number labeled on an ss' edge is the value of $\gamma(s, s')$.

We further need the following definition: Given a digraph D. We define an integer number α as follows: We let $\alpha = 0$ if D is not a rose. Otherwise, we let α be the number of common vertices of the cycles of the rose D. From the proof of Proposition 4, we know that α is also the number of irreducible components comprised of a single vertex.

With the definitions and notation above, we establish the following result.

Proposition 7. *Let D be a dependency graph associated with a CBN. Let s_i and s_j be two periodic orbits (which can be identified as two binary necklaces). Then, the following holds:*

$$P(s_i, s_j) = \begin{cases} \frac{\gamma(s_i,s_j)}{p^*} & \text{if } s_i \succ s_j \\ & \text{and } \sigma(s_i) - \sigma(s_j) = 1, \\ \frac{\alpha\gamma(s_j,s_i)}{np^*} & \text{if } s_i \prec s_j \\ & \text{and } \sigma(s_j) - \sigma(s_i) = 1, \\ \frac{(p^*-\sigma(s_i))(n-\alpha)}{np^*} & \text{if } s_i = s_j \\ & \text{and } \sigma(s_i) \neq p^*, \\ 0 & \text{otherwise}. \end{cases}$$

Remark 6. *We note here that if the graph D is not a rose, then the transition weights depend only on the loop number of D. We provide an example in Fig. 3.7 for the case $p^* = 4$.*

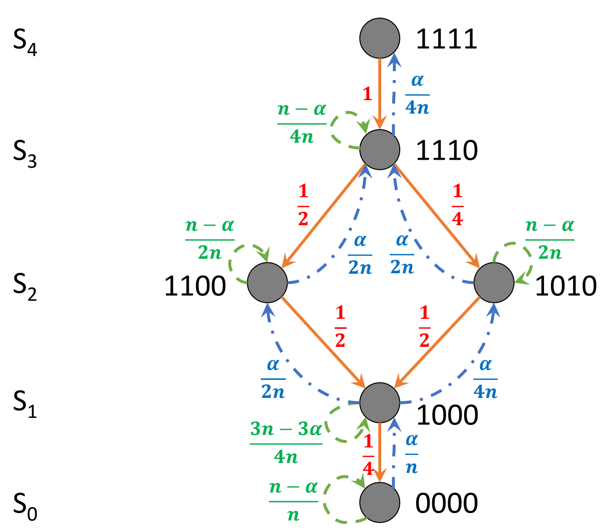

Figure 3.7: The values of the transition weights $P(s_i, s_j)$ are labeled on the edge of the stability structure H for the case where D has loop number $p^* = 4$.

Proof of Proposition 7. Let $s_i = \{x(t_0), \ldots, x(t_0 + p - 1)\}$ be a periodic orbit, and s_j be a successor of s_i. We first introduce some notations. For a time step t, for $t_0 \leq t \leq t_0 + p^* - 1$, we let $\mu_t^*(s_i, s_j)$ be the number of pairs $(x(t), x')$, for $x' \in \mathcal{I}(x(t))$, such that the trajectory of the CBN, with x' the initial condition, enters into s_j. We further let $\mu^*(s_i, s_j) = \sum_{t=t_0}^{t_0+p^*-1} \mu_t^*(s_i, s_j)$. Then, from its definition, we have the following relation:

$$P(s_i, s_j) = \frac{\mu(s_i, s_j)}{np} = \frac{\mu^*(s_i, s_j)}{np^*}.$$

We now evaluate $\mu_t^*(s_i, s_j)$ for each $t = t_0, \ldots, t_0 + p^* - 1$.

Let $G_k = (U_k, F_k)$, for $k = 0, \ldots, p^* - 1$, be irreducible components of D. From Corollary 1, we can write $x_{U_k}(t) = y_k(t)\mathbf{1}$ for all $k = 0, \ldots, p^* - 1$. We identify s_i with $y_0(t) \ldots y_{p^*-1}(t)$, and s_j with $y'_0 \ldots y'_{p^*-1}$. We further let $\Gamma(t)$ be a subset of $\{0, \ldots, p^* - 1\}$ defined as follows: an index k is in $\Gamma(t)$ if the binary necklace $y'_0 \ldots y'_{p^*-1}$ can be obtained from $y_0(t) \ldots y_{p^*-1}(t)$ by negating the value of $y_k(t)$.

We now relate $\Gamma(t)$ and $\Gamma(t')$ for two different time steps t and t'. In particular, we show that if $k \in \Gamma(t)$, then

$$((k + t' - t) \bmod p^*) \in \Gamma(t'). \tag{3.6}$$

To see this, note that from the second item of Theorem 1, we have that for all $k = 0, \ldots, p^* - 1$,

$$x_{U_{(k+t'-t) \bmod p^*}}(t') = x_{U_k}(t),$$

and hence

$$y_{(k+t'-t) \bmod p^*}(t') = y_k(t),$$

which implies (3.6).

We first evaluate the transition weights for down-edges. Note that since $s_i \succ s_j$, $y_k(t) = 1$ for all $k \in \Gamma(t)$, and moreover, $|\Gamma(t)| = \gamma(s_i, s_j)$. To proceed, we fix an index $k \in \{0, \ldots, p^* - 1\}$, and assume that $x_{U_k}(t) = \mathbf{1}$, and let $x' \in \mathcal{I}(x(t))$ be derived by negating an entry of x_{U_k}. Then, from Proposition 6, the trajectory, with x' the initial condition, will enter a periodic orbit, which can be identified as the following binary necklace:

$$y_0(t) \ldots y_{k-1}(t)\, 0\, y_{k+1}(t) \ldots y_{p^*-1}(t).$$

So, $y'_0 \dots y'_{p^*-1}$ coincides with the binary necklace above if and only if $k \in \Gamma(t)$. It then follows that

$$\mu_t^*(s_i, s_j) = \sum_{k \in \Gamma(t)} |U_k|. \tag{3.7}$$

Then, by combining (3.6) and (3.7) with the fact that $|\Gamma(t)| = \gamma(s_i, s_j)$ for all t, we obtain

$$\begin{aligned} \mu^*(s_i, s_j) &= \textstyle\sum_{t=0}^{p^*-1} \mu_t^*(s_i, s_j) \\ &= \textstyle\sum_{t=0}^{p^*-1} \sum_{k \in \Gamma(t)} |U_k| \\ &= \gamma(s_i, s_j) \textstyle\sum_{k=0}^{p^*-1} |U_k| = \gamma(s_i, s_j) n. \end{aligned}$$

Thus, for the case $s_i \succ s_j$ and $\sigma(s_i) - \sigma(s_j) = 1$, we obtain $P(s_i, s_j) = \gamma(s_i, s_j)/p^*$.

We next evaluate the transition weights for up-edges. Note that since $s_i \prec s_j$, $y_k(t) = 0$ for all $k \in \Gamma(t)$, and moreover, $|\Gamma(t)| = \gamma(s_j, s_i)$. To proceed, we fix an index $k \in \{0, \dots, p^* - 1\}$, and assume that $x_{U_k}(t) = \mathbf{0}$, and let $x' \in \mathcal{I}(x(t))$ be derived by negating an entry of x_{U_k}. We know from Proposition 6 that if $|U_k| = 1$, then the trajectory, with x' the initial condition, will enter a periodic orbit identified as:

$$y_0(t) \dots y_{k-1}(t)\, 1\, y_{k+1}(t) \dots y_{p^*-1}(t),$$

and vice versa. So, $y'_0 \dots y'_{p^*-1}$ coincides with the binary necklace above if and only if $k \in \Gamma(t)$ and $|U_k| = 1$. It then follows that

$$\mu_t^*(s_i, s_j) = \sum_{k : \left\{ \substack{k \in \Gamma(t) \\ |U_k| = 1} \right\}} |U_k|. \tag{3.8}$$

Then, by combining (3.6) and (3.8) with the fact that $|\Gamma(t)| = \gamma(s_j, s_i)$ for all t, we obtain

$$\begin{aligned} \mu^*(s_i, s_j) &= \textstyle\sum_{t=0}^{p^*-1} \mu_t^*(s_i, s_j) \\ &= \textstyle\sum_{t=0}^{p^*-1} \sum_{k : \left\{ \substack{k \in \Gamma(t) \\ |U_k| = 1} \right\}} |U_k| \\ &= \gamma(s_j, s_i) \textstyle\sum_{\substack{k = 0, \dots, p^*-1 \\ |U_k| = 1}} |U_k| = \gamma(s_j, s_i) \alpha. \end{aligned}$$

Thus, for the case $s_i \succ s_j$ and $\sigma(s_i) - \sigma(s_j) = 1$, we obtain $P(s_i, s_j) = \alpha \gamma(s_j, s_i)/(np^*)$.

As a final step, we evaluate the transition weights for self-loops. To proceed, we fix an index $k \in \{0, \ldots, p^* - 1\}$, and assume that $x_{U_k}(t) = \mathbf{0}$, and let $x' \in \mathcal{I}(x(t))$ be derived by negating an entry of x_{U_k}. We know from Proposition 6 that if $|U_k| > 1$, then the trajectory, with x' the initial condition, will enter a periodic orbit identified as:

$$y_0(t) \ldots y_{k-1}(t)\, 0\, y_{k+1}(t) \ldots y_{p^*-1}(t),$$

and vice versa. So, $y'_0 \ldots y'_{p^*-1}$ coincides with the binary necklace above if and only if $x_{U_k}(t) = \mathbf{0}$ and $|U_k| > 1$. It then follows that

$$\mu^*_t(s_i, s_j) = \sum_{k : \left\{ \substack{x_{U_k}(t) = \mathbf{0} \\ |U_k| > 1} \right\}} |U_k|. \tag{3.9}$$

Following the second item of Theorem 1, we have that if $k \in \{k : x_{U_k}(t) = \mathbf{0}\}$, then

$$((k + t' - t) \bmod p^*) \in \{k : x_{U_k}(t') = \mathbf{0}\}. \tag{3.10}$$

Now, by combining (3.9) and (3.10) with the fact that $|\{k : x_{U_k}(t) = \mathbf{0}\}| = (p^* - \sigma(s_i))$ for all t, we obtain

$$\begin{aligned} \mu^*(s_i, s_j) &= \textstyle\sum_{t=0}^{p^*-1} \mu^*_t(s_i, s_j) \\ &= \textstyle\sum_{t=0}^{p^*-1} \sum_{k : \left\{ \substack{x_{U_k}(t) = \mathbf{0} \\ |U_k| > 1} \right\}} |U_k| \\ &= (p^* - \sigma(s_i)) \textstyle\sum_{\substack{k = 0, \ldots, p^*-1 \\ |U_k| > 1}} |U_k| \\ &= (p^* - \sigma(s_i))(n - \alpha). \end{aligned}$$

Thus, for the case $s_i = s_j$ and $\sigma(s_i) \neq p^*$, we obtain $P(s_i, s_j) = (p^* - \sigma(s_i))(n - \alpha)/(np^*)$. ■

Chapter 4

CONTROLLABILITY ANALYSIS

4.1 Problem Formulation

In this section, we formally introduce the problem of how to control a CBN. Specifically, we assume that there is a selected subset of nodes whose Boolean values can be controlled at any time. We address in this chapter the following controllability question:

Q: How can one steer a CBN from any initial state to any final state (or any periodic orbit) by controlling the values of the selected nodes?

We provide a complete answer to this question toward the end of this chapter.

To proceed, we first introduce the control model in precise terms. Let $D = (V, E)$ be the dependency graph of a CBN. A node v_i of D is said to be a **control node** if its value at any time step is determined completely by an external control input. We denote by V^* the subset of V, comprising all the control nodes in the network. Then, the control model can be described as follows:

$$x_i(t) = \begin{cases} u_i(t) & \text{if } v_i \in V^*, \\ f_i(x(t-1)) & \text{otherwise,} \end{cases} \tag{4.1}$$

where the $u_i(\cdot)$'s are the external control inputs, and the f_i's are the Boolean functions given by (2.2). For example, if the u_i's are constant, then (4.1) simply models the mutants in genetic networks (i.e., $u_i = 0$ represents a knock out of gene i). We now introduce the following definitions:

Definition 10 (Orbit-controlling set)**.** *A subset $V^* \subseteq V$ is an* **orbit-controlling set** *for* (2.2) *if for any initial condition $x \in \mathbb{F}_2^n$ and any periodic orbit $\mathcal{O}$ of system* (2.2)*, there exists a time T and a set of control laws $u_i(t)$, for $v_i \in V^*$ and $0 \leq t \leq T$, such that the trajectory generated by system* (4.1) *with $x(0) = x$, reaches a state in $\mathcal{O}$ at $t = T$.*

Definition 11 (State-controlling set)**.** *A subset $V^* \subseteq V$ is a* **state-controlling set** *for* (2.2) *if for any initial condition x and any final state x^*, there exists a time T and a set of control laws $u_i(t)$ for $v_i \in V^*$ and $0 \leq t \leq T$ such that the trajectory generated by system* (4.1) *with $x(0) = x$, reaches x^* at $t = T$.*

Note that a state-controlling set is an orbit-controlling set, but the converse is not necessarily true. Also, note that a state-controlling set always exists as one can set $V^* = V$. In this case, each node is a control node, and if we let $u_i(0) = x_i^*$, for all $v_i \in V$, then $x(0) = x^*$. However, the cost of controlling every node in the network could be extremely high, especially when the size of the network is large. From the biological perspective, controlling all genes in a bio-system is generally not feasible. One thus looks for a proper subset V^*, with $|V^*| \ll |V|$, such that V^* is an orbit-controlling set (resp. state-controlling set). We take in this chapter the first step to solve such a minimal controllability problem by providing a necessary and sufficient condition for a set V^* to be an orbit-controlling (resp., a state-controlling) set.

We recall that for a node v_i, with $v_i \notin V^*$, the value $x_i(t)$ depends on the values of its incoming neighbors at time $(t-1)$:

$$x_i(t) = \prod_{v_j \in \mathcal{N}_{\text{in}}(v_i)} x_j(t-1). \tag{4.2}$$

The in-edges of v_i thus demonstrate the information flow at the node v_i. On the other hand, if v_i is a control node, then from the model (4.1), the value $x_i(t)$, at any time t, is determined completely by an external input, rather than the values of its incoming neighbors. Thus, the in-edges of v_i in the dependency graph D are unnecessary for the control model (4.1). We thus modify the definition of the dependency graph to accommodate the existence of control nodes by deleting the in-edges of each control node in V^*. Specifically, we have the following definition:

Definition 12 (Derived graph [49])**.** *Let $D = (V, E)$ be the dependency graph associated with a CBN. Let $V^* \subset V$ be the set of control nodes associated with system* (4.1)*. The* **derived graph** *$D' = (V, E')$ is a digraph, with V the node set and $E' = E \setminus \cup_{u \in V^*} \mathcal{E}_{\text{in}}(u)$ the edge set.*

4.2 Orbit-controllability

We investigate in this section the orbit-controllability of a CBN. To proceed, we first note that the asymptotic behavior of a CBN was investigated mostly over strongly connected digraphs, and little is known for other cases. In particular, it is known that the periodic orbits of strongly connected CBNs can be identified with binary necklaces of a certain length: Let $D = (V, E)$ be strongly connected, and denote by $D_1 = (V_1, E_1), \ldots, D_N = (V_N, E_N)$, with $V_i \subset V$ and $E_i \subset E$, the cycles of D. Let n_i be the length of D_i, and p^* be the greatest common divisor of n_i, for $i = 1, \ldots, N$:

$$p^* := \gcd\{n_1, n_2, ..., n_N\},$$

which is also known as the *loop number* of D [23]. We need the following fact:

Lemma 8. *If the dependency graph is strongly connected, then the period of the associated CBN is a divisor of p^*. Furthermore, there is a bijection between the set of periodic orbits and the set of binary necklaces of length p^*: We identify a periodic orbit $\{x(t_0), \ldots, x(t_0 + p - 1)\}$ with the corresponding binary necklace $x_i(t_0)x_i(t_0+1)\ldots x_i(t_0+p^*-1)$, where the choice of a vertex v_i can be arbitrary.*

We refer to [26, 47, 77] for proofs of Lemma 8. As in Chapter 3, we let S be the set of periodic orbits. Note, in particular, that from Lemma 8 the two binary necklaces $s = 0\ldots0$ and $s = 1\ldots1$ correspond to the fixed points $x = (0, \ldots, 0)$ and $x = (1, \ldots, 1)$, respectively. We further introduce the following definition: With the preliminaries above, we establish the first main result of this chapter:

Theorem 3. *Let the dependency graph $D = (V, E)$ of a conjunctive Boolean network be strongly connected. Then, a subset V^* is an orbit-controlling set if and only if the associated derived graph D' is acyclic.*

Remark 7. *Recall that a source node is defined as a vertex with no in-edges. Since D is strongly connected, there is no source node in D. In D', however, we have eliminated all in-edges of vertices in V^*. Thus, if D' is acyclic, then the nodes in V^* are necessarily the source nodes of D' and vice versa.*

Recall that $V_1, \ldots, V_N$ are the vertex sets of the cycles of D. Then, the statement of Theorem 3 is equivalent to the following statement: $V^* \subseteq V$ is an orbit-controlling set if and only if

$$V^* \cap V_i \neq \varnothing, \ \ \forall i = 1, \ldots, N. \tag{4.3}$$

Illustration of Theorem 3. We consider here a CBN with two different sets of control nodes, as shown in Fig. 4.1. The associated derived graphs are shown in Fig. 4.2, which are acyclic. Thus in both cases, the control nodes (vertices colored blue) form an orbit-controlling set. To check (4.3), we note that there are two cycles in the graph, whose vertex sets are $V_1 = \{v_1, v_2, v_3, v_4, v_5, v_6\}$ and $V_2 = \{v_1, v_2, v_7, v_8\}$, respectively. On the left of Fig. 4.1 (and Fig. 4.2), $V^* = \{v_2\}$, and thus

$$V^* \cap V_1 = V^* \cap V_2 = \{v_2\} \neq \varnothing.$$

On the right of Fig. 4.1 (and Fig. 4.2), $V^* = \{v_4, v_7\}$, and thus

$$V^* \cap V_1 = \{v_4\} \neq \varnothing, \quad V^* \cap V_2 = \{v_7\} \neq \varnothing.$$

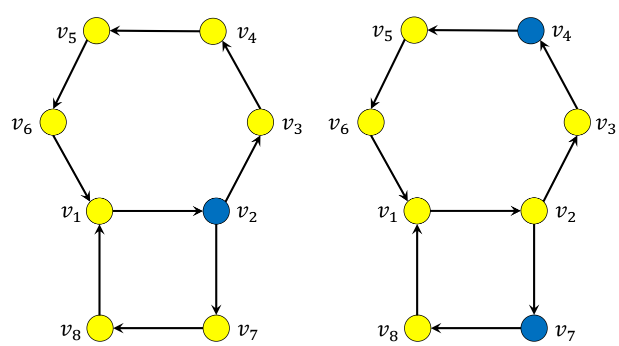

Figure 4.1: Two examples of orbit-controlling sets. Vertices colored blue are in the orbit-controlling set. The graph has two cycles. In the left figure, the only vertex in the orbit-controlling set is shared by both cycles. In the right figure, we have picked one vertex in each cycle to be in the orbit-controlling set.

The remainder of this section is devoted to the proof of Theorem 3. We first introduce a notation: For a subset $V' = \{v_{i_1}, \ldots, v_{i_m}\}$ of V, we define $x_{V'} := (x_{i_1}, \ldots, x_{i_m})$. We then first prove the necessity, i.e., if V^* is an orbit-controlling set, then $V^* \cap V_i \neq \varnothing$, $\forall i = 1, \ldots, N$.

Proof of necessity of (4.3). The proof is carried out by contradiction. Suppose to the contrary that for some cycle D_i, $V^* \cap V_i = \varnothing$. Then, given an initial condition $x(0) = (0, \ldots, 0) \in \mathbb{F}_2^n$, it is never possible for the trajectory to reach the periodic orbit $s = 1 \ldots 1$. To see this, recall that $s = 1 \ldots 1$ corresponds to the fixed point $x = (1, \ldots, 1)$, which is the only state in s. Then, for each vertex $v_j \in V_i$, there is

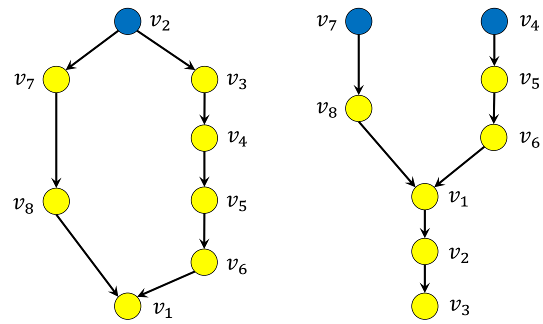

Figure 4.2: Two examples of D'. The left (right) figure is obtained by removing the in-edges of vertices in the orbit-controlling set in the left (right) figure of Fig. 4.1. It can be seen that the D' obtained this way is acyclic, and the set of source nodes is exactly the orbit-controlling set.

a vertex $v_k \in V_i$ such that $v_k \in \mathcal{N}_{\text{in}}(v_j)$. Since $x_k(0) = 0$, $x_j(1) = 0$ by the value update rule. Thus,

$$x_{V_i}(t) = x_{V_i}(t-1) = \cdots = x_{V_i}(0) = (0, \ldots, 0),$$

which implies that the trajectory will never enter $s = (1, \ldots, 1)$. This contradicts our initial assumption that V^* is an orbit-controlling set. ■

We next prove the sufficiency, i.e., if (4.3) is satisfied, then V^* is an orbit-controlling set. We will first provide an algorithm, Algorithm 1, in which we assign values to the control nodes (i.e., the entries of x_{V^*}) along time so that the trajectory generated by the control system, with any given initial condition $x(0)$, will enter the desired periodic orbit $s = y_0 \ldots y_{p^*-1}$. The algorithm comprises two parts. The first part is from line 2 to line 7, where we always assign "1" to all entries of x_{V^*} until the trajectory enters the periodic orbit $s' = 1 \ldots 1$. We note that from a biological perspective, assigning "1" to a vertex v_i means providing the product of the corresponding gene i (usually proteins) to the system. Equivalently, the gene i can be equivalently viewed as at "on" status in the system. The second part is from line 8 to line 11, where we sequentially assign the values from the desired periodic orbit (represented by a binary necklace $y_0 \ldots y_{p^*-1}$) to any single vertex in V^*.

Illustration of Algorithm 1. We consider the CBN whose dependency graph is shown in Fig. 4.1. The loop number p^* is 2, and hence a periodic orbit of the system is identified with a binary necklace of length 2. Suppose that the desired

Algorithm 1 Control law for orbit-controlling

procedure CONTROL(V^*, s)
    $t \leftarrow 0$
    while $x(t) \neq (1, \ldots, 1) \in \mathbb{F}_2^n$ **do**
        $x_{V^*}(t) \leftarrow (1, \ldots, 1)$
        $t \leftarrow t + 1$
    end while
    $\tau \leftarrow t$
    pick any $v_i \in V^*$
    for $t' := 0$ **to** $p^* - 1$ **do**
        $x_i(\tau + t') \leftarrow y_{p^*-1-t'}$;
    end for
end procedure

periodic orbit is $s = 01$. Then, for the control system on the left of Fig. 4.1 with $V^* = \{v_2\}$, the control inputs obtained from Algorithm 1 are given by

Step t	0	1	2	3	4	5	6	7
$x_2(t)$	1	1	1	1	1	1	0	1

In this case, $\tau = 6$. The system will enter the periodic orbit $s = 01$ at time step $(\tau + 7)$ as illustrated in Fig. 4.3.

For the control system on the right of Fig. 4.1 with $V^* = \{v_4, v_7\}$, the control inputs are given by

Step t	0	1	2	3	4	5	6	7
$x_4(t)$	1	1	1	1	1	1	1	1
$x_7(t)$	1	1	1	1	1	1	0	1

In either case, the control inputs will drive the system from any initial condition to enter the periodic orbit s.

Validating Algorithm 1. According to Algorithm 1, the proof of the validity is divided into two parts.

Part I: Driving the system to the state $x = (1, \ldots, 1)$ We show here that the first part of Algorithm 1 (specifically, the "while" loop) will be terminated in at most n time steps:

Proposition 8. *If the derived graph D' associated with the control system* (4.1) *is acyclic, then by setting $u_i(t) = 1$ for all $v_i \in V^*$ and $0 \leq t \leq n - 1$, we have that $x(n - 1) = (1, \ldots, 1)$. In particular, $\tau \leq (n - 1)$.*

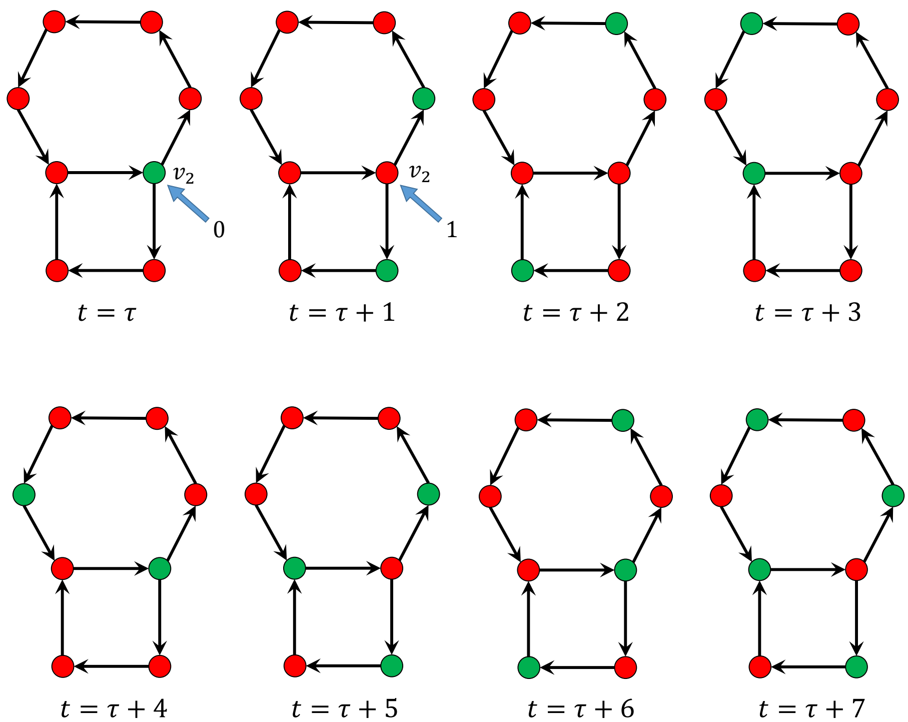

Figure 4.3: Illustrations of the second part of the control procedure described in Algorithm 1. Specifically, it shows the system states from $t = \tau$ to $t = \tau + 7$. We use the red (resp. green) color to denote that the corresponding node is holding value "1" (resp. "0"). We assign to the node v_2 the values 0 and 1 at the time steps $t = \tau$ and $t = \tau + 1$, respectively. With these assignments, the system will enter the periodic orbit $s = 01$ at the time step $t = \tau + 7 = 13$.

Proof. Suppose that, to the contrary, $x(n-1) \neq (1, \ldots, 1)$. Without loss of generality, take $x_i(n-1) = 0$. Since the value of each control node is fixed to be "1", $v_i \notin V^*$, and hence $\mathcal{N}_{\text{in}}(v_i; D') \neq \varnothing$. By value update rule, there exists a vertex $v_{i_1} \in \mathcal{N}_{\text{in}}(v_i; D')$ with $x_{i_1}(n-2) = 0$. Similarly, we have that $v_1 \notin V^*$ and there exists a vertex $v_{i_2} \in \mathcal{N}_{\text{in}}(v_1; D')$ with $x_{i_2}(n-3) = 0$. Repeating this argument, we find vertices $v_{i_1}, \ldots, v_{i_{n-1}} \notin V^*$ such that

$$x_i(n-1) = x_{i_1}(n-2) = \cdots = x_{i_{n-1}}(0) = 0.$$

On the other hand, there are only n vertices in D'. We thus have $v_{i_j} = v_i$ for some $j \in \{1, \ldots, n-1\}$. But then, there is a cycle $v_{i_j} v_{i_{j-1}} \ldots v_{i_1} v_i$ in D' which is a contradiction. ■

Part II: Driving the system from $x = (1, \ldots, 1)$ to the periodic orbit s We show here that after performing the "for" loop of Algorithm 1, the trajectory of the system states will enter the periodic orbit s. Recall that s is represented by a binary necklace of length p^*: $s = y_0 \ldots y_{p^*-1}$. If $s = 1 \ldots 1$, then we are done by the first part of the Algorithm 1 (lines 2-7). Otherwise, we need to execute the second part of the algorithm (lines 8-11). As a result, we provide the following proposition, whose proof is given in the Appendix.

Proposition 9. *Fix a vertex $v_i \in V$, and write $s = y_0 \ldots y_{p^*-1}$. After executing the control law given in Algorithm 1, the state x at time $\tau + p^* - 1$ is given by*

$$\begin{aligned} x_{\mathcal{N}^j_{\text{out}}(v_i)}(\tau + p^* - 1) &= y_j \mathbf{1},\ \forall j = 0, \ldots, p^* - 1 \\ x_r(\tau + p^* - 1) &= 1,\ \ \forall v_r \notin \cup_{j=0}^{p^*-1} \mathcal{N}^j_{\text{out}}(v_i), \end{aligned} \tag{4.4}$$

where $\mathbf{1}$ is a vector of all ones with an appropriate dimension. Moreover, a trajectory generated by the system (2.2)*, with the initial condition* (4.4)*, will enter the periodic orbit s after finite time steps.*

Remark 8. *Recall that the "while" loop takes a maximum of $(n - 1)$ time steps, and the "for" loop takes p^* time steps. Therefore, the maximum total time it takes to control the network is $(n + p^* - 1)$. The time it takes for the system to finally enter the periodic orbit, however, can be longer.*

Combining Proposition 8 and Proposition 9 leads to the sufficiency part of Theorem 3. The rest of this section is devoted to the proof of Proposition 9. It should be clear that after executing the "while" loop of Algorithm 1, the state of the system is given by $x(\tau - 1) = (1, \ldots, 1)$. Then, by assigning y_0 to x_i at time τ, we have $x_i(\tau) = y$ and $x_j(\tau) = 1$ for all $v_j \neq v_i$. We first have the following lemma.

Lemma 9. *Let $D = (V, E)$ be the dependency graph of a CBN. Let $v_i \in V$ be arbitrary, and without loss of generality, assume that $v_i \in U_0$. Let the initial condition be $x_i(0) = y$ and $x_j(0) = 1$ for all $v_j \in U_0$. Then, for $t' = 0, \ldots, p^* - 1$, we have*

$$x_{\mathcal{N}^{t'}_{\text{out}}(v_i)}(t') = y\mathbf{1}. \tag{4.5}$$

Proof. The proof is carried out by induction on t'. For the base case $t' = 0$, it is true since $\mathcal{N}^0_{\text{out}}(v_i) = \{v_i\}$, and hence $x_{\mathcal{N}^0_{\text{out}}(v_i)}(0) = x_i(0) = y$ by assumption.

For the induction step, we assume that (4.5) holds for $t' = k$, where $0 \leq k < p^* - 1$; then we show that (4.5) holds for $t' = k + 1$.

Let v_a be an arbitrary vertex in $\mathcal{N}_{\text{out}}^{k+1}(v_i)$, and $v_b \in \mathcal{N}_{\text{in}}(v_a) \cap \mathcal{N}_{\text{out}}^{k}(v_i)$. Then, by Lemma 3, $v_a \in U_{k+1}$ and $v_b \in U_k$. Thus, $\mathcal{N}_{\text{in}}(v_a) \subseteq U_k$. By induction assumption, $x_b(k) = y$. If $y = 0$, then $x_a(k + 1) = x_b(k) = 0 = y$. If $y = 1$, then $x_U(0) = \mathbf{1}$ by assumption. Again from Lemma 3, $\mathcal{N}_{\text{in}}(U_1) = U_0, \mathcal{N}_{\text{in}}(U_2) = U_1, \ldots, \mathcal{N}_{\text{in}}(U_{k+1}) = \mathcal{N}_{\text{in}}(U_k)$. Thus, $x_{U_{k+1}}(k + 1) = x_{U_k}(k) = \ldots = x_{U_0}(0) = \mathbf{1}$. This leads to $x_a(k + 1) = 1 = y$. ■

To proceed, we need to revisit a fact that we provided in Section 3.2.1. Recall that in Proposition 5, we have shown that there is a bijection between the set of periodic orbits and the set of binary necklaces of length p^*. The bijection map can be described as follows: First, in Corollary 1, we have shown that a state $x \in \mathbb{F}_2^n$ is in a periodic orbit if and only if for each $k = 0, \ldots, p^* - 1$, the entries of x_{U_k} hold the same value. Therefore, we represent this periodic orbit as a binary necklace $s = y_0 \ldots y_{p^*-1}$, by taking the value of the entries of x_{U_k} as y_k, for all $k = 0, \ldots, p^* - 1$.

With the above fact and Lemma 9 at hand, we now prove Proposition 9.

Proof of Proposition 9. We first show that the state x at time $(\tau + p^* - 1)$ is given by (4.4).

Without loss of generality, assume that $v_i \in U_0$. Then, by assigning y_{p^*-1} to x_i at time τ, we have $x_i(\tau) = y_{p^*-1}$ and $x_j(\tau) = 1$ for all $v_j \neq v_i$. Then, by applying Lemma 9 with $t' = p^* - 1$, we obtain that $x_{\mathcal{N}_{\text{out}}^{p^*-1}(v_i)}(T + p^* - 1) = y_{p^*-1}\mathbf{1}$. At time $\tau + 1$, we are assigning $x_i(\tau + 1) = y_{p^*-2}$. Note that $U_0, \ldots, U_{p^*-1}$ are pairwise distinct since they form a partition of V. Thus, $x_{U_0}(\tau + 1) = x_{U_{p^*-1}}(\tau) = \mathbf{1}$. We can then apply Lemma 9 again with $t' = p^* - 2$ to obtain that $x_{\mathcal{N}_{\text{out}}^{p^*-2}(v_i)}(\tau + p^* - 1) = y_{p^*-2}\mathbf{1}$. Continuing on this pattern, we will finally obtain that $x_{\mathcal{N}_{\text{out}}^{j}(v_i)}(\tau + p^* - 1) = y_j\mathbf{1}$ for all $j = 0, \ldots, p^* - 1$. Any vertices not reached by the assigned values at time $\tau + p^* - 1$ still hold "1". Thus, the state x at time $(\tau + p^* - 1)$ is given by (4.4).

We then show that the system (2.2), with (4.4) being the initial condition, will enter the periodic orbit s. Without loss of generality, assume that $v_i \in U_0$; then $\mathcal{N}_{\text{out}}^{j}(v_i) \subseteq U_j$ for $j = 0, \ldots, p^* - 1$.

If $y_j = 0$, then $x_{U_j}(0)$ contains an entry of value 0. Consider the induced dynamics on G_j: First, from the value update rule and the first item of Proposition 1, if $x_{U_j}(0)$ contains an entry of value 0, then so does $x_{U_j}(tp^*)$ for all $t \geq 0$. Second, since G_0 is irreducible, a periodic orbit of the induced dynamics has to be a fixed point [26, 77]. Combining these two facts, we know that there is a time $t_0 \geq 0$ such that $x_{U_j}(tp^*) = \mathbf{0}$ for all $t \geq t_0$.

If $y_j = 1$, then $x_{U_j}(0) = \mathbf{1}$. We appeal again to the first item of Theorem 1 and obtain

$$x_{U_j}(tp^*) = f_{U_j}^{tp^*}(x_{U_j}(0)) = g_j^t(x'_{U_j}(0)) = x_{U_j}(0) = \mathbf{1}.$$

Therefore, we conclude that $x_{U_j}(t_0 p^*) = y_j \mathbf{1}$, and this holds for all $j = 0, \ldots, p^* - 1$. The system is thus in periodic orbit $s = y_0 \ldots y_{p^*-1}$. ■

4.3 State-controllability

In this section, we investigate the state-controllability of a CBN. We do *not* require that the dependency graph D be strongly connected. The main result of the section is stated as follows:

Theorem 4. *A subset $V^* \subseteq V$ is a state-controlling set if and only if the associated derived graph D' satisfies the following conditions:*

1. *The derived subgraph D' is acyclic.*
2. *For any $v \in V$, there exists a control node $u \in V^*$ and an integer $k \geq 0$ such that $\mathcal{N}_{\mathrm{out}}^k(u; D') = \{v\}$.*

Note that the first item of Theorem 4 is itself a necessary and sufficient condition for V^* to be an orbit-controlling set. The second item is thus a necessary and sufficient condition for an orbit-controlling set to be a state-controlling set.

Illustration of Theorem 4. We consider again the example shown in Fig. 4.1, where we have a CBN with two different sets of control nodes. Recall that the associated derived graphs are acyclic in both cases (given in Fig. 4.2). Thus, the two sets of control nodes are both orbit-controlling sets. However, only the control nodes on the right of Fig. 4.1 form a state-controlling set. Indeed, we have

$$\begin{aligned}
&\mathcal{N}^2_{\text{out}}(v_7) = \mathcal{N}^3_{\text{out}}(v_4) = \{v_1\},\\
&\mathcal{N}^3_{\text{out}}(v_7) = \mathcal{N}^4_{\text{out}}(v_4) = \{v_2\},\\
&\mathcal{N}^4_{\text{out}}(v_7) = \mathcal{N}^5_{\text{out}}(v_4) = \{v_3\},\\
&\mathcal{N}^0_{\text{out}}(v_4) = \{v_4\},\\
&\mathcal{N}^1_{\text{out}}(v_4) = \{v_5\},\\
&\mathcal{N}^2_{\text{out}}(v_4) = \{v_6\},\\
&\mathcal{N}^0_{\text{out}}(v_7) = \{v_7\},\\
&\mathcal{N}^1_{\text{out}}(v_7) = \{v_8\},
\end{aligned}$$

where all the out-neighbors are taken within D'. Thus, the second condition of Theorem 4 is satisfied. On the other hand, the set of control nodes on the left of Fig. 4.1 is *not* a state controlling set. To see this, we note that the node v_4 of the left DAG only lies in $\mathcal{N}^2_{\text{out}}(v_2)$, but $\mathcal{N}^2_{\text{out}}(v_2) = \{v_4, v_8\} \neq \{v_4\}$, and hence the second condition of Theorem 4 is not satisfied.

We prove in the remainder of this section Theorem 4. The necessity and sufficiency of the two conditions listed in Theorem 4 are established subsequently in the following subsections.

4.3.1 Necessity

We prove here the necessity part of Theorem 4. Specifically, we show that if V^* is a state-controlling set, then the two conditions in Theorem 4 must hold. The necessity of the first condition should be clear as a state-controlling set is necessarily an orbit-controlling set.

We establish below the necessity of the second condition. The proof will be carried out by contradiction. Specifically, we assume that the derived graph D' is a DAG which does not satisfy the second item in Theorem 4. We then show that system (4.1) is not controllable. To proceed, we first have some preliminaries on the control dynamics (4.1). From (4.2), we have that for any $v_i \notin V^*$,

$$x_i(t) = \prod_{v_j \in \mathcal{N}_{\text{in}}(v_i; D')} x_j(t-1).$$

For each $v_j \in \mathcal{N}_{\text{in}}(v_i; D')$, we have two cases: If v_j is a control node, then we keep the factor $x_j(t-1)$ in (4.2). If v_j is not a control node, then v_j has a nonempty set of incoming neighbors. We can thus appeal again to (4.2) and replace the factor $x_j(t-1)$ in (4.2) with the following expression:

$$x_j(t-1) = \prod_{v_k \in \mathcal{N}_{\text{in}}(v_j; D')} x_k(t-2).$$

Since D' is a DAG, by recursively applying the arguments above, we obtain that

$$x_i(t) = \prod_{v_j \in V_i^*} \prod_{p \in P_{ji}} x_j(t - l(p)), \tag{4.6}$$

where $V_i^* \subseteq V^*$ is a subset of the set of source nodes such that there is at least one path from v_j to v_i for all $v_j \in V_i^*$. We recall that P_{ji} is the set of paths (within D') from v_j to v_i and $l(p)$ is the length of path p. Since the nodes v_j's in (4.6) are the control nodes of D', we call (4.6) the **control expression** of $x_i(t)$. In Fig. 4.4, we provide an example where we write the values of all nodes in their control expression form.

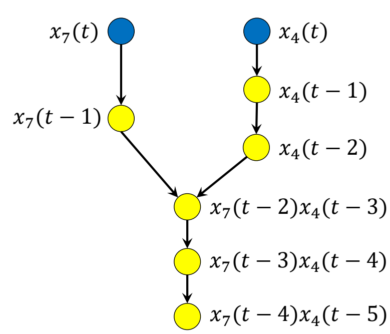

Figure 4.4: The DAG in this figure is the derived graph of the dependency graph shown on the right of Fig. 4.1. The two nodes v_7 and v_4 (marked in blue) form a state-controlling set. The values of all nodes at time t are expressed in their control expression form.

With the preliminaries above, we are now in a position to prove the necessity of the second condition of Theorem 4.

Proof of necessity of condition 2. Let $v_i \in V$ be a node such that $\mathcal{N}^k_{\text{out}}(u; D') \neq \{v_i\}$ for any $u \in V^*$ and any $k \geq 0$. We now show that system (4.1) cannot be driven from an initial state $(1, \ldots, 1)$ to the final state x^* where $x_i^* = 0$ and $x_s^* = 1$ for all $v_s \neq v_i$. The proof is carried out by contradiction, i.e., we assume that there is a set of control laws using which we can steer the system to reach $x(t) = x^*$ for some $t \geq 0$.

We let the control expression of $x_i^*(t)$ be given by (4.6). We then pick an arbitrary factor in (4.6), say $x_j(t - l(p_1))$, with $v_j \in V_i^* \cap \mathcal{N}_{\text{in}}^{l(p_1)}(v_i; D')$. By assumption, we have $\mathcal{N}_{\text{out}}^{l(p_1)}(v_j; D') \neq \{v_i\}$. Thus, there exists a node v_s, other than v_i, such that $v_s \in \mathcal{N}_{\text{out}}^{l(p_1)}(v_j; D')$. We then apply the control expression to x_s^*. Note, in particular, that the factor $x_j(t - l(p_1))$ we picked in the control expression of $x_i^*(t)$ is also a factor in the control expression of $x_s^*(t)$. Moreover, since $v_s \neq v_i$ and $x_s^*(t) = 1$, it is necessary that $x_j(t - l(p_1)) = 1$. Since the factor $x_j(t - l(p_1))$ in the control expression of $x_i^*(t)$ is picked arbitrarily, it is necessary that any such factor holds value "1". Thus, $x_i^*(t) = 1$, which is a contradiction. This completes the proof. ■

4.3.2 Sufficiency

We next prove the sufficiency part of Theorem 4. Specifically, we show that if $V^* \subseteq V$ satisfies the two conditions listed in Theorem 4, then V^* is a state-controlling set. The proof will be carried out by exhibiting an explicit control law for steering the system from an arbitrary initial condition to the desired final state x^*. Toward that end, let T be the length of a longest path in the derived graph D'. The following algorithm assigns the values to $x_{V^*}(t)$, for $0 \leq t \leq T$, such that the trajectory generated by the control system (4.1), from an arbitrary initial condition, reaches x^* at time T.

Algorithm 2 Control law for state-controlling

procedure CONTROL(V^*, x^*)
    $T \leftarrow$ length of the longest path in D'
    for $t := 0$ **to** T **do**
        for $v_i \in V^*$ **do**
            if $|\mathcal{N}_{\text{out}}^{T-t}(v_i; D')| == 1$ && $x^*_{\mathcal{N}_{\text{out}}^{T-t}(v_i;D')} == 0$ **then**
                $u_i(t) \leftarrow 0$
                continue
            end if
            $u_i(t) \leftarrow 1$
        end for
    end for
end procedure

The assignment of Algorithm 2 can be interpreted as follows: At time step t and for each control node $v_i \in V^*$, there are two cases: If there exists a node $v_j \in V$ such that $\mathcal{N}_{\text{out}}^{T-t}(v_i) = \{v_j\}$ and $x_j^* = 0$, then we let $u_i(t) = 0$. Otherwise, we let $u_i(t) = 1$. We also note that the values of control nodes assigned by the algorithm above do *not* depend on the initial condition.

Illustration of Algorithm 2. We consider the CBN whose dependency graph (resp. derived graph) is shown on the right of Fig. 4.1 (resp. Fig. 4.2). Suppose that the desired final state is $x^* = \{x_1^*, \ldots, x_8^*\} = \{1, 1, 0, 0, 0, 1, 0, 1\}$; then, the control inputs for x_4 and x_7 obtained from Algorithm 2 are given by:

Step t	0	1	2	3	4	5
$x_4(t)$	0	1	1	1	0	0
$x_7(t)$	1	0	1	1	1	0

With the these inputs, the system will enter the state $x^* = \{1, 1, 0, 0, 0, 1, 0, 1\}$ at time step $t = 5$ as illustrated in Fig. 4.5.

Validating Algorithm 2. We show below that for any $v_j \in V$, the Algorithm 2 leads to $x_j(T) = x_j^*$. There are two cases.

Case I: $x_j^* = 0$. If $v_j \in V^*$, then $\mathcal{N}_{\text{out}}^{T-T}(v_j) = \{v_j\}$, and both "if" conditions in Algorithm 2 are satisfied. Thus, we have that

$$x_j(T) = u_j(T) = 0.$$

If $v_j \notin V^*$, then by the second condition in Theorem 4, there exists a control node $v_i \in V^*$ and an integer k, with $0 < k \leq T$, such that $\mathcal{N}_{\text{out}}^{k}(v_i; D') = \{v_j\}$. At time $t = T - k$, we have that $|\mathcal{N}_{\text{out}}^{T-t}(v_i)| = 1$. Both "if" conditions in Algorithm 2 are satisfied. Thus,

$$x_i(T - k) = u_i(T - k) = 0.$$

Also, $\mathcal{N}_{\text{out}}^{k}(v_i; D') = \{v_j\}$ indicates that there is a path (within D') of length k from v_i to v_j. Appealing to (4.6), we obtain that $x_i(T - k)$ is a factor of the control expression of $x_j(T)$, which leads to

$$x_j(T) = x_i(T - k) = 0.$$

Case II: $x_j^* = 1$. From the control expression (4.6), we obtain

$$x_j(T) = \prod_{v_i \in V_j^*} \prod_{p \in P_{ij}} x_i(T - l(p)).$$

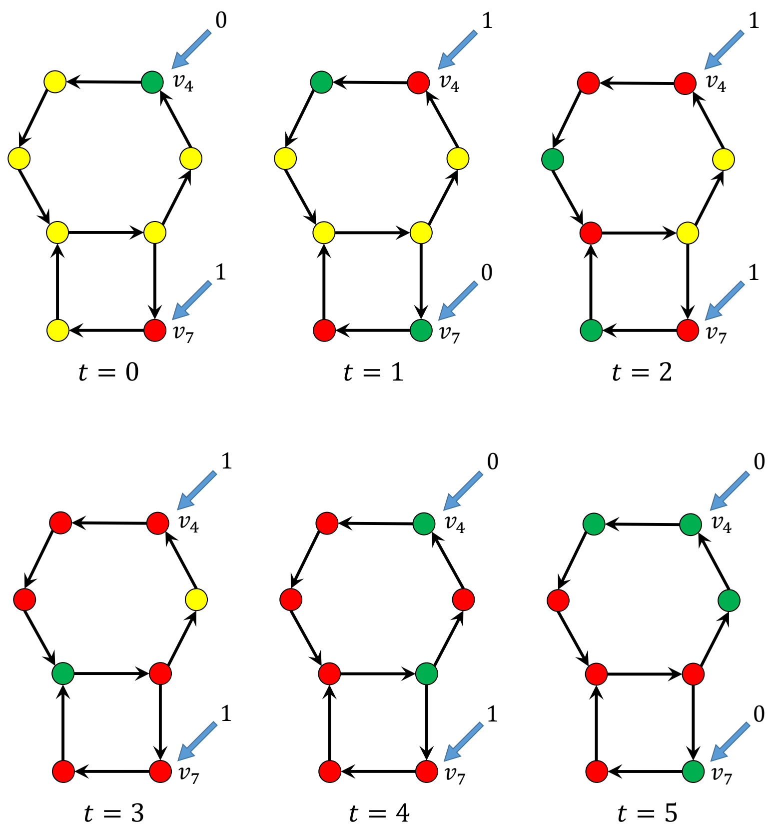

Figure 4.5: Illustration of the control procedure described in Algorithm 2. Specifically, it shows the system states from $t = 0$ to $t = 5$. We use the red (resp. green) color to denote that the corresponding node is holding value "1" (resp. "0"). Vertices are colored yellow if their values are irrelevant, i.e., their values do not affect the control procedure. We assign to the nodes v_4 and v_7 at the time steps $t = 0$ to $t = 5$. With these assignments, the system will enter the state $x^* = \{1, 1, 0, 0, 0, 1, 0, 1\}$ at the time step $t = 5$.

Note that $l(p) \leq T$ because T is the length of a longest path in D'. It now suffices to show that each factor $x_i(T - l(p))$ above is assigned the value "1" under Algorithm 2. Note that there is a path of length $l(p)$ from v_i to v_j, i.e., $v_j \in \mathcal{N}_{\text{out}}^{l(p)}(v_i; D')$. If $|\mathcal{N}_{\text{out}}^{T-(T-l(p))}(v_i)| \neq 1$, then the "if" condition in line 5 of Algorithm 2 is not satisfied. Thus, by the value assignment rule in line 11, we have that

$$x_i(T - l(p)) = u_i(T - l(p)) = 1.$$

If $\mathcal{N}_{\text{out}}^{T-(T-l(p))}(v_i; D') = \{v_j\}$, then the "if" condition in line 5 of Algorithm 2 is satisfied. However, since $x_j^* = 1$, the "if" condition in line 6 is not satisfied. Thus, by the value assignment rule in line 11, we again have that

$$x_i(T - l(p)) = u_i(T - l(p)) = 1.$$

This then establishes the validity of Algorithm 2. We thus complete the proof of Theorem 4. ■

Chapter 5

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

5.1 Conclusions

As a summary, we have investigated in this thesis both stability and controllability problems associated with CBNs.

For stability analysis, we have first introduced a new approach to study the dynamics of a CBN, and investigated the stability structure of the periodic orbits. Specifically, we have proposed a vertex set partition of the dependency graph associated with the CBN, and decomposed the digraph into multiple irreducible components. We have then introduced the induced dynamics on each of the irreducible components, and established in Theorem 1 a relationship between the original CBN and the induced dynamics on the irreducible components. Following this relationship, we have further identified the periodic orbits of the CBN with binary necklaces. By introducing a partial ordering on the set of binary necklaces, we have established in Theorem 2 the stability structure of the periodic orbits. In particular, we have provided in the theorem a necessary and sufficient condition for the existence of a transition from one periodic orbit to another under the condition that a single perturbation occurs to a state of the periodic orbit. The transition weights are also evaluated in Section 3.2.3.

For controllability analysis, we have posed and answered the following two-part controllability question: Given a subset of nodes of the dependency graph, what are the necessary and sufficient conditions for a subset to be an orbit-controlling set or a state-controlling set? The answers were given in Theorem 3 and Theorem 4. In particular, we related the orbit-controllability as well as controllability of system (4.1) to the structure of the derived graph. We have also presented, in Algorithm 1 (resp. Algorithm 2), a method of assigning the values of the control inputs to steer system (4.1) to a desired periodic orbit (resp. final state). Algorithm 1 takes at most $(n + p^* - 1)$ time steps, with n being the number of vertices in the dependency graph and p^* the greatest common divisor of cycle lengths. Algorithm 2 takes at most T time steps, with T being the length of the longest path in the derived graph.

Although systems biology has served as the main motivation for our research, applications of this work are by no means limited to gene regulated networks. CBNs are also suitable to model, for example, water quality networks. In such networks, each Boolean variable can be viewed as the water quality within a pipe. The Boolean variable takes the value "1" if the water is not polluted, and the value "0" if the water is polluted. The water in each pipe comes from some other pipes, and is polluted if the water in one of those other pipes was polluted. Other examples which can be modeled by CBNs include social networks (information flow on Twitter or Facebook), and supply chain networks (movement of materials), and the results of this thesis would also apply to all these networks.

5.2 Directions for Future Research

There are a number of research directions in this area that could be pursued in the future, and we mention here a few of them. First, we recall that the stability structure is constructed by assuming that only a single entry of a state in a periodic orbit is perturbed. A natural question is then to ask what the stability structure would be like if more than one entry of the state is perturbed. We also recall from Proposition 5 and Corollary 2 that the loop number itself is sufficient to determine the set of periodic orbits, and also the stability structure (provided that the dependency graph is not a rose). A future direction following this would be to develop algorithms for computing the loop number (so as to construct the stability structure), and to evaluate the computational complexity of these algorithms.

Another direction is to study the problem of finding the orbit-controlling set and state-controlling set with minimal cardinalities. We note that finding the orbit-controlling set with minimum cardinality is in fact equivalent to finding the minimum cardinality of the so-called **feedback vertex set**, the set of vertices (nodes) whose removal leads to DAG. This problem has been shown to be NP-hard for general graphs in [81], and it has been shown in [82] that finding a minimum feedback vertex set of general undirected graphs with n nodes can be solved in time $\mathcal{O}(1.7347^n)$. For general directed graphs, an algorithm has been provided in [83], solving the problem in time $\mathcal{O}(1.9977^n)$. A faster algorithm for finding the minimum feedback vertex set in strongly connected graphs may be developed in the future. Most recently, it has been shown in [51] that finding the minimum state-controlling set is NP-hard. An algorithm for finding the minimum state-controlling set may be developed as well.

We also note here that CBNs have been studied mostly over strongly connected digraphs. It is still not clear how to identify the periodic orbits of a weakly connected conjunctive Boolean network. One promising approach is to apply the strong component decomposition to the weakly connected digraph (see, for example, [84]) which partitions the digraph into strongly connected subgraphs. A few results obtained in this thesis can be used to establish certain properties of a periodic orbit when restricted to each connected component. Yet, a complete understanding of the periodic behavior is still lacking. This will be our main focus next, and we have obtained some preliminary results in this direction most recently [85]. We will continue on the work of characterizing periodic orbits of weakly connected CBNs and analyzing their stability structures as well as orbit-controllability problems.

Last, but not least, research on the dynamics of non-conjunctive BNs, such as those BNs whose value update rules are given by XOR (XNOR) and NAND (NOR) operations, as well as their stability structures and controllability problems, may be of interest.

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Appendix A

A COUNTER EXAMPLE FOR THE CONVERSE OF LEMMA 5

Recall the statement of Remark 4 that the converse of Lemma 5 does not hold; i.e., if there is a cycle of length m in each irreducible component G_k, it is not necessarily true that the original digraph D has a cycle of length mp^*. We now provide a counterexample for the converse of Lemma 5.

By slightly modifying the digraph shown in Fig. 3.1, namely, by adding a new cycle of length 4, we obtain a new digraph shown in Fig. A.1. This digraph has four cycles and the loop number is still 4.

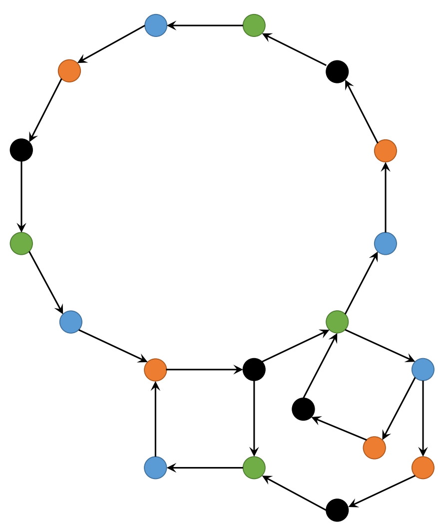

Figure A.1: This digraph has four cycles whose lengths are 4, 4, 8, and 12, respectively. Let $p = 4$ be a common divisor of the cycle lengths. Then, the associated partition yields 4 disjoint subsets, with the vertices of the same color belonging to the same subset.

Following Definition 4, the irreducible components, denoted by G_0, G_1, G_2, G_3, are shown in Fig. A.2. It can be seen that there exists a cycle of length 4 in each irreducible component. Yet, the original digraph in Fig. A.1 does not contain a cycle of length 16.

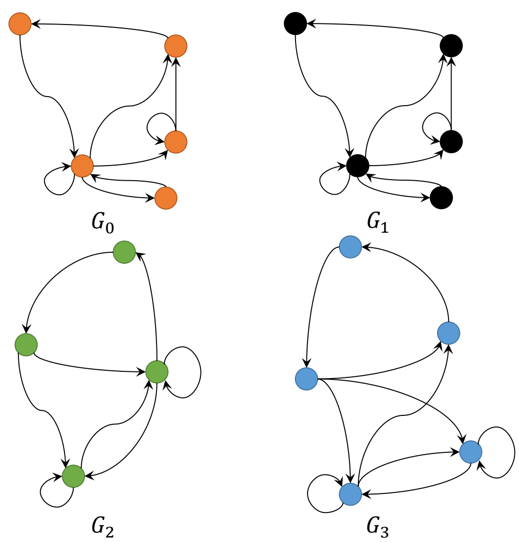

Figure A.2: Irreducible components of the digraph shown in Fig. A.1.