Cyclic attractors of nonexpanding $n$-ary networks

Etan Basser-Ravitz  
Department of Mathematics  
Yale University  
New Haven, CT, USA  
etan.basser@yale.edu

Arman Darbar  
New York University  
New York, NY, USA  
agd8612@nyu.edu

Julia Chifman*  
Department of Mathematics and Statistics  
American University  
Washington DC, USA  
chifman@american.edu

ABSTRACT

Discrete dynamical systems in which model components take on categorical values have been successfully applied to biological networks to study their global dynamic behavior. Boolean models in particular have been used extensively. However, multi-state models have also emerged as effective computational tools for the analysis of complex mechanisms underlying biological networks. Models in which variables assume more than two discrete states provide greater resolution, but this scheme introduces discontinuities. In particular, variables can increase or decrease by more than one unit in one time step. This can be corrected, without changing fixed points of the system, by applying an additional rule to each local activation function. On the other hand, if one is interested in cyclic attractors of their system, then this rule can potentially introduce new cyclic attractors that were not observed previously. This article makes some advancements in understanding the state space dynamics of multi-state network models with a synchronous update schedule and establishes conditions under which no new cyclic attractors are added to networks when the additional rule is applied. Our analytical results have the potential to be incorporated into modeling software and aid researchers in their analyses of biological multi-state networks.

Keywords  Discrete multi-state models · Cyclic attractors · Nonexpanding function · Synchronous update

1 Introduction

Biological networks can be modeled through a variety of mathematical formalisms and the choice depends on the type of questions and data available. Quantitative models require detailed knowledge of the kinetics involved, which at times is very limited. Thus, many biological systems are modeled by discrete dynamical systems, qualitative models in which variables take on categorical values, such as on/off or low/medium/high. Much of literature and computational tools are devoted to Boolean models, however, not all biological networks are Boolean. The interest in models where variables take on more than two values can be traced back to R. Thomas [1]. Examples of such biological models are: (i) multi-state models [2,3], (ii) models that employ a combination of Boolean and ternary variables [4-6], (iii) strictly ternary models [7] and (iv) four state models [8]. Networks of large biosystems in which variables assume more than two discrete states do present a computational challenge, but with the development of faster computational tools, it is only plausible to assume that the scientific community will see a rise in the use of multi-state models. The aim of this article is to provide analytical results that have the potential to be incorporated into a software, including our own

*Corresponding author
Cyclic attractors of nonexpanding \( n \)-ary networks

This work was motivated by our extensive analyses of biological networks. In particular, the focus of our team is on intracellular iron metabolism in epithelial cells and its dysregulation in cancer \([7,10]\). We have also explored iron handling in macrophages \([11]\). Our current model includes multiple oncogenic pathways, iron homeostasis and utilization pathways, oxidative stress response and a cell G1/S phase component, totaling 64 species. With the exception of an ODE model \([10]\), we chose ternary logic for all models since several species in our network, including iron levels, could not be modeled as On/Off or Active/Inactive. Allowing three states provided us with much greater resolution, but this scheme also introduced discontinuities, meaning that variables can jump \( \pm 2 \) units in one time step. If more states are required for each species, these jumps become even greater. Many multi-state models have been constructed under the constraint that species change by at most one unit (e.g., \([6,7]\)). This can be achieved by applying an additional rule to each local activation function (Section 2.3). Intuitively, this rule takes into consideration the current state of the node at time \( t \) and its next value at time \( t + 1 \). For example, in the ternary case, if the current state of the node is low (0), but a local update function for the same node assigns a high (2) value, then the actual value this node would receive at time \( t + 1 \) will be normal (1). This observation does not change fixed points (Remark 2.5), yet, cyclic attractors of ternary networks can present a challenge.

For clarity, let \( \mathcal{N} \) represent a ternary network in which \( \pm 2 \) jumps are present, and let \( \mathcal{H} \) be the corresponding network in which the additional rule was added to all local activation functions of \( \mathcal{N} \) to ensure that variables change by at most one unit. We have simulated and analyzed many networks under a synchronous update schedule and found that some of the networks had rather intuitive connections between cyclic attractors: (i) cyclic attractors that had \( \pm 2 \) jumps in \( \mathcal{N} \) were absorbed in \( \mathcal{H} \) by the basins of fixed points or by the basins of other remaining cyclic attractors, (ii) cyclic attractors that had only \( \pm 1 \) jumps remained in \( \mathcal{H} \) and (iii) no new cyclic attractors were introduced. However, we have also noticed that many networks, even those with the same interaction graph and nearly identical local activation functions, had entirely new cyclic attractors created in \( \mathcal{H} \) (see Example 2.1 and Figures 1(d)-(e)). This observation prompted our team to investigate this phenomenon further. Additionally, we have noticed that the state space of the network \( \mathcal{H} \) without new cyclic attractors preserved some rigid structure: trajectories of the networks \( \mathcal{N} \) and \( \mathcal{H} \) merged after some iteration, which was not true for the networks that added additional cyclic attractors (examples can be found at the beginning of the Section 3). Other differences in the state space dynamics between \( \mathcal{N} \) and \( \mathcal{H} \) networks are mentioned in the Discussion Section 5.

Attractors of discrete dynamical systems are of particular importance since in the biological context they correspond to different phenotypes, a concept that appeared in seminal works by S.A. Kauffman, L. Glass and S. Huang \([12,14]\). Deciding when an attractor (cyclic or fixed point) is biologically relevant has been addressed by several authors ranging from the idea of stability \([15]\), the size of the basin of attraction \([16,17]\) to ergodic attractors \([18]\). We encourage the reader to consult a concise review by J. D. Schwab et al. \([19]\) about Boolean models. From our own experience we have found that both fixed points and cyclic attractors can be of biological interest. While working with ternary models, we have learned that having a network that does not introduce new cyclic attractors after imposing \( \pm 1 \) jumps produced biologically relevant dynamics, at least in our case of iron metabolism. Whether or not it is true in general will require further investigations, but to our knowledge, the correspondence between trajectories and cyclic attractors of the biological multi-state networks with and without jumps has not been rigorously addressed. This article makes the first step in describing some conditions under which no new cyclic attractors are added to networks when \( \pm 1 \) jumps are enforced under a synchronous update schedule. The results in this article make a contribution not only to the analysis of biological multi-state networks but also to discrete applied mathematics in general.

The article is organized as follows. Section 2 provides some general terminology and definitions of \( n \)-ary networks, including the ones in which \( \pm 1 \) jumps are enforced. We call these networks one-step networks. Additionally, this section singles out one class of biological networks named in this article as generalized Boolean \( n \)-ary networks. Section 3 defines a new class of networks: nonexpanding networks with respect to the Chebyshev distance. Boolean non-expansive networks under the Hamming distance were analyzed in \([20,21]\) with a focus on fixed points. In this article, our main focus is on cyclic attractors, and also on the differences and the similarities between \( n \)-ary networks and their corresponding one-step networks. In the same section, we then prove our first result that generalized Boolean \( n \)-ary networks are nonexpanding (Theorem 3.3). We also discuss our observation about trajectories and prove our second result (Theorem 3.6) about the interplay between global activation functions of nonexpanding networks and their corresponding one-step networks. This then leads to our main result that corresponding one-step networks of nonexpanding networks do not add new cyclic attractors (Theorem 3.7). We conclude the article with the application of our results to intracellular iron networks (Section 4) and with the Discussion (Section 5).

The article is organized as follows. Section 2 provides some general terminology and definitions of \( n \)-ary networks, including the ones in which \( \pm 1 \) jumps are enforced. We call these networks one-step networks. Additionally, this section singles out one class of biological networks named in this article as generalized Boolean \( n \)-ary networks. Section 3 defines a new class of networks: nonexpanding networks with respect to the Chebyshev distance. Boolean non-expansive networks under the Hamming distance were analyzed in \([20,21]\) with a focus on fixed points. In this article, our main focus is on cyclic attractors, and also on the differences and the similarities between \( n \)-ary networks and their corresponding one-step networks. In the same section, we then prove our first result that generalized Boolean \( n \)-ary networks are nonexpanding (Theorem 3.3). We also discuss our observation about trajectories and prove our second result (Theorem 3.6) about the interplay between global activation functions of nonexpanding networks and their corresponding one-step networks. This then leads to our main result that corresponding one-step networks of nonexpanding networks do not add new cyclic attractors (Theorem 3.7). We conclude the article with the application of our results to intracellular iron networks (Section 4) and with the Discussion (Section 5).
2 Preliminaries

We generalize the concept of a Boolean Network on \( m \) components (species) to networks in which each node of a network has an associated state in \( \{0, 1, 2, \ldots, n-1\} \). Some notation in this section concerning graphs is standard (see for example [22] [23]).

2.1 Digraphs

Let \( G = (V(G), E(G)) \) be a finite digraph with a vertex set and an arc set denoted by \( V(G) \) and \( E(G) \), respectively. An arc joining two vertices \( v, u \in V(G) \) directed from \( u \) to \( v \) will be denoted by \( (u, v) \). The first vertex \( u \) is called the tail (source) and the second vertex \( v \) is the head (target) of the arc. The number of incoming arcs of a vertex \( v \in V(G) \) is called the in-degree of \( v \) and the number of outgoing arcs is called the out-degree of \( v \). For a vertex \( v \in V(G) \) the in-neighborhood (predecessor set) and out-neighborhood (successor set) of \( v \) are defined by \( N^-(v) = \{u \in V(G) | (u, v) \in E(G)\} \) and \( N^+(v) = \{u \in V(G) | (v, u) \in E(G)\} \), respectively.

An arc that joins a vertex to itself is called a loop, and two or more arcs that join the same pair of vertices are called multiple (parallel) edges. A graph that has no loops or multiple edges is a simple graph. A graph \( G \) could be a signed digraph, meaning there is a sign function \( \sigma: E(G) \to \{+,-\} \). In this case, each arc receives either a positive (+) or negative (-) assignment. In a biological context, such arcs are often called activation (positive arc) or inhibition (negative arc).

A directed path is a sequence of distinct vertices \( v_1, v_2, \ldots, v_k \) such that there is an arc \((v_i, v_{i+1})\) for all \( i \in \{1, 2, \ldots, k-1\} \). If, in addition, there is an arc from \( v_k \) to \( v_1 \) then a directed path is called a cycle. Note, directed paths and cycles are simple subgraphs. A digraph \( G \) is strongly connected or strong if for any \( v, u \in V(G) \) with \( v \neq u \) there is a directed path from \( u \) to \( v \) and from \( v \) to \( u \).

2.2 \( n \)-ary Networks

Let \( X_n := \{0, 1, 2, \ldots, n-1\} \) be a finite set on \( n \) elements equipped with a linear order. In the biological context the elements of \( X_n \) can be associated with concentration/activity levels of biological species.

An \( n \)-ary network \( \mathcal{N} = (G, F) \) with \( n \geq 2 \) is a discrete dynamical system where \( G = (V(G), E(G)) \) is a digraph on \( m \) nodes, called an interaction graph, and \( F \) is a global transition function

\[
F = (f_1, f_2, \ldots, f_m) : X_n^m \to X_n^m.
\]

Each node \( v \in V(G) \) has an associated state in \( X_n \) and the value of \( v \) is updated by a coordinate local activation function \( f_v : X_n^m \to X_n \), whose value depends on the values of the nodes in \( N^-(v) \). Note, with this definition, if \( n = 2 \) and each local activation function is a Boolean function, then \( \mathcal{N} = (G, F) \) is a Boolean network.

In this article we assume a synchronous update, meaning all nodes are updated simultaneously based on the values of their input/incident nodes at the previous time step and a local activation function. Thus, the dynamics of the network \( \mathcal{N} \) is described by the successive iterations of \( F \) and each state \( \mathbf{x} = (x_1, x_2, \ldots, x_m) \in X_n^m \) leads to another state, eventually converging to a fixed point or a cyclic attractor of length \( k \), also termed a \( k \)-cycle (see diagram below).

\[
\begin{align*}
\text{fixed point} & \quad \mathbf{x} \longrightarrow F(\mathbf{x}) \longrightarrow F^2(\mathbf{x}) \longrightarrow \cdots \longrightarrow F^i(\mathbf{x}) \\
\text{k-cycle} & \quad \mathbf{x} \longrightarrow F(\mathbf{x}) \longrightarrow \cdots \longrightarrow F^i(\mathbf{x}) \longrightarrow \cdots \longrightarrow F^{i+j}(\mathbf{x}) \\
& \quad \uparrow \quad \vdots \quad \downarrow \quad \leftarrow \quad \cdots \quad \leftarrow \quad F^{i+(k-1)}(\mathbf{x}) \quad \cdots \quad \leftarrow \quad F^{i+j+k}(\mathbf{x})
\end{align*}
\]

In the above diagram, \( F^i(\mathbf{x}) \) means a composition of \( F \) with itself \( i \) times. Since the interaction graph is finite we will have \( n^m \) states and each state \( \mathbf{x} \in X_n^m \) will belong to the basin of attraction of only one attractor, a fixed point or a cycle attractor.

We conclude this subsection with three examples that have the same interaction graph but different global transition functions. We will use these examples throughout the text to demonstrate our ideas. We would like to emphasize that our results in this article hold for graphs with multiple arcs and/or loops, and do not require the interaction graph to be signed.
Example 2.1. Let $G$ be a digraph as depicted in Figure 1(a) and let $X_3 = \{0, 1, 2\}$.

Network $N_1$: Consider a global transition function $F_1 = (f_1, f_2, f_3) : X_3^3 \to X_3^3$ given by

$$f_1(x) = \min(x_2, x_3)$$
$$f_2(x) = x_3$$
$$f_3(x) = 2 - x_1.$$

Local update rules can also be represented by transition tables (Table 1). Notice that each local activation function will either increase or decrease the future value of its target node. Thus, with this definition of a global transition function, the interaction graph $G$ is a signed digraph with arcs $(v_2, v_1)$, $(v_3, v_2)$ and $(v_3, v_1)$ being positive (+), while the arc $(v_1, v_3)$ is negative (−). The network $N_1 = (G, F_1)$ has one fixed point and two 5-cycles (Figure 1(b)).

| $x_2$ | $x_3$ | $f_1 = \min(x_2, x_3)$ | $x_3$ | $f_2 = x_3$ | $x_1$ | $f_3 = 2 - x_1$ |
|-------|-------|------------------------|-------|-------------|-------|-----------------|
| 0     | 0     | 0                      | 0     | 0           | 0     | 2               |
| 0     | 1     | 0                      | 1     | 1           | 1     | 1               |
| 0     | 2     | 2                      | 2     | 2           | 2     | 0               |
| 1     | 0     | 1                      | 1     | 1           | 2     | 2               |
| 1     | 1     | 2                      | 2     | 2           | 2     | 0               |

Network $N_2$: Now consider a global transition function $F_2 = (f_1, f_2, f_3) : X_3^3 \to X_3^3$ given by

$$f_1(x) = \min(x_2, x_3)$$
$$f_2(x) = 2x_3 + x_3^2 \mod 3$$
$$f_3(x) = 2 + x_1^2 \mod 3.$$

In this case the interaction graph $G$ is also a signed digraph. The difference between network $N_1$ and $N_2$ can be seen by comparing Table 1 and Table 2. The network $N_2$ has one 5-cycle (Figure 1(d)).

| $x_3$ | $f_2 = 2x_3 + x_3^2 \mod 3$ | $x_1$ | $f_3 = 2 + x_1^2 \mod 3$ |
|-------|-------------------------------|-------|---------------------------|
| 0     | 0                             | 0     | 2                         |
| 1     | 0                             | 1     | 0                         |
| 2     | 2                             | 2     | 0                         |

Network $N_3$: Now consider a global transition function $F_3 = (f_1, f_2, f_3) : X_3^3 \to X_3^3$ given by

$$f_1(x) = \min(x_2, x_3)$$
$$f_2(x) = 2x_3 + 2x_3^2 \mod 3$$
$$f_3(x) = 2 - x_1.$$

In this case, the interaction graph $G$ is not a signed graph. The future value of the node $v_2$ first increases from 0 to 1 when the input node $v_3$ takes on the values of 0 and 1, respectively. However the value of the node $v_2$ then decreases back to 0 when the input node $v_3$ is 2 (Table 3). Thus, the arc from $v_3$ to $v_2$ cannot be assigned a unique sign. The network $N_3$ has two fixed points and two 3-cycles (Figure 1(f)).

| $x_3$ | $f_2 = 2x_3 + 2x_3^2 \mod 3$ |
|-------|-------------------------------|
| 0     | 0                             |
| 1     | 1                             |
| 2     | 0                             |
Cyclic attractors of nonexpanding $n$-ary networks

Figure 1: Example of ternary network. Panel (a) Interaction graph. Panels (b), (d) and (f) display state space dynamics for each network as described in Example 2.1. Panels (c), (e) and (g) display dynamics of the corresponding one-step network; one-step networks defined and described in Section 2.3. Fixed points and cycle attractors are colored in red. For simplicity we represent each state $(x_1, x_2, x_3)$ as $x_1 x_2 x_3$, e.g., the state $(1, 1, 2)$ is the same as 112.
2.3 one-step n-ary Networks

Dynamics in Figures 1(b), 1(d) and 1(f) demonstrate an important fact about n-ary networks when \( n \geq 3 \). A value of a node \( v_i \) can increase, for example, from 0 to 2 in one time step and vice versa, e.g., \( 202 \rightarrow 020 \rightarrow 002 \rightarrow 022 \rightarrow \) etc. For \( n = 4 \) the value can jump three units. In some applications it is desirable that the value of a node changes at most one unit in one time step (e.g., \( \varepsilon \)). This can be accomplished by defining another function that depends on the current state of the node at time \( t \) and its next value at time \( t + 1 \), which is updated by a local activation function \( [24] \).

**Definition 2.2.** Let \( \mathcal{N} = (G, F) \) be an n-ary network and let \( f_v : X_n^m \rightarrow X_n \) be a local activation function for \( v \in V(G) \). A one-step local activation function \( h_v \) is defined by

\[
h_v(x) = \begin{cases} 
  x_v + 1 & \text{if } x_v < f_v(x) \\
  x_v & \text{if } x_v = f_v(x) \\
  x_v - 1 & \text{if } x_v > f_v(x)
\end{cases}
\]  

(1)

where \( x = (x_1, x_2, \ldots, x_v, \ldots, x_m) \in X_n^m \) is the input vector and \( x_v \in X_n \) is the current state of the node \( v \). A one-step global transition function is then

\[
h = (h_1, h_2, \ldots, h_m) : X_n^m \rightarrow X_n^m.
\]

An n-ary one-step network will be denoted by \( \mathcal{H} = (\mathcal{N}, h) \).

**Example 2.3.** Consider network \( \mathcal{N}_1 \) as defined in Example 2.7. Then

\[
F_1(2, 1, 0) = (f_1(2, 1, 0), f_2(2, 1, 0), f_3(2, 1, 0)) = (0, 0, 0).
\]

Now, since \( f_1(2, 1, 0) = 0 \) and \( x_1 = 2 > 0 \), then \( h_1(2, 1, 0) = x_1 - 1 = 1 \). Similarly we compute \( h_2 \) and \( h_3 \). Thus, \( h(2, 1, 0) = (1, 0, 0) \).

**Remark 2.4.** A one-step local activation function \( h_v(x) \) can also be written in the following form:

\[
h_v(x) = x_v + \text{sgn}(f_v(x) - x_v),
\]  

(2)

where

\[
\text{sgn}(w) = \begin{cases} 
  1 & \text{if } w > 0 \\
  0 & \text{if } w = 0 \\
  -1 & \text{if } w < 0
\end{cases}
\]

Note that a one-step function \( h_v(x) = f_v(x) \) if and only if \( |x_v - f_v(x)| = 1 \). Thus, for binary (2-ary) networks global transition functions \( F \) and \( h \) are identical. We would like to point out that in \( [24] \) and \( [7] \) function \( h_v \) was termed continuous. To avoid confusion between continuous networks in which dynamics are described by a system of differential equations, we have decided to use the terms one-step function and one-step network to describe systems that are discrete but require that each node change at most one unit in one time step. This terminology also allows for future investigations of k-step networks.

**Remark 2.5.** Fixed points of \( \mathcal{N} = (G, F) \) and the corresponding one-step network \( \mathcal{H} = (\mathcal{N}, h) \) are the same. Suppose \( x \in X_n^m \) is a fixed point of \( \mathcal{N} \). Then \( F(x) = x \). This means that \( f_v(x) = x_v \) for each local activation function, and consequently Definition 2.2 implies that \( h_v(x) = x_v \). Conversely, if \( x \) is a fixed point of \( \mathcal{H} \) then \( h(x) = x \) and \( h_v(x) = x_v \), which is only true if \( x_v = f_v(x) \). Thus \( x \) is a fixed point of \( \mathcal{N} \) as well. This is not the case for cyclic attractors.

Figures 1(c), 1(e) and 1(g) display dynamics of the one-step networks. Notice, the 5-cycle of the network \( \mathcal{N}_1 \) with two step jumps in Figure 1(b) now has been absorbed by the basins of the fixed point and the other 5-cycle in the corresponding one-step network \( \mathcal{H}_1 \). The remaining 5-cycle and the fixed point in \( \mathcal{H}_1 \) are identical to those in \( \mathcal{N}_1 \). For \( \mathcal{N}_2 \) and \( \mathcal{H}_2 \), the attractors are the same, though a fixed point 002 in \( \mathcal{H}_2 \) lost all states in its basin. One similarity between \( \mathcal{H}_1 \) and \( \mathcal{H}_3 \) is that no new attractors have been introduced. This is not the case for the one-step network \( \mathcal{H}_3 \), which has lost its 5-cycle and two new cycles have been introduced (a 2-cycle and a 7-cycle). In Section 3 we present conditions under which one-step networks do not add new cyclic attractors, but before we turn to our main results, we describe a subclass of n-ary networks.
2.4 Generalized Boolean n-ary Networks

A subclass of n-ary networks that we would like to single out is the one in which each local activation function \( f_v \) is constructed from three operators

\[
\max(x), \quad \min(x), \quad \text{and } \not(x_i) = (n - 1) - x_i.
\]

(3)

where \( x = (x_1, x_2, \ldots, x_m) \in X^n \) and \( x_i \in X_n \). Our team utilizes this scheme for ternary protein-protein networks as it allows us to intuitively describe interactions among biological species (see [7]). Notice that the \( \not \) operator is self inverting, meaning \( \not(\not(x_i)) = x_i \). If the node \( v \) has only one incident node \( u \) and no loop, then depending on the biological context, the local activation function \( f_v \) can be defined as logical identity \( f_v(x) = x_u \) or as \( f_v(x) = (n - 1) - x_u \). The \( \max \) and \( \min \) operators are idempotent since \( \max(x_1, x_i) = x_i \) and \( \min(x_i, x_i) = x_i \) for all \( x_i \in X_n \), which means that they are semilattice operators (see [25] about semilattice networks). Some familiar properties that are satisfied by \( \max \), \( \min \), and \( \not \) operators are listed in Appendix A. Various compositions of \( \min/\max/\not \) are also possible. In the case when \( n = 2 \), the operators \( \max \), \( \min \), and \( \not \) are just the traditional OR, AND and NOT operators, respectively. This leads to a natural definition below.

**Definition 2.6.** Networks in which each local activation function is a composition of the operators \{\( \min, \max, \not \)\} given by Equation (3) will be called **generalized Boolean n-ary networks**, denoted by \( N_{GB} \).

An example of the \( N_{GB} \) 3-ary (ternary) network is \( N_2 \) in Example 2.1. Networks \( N_2 \) and \( N_3 \) are not generalized Boolean. Our next definition is an analogue of the disjunctive normal form for Boolean expressions with the difference being that we allow for both \( x_i \) and \( \not(x_i) \) to appear in some terms. In the Boolean formalism, \( \min(x, \not(x)) = 0 \) for \( x \in \{0, 1\} \) with \( n > 2 \), unless \( x = 0 \) or \( x = n - 1 \).

**Definition 2.7.** Let \( N_{GB} \) be a generalized Boolean n-ary network and \( x \in X^n \). A local activation function \( f_v : X^n \to X_n \) is in **max−min form** if it is of the form

\[
f_v(x) = \max(M_1(x), M_2(x), \ldots, M_r(x)),
\]

(4)

where each \( M_i(x) = \min(a_{i1}, a_{i2}, \ldots, a_{ik}) \), with \( a_{ij} = x_k \) or \( a_{ij} = \not(x_k) \), \( x_k \) being one of the entries of the vector \( x \). In this context, each \( M_i \) is the \( \min \) of some or all entries of the vector \( x = (x_1, x_2, \ldots, x_n) \) with a possibility of having both \( x_k \) and \( \not(x_k) \) as part of the same \( M_i \) term. In the case \( r = 1 \), \( f_v(x) = M_1(x) \).

**Lemma 2.8.** Each local activation function \( f_v \) of a generalized Boolean n-ary network can be written in max − min form.

**Proof.** Repeated application of the De Morgan’s laws [12e] - [12f] and the Distributive property [12c] (see Appendix A) will transform \( f_v \) into max − min form. Identical terms can be eliminated by using the fact that the max operator is idempotent. \( \square \)

**Example 2.9.** Consider \( f_v : X^3 \to X_n \) defined by

\[
f_v(x) = \min(x_2, \max(x_1, \not(\min(x_2, x_3)))).
\]

We are going to transform \( f_v \) into max − min form. Note that

\[
\max(x, y, z) = \max(\max(x, y), z) = \max(x, \max(y, z)).
\]

(5)

The same is true for the min operator. Now,

\[
\min(x_2, \max(x_1, \not(\min(x_2, x_3))))
\]

[12e] \quad \max(\min(x_2, x_1), \min(x_2, \not(\min(x_2, x_3))))

[12f] \quad \max(\min(x_2, x_1), \min(x_2, \max(\not(x_2), \not(x_3))))

[12c] \quad \max(\min(x_2, x_1), \max(\min(x_2, \not(x_2)), \min(x_2, \not(x_3))))

[12c] \quad \max(\min(x_1, x_2), \min(x_2, \not(x_2)), \min(x_2, \not(x_3))).
\]

Thus, \( f_v(x) = \max(M_1(x), M_2(x), M_3(x)) \), where \( M_1(x) = \min(x_1, x_2), M_2(x) = \min(x_2, \not(x_2)) \) and \( M_3(x) = \min(x_2, \not(x_3)) \).
3 Nonexpanding Networks

The main objective of this section is to establish conditions under which no new cyclic attractors are introduced in one-step networks. It is quite clear from Figure 1 that a one-step global transition function does change trajectories. It is not quite obvious, though, if there is a connection between the trajectories in Figure 1(b) and Figure 1(c), for example. We initially speculated that a global transition function of the one-step network acts “chaotically” on a trajectory of an initial vector. To our surprise, we found that if a global transition function $F$ has some desirable properties then the corresponding one-step global transition function preserves some rigid structure, allowing us to establish our main results. To make these ideas concrete we begin with a few examples.

Consider networks $N_1$ and $H_1$ in Example 2.1 and its corresponding state spaces in Figure 1(b) and Figure 1(c). Let $x = (2, 0, 0)$ be an initial state, then

$$
\text{trajectory under } H_1: \quad 200 \rightarrow 100 \rightarrow 001 \rightarrow 012 \rightarrow \cdots
$$

$$
x \quad h(x) \quad h^2(x) \quad h^3(x) \quad \cdots
$$

One can see that when $h(x) = h(2, 0, 0) = (1, 0, 0)$ is computed, the trajectory from the point $h(x) = (1, 0, 0)$ is the same for both $H_1$ and $H_2$ networks. This is true for all initial states in $H_1$. One also checks that the same phenomenon occurs for $N_3$ and $H_3$ networks even though this network is not generalized Boolean and the interaction graph is not signed.

Now, consider network $N_2$ and $H_2$ (state spaces are in Figure 1(d) and Figure 1(e)) and let $x = (2, 1, 2)$. Then

$$
\text{trajectory under } H_2: \quad 212 \rightarrow 121 \rightarrow 110 \rightarrow 000 \rightarrow \cdots
$$

$$
x \quad h(x) \quad h^2(x) \quad h^3(x) \quad \cdots
$$

$$
\text{trajectory under } N_2: \quad 121 \rightarrow 100 \rightarrow 000 \rightarrow 002 \rightarrow \cdots
$$

The trajectories starting from $h(x) = h(2, 1, 2) = (1, 2, 1)$ are quite different and while they do coincide at some states they never merge, meaning there is no state from which the trajectory is the same for both $N_2$ and $H_2$ networks.

To study this phenomenon, as demonstrated by examples above, we need to be able to measure a distance between a pair of points $x, y \in X^m$. The choice of a distance below is influenced by Definition 1.2.1 and its implication: a one-step local activation function $h_v(x) = f_v(x)$ if and only if $|x_v - f_v(x)| \leq 1$, where $x_v$ is the current state of the node $v$ and $f_v$ is the local update function for $v$. Keeping this observation in mind, we use the maximum distance, also called the Chebyshev distance, between two elements $x, y \in X^m$ defined by

$$
d_{\infty}(x, y) = \max_{i \leq m}|x_i - y_i|.
$$

This now leads to a natural definition of closeness.

**Definition 3.1.** Let $N = (G, F)$ be an $n$-ary network and let $x, y \in X^m$.

(i) A point $x$ is close to a point $y$ if $d_{\infty}(x, y) \leq 1$.

(ii) A global transition function $F$ is nonexpanding if for all $x, y \in X^m$ such that $d_{\infty}(x, y) \leq 1$ we have $d_{\infty}(F(x), F(y)) \leq 1$. In this case we also say that an $n$-ary network $N$ is a nonexpanding network.

The term nonexpanding is motivated by the fact that in nonexpanding networks a global transition function is a discrete analogue of a mapping satisfying the Lipschitz condition with a constant equal to one. Such mappings are called nonexpansive or nonexpanding. Also note, Boolean (2-ary) networks are necessarily nonexpanding.

**Lemma 3.2.** Let $N = (G, F)$ be an $n$-ary network. $N$ is nonexpanding if and only if $d_{\infty}(F(x), F(y)) \leq d_{\infty}(x, y)$ for all $x, y \in X^m$.

**Proof.** If $d_{\infty}(F(x), F(y)) \leq d_{\infty}(x, y)$ for all $x, y \in X^m$ then $d_{\infty}(F(x), F(y)) \leq 1$ whenever $d_{\infty}(x, y) \leq 1$. For the other direction, suppose $N$ is nonexpanding and let $x, y \in X^m$. If $x = y$ then the inequality holds trivially.

Let $d_{\infty}(x, y) = k$ for some $k \in X_m$. This means that each coordinate $x_i$ of $x$ differs from the coordinate $y_i$ of the vector $y$ by at most $k$ units. Thus, we can find $k - 1$ vectors $z_i \in X^m$ such that $d_{\infty}(x, z_1) \leq 1$, $d_{\infty}(a_{k-1}, y) \leq 1$ and $d_{\infty}(z_i, z_{i+1}) \leq 1$ for $i \in \{1, 2, \ldots, k - 2\}$. Now using the triangle inequality and the assumption that $N$ is nonexpanding we obtain
\[ d_\infty(F(x), F(y)) \leq d_\infty(F(x), F(z_1)) + d_\infty(F(z_{k-1}), F(y)) + \sum_{i=1}^{k-2} d_\infty(F(z_i), F(z_{i+1})) \]
\[ \leq 1 + 1 + \cdots + 1 \]
\[ = k \]
\[ = d_\infty(x, y). \]

Networks \( N_1 \) and \( N_2 \) in Example 2.1 are nonexpanding, though \( N_3 \) is not a generalized Boolean network. The network \( N_2 \) fails to be nonexpanding since \( d_\infty((1, 1, 2), (0, 0, 1)) = 1 \) but \( d_\infty(F_2(1, 1, 2), F_2(0, 0, 1)) = 2 \).

Our first main result of this section concerns generalized Boolean networks.

**Theorem 3.3.** A generalized Boolean \( n \)-ary network \( N_{GB} \) is nonexpanding.

**Proof.** Let \( x, y \in X_n \) so that \( d_\infty(x, y) \leq 1 \). Since
\[ d_\infty(F(x), F(y)) = \max_{v \leq m} |f_v(x) - f_v(y)|, \]
we only need to show that \( |f_v(x) - f_v(y)| \leq 1 \) for each local activation function. By Lemma 2.8, \( f_v \) of the generalized Boolean \( n \)-ary network can be written in \( \max - \min \) form. Thus, \( f_v(x) \) and \( f_v(y) \) can be expressed in the form of Equation 4.1, where \( M_i(x) = \min(a_{i1}, a_{i2}, \ldots, a_{is}) \) and \( M_i(y) = \min(b_{i1}, b_{i2}, \ldots, b_{is}) \) with \( a_{ij} = x_k \) or \( a_{ij} = \text{not}(x_k) \) and \( b_{ij} = y_k \) or \( b_{ij} = \text{not}(y_k) \). Now, \( x_k \) and \( y_k \) are some entries of the vectors \( x \) and \( y \), respectively, corresponding to the same index \( k \). Since \( x \) is close to \( y \), \( y_k \) differs from \( x_k \) by at most one unit. Clearly, \( \text{not}(x_k) \) and \( \text{not}(y_k) \) also differ by at most one unit. Consequently, for all \( j \in \{1, \ldots, s\} \)
\[ |b_{ij} - a_{ij}| \leq 1. \] (6)

Without loss of generality, assume that \( a_{i1} \leq a_{ij} \) for all \( j \in \{1, \ldots, s\} \). That is \( a_{i1} = \min(a_{i1}, a_{i2}, \ldots, a_{is}) \). Suppose \( b_{ij} = \min(b_{i1}, b_{i2}, \ldots, b_{is}) \) for some \( j \in \{1, \ldots, s\} \). Then by Eq. 6 and the fact that \( a_{i1} \) and \( b_{ij} \) are the minima, we get
\[ a_{i1} - 1 \leq a_{ij} - 1 \leq b_{ij} \leq b_{i1} \leq a_{i1} + 1. \]

Thus we conclude \( |M_i(x) - M_i(y)| \leq 1 \) for all \( i \in \{1, \ldots, r\} \).

We can apply similar logic to the \( \max \) operator to show that for all \( v \in \{1, \ldots, m\} \)
\[ |f_v(x) - f_v(y)| = |\max(M_1(x), \ldots, M_r(x)) - \max(M_1(y), \ldots, M_r(y))| \leq 1. \]

Hence, \( d_\infty(F(x), F(y)) = \max_{v \leq m} |f_v(x) - f_v(y)| \leq 1. \)

\[ \square \]

### 3.1 One-step Networks and Cyclic Attractors

As we have already stated, networks \( N_1 \) and \( N_3 \) in Example 2.1 are nonexpanding, while the network \( N_2 \) is not (e.g., close points \((1, 1, 1)\) and \((0, 0, 1)\) are mapped by \( F_2 \) to \((1, 0, 0)\) and \((0, 0, 2)\), respectively). The corresponding one-step networks also have the same feature, meaning that \( H_1 \) and \( H_2 \) are nonexpanding, while \( H_2 \) is not. It could also happen that a network that fails to be nonexpanding has a corresponding one-step network that maps all close points to close points. For example, a global transition function \( F = (f_1, f_2) : X_3^2 \to X_3^2 \) of the ternary network on two nodes (Equation 7 below), will not map all close points to close points, however, the corresponding one-step network will (state space for this example is provided in Appendix A Example 3.3 and Figure 3)
\[ f_1(x_1, x_2) = (2 + x_1 + x_2 + 2x_1x_2 + x_1^2x_2^2) \mod 3 \]
\[ f_2(x_1, x_2) = x_1. \]

The lemma below summarizes this discussion. A proof can be found in Appendix A.
Lemma 3.4. Suppose $N = (G, F)$ is an $n$-ary network with the corresponding one-step network $H = (N, h)$. If $N$ is nonexpanding, then so is $H$.

Another important observation that will be used in our proofs follows from Definition 3.1 and Section 2.3. Given any $n$-ary network $N = (G, F)$ and a corresponding one-step network $H = (N, h)$, $F(x) = h(x)$ if and only if $F(x)$ is close to $x$. Additionally, $h^{k-1}$ is always close to $h^k$, that is $d_\infty(h^k(x), h^{k-1}(x)) \leq 1$, where $h^i$ is the composition of $h$ with itself $i$ times.

Before we introduce and prove our main results we will need the following lemma. In Appendix X we introduce a few other small results.

Lemma 3.5. Suppose $N = (G, F)$ is a nonexpanding $n$-ary network with the corresponding one-step network $H = (N, h)$. Let $x \in X_n^m$ and $i \in \mathbb{N}$. If $F(x) = h(x)$ then $F^i(x) = h^i(x)$.

Proof. Note that $F(x) = h(x)$ if and only if $d_\infty(F(x), x) \leq 1$. When $i = 1$, the base case holds by assumption. Now suppose $F^{i-1}(x) = h^{i-1}(x)$. Since $F$ is nonexpanding, we can apply Lemma 3.2 repeatedly to obtain desired result:

$\begin{align*}
d_\infty(F^i(x), F^{i-1}(x)) &= d_\infty(F(F^{i-1}(x)), F(F^{i-2}(x))) \\
&\leq d_\infty(F^{i-1}(x), F^{i-2}(x)) \\
&\leq d_\infty(F^{i-2}(x), F^{i-3}(x)) \\
&\vdots \\
&\leq d_\infty(F(x), x) \\
&\leq 1.
\end{align*}$

Thus, $F^i(x) = h(F^{i-1}(x)) = h(h^{i-1}(x)) = h^i(x)$.

Our next Theorem addresses the discussion at the beginning of Section 3 about trajectories. The vital observation we have made about trajectories of nonexpanding networks is that they eventually merge. The maximum number of compositions a one-step function $h$ must make before the trajectory of the one-step network $H$ becomes the same as for the network $N$, depends on the number of states $n$ but not the number of nodes $m$.

Theorem 3.6. Suppose $N = (G, F)$ is an $n$-ary nonexpanding network with the corresponding one-step network $H = (N, h)$. Then, for all $x \in X_n^m$ and $i \in \mathbb{N}$

$F^i(h^{n-2}(x)) = h^i(h^{n-2}(x)).$

Proof. First we show that for $0 \leq i \leq n-2$ and $x \in X_n^m$

$\begin{align*}
d_\infty(F(h^i(x)), h(h^i(x))) &= \max_{v \leq m} |f_v(h^i(x)) - h_v(h^i(x))| \\
&\leq (n - 2) - i.
\end{align*}$

In particular, we show the above inequality holds for each local activation function. Recall, $|f_v(h^i(x)) - h_v(h^{i-1}(x))| \leq 1$ if and only if $f_v(h^i(x)) = h_v(h^i(x))$.

Thus, we may assume that $f_v(h^i(x)) > h_v(h^i(x))$. The other inequality follows analogously. With this assumption,

$\begin{align*}
h_v(h^i(x)) &= h_v(h^{i-1}(x)) + 1 \\
&\text{and } f_v(h^i(x)) - h_v(h^{i-1}(x)) > 1. \quad (8)
\end{align*}$

Additionally, since $h^{i-1}(x)$ is close to $h^i(x)$ and $F$ is nonexpanding, we get

$\begin{align*}
f_v(h^{i-1}(x)) + 1 &\geq f_v(h^i(x)) \\
&> h_v(h^i(x)) \\
&= h_v(h^{i-1}(x)) + 1.
\end{align*}$

Specifically,

$f_v(h^{i-1}(x)) > h_v(h^{i-1}(x)). \quad (9)$
Applying this argument repeatedly, we can show that Equations (8) – (9) hold for any \( k \in \{0, 1, \ldots, i\} \). Therefore, by the definition of a one-step function and Remark 2,

\[
h_v(h^i(x)) = x_v + \sum_{k=0}^{i} \text{sgn}(f_v(h^k(x)) - h_v(h^{k-1}(x))) = x_v + (i + 1),
\]

where \( h_v(h^{k-1}(x)) = x_v \) for \( k = 0 \). Since the largest possible value for \( f_v(h^i(x)) \) is \( n - 1 \) and \( h_v(h^i(x)) \geq i + 1 \) by Equation (10),

\[
f_v(h^i(x)) - h_v(h^i(x)) \leq (n - 1) - (i + 1) = (n - 2) - i.
\]

Using similar logic for the other assumption, \( f_v(h^i(x)) < h_v(h^i(x)) \) we get

\[
h_v(h^i(x)) - f_v(h^i(x)) \leq (n - 1) - (i + 1) = (n - 2) - i.
\]

Thus, we conclude that for all \( 0 \leq i \leq n - 2 \)

\[
d_{\infty}(F(h^i(x)), h(h^i(x))) \leq (n - 2) - i.
\]

In particular, when \( i = n - 2 \) then \( d_{\infty}(F(h^{n-2}(x)), h(h^{n-2}(x))) = 0 \). This means that \( F(h^{n-2}(x)) = h(h^{n-2}(x)) \).

Now Lemma 3.5 implies

\[
F^i(h^{n-2}(x)) = h^i(h^{n-2}(x)).
\]

Equipped with Theorem 3.6 we are now ready to prove our main objective of this article. In particular, we show that when a network is nonexpanding then a cyclic attractor of the network \( \mathcal{H} \) is also an attractor of the network \( \mathcal{N} \), implying that no new cyclic attractors are introduced in one-step networks.

**Theorem 3.7.** Let \( \mathcal{N} = (G, F) \) be an \( n \)-ary nonexpanding network with the corresponding one-step network \( \mathcal{H} = (\mathcal{N}, h) \). If \( C \) is a k-cycle of the network \( \mathcal{H} \) then \( C \) is a k-cycle of the network \( \mathcal{N} \).

**Proof.** Let \( C = \{x, h(x), h^2(x), \ldots, h^{k-1}(x)\} \) be any k-cycle of the network \( \mathcal{H} \), where \( h^k(x) = x \) for \( k \geq 1 \) and \( h^j(h^k(x)) \in C \) for any \( j \in \mathbb{N} \). Thus, if \( k \leq n - 2 \) then \( n - 2 = k + j \), for some \( j \in \mathbb{N} \), and

\[
h^{n-2}(x) = h^{k+j}(x) = h^j(h^k(x)) = h^j(x) \in C.
\]

Also, if \( k > n - 2 \) then trivially \( h^{n-2}(x) \in C \). Thus, \( h^i(h^{n-2}(x)) = h^k(x) = x \) for some \( i \). Applying Theorem 3.6 repeatedly, we get

\[
F^i(h^{n-2}(x)) = h^i(h^{n-2}(x)) = x
\]

\[
F^{i+1}(h^{n-2}(x)) = h^{i+1}(h^{n-2}(x)) = h(x)
\]

\[
\vdots
\]

\[
F^{i+k}(h^{n-2}(x)) = h^{i+k}(h^{n-2}(x)) = h^k(x).
\]

Thus, \( C \) is also a k-cycle of \( \mathcal{N} \).

**4 Application to Intracellular Iron Metabolism**

To demonstrate the utility of our analytical results, we use our previously published model of intracellular iron regulation specific to normal breast epithelial cells [7]. This model dynamically links the iron core network (depicted in green in Figure 1) to iron utilization, oxidative stress response and oncogenic pathways. Briefly, almost all living organisms require iron for cellular respiration, oxygen transport, DNA synthesis and energy production. However, iron has an ability to exist in various oxidation states and can contribute to the formation of reactive oxygen species (ROS) that can damage DNA and other cellular structures. Iron dysregulation can lead to iron overload or deficiency, both of which are detrimental to the organism. Additionally, altered iron metabolism, signified by the reduced intracellular iron export (Fpn) and increased iron import (TfR1), has been well documented in tumors (see recent review by Brown et al. [26]). The model presented in [7] was one of the first attempts to better understand the connection between intracellular iron metabolism and cancer.
Iron Homeostasis Pathway
Iron Utilization Pathway
Oxidative Stress Response Pathway
Oncogenic Pathway

Figure 2: Intracellular Iron Network. Original image as published in Chifman et al. (2017) [7]. Activation/upregulation is represented by arrows and inhibition/downregulation by hammer heads.

For ease of notation, we use $x_i$ in place of the biological species, as listed below. See original article for the description of each variable and biological background in general.

| LIP | TfR1 | Fpn | Ft | IRP1 | IRP2 | Hep | HO-1 | ALAS1 | Heme | ROS | AE |
|-----|------|-----|----|------|------|-----|------|-------|------|-----|----|
| $x_1$ | $x_2$ | $x_3$ | $x_4$ | $x_5$ | $x_6$ | $x_7$ | $x_8$ | $x_9$ | $x_{10}$ | $x_{11}$ | $x_{12}$ |
| Nrf2 | Keap1 | IL-6 | Ras | SOS | ERK | c-Myc | GAPs | EGFR | LIPmt | Mfn | Fmtn |
| $x_{13}$ | $x_{14}$ | $x_{15}$ | $x_{16}$ | $x_{17}$ | $x_{18}$ | $x_{19}$ | $x_{20}$ | $x_{21}$ | $x_{22}$ | $x_{23}$ | $x_{24}$ |

A global transition function $F : \{0, 1, 2\}^{24} \rightarrow \{0, 1, 2\}^{24}$ is given by

$$
\begin{align*}
  f_1 &= \min(\max(x_2, x_8), \min(\not(x_3), \not(x_4), \not(x_{23}))) \\
  f_2 &= \max(x_5^2 \mod 3, x_6, x_{19}) \\
  f_3 &= \min(2 + 2x_2^2 \mod 3, \not(x_6), \not(x_7)) \\
  f_4 &= \min(2 + 2x_2^2 \mod 3, \not(x_6)) \\
  f_5 &= \not(x_1) \\
  f_6 &= \max(\not(x_1), x_{19}) \\
  f_7 &= x_{15} \\
  f_8 &= \max(x_{10}, x_{13}) \\
  f_9 &= \min(\not(x_{10}), x_{22}) \\
  f_{10} &= \min(\not(x_8), x_9)
\end{align*}
$$
This network is almost a generalized Boolean network with the exception of four local activation functions: $f_2$, $f_3$, $f_4$ and $f_{14}$. For example, the input nodes for $f_4$ are $x_5$ and $x_6$, but inside the min operator the variable $x_5$, which corresponds to the iron regulatory protein 1 (IRP1), appears in a polynomial function. The reason is that active IRP1 contributes less to the regulation of ferritin ($Ft$), the iron storage protein, meaning that when IRP1 = 2 it will have a weaker inhibitory impact than active IRP2. We termed such rules “adjusted regulations” in [7] and they were necessary in order to adequately represent the strength of one biological species’ control over another.

We would like to argue that we can use Theorem 3.3 to conclude that this iron network is nonexpanding. Consider

$$f_4 = \min(2 + 2x_5^2 \mod 3, \not(x_6))$$

and let $g(x_5) = 2 + 2x_5^2 \mod 3$. Notice that $f_4$ is almost in max $-$ min form with one $M_1(x)$ term:

$$f_4 = \min(g(x_5), \not(x_6)) \cdot M_1(x)$$

The proof of Theorem 3.3 relies on the fact that for all close points $x, y \in X^n$, the corresponding entries $a_{ij}$ and $b_{ij}$ in $M_i(x) = \min(a_{i1}, a_{i2}, \ldots, a_{is})$ and $M_i(y) = \min(b_{i1}, b_{i2}, \ldots, b_{is})$ differ by at most one unit. Thus, all we need to check if for all $x_5, y_5 \in \{0, 1, 2\}$ such that $|x_5 - y_5| \leq 1$ we have $|g(x_5) - g(y_5)| \leq 1$. Simple computation shows that this is true. Same logic and conclusions apply to $f_2$, $f_3$ and $f_{14}$. Therefore, we conclude that the iron network is nonexpanding and hence, by Theorem 3.7 the corresponding one-step network does not have new cyclic attractors.

When this iron network was first studied, having the information above would have been helpful. Our main goal in [7] was to show that an oncogenic pathway alters the iron homeostasis pathway under a variety of experimental settings, such as knockout or overexpression of critical species. Thus, we focused on attractors only. We noticed early on that our original model included multiple cyclic attractors with $\pm 2$ jumps in addition to others, and we knew that running a corresponding one-step model would eliminate all cyclic attractors with jump discontinuities. However, we did not know if the corresponding one-step network would have new cyclic attractors at the time. As a result, we had to run multiple models exhaustively. With current knowledge of nonexpanding networks, we could have extracted information from the original model about fixed points and cyclic attractors with $\pm 1$ jumps only, and then argued that under a one-step structure, the exact same attractors would be present, eliminating the need to run multiple models.

### 4.1 Iron Model that Fails to be Nonexpanding

To demonstrate how quickly a network can fail the nonexpanding property, we can adjust, for example, the local activation function $f_{16}$ for Ras. The activity of Ras is controlled by a regulated GDP/GTP cycle, and its level of activation (GTP-bound form / total Ras) is regulated by the guanine nucleotide exchange factors and GTPase-activating proteins (GAPs). Since the degree of Ras activation matters [27] [28], our original model considered three levels for Ras activation. On the other hand, if one is only concerned with Ras activity and not the levels, then Ras can be modeled as an on/off switch. One intuitive way to model this is to consider 0 as inactive and both {1, 2} as active, meaning when the activator of Ras, Son of Sevenless (SOS), is {1, 2} then Ras = 2 (active), and when GAPs are {1, 2}
then Ras = 0 (inactive). The adjusted local activation function for Ras that reflects the above discussion is then

\[ f_{16} = \min(\max(x_{15}, 2x_{17} \mod 3), 2 + x_{20}^2 \mod 3). \]

Now, this network fails the nonexpanding property, since there are multiple close points \( x, y \in \{0, 1, 2\}^2 \) such that \( |f_{16}(x) - f_{16}(y)| = 2 \). For example, one such pair of vectors would be obtained by setting all entries in \( x \) to zero and all entries in \( y \) to zero except for \( y_{17} = 1 \).

We have performed stochastic simulations with 10-million random initial conditions and have found that the corresponding one-step model has at least three new cyclic attractors of length seven. To confirm that these three 7-cycles are not attractors without one-step structure, we have traced a trajectory of one of the points from each 7-cycle. All trajectories converged to a different cyclic attractor. Interestingly, the trajectories of vectors from each of the three cycles converged to the same discontinuous 7-cycle in the original network with modified local activation function for Ras. For simulations we have used our software [https://steadycellphenotype.github.io](https://steadycellphenotype.github.io).

We have written a short R script that checks if an \( n \)-ary network is nonexpanding whenever Theorem 3.3 cannot be applied directly. We tested this script on the models discussed in this section and confirmed that the original model is nonexpanding, while the model with the adjusted local activation function for Ras fails the property. The script is available at [https://github.com/chifman/Nonexpanding-networks](https://github.com/chifman/Nonexpanding-networks).

### 5 Discussion

Networks in which variables take on \( n > 2 \) discrete states have multiple scales of change for each variable, meaning that from one time step to the next a node can change by as much as \( n - 1 \) units. To ensure that all nodes change by at most one unit, a one-step network was defined that depends on the structure and the global activation function of the original network. While these two networks are connected, the dynamics of their state spaces can be quite disparate. The results about cyclic attractors and trajectories of nonexpanding networks presented here are the first steps in understanding the state space dynamics between these networks. In particular, we have established that no new cyclic attractors are introduced in one-step networks, provided the original network was nonexpanding. Although the results in this article are specific to networks in which all variables take on the same number of discrete states and a synchronous update schedule, we hypothesize that our results can be extended to other schemes, and in some cases the extensions might be trivial.

Additionally, in this article we only considered the Chebyshev distance to define nonexpanding networks. The choice of this distance was motivated by the relation of the global function \( F \) to its one-step function \( h \). While other distances might lead to interesting conclusions and a class of networks with desirable properties, they do present subtle differences. Here, we briefly discuss the Taxicab distance (1-norm distance) and the Euclidean distance (2-norm distance) denoted by \( d_1 \) and \( d_2 \), respectively:

\[
\begin{align*}
d_1(x, y) &= \sum_{v=1}^{m} |x_v - y_v|, \quad d_2(x, y) = \left( \sum_{v=1}^{m} |x_v - y_v|^2 \right)^{1/2}.
\end{align*}
\]

We can modify the definition of “closeness” as follows. Let \( x, y \in X_n^m \) and \( i \in \{1, 2\} \). We say that \( x \) is \( d_i \)-close to \( y \) if \( d_i(x, y) \leq 1 \). Recall, \( X_n = \{0, 1, 2, \ldots, n-1\} \), thus this new definition implies that \( x \) and \( y \) differ by one unit in exactly one coordinate for both \( d_1 \) and \( d_2 \). Now we can say that a network is “\( d_i \)-nonexpanding” if \( d_i(x, y) \leq 1 \) implies \( d_i(F(x), F(y)) \leq 1 \) for all \( x, y \in X_n^m \). One can show that if network \( N \) is \( d_i \)-nonexpanding then for all \( x, y \in X_n^m \)

\[
\begin{align*}
d_1(F(x), F(y)) &\leq d_1(x, y), \quad d_2(F(x), F(y)) \leq \sqrt{m} \cdot d_2(x, y).
\end{align*}
\]

However, if \( N \) is \( d_i \)-nonexpanding, the corresponding one-step network \( H \) may fail this property. For example, consider a ternary network \( N \) on two nodes given by

\[
F = (f_1, f_2) = (2 + 2x_1^2 + x_1^2x_2^2 \mod 3, x_2 + 2x_1^2x_2^2 \mod 3).
\]

This network is \( d_i \)-nonexpanding, but the corresponding \( H \) network is not. For instance, let \( x = (0, 2) \) and \( y = (1, 2) \). Then

\[
\begin{align*}
d_1(x, y) &= 1 \quad \text{and} \quad d_1(F(x), F(y)) = d_1((2, 2), (2, 1)) = 1, \quad \text{but} \\
& d_1(h(x), h(y)) = d_1((1, 2), (2, 1)) = 2 \\
& d_2(h(x), h(y)) = d_2((1, 2), (2, 1)) = \sqrt{2}.
\end{align*}
\]
Additionally, this new definition does not guarantee that \( h^{k-1} \) is \( d_i \)-close to \( h^k \). Using the same example above, 
\[
d_1(y, h(y)) = 2 \quad \text{and} \quad d_2(y, h(y)) = \sqrt{2}.
\]
These properties played an important role in our proofs of Theorem 3.6 and Theorem 3.7. Moreover, we would like to point out that \( d_i(F(x), F(y)) \) may fail to be less than or equal to 1 for \( d_i \)-close points, and yet the network might have the property that no new cyclic attractors are added. Consider network \( N'_1 \) in Example 2.1. Let \( x = (0, 1, 1) \) and \( y = (0, 1, 0) \). Then \( d_i(x, y) = 1 \) but 
\[
d_1(F(x), F(y)) = d_1((1, 1, 2), (0, 0, 2)) = 2 > 1.
\]
Similarly, \( d_2(F(x), F(y)) > 1 \).

We believe that networks in which \( d_i(x, y) \leq 1 \) implies \( d_i(F(x), F(y)) \leq 1 \) for \( i \in \{1, 2\} \) constitute a class of networks that has an interaction with the class of nonexpanding networks studied in this article in which no new cyclic attractors are added under the one-step function. However, it is not clear if \( d_i \)-closeness is sufficient to guarantee the results of Theorem 3.7. For the time being we only pose this as a conjecture.

These observations are important and will require careful investigation, which is the aim of our future work. We will also consider other definitions of closeness in an attempt to generalize our results and extend them to a wider class of networks. Another important question to consider is the stability of attractors in one-step networks, including fixed points. For example a basin of a fixed point can entirely disappear, raising a question about the importance of this particular fixed point (see Figure 1(f) - (g)). Since fixed points between one-step networks and their original ones stay the same, it might be tempting to just compute fixed points and estimate their basins without passing to a one-step structure, missing the fact that this attractor might be biologically less meaningful if its basin can be dramatically reduced under a one-step function. We believe in the importance of pursuing these questions and providing analytical results, as they have the potential to be incorporated into modeling software and aid researchers in their analyses of biological multi-state networks.

**Author contributions**

Julia Chifman conceptualized, designed and directed the project. Original results for the nonexpanding ternary networks were derived by Etan Basser-Ravitz and Arman Darbar. All authors contributed to the extension of original results to multi-state networks. The first version of the manuscript was written by Julia Chifman and all authors commented and edited on subsequent versions of the manuscript. All authors read and approved the final manuscript.

**References**

1. René Thomas. Regulatory networks seen as asynchronous automata: A logical description. *Journal of Theoretical Biology*, 153(1):1–23, 1991.
2. Denis Thieffry and René Thomas. Dynamical behaviour of biological regulatory networks—ii. immunity control in bacteriophage lambda. *Bulletin of Mathematical Biology*, 57(2):277–297, 1995.
3. LUCAS SÁNCHEZ and DENIS THIEFFRY. A logical analysis of the drosophila gap-gene system. *Journal of Theoretical Biology*, 211(2):115–141, 2001.
4. Carlos Espinosa-Soto, Pablo Padilla-Longoria, and Elena R. Alvarez-Buylla. A Gene Regulatory Network Model for Cell-Fate Determination during Arabidopsis thaliana Flower Development That Is Robust and Recovers Experimental Gene Expression Profiles. *The Plant Cell*, 16(11):2923–2939, 11 2004.
5. Elisabeth Remy, Sandra Rebouissou, Claudine Chaouiya, Andrei Zinovyev, François Radvanyi, and Laurence Calzone. A modeling approach to explain mutually exclusive and co-occurring genetic alterations in bladder tumorigenesis. *Cancer Research*, 75(19):4042–4052, 2015.
6. Wassim Abou-Jaoude, Djomangan A. Ouattara, and Marcelle Kaufman. From structure to dynamics: Frequency tuning in the p53–mdm2 network: I. logical approach. *Journal of Theoretical Biology*, 258(4):561–577, 2009.
7. Julia Chifman, Seda Arat, Zhiyong Deng, Erica Lemler, James C. Pino, Leonard A. Harris, Michael A. Kochen, Carlos F. Lopez, Steven A. Akman, Frank M. Torti, Suzy V. Torti, and Reinhard Laubenbacher. Activated oncogenic pathway modifies iron network in breast epithelial cells: A dynamic modeling perspective. *PLOS Computational Biology*, 13(2):1–24, 02 2017.
8. Y. Setty, A. E. Mayo, M. G. Surette, and U. Alon. Detailed map of a cis-regulatory input function. *Proceedings of the National Academy of Sciences*, 100(13):7702–7707, 2003.
9. Adam C. Knapp, Luis Sordo Vieira, Reinhard Laubenbacher, and Julia Chifman. Steadycellphenotype: A web-based tool for the modeling of biological networks with ternary logic. *bioRxiv*, 2021.
10. J. Chifman, A. Kniss, P. Neupane, I. Williams, B. Leung, Z. Deng, P. Mendes, V. Hower, F.M. Torti, S.A. Akman, S.V. Torti, and R. Laubenbacher. The core control system of intracellular iron homeostasis: A mathematical model. *Journal of Theoretical Biology*, 300(0):91 – 99, 2012.
Cyclic attractors of nonexpanding $n$-ary networks

[11] Luis Sordo Vieira, Joseph Masison, Jacqueline Adams, Suzy Torti, Reinhard Laubenbacher, and Julia Chifman. Abstract 2442: Assessing how macrophages attain distinct iron handling phenotypes in a tumor via a mathematical model. *Cancer Research*, 79(13 Supplement):2442–2442, 2019.

[12] S.A. Kauffman. Metabolic stability and epigenesis in randomly constructed genetic nets. *Journal of Theoretical Biology*, 22(3):437–467, 1969.

[13] Leon Glass and Stuart A. Kauffman. The logical analysis of continuous, non-linear biochemical control networks. *Journal of Theoretical Biology*, 39(1):103–129, 1973.

[14] Sui Huang. Gene expression profiling, genetic networks, and cellular states: An integrating concept for tumorigenesis and drug discovery. *Journal of molecular medicine (Berlin, Germany)*, 77:469–80, 07 1999.

[15] Konstantin Klemm and Stefan Bornholdt. Stable and unstable attractors in boolean networks. *Physical review. E, Statistical, nonlinear, and soft matter physics*, 72:055101, 12 2005.

[16] S. Bornholdt. Boolean network models of cellular regulation: prospects and limitations. *Journal of The Royal Society Interface*, 5:S85 – S94, 2008.

[17] Lea Siegle, Julian D. Schwab, Silke D. Kühlwein, Ludwig Lausser, Stefan Tümpel, Astrid S. Pfister, Michael Kühl, and Hans A. Kestler. A boolean network of the crosstalk between igf and wnt signaling in aging satellite cells. *PLOS ONE*, 13(3):1–24, 03 2018.

[18] Andre S. Ribeiro and Stuart A. Kauffman. Noisy attractors and ergodic sets in models of gene regulatory networks. *Journal of Theoretical Biology*, 247(4):743–755, 2007.

[19] Julian D. Schwab, Silke D. Kühlwein, Nensi Ikonomi, Michael Kühl, and Hans A. Kestler. Concepts in boolean network modeling: What do they all mean? *Computational and Structural Biotechnology Journal*, 18:571–582, 2020.

[20] Adrien Richard. Local negative circuits and fixed points in non-expansive boolean networks. *Discrete Applied Mathematics*, 159(11):1085–1093, 2011.

[21] Adrien Richard. Fixed point theorems for boolean networks expressed in terms of forbidden subnetworks. *Theoretical Computer Science*, 583:1–26, 2015.

[22] Douglas B. West. *Introduction to Graph Theory*. Prentice Hall, 2 edition, September 2000.

[23] G. Chartrand and O.R. Oellermann. *Applied and Algorithmic Graph Theory*. International series in pure and applied mathematics. McGraw-Hill, 1993.

[24] Alan Veliz-Cuba, Abdul Salam Jarrah, and Reinhard Laubenbacher. Polynomial algebra of discrete models in systems biology. *Bioinformatics*, 26(13):1637–1643, 05 2010.

[25] Alan Veliz-Cuba and Reinhard Laubenbacher. Dynamics of semilattice networks with strongly connected dependency graph. *Automatica*, 99:167 – 174, 2019.

[26] Rikki A. M. Brown, Kirsty L. Richardson, Tasnuva D. Kabir, Debbie Trinder, Ruth Ganss, and Peter J. Leedman. Altered iron metabolism and impact in cancer biology, metastasis, and immunology. *Frontiers in Oncology*, 10:476, 2020.

[27] K Muroya, S Hattori, and S Nakamura. Nerve growth factor induces rapid accumulation of the gtp-bound form of p21ras in rat pheochromocytoma pc12 cells. *Oncogene*, 7(2):277—281, February 1992.

[28] Sean Boykevish, Chen Zhao, Holger Sondermann, Polixeni Philippidou, Simon Hagleoua, John Kuriyan, and Dafna Bar-Sagi. Regulation of ras signaling dynamics by sos-mediated positive feedback. *Curr Biol*, 16(21):2173–2179, Nov 2006.
Appendix

A Additional properties, proofs and examples

Some properties of max, min and not operators.

Let \( x, y, z \in X_n = \{0, 1, \ldots, n - 1\} \).

Associative property:

\[
\begin{align*}
\max(x, \max(y, z)) &= \max(\max(x, y), z) \\
\min(x, \min(y, z)) &= \min(\min(x, y), z).
\end{align*}
\] (12a)

Distributive property:

\[
\begin{align*}
\min(x, \max(y, z)) &= \max(\min(x, y), \min(x, z)) \\
\max(x, \min(y, z)) &= \min(\max(x, y), \max(x, z)).
\end{align*}
\] (12d)

De Morgan’s laws:

\[
\begin{align*}
\min(\not(x), \not(y)) &= \not(\max(x, y)) \\
\max(\not(x), \not(y)) &= \not(\min(x, y)).
\end{align*}
\] (12f)

Absorption properties:

\[
\begin{align*}
\max(x, \min(x, y)) &= x \\
\min(x, \max(x, y)) &= x.
\end{align*}
\] (12h)

Other properties:

\[
\begin{align*}
\max(x, 0) &= x \\
\min(x, n - 1) &= x \\
\not(\not(x)) &= x.
\end{align*}
\] (12k)

Proof of Lemma 3.4

Let \( x, y \in X_n \) so that \( d_{\infty}(x, y) \leq 1 \). Since \( x \) is close to \( y \) then

\[
y_v = x_v - 1 \quad \text{or} \quad y_v = x_v \quad \text{or} \quad y_v = x_v + 1,
\] (13)

where \( x_v, y_v \in X_n \) are the current states of the node \( v \). Let \( f_v(x) = k \) for some \( k \in X_n \). This means that \( f_v(y) \) takes on the values in the set \( \{k - 1, k, k + 1\} \) because \( F \) is nonexpanding.

Case 1. Suppose \( x_v < k \), then according to Definition 2.2, \( h_v(x) = x_v + 1 \).

If \( f_v(y) = k - 1 \) then Definition 2.2 and (13) together with the assumption that \( x_v < k \) imply

\[
h_v(y) = \begin{cases} 
  x_v & \text{if } y_v = x_v - 1 \\
  x_v + 1 & \text{or } x_v \\
  x_v + 2 & \text{or } x_v + 1 \text{ or } x_v
\end{cases}
\]

If \( f_v(y) = k \) then using the same assumptions as above we get

\[
h_v(y) = \begin{cases} 
  x_v & \text{if } y_v = x_v - 1 \\
  x_v + 1 & \text{if } y_v = x_v \\
  x_v + 2 & \text{or } x_v + 1 \text{ or } x_v
\end{cases}
\]

Finally, when \( f_v(y) = k + 1 \) then

\[
h_v(y) = \begin{cases} 
  x_v & \text{if } y_v = x_v - 1 \\
  x_v + 1 & \text{if } y_v = x_v \\
  x_v + 2 & \text{if } y_v = x_v + 1
\end{cases}
\]
Thus all possibilities lead to $|h_v(x) - h_v(y)| \leq 1$.

**Case 2.** Suppose $x_v = k$, then according to Definition 2.2, $h_v(x) = x_v$. Using similar logic as in Case 1, we get that the possible values for $h_v(y)$ are $x_v - 1, x_v$ or $x_v + 1$, implying that $|h_v(x) - h_v(y)| \leq 1$.

**Case 3.** Suppose $x_v > k$, then according to Definition 2.2, $h_v(x) = x_v - 1$. Now, we get that the possible values for $h_v(y)$ are $x_v - 2, x_v - 1$ or $x_v$, which also leads to $|h_v(x) - h_v(y)| \leq 1$.

In all cases, $d_{\infty}(h(x), h(y)) = \max_{v \leq m} |h_v(x) - h_v(y)| \leq 1$. Thus, $\mathcal{H}$ is nonexpanding.

**Lemma A.1.** Suppose $\mathcal{N} = (G, F)$ is an $n$-ary network with the corresponding one-step network $\mathcal{H} = (\mathcal{N}, h)$, then $d_{\infty}(h(x), F(x)) \leq n - 2$ for all $x \in X_n^m$.

**Proof.** Since $d_{\infty}(h(x), F(x)) = \max_{v \leq m} |h_v(x) - f_v(x)|$, we only need to show that $|h_v(x) - f_v(x)| \leq n - 2$ for each local activation function. Suppose $f_v(x) = k$ for some $k \in X_n$. Then according to Definition 2.2, the values of $h_v$ will depend on the values of $x_v$, which is the current state of the node $v$. Note, if the value of $x_v$ were $k - 1, k$, or $k + 1$, then $f_v(x) = h_v(x)$ and $|h_v(x) - f_v(x)| = 0$.

If $x_v \notin \{k - 1, k, k + 1\}$ then $h_v(x) = x_v + 1$ if $x_v < k$ or $h_v(x) = x_v - 1$ if $x_v > k$. Since $x_v, k \in X_n$, the largest possible distance between $h_v(x)$ and $f_v(x)$ is $n - 2$. In particular, $d_{\infty}(h(x), F(x)) \leq n - 2$.

**Lemma A.2.** Suppose $\mathcal{N} = (G, F)$ is a nonexpanding $n$-ary network with the corresponding one-step network $\mathcal{H} = (\mathcal{N}, h)$. Let $x \in X_n^m$ and $i \in \mathbb{N}$. If $F(h_i(x)) = h(h_{i-1}(x))$ then $F(h_i(x)) = h_i(x)$.

**Proof.** Suppose $F(h_i(x)) = h_i(x)$. Since $h_{i-1}(x)$ is close to $h_i(x)$ and $F$ is nonexpanding, we get $d_{\infty}(F(h_i(x)), h_i(x)) = d_{\infty}(F(h_i(x)), F(h_{i-1}(x))) \leq 1$.

Thus we conclude that $F(h_i(x)) = h_i(x)$.

**Example A.3.** Let $G$ be a digraph as depicted in Figure 3(a) and let $X_3 = \{0, 1, 2\}$. Let a global transition function $F = (f_1, f_2) : X_3^2 \to X_3^2$ given by

- $f_1(x) = (2 + x_1 + x_2 + 2x_1x_2 + x_1^2x_2^2) \mod 3$
- $f_2(x) = x_1$.

The network $\mathcal{N}$ fails to be nonexpanding and has one fixed point. The corresponding one-step network $\mathcal{H}$ is nonexpanding, but notice it now has a new 3-cycle.

![Graph Image](image)

**Figure 3:** Example of ternary network. Panel (a) Interaction graph. Panel (b) displays state space dynamics for network as described in Example A.3. Panel (c) displays dynamics of the corresponding one-step network; one-step networks are described in the Section 2.3. Fixed points and cycle attractors are colored in red.