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Correspondence of Trap Spaces in Different Models of Bioregulatory Networks

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Correspondence of Trap Spaces in Different Models of Bioregulatory Networks¹

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Abstract

Mathematical models for bioregulatory networks can be based on different formalisms, depending on the quality of available data and the research question to be answered. Discrete Boolean models can be constructed based on qualitative data, which are frequently available. On the other hand, continuous models in terms of ordinary differential equations (ODEs) can incorporate time-series data and give more detailed insight into the dynamics of the underlying system. A few years ago, a method based on multivariate polynomial interpolation and Hill functions has been developed for an automatic conversion of Boolean models to systems of ordinary differential equations. This method is frequently used by modellers in systems biology today, but there are only a few results available about the conservation of mathematical structures and properties across the formalisms. Here, we consider subsets of the phase space where some components stay fixed, called trap spaces, and demonstrate how Boolean trap spaces can be linked to invariant sets in the continuous state space. This knowledge is of practical relevance since finding trap spaces in the Boolean setting, which is relatively easy, allows for the construction of reduced ODE models.

1 Introduction

Biological systems usually consist of numerous subsystems interacting through various feedback mechanisms, whose relevant scales in space and time span multiple orders of magnitude. The exact nature of many of these processes and the relevant values of the parameters involved are in many cases unknown, and quantitative data is often lacking. This often hinders the use of ordinary differential equation (ODE) models, a standard tool in systems biology for the quantitative simulation of concentration changes or activity profiles of biochemical molecules over time. Although extremely useful, exploration of the complete parameter space and possible dynamical behavior of a system is usually out of scope, and calls for alternative modeling paradigms. Logic-based models can utilize qualitative data, describing states of system components using activity

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levels, e.g., representing ranges of concentrations, that are responsible for a specific qualitative effect [21]. The resulting dynamics can be represented by a finite state transition graph, which allows for exploitation of methods and tools not applicable in the ODE setting such as graph theoretical algorithms or formal verification [8, 9, 24, 27, 2, 12].

Aside of aspects of computability, switching between the different formalisms or combining them in hybrid models is of great benefit for many applications where the available data sets are highly inhomogeneous, containing data on different levels of resolution. In addition, logical models are much more accessible for non-experts, making it convenient to use them for testing hypotheses that can then be transferred to more detailed models. However, such integrated approaches can only go beyond heuristics if conservation of certain mathematical structures and properties across the formalisms can be proven.

Different methods have been proposed to transfer either Boolean networks to ODE models in an automated framework (see, e.g., [25, 11]) or vice versa (see, e.g., [20, 5]). Since the most common way of modelling is to first construct a Boolean network and to derive an ODE system in the second step, we concentrate on the algorithm presented in [25]. This algorithm aims at preserving the network topology and the type of influence (stimulatory or inhibitory) during the conversion process by using multivariate polynomial interpolation and Hill functions. The value of this approach crucially depends on our ability to transfer knowledge from the Boolean model to the continuous model. Results available so far are limited. Information about the location and number of steady states can already be deduced from the Boolean model (see, e.g., [22, 25]), but less is known about other dynamical features like oscillations or reachability. There are some results about oscillatory behavior for piecewise-linear differential equations, for example in [19, 23]. However, studies on example systems show that these dynamical features, in general, are not necessarily preserved in Hill-type continuous models (e.g. [16, 3]).

In this paper we focus on a characteristic feature of dynamical systems that generalizes the concept of steady states - namely subspaces of the state space where only some of the components remain fixed, called trap spaces. Trap spaces have also been studied by other researchers [27, 26, 15, 18]. We show that the trap spaces of a Boolean dynamical system correspond to invariant sets of the continuous dynamical system, whereby the size of these sets can be controlled by the Hill exponents. Trap spaces in a Boolean network can be computed efficiently (see [8]). This hints to possible model reductions whereby only a specific subnetwork of the original Boolean network needs to be translated into an ODE model.

The paper is organized as follows. In Sec. 2 we introduce the notation and briefly review the transformation algorithm from [25]. In Sec. 3 we show that trap spaces of a Boolean network cannot directly be linked to trap spaces in the ODE model in the general case. This can only be done if normalized Hill functions are used for the translation, as we demonstrate in Sec. 4. In Sec. 5, we show that, even if the Hill functions are not normalized, a correspondance to invariant sets is possible. The size of these sets can be controlled by the parameters of the Hill functions, as we will demonstrate in Sec. 6. Finally, we demonstrate the applicability of our approach on a 4-dimensional dynamical system in Sec. 7.

2 Preliminaries

Consider an arbitrary Boolean function $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$, $N \in \mathbb{N}$. This function could either decode an asynchronous or a synchronous update scheme. For our purpose it is enough to consider only the synchronous update scheme since steady states as well as trap spaces (see Definition 1) remain the same in both formalisms [8]. Hence, we consider the following Boolean dynamical system:

$$\begin{aligned} x^{t+1} &= f(x^t), t \in \mathbb{N} \\ x^0 &:= x_0 \in \{0, 1\}^N \end{aligned} \tag{1}$$

We will associate to f a family of two-parametric continuous functions $(\overline{f}^{\vec{k}, \vec{\theta}})_{\vec{k} \in \mathbb{R}_{>0}^N, \vec{\theta} \in (0, 1)^N}$, where $\overline{f}^{\vec{k}, \vec{\theta}} : [0, 1]^N \rightarrow [0, 1]^N$, which should be understood as a continuous continuation of f on $[0, 1]^N$. This means that $\overline{f}^{\vec{k}, \vec{\theta}}$ agrees with f on $\{0, 1\}^N$ or, vaguely speaking, takes at least similar values on $\{0, 1\}^N$. Throughout the paper, the line over variables and functions is used only in the continuous setting. The construction of $\overline{f}^{\vec{k}, \vec{\theta}}$ and the meaning of the parameters \vec{k} and $\vec{\theta}$ will be explained later. This leads to a time-discrete but state-continuous dynamical system of the form:

$$\begin{aligned} \overline{x}^{t+1} &= \overline{f}^{\vec{k}, \vec{\theta}}(\overline{x}^t), t \in \mathbb{N} \\ \overline{x}^0 &:= \overline{x}_0 \in [0, 1]^N \end{aligned}$$

Finally we construct for any $\vec{k} \in \mathbb{R}_{>0}^N$ an ODE system of the form:

$$\begin{aligned} \dot{\overline{x}} &= D \cdot (\overline{f}^{\vec{k}, \vec{\theta}}(\overline{x}) - \overline{x}) \\ \overline{x}(0) &= \overline{x}_0 \in [0, 1]^N \end{aligned} \tag{2}$$

where D is a strictly positive diagonal matrix, $D = \text{diag}(d_1, \dots, d_N)$ with $d_i > 0$ for $i \in \{1, \dots, N\}$ ¹. A solution $\overline{x} : \mathbb{R}_{\geq 0} \rightarrow [0, 1]^N$ of (2) could for example represent the course of mRNA or protein concentrations over time. A steady state $\overline{x} \in [0, 1]^N$ of the ODE system is defined as the zero locus of (2),

$$\vec{0} = \overline{f}^{\vec{k}, \vec{\theta}}(\overline{x}) - \overline{x}.$$

Trap spaces represent a generalization of steady states in that only a few components remain unchanged, whereas in steady states all components remain fixed. We now give a formal definition of trap spaces. To simplify matters we will restrict ourselves to the case where the first $n \leq N$ components stay fixed. However, the results remain of course true in the general case because we can always permute the components of f in such a way that we arrive at this special case.

¹We could also consider the ODE system $\dot{x} = \text{diag}(\vec{\alpha})\overline{f}^{\vec{k}}(x) - \text{diag}(\vec{\beta})x$. However, after a normalization step we arrive at a system of the form (2) (see [25]).

Definition 1. Consider a dynamical system (G, X^N, ϕ) with time domain $G = \mathbb{N}$ or $G = \mathbb{R}_{\geq 0}$, $N \in \mathbb{N}$, a non-empty set X , and evolution ϕ given by

$$\begin{aligned} \phi : G \times X^N &\rightarrow X^N \\ (t, x) &\mapsto \phi(t, x). \end{aligned}$$

We define the set

$$(p, *)_X = \{x \in X^N \mid x_i = p_i \text{ for } i \leq n\}$$

with $p \in X^n$, $n \in \{1, \dots, N\}$. We call a set of the form $(p, *)_X$ a trap space of the dynamical system if it is invariant with respect to the evolution, i.e.

$$\phi(t, x) \in (p, *)_X \quad \forall x \in (p, *)_X, t \in G.$$

If the meaning of X is clear from the context, we write $(p, *)$ instead of $(p, *)_X$.

If we choose in the above definition $n = N$ then we arrive at the definition of a steady state. Therefore, every steady state is as well a trap space. On the other hand we excluded the trivial case where no component is fixed from the definition.

Now we turn our attention to the construction of the functions $\bar{f}^{\vec{k}, \vec{\theta}}$. According to [25], we will analyze here two ways to construct the family $\bar{f}^{\vec{k}, \vec{\theta}}$, $\vec{k} \in \mathbb{R}_{>0}^N$, $\vec{\theta} \in (0, 1)^N$, one based on Hill cubes and the other one based on normalized Hill cubes. The basic procedure in both approaches is the same. First, a multivariate polynomial interpolation of f is constructed to obtain a continuous continuation of f . Afterwards, Hill functions are used to induce a behavior of the resulting continuous function similar to step functions. The exact shape of these Hill functions can be controlled by specific parameters.

Definition 2. Let $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$ be a Boolean function. Its multivariate polynomial interpolation is a function $\bar{I}(f) : [0, 1]^N \rightarrow [0, 1]^N$ with $\bar{I}(f)_i := \bar{I}(f_i) : [0, 1] \rightarrow [0, 1]$ that assigns polynomials to the Boolean functions f_i given explicitly by

$$\bar{I}(f_i)(\bar{x}_1, \dots, \bar{x}_N) = \sum_{x \in \{0, 1\}^N} f_i(x) \prod_{j=1}^N (x_j \bar{x}_j + (1 - x_j)(1 - \bar{x}_j)). \quad (3)$$

As shown in [25, p.16-17] the multivariate polynomial interpolation $\bar{I}(f_i)$ is the unique polynomial of minimal degree² that coincides with f_i on the vertices $x \in \{0, 1\}^N$ of the hypercube.

We illustrate this process with a small example which will be used again later on:

Example 3. Consider the Boolean function $f : \{0, 1\}^3 \rightarrow \{0, 1\}^3$ defined in Tab. 1. Using (3) we obtain the polynomial map $\bar{I}(f)$:

$$\begin{aligned} \bar{I}(f) &= \begin{pmatrix} (1 - \bar{x}_1)(1 - \bar{x}_2)(1 - \bar{x}_3) + \bar{x}_1(1 - \bar{x}_2)\bar{x}_3 + \bar{x}_1\bar{x}_2\bar{x}_3 + \bar{x}_1\bar{x}_2(1 - \bar{x}_3) + \bar{x}_1(1 - \bar{x}_2)(1 - \bar{x}_3) \\ \bar{x}_1(1 - \bar{x}_2)\bar{x}_3 + \bar{x}_1\bar{x}_2\bar{x}_3 + (1 - \bar{x}_1)(1 - \bar{x}_2)\bar{x}_3 + (1 - \bar{x}_1)\bar{x}_2\bar{x}_3 \\ (1 - \bar{x}_1)(1 - \bar{x}_2)(1 - \bar{x}_3) + \bar{x}_1(1 - \bar{x}_2)\bar{x}_3 + \bar{x}_1(1 - \bar{x}_2)(1 - \bar{x}_3) + (1 - \bar{x}_1)(1 - \bar{x}_2)\bar{x}_3 \end{pmatrix} \\ &= \begin{pmatrix} (1 - \bar{x}_1)(1 - (\bar{x}_2 + \bar{x}_3 - \bar{x}_2\bar{x}_3)) + \bar{x}_1 \\ \bar{x}_3 \\ 1 - \bar{x}_2 \end{pmatrix} \end{aligned}$$

²The degree of a polynomial $P(X_1, \dots, X_N) = \sum_{(m_1, \dots, m_N) \in \mathbb{N}^N} a_{m_1, \dots, m_N} X_1^{m_1} \dots X_N^{m_N}$ is defined as $\deg(P) = \max_{(m_1, \dots, m_N) \in \mathbb{N}^N, a_{m_1, \dots, m_N} \neq 0} \sum_{i=1}^N m_i$.

Table 1: Truth table for $f : \{0, 1\}^3 \rightarrow \{0, 1\}^3$ in Example 3.

x_1	x_2	x_3	$f_1(x)$	$f_2(x)$	$f_3(x)$
0	0	0	1	0	1
0	0	1	0	1	1
0	1	0	0	0	0
0	1	1	0	1	0
1	0	0	1	0	1
1	0	1	1	1	1
1	1	0	1	0	0
1	1	1	1	1	0

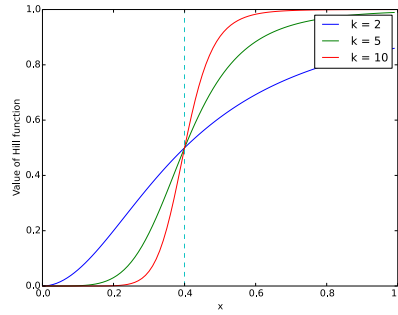


Figure 1: Different Hill functions for $\theta = 0.4$.

Let's return to the construction of $f^{\vec{k}, \vec{\theta}}$. For this purpose we need the notion of Hill functions.

Definition 4. A multivariate Hill function is defined by

$$H^{\vec{k}, \vec{\theta}} : [0, 1]^N \rightarrow [0, 1]^N$$

$$H^{\vec{k}, \vec{\theta}}(x) = (h_{k_1, \theta_1}(x_1), \dots, h_{k_N, \theta_N}(x_N))$$

with univariate Hill functions

$$h_{k, \theta} : [0, 1] \rightarrow [0, 1]$$

$$h_{k, \theta}(x) = \frac{x^k}{x^k + \theta^k}, \quad k \in \mathbb{R}_{>0}, \theta \in (0, 1).$$

The parameter k is called *Hill coefficient* and θ is called *threshold*. In Fig. 1 the graphs of several Hill functions with different Hill coefficients are depicted. A larger Hill coefficient leads to a steeper Hill function. By construction it holds $h_{k, \theta}(0) = 0$ and $h_{k, \theta}(1) < 1$ for any $\theta \in (0, 1)$, $k \in \mathbb{R}_{>0}$.

Lemma 5. The Hill functions $h_{k, \theta}$ as well as the normalized Hill functions $\frac{h_{k, \theta}}{h_{k, \theta}(1)}$ converge on any interval $[a, b] \subset [0, \theta)$ uniformly to 0 and for $[a, b] \subset (\theta, 1]$ uniformly to 1.

Proof. For $x \in [a, b] \subset [0, \theta)$ it holds $x < \theta$, and for $x \in [a, b] \subset (\theta, 1]$ it holds $x > \theta$. Using Dini's theorem [4, p. 165] the above Lemma follows from

$$\lim_{k \rightarrow \infty} h_{k, \theta}(x) = \lim_{k \rightarrow \infty} \frac{x^k}{x^k + (\frac{\theta}{x})^k} = \lim_{k \rightarrow \infty} \frac{1}{1 + (\frac{\theta}{x})^k} = \begin{cases} 0 & \text{if } x < \theta \\ \frac{1}{2} & \text{if } x = \theta \\ 1 & \text{if } x > \theta \end{cases}.$$

□

We now consider two ways to construct the family $(\vec{f}^{\vec{k}, \vec{\theta}})_{\vec{k} \in \mathbb{R}_{>0}^N, \vec{\theta} \in (0, 1)^N}$ from $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$ and $H^{\vec{k}, \vec{\theta}}$.

Definition 6. A Hill cube is defined as ([25, p. 5]):

$$\begin{aligned} \vec{f}^{\vec{k}, \vec{\theta}} : [0, 1]^N &\rightarrow [0, 1]^N \\ \vec{f}^{\vec{k}, \vec{\theta}} &:= \bar{I}(f) \circ H^{\vec{k}, \vec{\theta}} \end{aligned}$$

A normalized Hill cube is defined as ([25, p. 5]):

$$\begin{aligned} \vec{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}} : [0, 1]^N &\rightarrow [0, 1]^N \\ \vec{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}} &:= \bar{I}(f) \circ \frac{H^{\vec{k}, \vec{\theta}}}{H^{\vec{k}, \vec{\theta}}(\bar{1})}, \end{aligned}$$

where the division $\frac{H^{\vec{k}, \vec{\theta}}}{H^{\vec{k}, \vec{\theta}}(\bar{1})}$ is meant component wise.

We remark here that in [25] the Hill-coefficients \vec{k} and the thresholds $\vec{\theta}$ are allowed to differ in each of the components of the functions and variables. However, here we assume that they can only differ between different variables. This allows us to represent $\vec{f}^{\vec{k}, \vec{\theta}}$ as a concatenation of two functions.

3 Motivation

The normalization of the Hill cubes implies that $\vec{f}^{\vec{k}, \vec{\theta}}$ coincides with f on the vertices of the hypercube $[0, 1]^N$. If the Hill cubes are not normalized, the function $\vec{f}^{\vec{k}, \vec{\theta}}$ will differ slightly from f on $\{0, 1\}^N$. This raises the question which dynamical properties are preserved during the conversion from the state and time discrete model to the continuous model. In case of steady states it is guaranteed that for sufficiently large \vec{k} a steady state $\vec{x}_{\text{steady}}^{\vec{k}}$ of Eq. (2) can be found in a neighborhood $U(x_{\text{steady}})$, where x_{steady} is a steady state of f in Eq. (1). This result was derived in [25] and generalized in [22].

Theorem 7 ([25]). Assume $x_{\text{steady}} \in \{0, 1\}^N$ is a steady state of f in Eq. (1). If $\min_{i \in \{0, \dots, N\}} k_i$ is sufficiently large, then there is a neighborhood $U(x_{\text{steady}}) \subseteq [0, 1]^N$ of x_{steady} such that the ODE model (2) has a steady state $\vec{x}_{\text{steady}}^{\vec{k}} \in U(x_{\text{steady}})$. Moreover, for any sequence $(\vec{k}^j)_{j \in \mathbb{N}} \subset \mathbb{R}_{>0}^N$ that converges component-wise to infinity, it holds

$$\lim_{j \rightarrow \infty} \vec{x}_{\text{steady}}^{\vec{k}^j} = x_{\text{steady}}.$$

This motivates the following question: Do $\vec{f}^{\vec{k},\vec{\theta}}$ and $\vec{f}^{\vec{k},\vec{\theta}}_{\text{normalized}}$ inherit the trap spaces of f ? A natural idea would be to generalize Theorem 7 by assigning to each trap space of f a trap space of $\vec{f}^{\vec{k},\vec{\theta}}$. However, as the following example shows, this does not always work.

Example 8. Consider again the Boolean function $f : \{0,1\}^3 \rightarrow \{0,1\}^3$ from Example 3. We can write $\bar{I}(f)$ in the form

$$\bar{I}(f)(\bar{x}) = \begin{pmatrix} 1 - (1 - \bar{x}_1) \cdot \underbrace{(\bar{x}_2 + \bar{x}_3 - \bar{x}_2\bar{x}_3)}_{=: C(\bar{x}_2, \bar{x}_3)} \\ \bar{x}_3 \\ 1 - \bar{x}_2 \end{pmatrix}.$$

From the definition of f (see Tab. 1) it is clear that $(1, *) \subseteq \{0,1\}^3$ is a trap space of f . We want to know if there is a $\bar{p}_1 \in [0,1]$ such that $(\bar{p}_1, *) \subseteq [0,1]^3$ is a trap space of $\vec{f}^{\vec{k},\vec{\theta}}$. For simplicity, we assume $\vec{k} = (k \ k \ k)^T$ for some $k \in \mathbb{R}_{>0}$, $\vec{\theta} = (\theta \ \theta \ \theta)^T$, $\theta \in (0,1)$, and consequently write $\vec{f}^{k,\theta} = \vec{f}^{\vec{k},\vec{\theta}}$. This means, we need to find $\bar{x}_1 \in [0,1]$ such that

$$\forall \bar{x}_2, \bar{x}_3 \in [0,1] : 0 = \vec{f}_1^k(\bar{x}_1, \bar{x}_2, \bar{x}_3) - \bar{x}_1$$

holds. We have

$$\vec{f}_1^k(\bar{x}_1, \bar{x}_2, \bar{x}_3) - \bar{x}_1 = \bar{I}(f_1) \circ H^{k,\theta}(\bar{x}_1, \bar{x}_2, \bar{x}_3) - \bar{x}_1.$$

In order to find a trap space of $\vec{f}^{k,\theta}$, we can instead look at the function $g : [0,1]^3 \rightarrow [0,1]$

$$\bar{g}(\bar{x}_1, \bar{y}_1, \bar{y}_2) := \bar{I}(f_1)(h_{k,\theta}(\bar{x}_1), \bar{y}_1, \bar{y}_2) - \bar{x}_1,$$

since the input variables of the Hill functions are allowed to vary freely. Consequently, for a fixed $\bar{x}_1 \in [0,1]$, we can interpret the function $g(\bar{x}_1, \cdot, \cdot)$ as a polynomial $\bar{g}(\bar{x}_1, Y_1, Y_2)$ in $\mathbb{R}[Y_1, Y_2]$. Since the set $K := h_{k,\theta}([0,1]) \times h_{k,\theta}([0,1])$ has a nonempty interior, we have the following equivalence:

$$\begin{aligned} & \exists \bar{x}_1 \in [0,1] : 0 = \bar{g}(\bar{x}_1, Y_1, Y_2) \in \mathbb{R}[Y_1, Y_2] \\ \Leftrightarrow & \exists \bar{x}_1 \in [0,1] \forall (\bar{y}_1, \bar{y}_2) \in K : 0 = \bar{g}(\bar{x}_1, \bar{y}_1, \bar{y}_2) \\ \Leftrightarrow & \exists \bar{x}_1 \in [0,1] \forall \bar{x}_2, \bar{x}_3 \in [0,1] : 0 = \vec{f}_1^k(\bar{x}_1, \bar{x}_2, \bar{x}_3) - \bar{x}_1 \end{aligned}$$

Hence, for $(\bar{x}_1, *)$ being a trap space, the polynomial system of equations needs to be fulfilled:

$$\begin{aligned} 0 &= \bar{g}(\bar{x}_1, Y_1, Y_2) \\ \Leftrightarrow 0 &= 1 - \left(1 - \frac{\bar{x}_1^k}{\theta^k + \bar{x}_1^k}\right) \cdot C(Y_1, Y_2) - \bar{x}_1 \end{aligned} \quad (4)$$

Since the polynomial $C(Y_1, Y_2)$ is not the zero polynomial and it has no constant monomials, we obtain the system of equations

$$\begin{aligned} 1 - \frac{\bar{x}_1^k}{\theta^k + \bar{x}_1^k} &= 0, \\ 1 - \bar{x}_1 &= 0, \end{aligned}$$

which has no solution for $k > 0$, $\theta \in (0, 1)$. This means there is no $k \in \mathbb{R}_{>0}$ such that $\vec{f}^{k, \theta}$ has a trap space of the form $(\bar{x}_1, *)$, $\bar{x}_1 \in [0, 1]$.

This example shows that we cannot link the trap spaces of a Boolean system directly to the trap spaces of the ODE system if we use Hill functions. That means, we cannot generalize Theorem 7 directly. One reason why these difficulties arise at all lies in the fact that the functions $\vec{f}^{k, \theta}$ do not agree perfectly with their Boolean counterparts on $\{0, 1\}^N$. The situation changes if we use normalized Hill functions, as we will demonstrate in the following section.

4 Correspondence of trap spaces for normalized Hill functions

We will show now that if we use normalized Hill functions, the trap spaces remain the same during the conversion from the Boolean model (1) to the ODE system

$$\begin{aligned} \dot{\bar{x}} &= D \cdot (\vec{f}_{\text{normalized}}^{k, \theta}(\bar{x}) - \bar{x}) \\ \bar{x}(0) &= \bar{x}_0. \end{aligned} \quad (5)$$

Since the map $\frac{H^{k, \theta}}{H^{k, \theta}(1)}$ is a bijection from $[0, 1]^N$ to $[0, 1]^N$ for $\vec{k} \in \mathbb{R}_{>0}^N$ and $\vec{\theta} \in (0, 1)^N$ and its restriction to $\{0, 1\}^N$ is the identity map, it suffices to show that $\bar{I}(f)$ is inheriting the trap spaces of f . This result will also be useful later on with respect to $\vec{f}^{k, \theta}$. We introduce the following notation:

$$\bar{I}(f_i)(\bar{x}) = \underbrace{\sum_{x \in \{0, 1\}^N} f_i(x) \prod_{j=1}^N \underbrace{(x_j \bar{x}_j + (1 - x_j)(1 - \bar{x}_j))}_{:= P_j^x(\bar{x}_j)}}_{:= S_i^x(\bar{x})}.$$

First, we consider a special case:

Lemma 9. *Let $(\vec{0}, *) \subseteq \{0, 1\}^N$ be a trap space of f . Then*

$$\forall i \in \{1, \dots, n\} \forall x \in \{0, 1\}^N \exists j \in \{1, \dots, n\} : \bar{x}_j | S_i^x(\bar{x}),$$

where $|$ is the division relation in the polynomial ring $\mathbb{R}[\bar{x}] = \mathbb{R}[\bar{x}_1, \dots, \bar{x}_N]$ and $\vec{0} \in \mathbb{R}^n$, $n \leq N$. In particular, this implies that $(\vec{0}, *)$ is a trap space of $\bar{I}(f)$.

Proof. Let $x \in (\vec{0}, *)$. Then, for all $i \in \{1, \dots, n\}$ we have $f_i(x) = 0$ and hence $S_i^x(\bar{x}) \equiv 0$. Therefore $\bar{x}_j | S_i^x(\bar{x})$ for all $j \in \{1, \dots, n\}$.

For $x \in \{0, 1\}^N \setminus (\vec{0}, *)$ there exists at least one $j \in \{1, \dots, n\}$ such that $x_j = 1$, hence $P_j^x(\bar{x}_j) = \bar{x}_j$. Since $P_j^x(\bar{x}_j) | S_i^x(\bar{x})$ for all $i \in \{1, \dots, n\}$, this proves $\bar{x}_j | S_i^x(\bar{x})$.

Let $\bar{x} \in (\vec{0}, *)$, i.e. $\bar{x}_j = 0 \forall j \in \{1, \dots, n\}$. Hence, $S_i^x(\bar{x}) \equiv 0$ for all $i \in \{1, \dots, n\}$ and $x \in \{0, 1\}^N$ since $\bar{x}_j | S_i^x(\bar{x})$. Consequently, $\bar{I}(f_i)(\bar{x}) = 0$ for all $i \in \{1, \dots, n\}$ and $\bar{x} \in (\vec{0}, *)$, proving that $(\vec{0}, *)$ is a trap space of $\bar{I}(f)$. \square

Now we generalize Lemma 9 to arbitrary trap spaces. For this purpose we consider a translation of the form $\tau_J : \{0, 1\}^N \rightarrow \{0, 1\}^N$ for $J \subseteq \{1, \dots, N\}$ with

$$(\tau_J)_i : \{0, 1\}^N \rightarrow \{0, 1\}$$

$$x \mapsto \begin{cases} 1 - x_i, & \text{if } i \in J \\ x_i, & \text{else} \end{cases}.$$

We define $\bar{\tau}_J := \bar{I}(\tau_J)$. It is easy to see from Definition 2 that

$$(\bar{\tau}_J)_i : \bar{x} \mapsto \begin{cases} 1 - \bar{x}_i, & \text{if } i \in J \\ \bar{x}_i, & \text{else} \end{cases}$$

holds and therefore $\tau_J^{-1} = \tau_J$ and $\bar{\tau}_J^{-1} = \bar{\tau}_J$.

Lemma 10. *Let $J \subseteq \{1, \dots, N\}$. Then the following diagram commutes:*

$$\begin{array}{ccc} g := \tau_J^{-1} \circ f \circ \tau_J & \xrightarrow{\bar{I}} & \bar{I}(g) \\ \tau_J^{-1} \circ \tau_J \uparrow & & \bar{\tau}_J^{-1} \circ \bar{\tau}_J \uparrow \\ f & \xrightarrow{\bar{I}} & \bar{I}(f) \end{array}$$

Proof. We need to show the following equality:

$$\bar{I}(g) = \bar{\tau}_J^{-1} \circ \bar{I}(f) \circ \bar{\tau}_J$$

For this purpose we need to show that $\bar{\tau}_J^{-1} \circ \bar{I}(f) \circ \bar{\tau}_J$ is a polynomial map with minimal degree, which coincides with g on $\{0, 1\}^N$. Equality follows due to the uniqueness of the multivariate polynomial interpolation.

Firstly, it is clear that $\bar{\tau}_J^{-1} \circ \bar{I}(f) \circ \bar{\tau}_J$ as a concatenation of polynomial maps is itself a polynomial map. Since $\bar{I}(f)$ as well as $\bar{\tau}_J = \bar{\tau}_J^{-1}$ coincide with their Boolean counterparts on $\{0, 1\}^N$, the same holds true for any concatenation of these functions, i.e. $\bar{\tau}_J \circ \bar{I}(f) \circ \bar{\tau}_J = \tau_J \circ f \circ \tau_J = g$ on $\{0, 1\}^N$. Furthermore, the transformation $\bar{I}(f) \mapsto \bar{\tau}_J \circ \bar{I}(f) \circ \bar{\tau}_J$ preserves the degree of each component $\bar{I}(f)_i$, $i \in \{1, \dots, N\}$. Therefore, we first obtain $\deg \bar{I}(f_i) = \deg(\bar{\tau}_J \circ \bar{I}(f_i) \circ \bar{\tau}_J) \geq \deg \bar{I}(g_i)$ and, since also $\bar{\tau}_J \circ \bar{I}(g) \circ \bar{\tau}_J = \tau_J \circ g \circ \tau_J = f$ holds on $\{0, 1\}^N$, we have $\deg(\bar{I}(g_i)) = \deg(\bar{\tau}_J \circ \bar{I}(g_i) \circ \bar{\tau}_J) \geq \deg \bar{I}(f_i)$. Consequently, $\deg \bar{I}(f_i) = \deg \bar{I}(g_i)$ and $\deg(\bar{\tau}_J \circ \bar{I}(f_i) \circ \bar{\tau}_J) = \deg(\bar{I}(g_i))$.

From the minimality of $\bar{I}(g)$ with regard to the function $\deg(\cdot)$ the equality $\bar{I}(g_i) = \bar{\tau}_J \circ \bar{I}(f_i) \circ \bar{\tau}_J$ finally follows. This shows that $\bar{\tau}_J \circ \bar{I}(f) \circ \bar{\tau}_J$ is indeed the multivariate polynomial interpolation of g . \square

We are now ready to prove the following proposition.

Proposition 11. *Let $(p, *)$ be any trap space of f , then $(\bar{p}, *)$ with $\bar{p} = p \in \{0, 1\}^n$ is a trap space of $\bar{I}(f)$.*

Proof. Choose $J = \{j \in \{1, \dots, n\} \mid p_j = 1\}$. It holds $\tau_J((\vec{0}, *)) = (p, *)$. Furthermore, define $g := \tau_J^{-1} \circ f \circ \tau_J$. Then $(\vec{0}, *) \subseteq \{0, 1\}^n$ is a trap space of g since $\tau_J^{-1} \circ f \circ \tau_J(\vec{0}, *) \subseteq (\vec{0}, *)$. Then, according to Lemma 9, $(\vec{0}, *) \subseteq [0, 1]^n$ is also

a trap space of $\bar{I}(g)$. According to Lemma 10, we have $\bar{\tau}_J^{-1} \circ \bar{I}(g) \circ \bar{\tau}_J = \bar{I}(f)$. Due to

$$\begin{aligned} \bar{\tau}_J^{-1} \circ \bar{I}(g) \circ \bar{\tau}_J(\bar{p}, *) &= \bar{\tau}_J^{-1} \circ \bar{I}(g)(\vec{0}, *) \\ &\subseteq \bar{\tau}_J^{-1}(\vec{0}, *) \\ &= (\bar{p}, *), \end{aligned}$$

$(\bar{p}, *)$ is also a trap space of $\bar{I}(f)$. \square

The last proposition shows that we can assign to each trap space of f a trap space of $\bar{I}(f)$. This result then transfers to $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$.

Corollary 12. *If $(p, *)$, $p \in \{0, 1\}^n$ is a trap space of f , then for any $\vec{k} \in \mathbb{R}_{>0}^N$ and $\vec{\theta} \in (0, 1)^N$, $(p, *)$ is a trap space of the flow map defined by a solution of the ODE system of the form (5).*

Proof. Let $x : \mathbb{R}_{\geq 0} \rightarrow [0, 1]^N$ be any solution of the above ODE system. Assume $x(t) \in (p, *)$, $t \in \mathbb{R}_{\geq 0}$. Since $(p, *)$ is a trap space of f , according to Proposition 11, $(p, *)$ is a trap space of $\bar{I}(f)$. The function $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$ is defined as the concatenation of normalized Hill cubes and $\bar{I}(f)$. Consequently, $(p, *)$ is a trap space of $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$. Therefore, for any $i \in \{1, \dots, n\}$ and $x(t) \in (p, *)$ the equality $\dot{x}_i(t) = d_i \cdot ((\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}})_i(x(t)) - p_i) = 0$ holds, and $(p, *)$ is an invariant set of any flow defined by the above ODE system. \square

Now we would like to know what happens if the fixed components of these trap spaces are perturbed slightly. Therefore, we consider an association to invariant sets that is possible even if we do not use normalized Hill functions.

5 Associating invariant sets to trap spaces

Instead of associating the trap spaces of f to trap spaces of $\bar{f}^{\vec{k}, \vec{\theta}}$ or $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$, we can associate them to certain invariant sets of these functions, whose size can be controlled by the Hill coefficients \vec{k} . In contrast to trap spaces the previously fixed components are allowed to change to a certain degree over time in these invariant sets. We will now state what we mean with this precisely.

Definition 13. *Let $\pi : [0, 1]^N \rightarrow [0, 1]^n$ be the projection on the first $n \leq N$ components. For any $\epsilon > 0$ and $(\bar{p}, *) \subseteq [0, 1]^N$, $\bar{p} \in [0, 1]^n$ we define (see Fig. 2)*

$$K(\bar{p}, \epsilon) := \{\bar{x} \in [0, 1]^N \mid \|\pi(\bar{x}) - \bar{p}\|_\infty \leq \epsilon\}.$$

We want to show that $K(\bar{p}, \epsilon)$ is an invariant set of the ODE system (2) constructed with either $\bar{f}^{\vec{k}, \vec{\theta}}$ or $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$ provided the Hill coefficients \vec{k} are large enough. The proof is carried out in two steps. First, we show that $K(\bar{p}, \epsilon)$ is an invariant set of the time-discrete dynamical systems

$$\begin{aligned} x^{t+1} &= \bar{f}^{\vec{k}, \vec{\theta}}(x^t), \\ x^{t+1} &= \bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}(x^t). \end{aligned} \tag{6}$$

Afterwards, we show the invariance for the corresponding ODE systems.

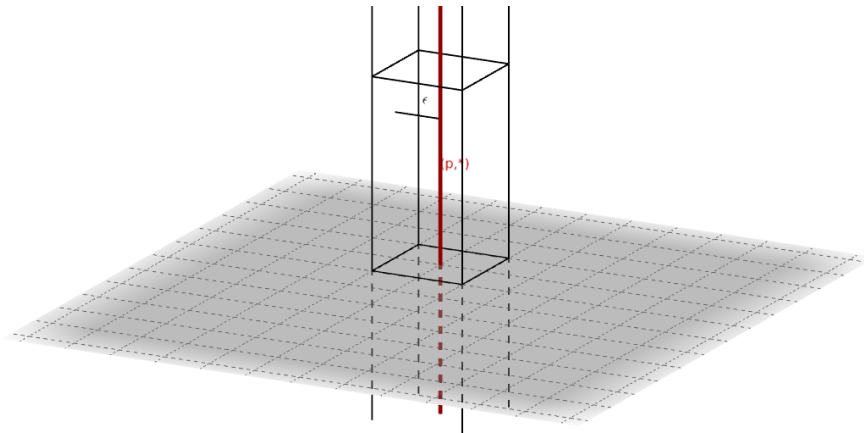


Figure 2: Illustration of the set $K(\bar{p}, \epsilon)$.

5.1 Invariance in the time-discrete dynamical system

Now we want to show that if $(\bar{p}, *)$ is a trap space of $\bar{f}^{\vec{k}, \vec{\theta}}$ or $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$, then for sufficiently large Hill coefficients \vec{k} the set $K(\bar{p}, \epsilon)$ is an invariant set of $\bar{f}^{\vec{k}, \vec{\theta}}$ or $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$ as well.

Proposition 14. *Let $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$, L be the Lipschitz constant of $\bar{I}(f)$ with respect to $\|\cdot\|_\infty$ and $(\bar{p}, *)$ be a trap space of $\bar{I}(f)$. Then for any $0 < \gamma, \epsilon < \min_{i \in \{1, \dots, n\}} \{\theta_i, 1 - \theta_i\}$ and sufficiently large \vec{k}_0 , the function $\bar{f}^{\vec{k}, \vec{\theta}}$ or, respectively, $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$ satisfies*

$$\begin{aligned} \forall \vec{k} \geq \vec{k}_0 : \bar{f}^{\vec{k}, \vec{\theta}}(K(\bar{p}, \epsilon)) &\subseteq K(\bar{p}, \gamma), \\ \forall \vec{k} \geq \vec{k}_0 : \bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}(K(\bar{p}, \epsilon)) &\subseteq K(\bar{p}, \gamma). \end{aligned} \quad (7)$$

The relation $\vec{k} \geq \vec{k}_0$ is meant component-wise here. This means, on the one hand, if \vec{k} grows, there is an increasingly thin tube $K(\bar{p}, \gamma)$ around the trap spaces which is not left by the trajectories of the dynamical systems (6). On the other hand, there is an increasingly wide tube $K(\bar{p}, \epsilon)$, whose boundaries approach the thresholds of the Hill cubes, and every trajectory starting in $K(\bar{p}, \epsilon)$ is drawn into $K(\bar{p}, \gamma)$.

For the proof of Proposition 14 we exploit that $\bar{f}^{\vec{k}, \vec{\theta}}$ as well as $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$ is a concatenation of the Hill functions and a multivariate polynomial interpolation. First, we prove that $K(\bar{p}, \epsilon)$ can be arbitrarily contracted by the Hill functions provided we choose the parameters \vec{k} large enough and $K(\bar{p}, \epsilon)$ does not overlap with any of the thresholds of the Hill functions. Afterwards, we continue showing that the multivariate interpolation $\bar{I}(f)$ stretches the set $K(\bar{p}, \epsilon)$ maximally with a constant that is bounded by the Lipschitz constant of $\bar{I}(f)$.

Having the Hill functions in mind, we prove the following lemma:

Lemma 15. *Let $H^k : [0, 1] \rightarrow [0, 1]$ be a sequence of functions, which converges uniformly towards 0 on $[0, \epsilon]$, $\epsilon \in (0, 1)$, and uniformly towards 1 on $[1 - \epsilon, 1]$,*

then

$$\forall \gamma \in (0, \epsilon] \exists k_0 \in \mathbb{N} \forall k \geq k_0 : H^k([0, \epsilon]) \subseteq [0, \gamma]$$

$$\text{and } \forall k \geq k_0 : H^k([1 - \epsilon, 1]) \subseteq [1 - \gamma, 1].$$

Proof. This follows directly from the definition of uniform convergence. \square

Applying Lemma 15 to each component of the Hill function $H^{\vec{k}, \vec{\theta}}$, which is a Hill function, we arrive at the following corollary:

Corollary 16. *For $n \leq N$ and $\vec{\theta} \in (0, 1)^N$, the following statement holds:*

$$\forall \vec{p} \in \{0, 1\}^n, \epsilon < \theta_{\min}, \gamma \in (0, 1] \exists \vec{k}_0 \in \mathbb{R}_{>0}^N \forall \vec{k} \geq \vec{k}_0 : H^{\vec{k}, \vec{\theta}}(K(\vec{p}, \epsilon)) \subseteq K(\vec{p}, \gamma)$$

with $\theta_{\min} := \min_{i \in \{1, \dots, n\}} \{\theta_i, 1 - \theta_i\}$. This remains true for normalized Hill cubes $\frac{H^{\vec{k}, \vec{\theta}}}{H^{\vec{k}, \vec{\theta}}(\vec{1})}$.

Proof. The components h_{k_i, θ_i} , $i \in \{1, \dots, n\}$, of the Hill function $H^{\vec{k}, \vec{\theta}}$ as well as the components $\frac{h_{k_i, \theta_i}}{h_{k_i, \theta_i}(\vec{1})}$, $i \in \{1, \dots, n\}$, of the normalized Hill function $\frac{H^{\vec{k}, \vec{\theta}}}{H^{\vec{k}, \vec{\theta}}(\vec{1})}$ satisfy the conditions of Lemma 15 as long as ϵ is strictly smaller than θ_i and $1 - \epsilon$ is strictly bigger than θ_i for every $i \in \{1, \dots, n\}$ (see Lemma 5). This is guaranteed by $\epsilon < \min_{i \in \{1, \dots, n\}} \{\theta_i, 1 - \theta_i\}$ for every $\vec{\theta} \in (0, 1)^N$. For each $\vec{x} \in K(\vec{p}, \epsilon)$, $i \in \{1, \dots, n\}$, we have either $\bar{x}_i \in [0, \epsilon]$ or $\bar{x}_i \in [1 - \epsilon, 1]$, which is mapped (for an arbitrary large $(k_0)_i$) into $[0, \gamma]$ in the first case or into $[1 - \gamma, 1]$ in the second case. This means, $\forall \vec{k} \geq \vec{k}_0 : H^{\vec{k}, \vec{\theta}}(K(\vec{p}, \epsilon)) \subseteq K(\vec{p}, \gamma)$. \square

We proceed with the multivariate interpolation of f .

Lemma 17. *Let $\bar{I} : [0, 1]^N \rightarrow [0, 1]^N$ be a Lipschitz continuous function with respect to $\|\cdot\|_\infty$ with Lipschitz constant L . Furthermore, let $(\vec{p}, *)$ be a trap space of \bar{I} . Then*

$$\forall \epsilon \in (0, 1) : \bar{I}(K(\vec{p}, \epsilon)) \subseteq K(\vec{p}, L\epsilon)$$

holds.

Proof. According to the definition of $K(\vec{p}, \epsilon)$ we need to show that

$$\|\pi(\vec{x}) - \vec{p}\|_\infty \leq \epsilon \Rightarrow \|\pi(\bar{I}(x)) - \vec{p}\|_\infty \leq L\epsilon$$

holds. Due to the Lipschitz continuity we have

$$\begin{aligned} \|\pi(\bar{I}(x)) - \vec{p}\|_\infty &= \inf_{y \in (\vec{p}, *)} \|\bar{I}(x) - y\|_\infty \\ &\leq \inf_{y \in (\vec{p}, *)} \|\bar{I}(x) - \bar{I}(y)\|_\infty \\ &\leq L \cdot \inf_{y \in (\vec{p}, *)} \|x - y\|_\infty \\ &= L \cdot \|\pi(x) - \vec{p}\|_\infty \\ &\leq L \cdot \epsilon. \end{aligned}$$

The first equality holds since $y \in (\bar{p}, *)$ can be chosen such that $\bar{I}(x)_i - y_i = 0$ for $i \in \{n+1, \dots, N\}$, and therefore $\|\bar{I}(x) - y\|_\infty = \|\pi(\bar{I}(x)) - p\|_\infty$ holds. For the same reason the fourth equality holds. The second inequality is true due to

$$\bar{I}(\bar{p}, *) \subseteq (\bar{p}, *).$$

□

Combining the two results (Corollary 16 and Lemma 17) we can now prove Proposition 14 from the beginning of this section.

Proof. (Proof of Proposition 14) According to Corollary 16, if we choose $\gamma' \leq \frac{\gamma}{L}$ such that $\gamma' \in (0, \epsilon]$, we have for sufficiently large \vec{k} :

$$\begin{aligned} \bar{f}^{\vec{k}, \vec{\theta}}(K(\bar{p}, \epsilon)) &= \bar{I}(f) \circ H^{\vec{k}, \vec{\theta}}(K(\bar{p}, \epsilon)) \\ &\subseteq \bar{I}(f)(K(\bar{p}, \gamma')) \end{aligned}$$

According to Lemma 17, we have

$$\bar{I}(f)(K(\bar{p}, \gamma')) \subseteq K(\bar{p}, L\gamma') \subseteq K(\bar{p}, \gamma).$$

The statement $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}(K(\bar{p}, \epsilon)) \subseteq K(\bar{p}, \gamma)$ follows analogously. □

5.2 Invariance in the ODE system

We show in this section the invariance of the set $K(\bar{p}, \epsilon)$ for a trap space $(\bar{p}, *)$ of the ODE system 2. The proof is carried out by exploiting the results on the time-discrete but state-continuous dynamical system of the previous 5.1 and combining them with a result by Nagumo on invariant sets [13].

Definition 18 ([1, p. 24]). *A subset K of a finite dimensional vector space X is said to be invariant under F if for any initial state $x_0 \in K$ all solutions to the differential equation*

$$\begin{aligned} \dot{x} &= F(x) \\ x(0) &= x_0 \end{aligned} \tag{8}$$

remain in K .

Definition 19 ([1, 6, p. 25]). *Let X be a normed space, $\emptyset \neq K \subseteq X$, $x \in X$. The tangent cone (Fig. 3) to K at x is the set*

$$T_K(x) := \{v \in X \mid \liminf_{h \rightarrow 0^+} \frac{\inf_{z \in K} \|(x + hv) - z\|}{h} = 0\}.$$

We use the following Theorem from [13]:

Theorem 20 ([6, 13]). *Let $K \subset \mathbb{R}^N$ be closed and convex, $F : \mathbb{R}^N \rightarrow \mathbb{R}^N$ continuous and assume 8 admits a globally unique solution for every $x_0 \in K$. Then K is an invariant set of this system if and only if*

$$\forall x \in \partial K : F(x) \in T_K(x). \tag{9}$$

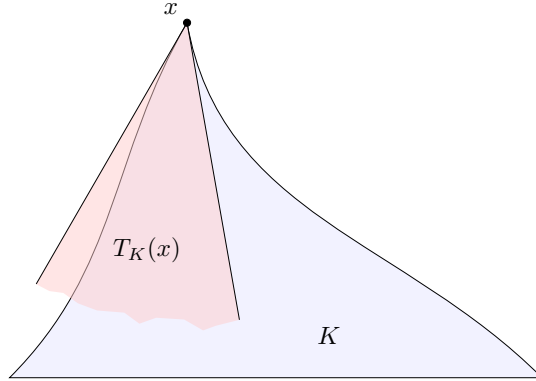


Figure 3: Illustration of the tangent cone $T_K(x)$ of K .

Now we are ready to prove the correspondence of trap spaces and invariant sets.

Proposition 21. *Let $(\bar{p}, *)$, $\bar{p} \in \{0, 1\}^N$ be a trap space of $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$. Then*

$$\forall \epsilon \in (0, \theta_{\min}) \exists \vec{k}_0 \in \mathbb{N}^N \forall \vec{k} \in \mathbb{N}^N \forall x_0 \in K(\bar{p}, \epsilon) : \forall t \in [0, \infty) : x(t) \in K(\bar{p}, \epsilon),$$

where $x(t)$ is the solution of 2 and with $\theta_{\min} := \min_{i \in \{1, \dots, n\}} \{\theta_i, 1 - \theta_i\}$.

Proof. We want to show that the ODE system 2 with $K(\bar{p}, \epsilon)$ satisfies the conditions of Theorem 20. Here, our function F in Theorem 20 has the form:

$$F^{\vec{k}, \vec{\theta}}(x) := D \cdot (\bar{f}^{\vec{k}, \vec{\theta}}(x) - x)$$

We need to show that 9 with $K := K(\bar{p}, \epsilon)$ is satisfied. Let $\xi \in \partial K(\bar{p}, \epsilon)$. Eq. (9) holds especially true if $\xi + hF(\xi) \in K$ is satisfied for small enough $h > 0$. Therefore, it would suffice to show

$$\xi + h[D \cdot (\bar{f}^{\vec{k}, \vec{\theta}}(\xi) - \xi)] = (1 - hD)\xi + hD \cdot \bar{f}^{\vec{k}, \vec{\theta}}(\xi) \in K(\bar{p}, \epsilon).$$

Indeed, this is true for sufficiently small $h > 0$ (to guarantee $(1 - hd_i) > 0$ for $i \in \{1, \dots, n\}$) due to the following inequality for $i \in \{1, \dots, n\}$ and sufficiently large \vec{k} :

$$\begin{aligned} \|(1 - hd_i)\xi_i + hd_i \bar{f}_i^{\vec{k}, \vec{\theta}}(\xi) - \bar{p}_i\| &= \|(1 - hd_i)(\xi_i - \bar{p}_i) + hd_i(\bar{f}_i^{\vec{k}, \vec{\theta}}(\xi) - \bar{p}_i)\| \\ &\leq (1 - hd_i) \cdot \underbrace{\|\xi_i - \bar{p}_i\|}_{\leq \epsilon} + hd_i \cdot \underbrace{\|\bar{f}_i^{\vec{k}, \vec{\theta}}(\xi) - \bar{p}_i\|}_{\leq \epsilon \text{ by Proposition 14}} \\ &\leq \epsilon \end{aligned} \tag{10}$$

$$\Rightarrow \xi + hD \cdot (\bar{f}^{\vec{k}, \vec{\theta}}(\xi) - \xi) \in K(\bar{p}, \epsilon)$$

The uniqueness of the solution of the ODE system (2) follows from the Lipschitz continuity of $\bar{f}^{\vec{k}, \vec{\theta}}$ (see, e.g., [17, p. 88]). \square

Again, the same argumentation is valid if we replace $\bar{f}^{\vec{k}, \vec{\theta}}$ by $\bar{f}_{\text{normalized}}^{\vec{k}, \vec{\theta}}$.

6 Computing explicit values for the Hill coefficients to guarantee invariance

Finally, we are interested in finding some explicit boundaries for the values \vec{k} and to find out how they are related to the network structure. Namely, assume we would like to find Hill coefficients \vec{k} such that $K(p, \epsilon)$ is mapped to $K(p, \gamma)$ by $\vec{f}^{\vec{k}, \vec{\theta}}$ for given $\epsilon, \gamma > 0$ in such a way that $K(p, \epsilon)$ is an invariant set of the corresponding ODE system.

We can approximate the Lipschitz constants of $\bar{I}(f)$ explicitly. First, notice that if we want to find the Lipschitz constant L of $\bar{I}(f) : [0, 1]^N \rightarrow [0, 1]^N$, i.e.

$$\forall x, y \in [0, 1]^N : \|\bar{I}(f)(x) - \bar{I}(f)(y)\|_\infty \leq L \cdot \|x - y\|_\infty, \quad (11)$$

we can do this by finding the Lipschitz constants of the components of $\bar{I}(f) = (\bar{I}(f_1), \dots, \bar{I}(f_N))$ and then taking the maximal Lipschitz constant for $\bar{I}(f)$. For the Lipschitz constants of the components $\bar{I}(f_i)$ we find an upper bound with the following theorem:

Theorem 22 ([14]). *Assume $f : [0, 1]^N \rightarrow [0, 1]$ is a Lipschitz continuous function. Then*

$$|f(x) - f(y)| \leq L_p \cdot \|x - y\|_q \quad (12)$$

and

$$L_p = \sup\{\|\nabla f(x)\|_p : x \in [0, 1]^N\}$$

with $\frac{1}{p} + \frac{1}{q} = 1$, $1 \leq p, q \leq \infty$.

Applying the theorem to the case $q = \infty$ we need to find $\sup_{x \in [0, 1]^N} \|\nabla \bar{I}(f_i)\|_1$ for all $i \in \{1, \dots, N\}$.

After having estimated the Lipschitz constant L of $\bar{I}(f)$, we can proceed as follows to obtain values for \vec{k} that guarantee that $K(p, \epsilon)$ is mapped to $K(p, \gamma)$ for a trap space $(p, *)$ of f . For fixed $\vec{\theta}$ we need to find k_i such that

$$\begin{aligned} h_{k_i, \theta_i}(\epsilon) &\leq \frac{\epsilon}{L} \text{ if } p_i = 0, \\ h_{k_i, \theta_i}(1 - \epsilon) &\geq 1 - \frac{\epsilon}{L} \text{ if } p_i = 1 \end{aligned} \quad (13)$$

holds to guarantee $H^{\vec{k}, \vec{\theta}}(K(\bar{p}, \epsilon)) \subseteq K(\bar{p}, \frac{\epsilon}{L})$. Then Lemma 17 implies

$$\vec{f}^{\vec{k}, \vec{\theta}}(K(\bar{p}, \epsilon)) \subseteq \bar{I}(f)(K(\bar{p}, \frac{\epsilon}{L})) \subseteq K(\bar{p}, \epsilon).$$

6.1 Using the Interaction graph to approximate the Lipschitz constant

While (13) is independent of the structure of the bioregulatory system, the size of the Lipschitz constant of $\bar{I}(f)$ is not. Therefore, it would be interesting to find out in what respect it depends on the structure of the discrete interaction graph.

Definition 23. Suppose V_1, V_2, \dots, V_k and W are vector spaces. A function

$$f : V_1 \times V_2 \times \dots \times V_k \rightarrow W$$

is called *multilinear* if it is linear in each of its variables, i.e.

$$\begin{aligned} \forall i \in \{1, \dots, k\} : f(v_1, \dots, av_i + bw_i, \dots, v_k) &= af(v_1, \dots, v_i, \dots, v_k) \\ &+ bf(v_1, \dots, w_i, \dots, v_k). \end{aligned}$$

An *affine multilinear function* $f : V_1 \times V_2 \times \dots \times V_k \rightarrow W$ is defined analogously.

We notice that due to Eq. (3) the images of the operator \bar{I} are affine multilinear functions. Before we proceed we will give two lemmas, which we need in the proceeding proofs:

Lemma 24. For a multilinear or an affine multilinear function $f : [0, 1]^N \rightarrow \mathbb{R}_{\geq 0}$, there exists $\bar{x}_{\max} \in \{0, 1\}^N$ such that f takes its maximum value at \bar{x}_{\max} .

Proof. Assume f is multilinear and $\bar{x}_{\max} := \arg \max_x f(x)$, $\bar{x}_{\max} \in [0, 1]^N \setminus \{0, 1\}^N$. If $f(\bar{x}_{\max}^{(1)}, \dots, \bar{x}_{\max}^{(N)}) = 0$, there is nothing to prove, since in this case $\forall x \in [0, 1]^N : 0 \geq f(x) \geq 0 \Rightarrow f \equiv 0$ holds. Therefore, we assume $f(\bar{x}_{\max}^{(1)}, \dots, \bar{x}_{\max}^{(N)}) > 0$. Since $\bar{x}_{\max} \in [0, 1]^N \setminus \{0, 1\}^N$, there must be an index $i \in \{1, \dots, N\}$ such that $\bar{x}_{\max}^{(i)} \notin \{0, 1\}$. Assume f depends on $\bar{x}^{(i)}$, i.e., f is not constant on the line $\{(x_{\max}^{(1)}, \dots, x_{\max}^{(i-1)}, \lambda, \bar{x}_{\max}^{(i+1)}, \dots, \bar{x}_{\max}^{(N)}) \mid \lambda \in \mathbb{R}\}$ ³. Then, for $\lambda = \frac{1}{\bar{x}_{\max}^{(i)}} > 1$,

$$\begin{aligned} f(\bar{x}_{\max}^{(1)}, \dots, \bar{x}_{\max}^{(N)}) &< \lambda \cdot f(\bar{x}_{\max}^{(1)}, \dots, \bar{x}_{\max}^{(N)}) \\ &= f(\bar{x}_{\max}^{(1)}, \dots, \bar{x}_{\max}^{(i-1)}, 1, \bar{x}_{\max}^{(i+1)}, \dots, \bar{x}_{\max}^{(N)}) \end{aligned}$$

holds, which is a contradiction to the assumption. The proof holds true for affine multilinear functions as well since we can shift the coordinate system accordingly. \square

Assume $\bar{f} : \mathbb{R}^N \rightarrow \mathbb{R}$ is an affine multilinear function. We can write \bar{f} always in the form

$$\bar{f}(\bar{x}) = \sum_{p \in \{0, 1\}^N} \bar{f}(p) \prod_{k=1}^N (\bar{x}_k p_k + (1 - p_k)(1 - \bar{x}_k)),$$

since a multilinear function from \mathbb{R}^N to \mathbb{R} is uniquely determined by its values on $\{0, 1\}^N$ (see also [25, p. 16-17]).

Lemma 25. Let $F = (f_1, \dots, f_N) : [0, 1]^N \rightarrow \mathbb{R}^N$ be a function whose components f_1, \dots, f_N are affine multilinear. Then the function $\|F\|_1 : \bar{x} \mapsto \|F(\bar{x})\|_1$ takes its maximum value on $\{0, 1\}^N$.

³If not $\bar{x}_{\max}^{(i)}$ can be replaced by 0 or 1.

Proof. We have for $\bar{x} \in [0, 1]^N$

$$\begin{aligned} \|F(\bar{x})\|_1 &= \sum_{i=1}^N |f_i(\bar{x})| \\ &\leq \sum_{i=1}^N \underbrace{\sum_{p \in \{0,1\}^N} |f_i(p)| \cdot \prod_{k=1}^N (\bar{x}_k p_k + (1-p_k)(1-\bar{x}_k))}_{\geq |f_i(\bar{x})|} \\ &=: g(\bar{x}). \end{aligned}$$

Furthermore, we have for $q \in \{0, 1\}^N$: $\|F(q)\|_1 = g(q)$ because

$$\begin{aligned} \|F(q)\|_1 &= \sum_{i=1}^N |f_i(q)| = \sum_{i=1}^N \sum_{p \in \{0,1\}^N} |f_i(p)| \cdot \underbrace{\prod_{k=1}^N (q_k p_k + (1-p_k)(1-q_k))}_{= \begin{cases} 0 & \text{if } p = q \\ 1 & \text{otherwise} \end{cases}} = g(q) \end{aligned}$$

holds true. The function $g : [0, 1]^N \rightarrow \mathbb{R}_{\geq 0}$ is affine multilinear. According to Lemma 24, g takes a maximum value in a point in $\{0, 1\}^N$. Therefore, also $\|F(\bar{x})\|_1$ takes a maximum value on $\{0, 1\}^N$. \square

We now define the interaction graph of a Boolean function f . For this purpose, we need the notion of discrete derivatives.

Definition 26. *The discrete derivative of a function $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$ is defined as*

$$\begin{aligned} (\partial_j f_i)(x) &:= \frac{f_i(x \oplus e_j) - f_i(x)}{(x_j \oplus 1) - x_j}, \\ &= \frac{f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_N) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_N)}{1 - 0} \\ &\in \{-1, 0, 1\}, \end{aligned}$$

where \oplus is the addition modulo 2. Furthermore, we denote with ∇f_i the vector $(\partial_1 f_i, \dots, \partial_N f_i)^t$.

This means especially that $\partial_j f_i(x)$ actually does not depend on its value in x_j .

Definition 27. *The local interaction graph $IG_f(x) := (V, E)$, $x \in \{0, 1\}^N$ of a Boolean function $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$ consists of N vertices $V := \{1, \dots, N\}$ and a signed edge-set E defined in the following way:*

$$(j, i, \epsilon) \in E \Leftrightarrow (\partial_j f_i)(x) = \epsilon$$

with $\epsilon \in \{-1, 1\}$.

So far, we defined the interpolation operator \bar{I} for functions from $\{0, 1\}^N$ to $\{0, 1\}^N$. However, Definition 2 can be easily extended to functions $\{0, 1\}^N \rightarrow \mathbb{R}^N$ by

$$\begin{aligned} \bar{I} : \{f : \{0, 1\}^N \rightarrow \mathbb{R}\} &\rightarrow \{g : \mathbb{R}^N \rightarrow \mathbb{R} \mid g \text{ is affine linear}\} \\ f &\mapsto \{\bar{x} \mapsto \sum_{x \in \{0, 1\}^N} f(x) \prod_{j=1}^N (x_j \bar{x}_j + (1 - x_j)(1 - \bar{x}_j))\}. \end{aligned} \quad (14)$$

With the following two lemmas we show that \bar{I} behaves well with respect to the interaction graph.

Lemma 28. *The function \bar{I} is linear. Furthermore, for $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$ it holds*

$$\begin{aligned} \bar{I}(f)(1, \cdot) &= \bar{I}(f(1, \cdot)) \\ \bar{I}(f)(0, \cdot) &= \bar{I}(f(0, \cdot)). \end{aligned}$$

Proof. Linearity follows immediately from (14). For the second claim let $p, q \in \{0, 1\}$. Since $p \cdot q + (1 - p)(1 - q) = \begin{cases} 1 & \text{if } p = q \\ 0 & \text{otherwise} \end{cases}$, we obtain with $\bar{x} = (\bar{x}_2, \dots, \bar{x}_N) \in [0, 1]^{N-1}$ and for any $q \in \{0, 1\}$:

$$\begin{aligned} \bar{I}(f_i)(q, \cdot) &= \sum_{p \in \{0, 1\}^N} [f_i(p) \cdot (p_1 q + (1 - p_1)(1 - q)) \cdot \prod_{j=2}^N (p_j \bar{x}_j + (1 - p_j)(1 - \bar{x}_j))] \\ &= \sum_{p \in \{0, 1\}^{N-1}} [f_i(q, p) \cdot \prod_{j=2}^N (p_j \bar{x}_j + (1 - p_j)(1 - \bar{x}_j))] \\ &= \bar{I}(f_i(q, \cdot)). \end{aligned}$$

□

Lemma 29. *Let $f : \{0, 1\}^N \rightarrow \{0, 1\}^N$. Then $\bar{I}(\partial_j f_i) = \partial_j \bar{I}(f_i)$ for $i, j \in \{1, \dots, N\}$.*

Proof. Let us assume that w.l.o.g. $j = 1$. $\bar{I}(f_i)$ is an affine multilinear function. Therefore, the partial derivative $\partial_1 \bar{I}(f_i)$ is given by

$$\partial_1 \bar{I}(f_i)(\bar{x}) = \left(\frac{\bar{I}(f_i)(1, \cdot) - \bar{I}(f_i)(0, \cdot)}{1 - 0} \right)(\bar{x}).$$

Due to linearity of \bar{I} and Lemma 28, it holds

$$\begin{aligned} \partial_1 \bar{I}(f_i)(\bar{x}) &= \left(\frac{\bar{I}(f_i)(1, \cdot) - \bar{I}(f_i)(0, \cdot)}{1 - 0} \right)(\bar{x}) \\ &= \left(\bar{I} \left(\frac{f_i(1, \cdot) - f_i(0, \cdot)}{1 - 0} \right) \right)(\bar{x}) \\ &= \left(\bar{I}(\partial_1 f_i) \right)(\bar{x}), \end{aligned}$$

which completes the proof. □

This allows us to apply Lemma 25 to $F := \nabla \bar{I}(f_i) = \bar{I}(\nabla f_i)$, $i \in \{1, \dots, N\}$, and we obtain the following.

Corollary 30. *The Lipschitz constant of $\bar{I}(f_i)$ with respect to $\|\cdot\|_\infty$, $i \in \{1, \dots, N\}$ is smaller or equal to*

$$\max_{x \in \{0,1\}^N} \|\nabla \bar{I}(f_i)(x)\|_1 = \max_{x \in \{0,1\}^N} \|\bar{I}(\nabla f_i)(x)\|_1 = \max_{x \in \{0,1\}^N} \|\nabla f_i(x)\|_1.$$

Proof. According to Theorem 22, the Lipschitz constant L of $\bar{I}(f_i)$ with respect to $\|\cdot\|_\infty$ can be approximated by $\sup_{\bar{x} \in [0,1]^N} \|\nabla \bar{I}(f_i)(\bar{x})\|_1$. According to Lemma 25, applied to $F := \nabla \bar{I}(f_i)$, we have $\sup_{\bar{x} \in [0,1]^N} \|\nabla \bar{I}(f_i)(\bar{x})\|_1 = \max_{x \in \{0,1\}^N} \|\nabla \bar{I}(f_i)(x)\|_1$, and due to Lemma 29 $\max_{x \in \{0,1\}^N} \|\nabla \bar{I}(f_i)(x)\|_1 = \max_{x \in \{0,1\}^N} \|\bar{I}(\nabla f_i)(x)\|_1$. Furthermore, for $x \in \{0,1\}^N$,

$$\bar{I}(\nabla f_i)(x) = \nabla f_i(x)$$

holds, which proves the above equality. \square

The expression $\max_{x \in \{0,1\}^N} \|\nabla f_i(x)\|_1$ can be read off directly from the interaction graph.

Corollary 31. *Let $IG_f(x)$ be the local interaction graph of $f : \{0,1\}^N \rightarrow \{0,1\}^N$. Then $\max_{x \in \{0,1\}^N} \|\nabla f_i(x)\|_1$ is the maximal in-degree of $i \in V = \{1, \dots, N\}$ over all local interaction graphs, i.e.,*

$$\max_{x \in \{0,1\}^N} \text{indeg}_{IG_f(x)}(i) = \max_{x \in \{0,1\}^N} \|\nabla f_i(x)\|_1.$$

Furthermore, the Lipschitz constant L of $\bar{I}(f)$ can be approximated by the maximum degree over all local interaction graphs of f^4 , i.e.,

$$\max_{x \in \{0,1\}^N, i \in \{1, \dots, N\}} \text{indeg}_{IG_f(x)}(i) \geq L, \quad (15)$$

where L is the Lipschitz constant of $\bar{I}(f)$.

Proof. The in-degree of a vertex $i \in \{1, \dots, N\}$ in the local interaction graph $IG_f(x)$ equals $\|\nabla f_i(x)\|_1$ since $|\partial_j f_i(x)| \in \{0,1\}$, i.e.,

$$\begin{aligned} \text{indeg}_{IG_f(x)}(i) &= \|\nabla f_i(x)\|_1 \\ \Rightarrow \max_{x \in \{0,1\}^N} \text{indeg}_{IG_f(x)}(i) &= \max_{x \in \{0,1\}^N} \|\nabla f_i(x)\|_1. \end{aligned}$$

Then Corollary 30 proves (15). \square

Consider an arbitrary Boolean function $f : \{0,1\}^N \rightarrow \{0,1\}^N$ with interaction graph $IG_f(x)$, $x \in \{0,1\}^N$ and a trap space $(p, *) \subseteq \{0,1\}^N$, $p \in \{0,1\}^n$, $n \leq N$. We give now a sufficient condition for the parameters $\vec{\theta}$ and \vec{k} of the ODE system (2) which guarantees that $K(p, \epsilon)$ is an invariant set of (2).

⁴This implies that $\max_{x \in \{0,1\}^N} \|\nabla f_i(x)\|_1$ is bounded by the maximal in-degree of the global interaction graph as well.

Proposition 32. *Let us denote with $d := \max_{x \in \{0,1\}^N, i \in \{1, \dots, N\}} \text{indeg}_{IG_f(x)}(i)$ the maximal in-degree of $IG_f(x)$ over all $x \in \{0,1\}^N$ of a Boolean function $f : \{0,1\}^N \rightarrow \{0,1\}^N$. Assume $(p, *) \subseteq \{0,1\}^N$, $p \in \{0,1\}^n$, $n \leq N$, is a trap space of f . For*

$$k_i \geq \begin{cases} \frac{\ln \epsilon - \ln(d-\epsilon)}{\ln \epsilon - \ln \theta_i}, & \text{if } p_i = 0 \\ \frac{\ln \left(\frac{d-\epsilon}{\epsilon}\right)}{\ln \left(\frac{1}{\theta_i} - \frac{1}{\theta_i} \epsilon\right)}, & \text{if } p_i = 1 \end{cases}$$

with $i \in \{1, \dots, N\}$, the set $K(p, \epsilon)$ is an invariant set of the ODE system (2) provided $\epsilon \in (0, \theta_{\min})$.

Proof. Due to Corollary 31, the Lipschitz constant L of \bar{I} with respect to $\|\cdot\|_\infty$ can be approximated by d . Therefore, it remains to prove

$$H^{\vec{k}, \vec{\theta}}(K(p, \epsilon)) \subseteq K(p, \frac{\epsilon}{d}).$$

We need to check for each component of $H^{\vec{k}, \vec{\theta}}$ the condition

$$\begin{cases} h_{k_i, \theta_i}(\epsilon) \leq \frac{\epsilon}{d}, & \text{if } p_i = 0 \\ h_{k_i, \theta_i}(1 - \epsilon) \geq 1 - \frac{\epsilon}{d}, & \text{if } p_i = 1 \end{cases}.$$

For $i \in \{1, \dots, n\}$ we obtain for $p_i = 0$ the condition

$$\begin{aligned} h_{k_i, \theta_i}(\epsilon) &\leq \frac{\epsilon}{d} \\ \Leftrightarrow \frac{\epsilon^{k_i}}{\epsilon^{k_i} + \theta_i^{k_i}} &\leq \frac{\epsilon}{d} \\ \Leftrightarrow k_i \cdot \underbrace{\ln \frac{\epsilon}{\theta_i}}_{< 0} &\leq \ln \frac{\epsilon}{d - \epsilon} \\ \Leftrightarrow k_i &\geq \frac{\ln \frac{\epsilon}{d - \epsilon}}{\ln \frac{\epsilon}{\theta_i}} = \frac{\ln \epsilon - \ln(d - \epsilon)}{\ln \epsilon - \ln \theta_i} \end{aligned}$$

and for $p_i = 1$ the condition

$$\begin{aligned} h_{k_i, \theta_i}(1 - \epsilon) &\geq 1 - \frac{\epsilon}{d} \\ \Leftrightarrow k_i &\geq \frac{\ln \left(\frac{d-\epsilon}{\epsilon}\right)}{\ln \left(\frac{1}{\theta_i} - \frac{1}{\theta_i} \epsilon\right)} \end{aligned}$$

□

We can obtain a similar result for the normalized ODE system.

7 Application

We want to illustrate how the theoretical results on trap spaces can be used to ease the analysis of ODE systems. For this purpose, we consider an example from [8], namely a Boolean dynamical system with update function

$$f : (x_1, x_2, x_3, x_4) \mapsto (x_1 \vee x_2, x_1 \wedge x_4, \neg x_1 \wedge x_4, \neg x_3).$$

The state transition graph $G(f)$ is depicted in Fig. 4. As it can be seen in the figure, $(1, 1, 0, 1)$, $(1, *, 0, 1)$, $(1, *, 0, *)$, $(1, *, *, *)$ and $(0, 0, *, *)$ are trap spaces of the Boolean dynamical system given by f . Hence, the state of the first component plays a decisive role in the behavior of the system. Once the first component is activated, it will never be deactivated afterwards. According to the results presented in this paper, this behavior should be similar in the corresponding ODE system as long as we choose sufficiently large Hill coefficients \vec{k} .

Example 33. Consider the trap space $(0, 0, *, *)$, where the maximal in-degree of the local interaction graph is 2. Let $\vec{\theta} = (0.5, 0.5, 0.5, 0.5)^T$, $D = \text{diag}(1, 1, 1, 1)$, and $\epsilon = 0.4$. We would like to find values for \vec{k} such that $K(p, \epsilon)$ is an invariant set. In Fig. 5 the conditions from Proposition 32 are depicted for the parameters $\theta = 0.5$ and maximal in-degree $d = 2$. Since all fixed components in our trap space are zero, we only need to consider the curve corresponding to the first condition in Proposition 32. We can learn from this that we need to choose $k_i \geq 6.213$ to guarantee invariance for $\epsilon = 0.4$. More precisely, the first condition in Proposition 32 becomes:

$$k_i \geq \frac{\ln \epsilon - \ln(d - \epsilon)}{\ln \epsilon - \ln \theta_i} \geq \frac{\ln 0.4 - \ln(2 - 0.4)}{\ln 0.4 - \ln 0.5} \approx 6.213.$$

Indeed, if we choose an initial state $x_0 = (0.4, 0.4, 0.1, 0.1)^T$, and Hill coefficients $k_i \geq 6.213$, then the first two components tend to zero. Exactly this behavior can be observed in Fig. 6a.

Let us see what happens if we change the value of the first component slightly, such that the initial state is no longer in an invariant set corresponding to the trap space $(0, 0, *, *)$ but in one associated to $p = (1, *)$. For this purpose we could again consider Fig. 5. Now we need to look at the curve corresponding to the second condition in Proposition 32, since all fixed components in the trap space p are 1. We can see that if we choose for example $\epsilon = 0.35$ the Hill exponent $k = 6.213$ is sufficiently large to guarantee that $K(p, \epsilon)$ is an invariant set of the corresponding ODE-system. More precisely, due to the inequality

$$6.213 \geq \frac{\ln\left(\frac{d-\epsilon}{\epsilon}\right)}{\ln\left(\frac{1}{\theta_i} - \frac{1}{\theta_i}\epsilon\right)} = \frac{\ln\left(\frac{2-0.35}{0.35}\right)}{\ln\left(\frac{1}{0.5} - \frac{1}{0.5} \cdot 0.35\right)},$$

we know that the trajectory of the solution is guaranteed to stay in $K(p, 0.35)$. Indeed, if we choose for example the initial value $x_0 = (0.65, 0.4, 0.1, 0.1)^T$, we observe in Fig. 6b that the trajectory of the solution remains in the set $K(p, \epsilon)$. Finally, let us consider a case, where we need to use both conditions from Proposition 32. I.e. for $p = (1, *, 0, *)$ to guarantee that $K(p, \epsilon)$ is an invariant set, we need to consider the maximum of both curves in Fig. 5. Again we observe that for $\epsilon = 0.35$ the Hill exponents can remain at 6.213 to guarantee invariance.

For more numerical experiments we refer to the supplementary, where we conducted some experiments on the T-cell activation model used as well in [25]. More numerical experiments concerning the conservation of trap spaces using normalized Hill cubes can be found in [27], too.

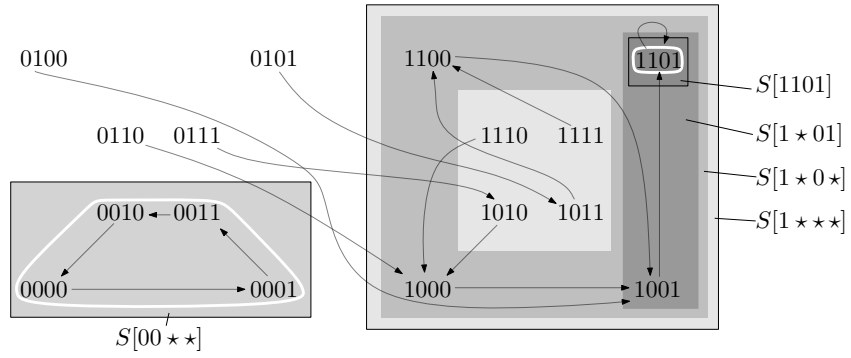


Figure 4: Example from [8].

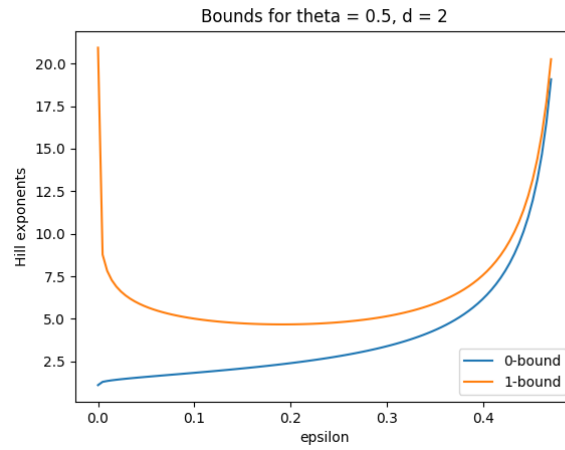
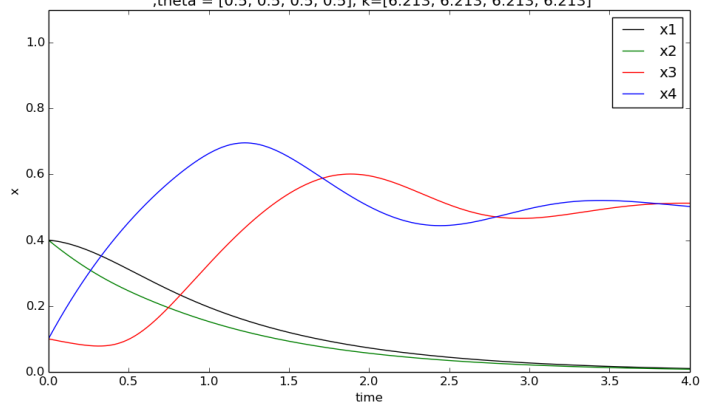


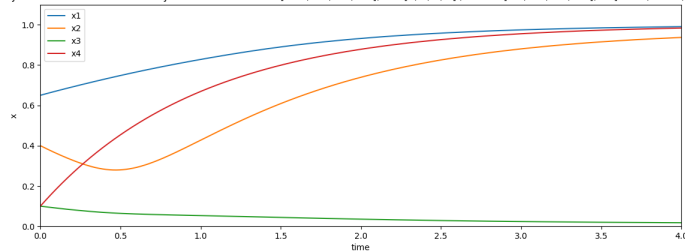
Figure 5: Plot of the conditions from Proposition 32. The curve denoted by 0-bound represents the condition in the first case in the proposition, while the second curve represents the condition in the second case. For an invariant set $K(p, \epsilon)$, corresponding to a trap space $(p, *)$, we can read off the minimal Hill exponent necessary for invariance from these curves.

Trajectory of the solutions of the ODE-system with initial state $[0.4, 0.4, 0.1, 0.1]$, $d = [1, 1, 1, 1]$, $\theta = [0.5, 0.5, 0.5, 0.5]$, $k = [6.213, 6.213, 6.213, 6.213]$



(a) A trajectory in the invariant set corresponding to $(0, 0, *, *)$

Trajectory of the solutions of the ODE-system with initial state $[0.65, 0.4, 0.1, 0.1]$, $d = [1, 1, 1, 1]$, $\theta = [0.5, 0.5, 0.5, 0.5]$, $k = [6.213, 6.213, 6.213, 6.213]$



(b) A trajectory in the invariant set corresponding to $(1, *)$.

Figure 6: Trajectories in the invariant set.

8 Conclusion

Statements about the correspondence between steady states of discrete dynamical systems and corresponding continuous dynamical systems cannot be generalized directly to trap spaces. However, in case of ODE systems that are created from Boolean systems by multivariate polynomial interpolation and Hill cubes, we can link the Boolean trap spaces to invariant sets whose size can be controlled by the Hill coefficients. This result is of practical relevance, since it allows to transfer knowledge about the location of trap spaces from one model to the other, which paves the way towards combining Boolean and ODE-models of bioregulatory networks. For future work, it would be interesting to see in how far the results presented here can be generalized to a wider class of models for bioregulatory networks.

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Appendix

We use the T-cell activation model published in [25, 7] to demonstrate that the conservation of the trap spaces holds as well in a bigger network, stemming from a biological setting. For our example we use the parameters computed in [25] and proposed as a possible parametrization of the system. As emphasized in [25] this is by far not the only possibility to obtain a good fit to the data used there. In this parametrization the influence of one component on the others is governed by different Hill coefficients and thresholds. This means that the simplifying assumption in the main text, namely that we can represent the right hand side of the ODE-system as a concatenation of the form $\vec{f}^{\vec{k},\vec{\theta}} = \bar{I}(f) \circ H^{\vec{k},\vec{\theta}}$ or $\vec{f}_{\text{normalized}}^{\vec{k},\vec{\theta}} = \bar{I}(f) \circ \frac{H^{\vec{k},\vec{\theta}}}{H^{\vec{k},\vec{\theta}}(\bar{1})}$, does not hold anymore. However, as we suspected in the main text, the conservation of trap spaces during the conversion seems to hold in the more general setting, too.

In the second part of the supplementary we test numerically in how far the results from the main text justify the usage of trap spaces for network reduction.

Conservation of trap spaces

We analyzed the Boolean model of T-cell activation published in [25, 7]. In Tab. 2 we see the Boolean function representing this regulatory network and in Fig. 7 its interaction graph. The Boolean regulatory network includes forty components. The nodes C4, CD45 and TCRlig are inputs while NFAT, NFkB, API and CRE are outputs. Here, we chose to set all input variables to one. The maximal in-degree of a component in the interaction graph is five. We used PyBoolNet [10] to compute all the trap spaces of the network (1000 trap spaces). From these trap spaces we subsequently chose the biggest⁵ trap space, which is not a fixed point, to demonstrate our results (Tab. 3). This trap space has 21 fixed components.

Next, we converted the Boolean network into an ODE-system using Hill cubes according to the method described in the main text stemming from [11]. The parameters (lifetimes, thresholds and Hill coefficients) were chosen according to [25, Table 1] (see Tab. 4 and Tab. 5). We inserted an additional parameter s affecting only the interactions between the components which are fixed in the trap space (see Tab. 4) and an additional parameter t affecting all Hill coefficients of the fixed components occurring anywhere in the network. We are interested in the effect of these parameters on the conservation of our trap space in the ODE-system. Even though we did not prove our results in the general scenario, considered in this supplementary, our numerical experiments here point towards the assumption that for sufficiently large Hill coefficients trap spaces are preserved as well in this more general setting.

However, since the presence of the invariant sets associated to the trap spaces in the Boolean network is only guaranteed for sufficiently large Hill coefficients (Proposition 21 in the main text), the parameter s needs to be chosen sufficiently large. This was confirmed by our simulations.

We simulated our ODE-system for several values of s ⁶. The result for $s = 4$ is depicted in Fig. 8. White represents the value zero and black the value one.

⁵with respect to the number of fixed components

⁶and t remains always zero.

Species	Boolean update function
CD45	1
CD4	1
TCRlig	1
Calcen	Ca
NFAT	Calcen
CRE	CREB
PKCth	DAG
Fos	ERK
Rsk	ERK
PAGCsk	Fyn !TCRbind
TCRphos	Fyn (TCRbind & Lck)
SLP76	Gads
Ras	Grb2Sos RasGRPI
NFkB	IkB
IkB	IKKbeta
Ca	IP3
Jun	JNK
JNK	SEK
API	Jun & Fos
Gads	LAT
Grb2Sos	LAT
PLCg_bind	LAT
Fyn	(Lck & CD45) (TCRbind & CD45)
Rlk	Lck
ERK	MEK
Lck	!PAGCsk & CD4 & CD45
RasGRPI	PKCth & DAG
IKKbeta	PKCth
SEK	PKCth
DAG	PLCg_act
IP3	PLCg_act
MEK	Raf
Raf	Ras
CREB	Rsk
TCRbind	TCRlig & !cCbl
ZAP70	TCRphos & Lck & !cCbl
PLCg_act	(ZAP70 & SLP76 & PLCg_bind & Itk) (ZAP70 & SLP76 & Rlk & PLCg_bind)
Itk	ZAP70 & SLP76
cCbl	ZAP70
LAT	ZAP70

Table 2: Boolean update function of the T-cell network [25, Fig. 2a]. '&' denotes the logical conjunction, '|' logical disjunction and '!' negation.

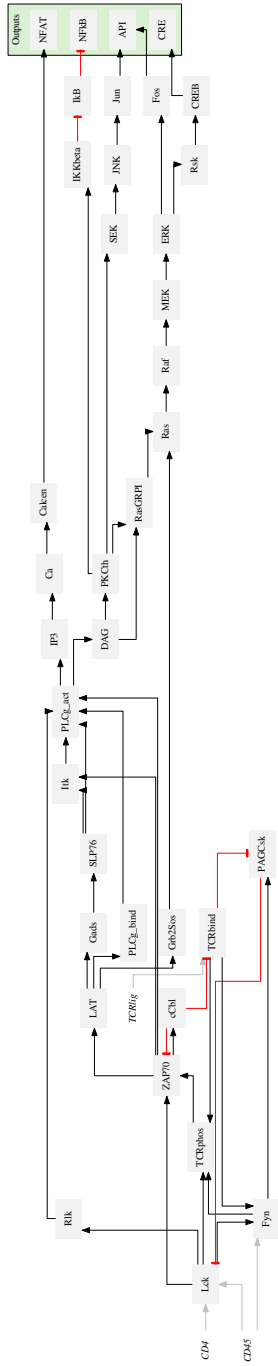


Figure 7: Interaction graph of the Boolean function in Tab. 2. Red edges are inhibiting and black edges activating.

Component	CD4	CD45	Ca	Calcen	Fyn	Gads	Grb2Sos
	1	1	0	0	1	0	0
Component	IP3	Itk	LAT	Lck	NFAT	PAGCsk	PLCg_act
	0	0	0	0	0	1	0
Component	PLCg_bind	Rlk	TCRbind	TCRlig	TCRphos	ZAP70	cCbl
	0	0	1	1	1	0	0

Table 3: Values of the components fixed in the biggest trap space, which is not a fixed point.

As stopping time for the simulations we chose $T = 10$. The initial value was chosen uniformly at random from values between 0 and 1 (see Tab. 6). Only the fixed components of the trap space we chose to be 0 or 1 according to their value in the trap space (see Tab. 3).

In the case $s = 4$ we observe an invariant set associated to our trap space as we predicted (Fig. 8). On the other hand, if we choose $s = 0$ then the trap space of the Boolean regulatory network is not preserved (see Fig. 9). This emphasizes that not necessarily for all parameterization trap spaces are transferred to the corresponding ODE-system. Only for Hill coefficients large enough the ODE-system behaves similar to the Boolean model. However, it seems that in practice often already small Hill coefficients are sufficient for conservation.

Network reduction using trap spaces

In our paper we proved that for sufficiently large Hill coefficients trap spaces are preserved as invariant sets whose size is controlled by the Hill coefficients. Furthermore, we suspect that this result can be used to reduce the dimension of the original network. More precisely, instead of considering the complete network, we can simulate it on one of the trap spaces for sufficiently large Hill coefficients by replacing the fixed components with their values in the trap space. This can be done by finding the trap space in the discrete setting, replacing the original Boolean network with its restriction on this trap space and converting it into an ODE-system. Alternatively, we could simulate the entire ODE-system obtained from the complete Boolean function, but project the solution on the components which are not fixed in the trap space. However, this would be more costly and more parameters would need to be specified. Therefore, a reduction in the Boolean network could be beneficial in many scenarios, provided both ways lead to a similar solution.

We use the example from the previous section to compare both methods with respect to the L^2 - and L^∞ -norm for different Hill coefficients whose size is controlled by the parameter t^7 in Tab. 4. In contrast to s , this parameter also has an impact on the influences of components fixed in the trap space on the remaining components. This is necessary, since we implicitly replace these Hill functions by one or zero as well, when restricting the Boolean function to its trap space and subsequently convert it into an ODE-system. We use again the trap space in Tab. 3. As initial value for the simulations we use the values from the previous section (Tab. 6)⁸. The result of the reduced Boolean function

⁷the parameter s remains here at zero.

⁸or its projection on the components occurring in the reduced system.

Species	Input	θ	k	Input	θ	k	Input	θ	k	Input	θ	k
Lck	PAGCsk	$2 + s + t$	0.3	CD45	$1 + s + t$	0.33	CD4	$2 + s + t$	0.37			
SEK	PKC θ	1	0.26									
Rsk	ERK	3	0.3									
DAG	PLCg_act	$3 + t$	0.28									
Ikk	Ikkbeta	3	0.3									
Ras	Grb2Sos	$17 + t$	0.39	RasGRPI	3	0.33						
PAGCsk	Fyn	$1 + s + t$	0.69	TCRbind	$1 + s + t$	0.32						
SLP70	Gads	$1 + t$	0.35									
Gads	LAT	$1 + s + t$	0.36									
Ikk	SLP70	1	0.3	ZAP70	$1 + s + t$	0.1						
CREB	Rsk	3	0.3									
Jun	JNK	3	0.3									
IP3	PLCg_act	$2 + s + t$	0.38									
NFKB	Ikk	3	0.3									
PKC θ	DAG	2	0.3									
Ca	IP3	$3 + s + t$	0.33									
ERK	MEK	2	0.28									
Fyn	Lck	$2 + s + t$	0.3	CD45	$4 + s + t$	0.37	TCRbind	$6 + s + t$	0.27			
LAT	ZAP70	$3 + s + t$	0.14									
ZAP70	Lck	$1 + s + t$	0.33	cCbl	$1 + s + t$	0.3	TCRphos	$2 + s + t$	0.29			
MEK	Raf	1	0.28									
RasGRPI	DAG	1	0.39	PKC θ	1	0.4						
NFAT	Calcien	$1 + s + t$	0.37									
CD4												
PLCg_bind	LAT	$5 + s + t$	0.36									
CD45												
JNK	SEK	4	0.57									
PLCg_act	SLP70	1	0.29	Rlk	$1 + s + t$	0.24	Ikk	$2 + s + t$	0.34	ZAP70	$1 + s + t$	0.3
Ikkbeta	PKC θ	18	0.33									
TCRphos	Lck	$1 + s + t$	0.34	Fyn	$1 + s + t$	0.13	TCRbind	$1 + s + t$	0.34			
Raf	Ras	3	0.3									
TCRHg												
cCbl	ZAP70	$1 + s + t$	0.7									
Calcien	Ca	$11 + s + t$	0.3									
Grb2Sos	LAT	$8 + s + t$	0.46									
Rlk	Lck	$1 + s + t$	0.36									
Fos	ERK	3	0.3									
CRE	CREB	3	0.3									
API	Jun	3	0.3	Fos	3	0.3						
TCRbind	TCRHg	$1 + s + t$	0.2	cCbl	$1 + s + t$	0.41						

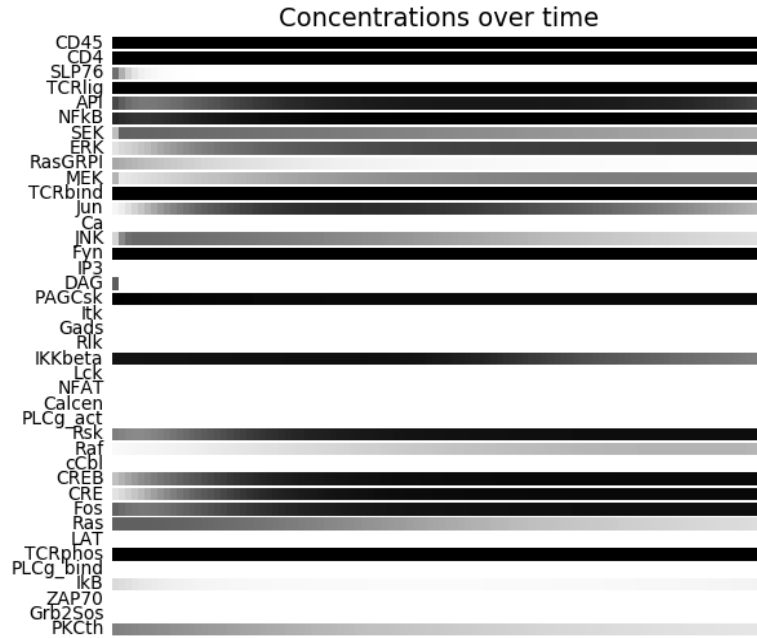
Table 4: Parametrization of the ODE-system taken from [25, Table 1]. The parameter s we inserted to increase/decrease the size of the invariant set. The parameter t is used in the second section.

d_Fos	1.0
d_CD45	0.6097560975609756
d_Calcen	0.22075055187637968
d_MEK	100.0
d_PLCg_bind	100.0
d_Lck	6.666666666666667
d_Grb2Sos	0.19011406844106465
d_CREB	1.0
d_IKKbeta	0.0947867298578199
d_NFkB	1.0
d_DAG	100.0
d_Rsk	1.0
d_ERK	10.0
d_PKCth	0.11547344110854503
d_Raf	0.0847457627118644
d_ZAP70	0.36101083032490977
d_Itk	100.0
d_RasGRPI	0.3623188405797102
d_Gads	8.333333333333334
d_Jun	1.0
d_Ras	0.13333333333333333
d_IkB	1.0
d_Fyn	2.1739130434782608
d_PLCg_act	100.0
d_TCRlig	0.78125
d_LAT	100.0
d_CRE	1.0
d_JNK	12.5
d_API	1.0
d_IP3	100.0
d_CD4	0.4444444444444444
d_NFAT	0.19880715705765406
d_SEK	100.0
d_TCRphos	33.333333333333336
d_cCbl	3.4482758620689657
d_Ca	5.0
d_Rlk	0.9803921568627451
d_PAGCsk	0.7518796992481203
d_TCRbind	1.6949152542372883
d_SLP76	4.166666666666667

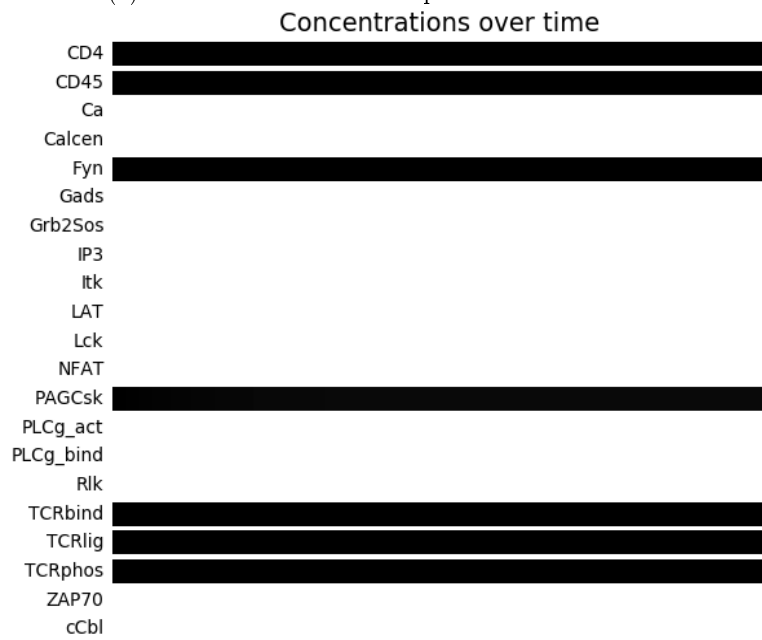
Table 5: Lifetimes of the species.

species	concentration
CD45	1
CD4	1
SLP76	0.6383074636864451
TCRlig	1
API	0.7710153667784586
NFkB	0.8674644188468164
SEK	0.36864521258257776
ERK	0.19894364354387672
RasGRPI	0.4385506551628684
MEK	0.4053605834313827
TCRbind	1
Jun	0.08284766843289271
Ca	0
JNK	0.2752331706050737
Fyn	1
IP3	0
DAG	0.7076011269333241
PAGCsk	1
Itk	0
Gads	0
Rlk	0
IKKbeta	0.9305312743703905
Lck	0
NFAT	0
Calcen	0
PLCg_act	0
Rsk	0.5849715505749411
Raf	0.04974369229436948
cCbl	0
CREB	0.35963640904474836
CRE	0.19590574360372903
Fos	0.684761045360155
Ras	0.6950465127721994
LAT	0
TCRphos	1
PLCg_bind	0
IkB	0.24608085019556414
ZAP70	0
Grb2Sos	0
PKCth	0.5742499725510135

Table 6: Initial values corresponding to Fig. 8.



(a) Concentrations of all components over time.



(b) Components which are fixed in the trap space.

Figure 8: Numerical results for $s = 4$ until $T = 10$.

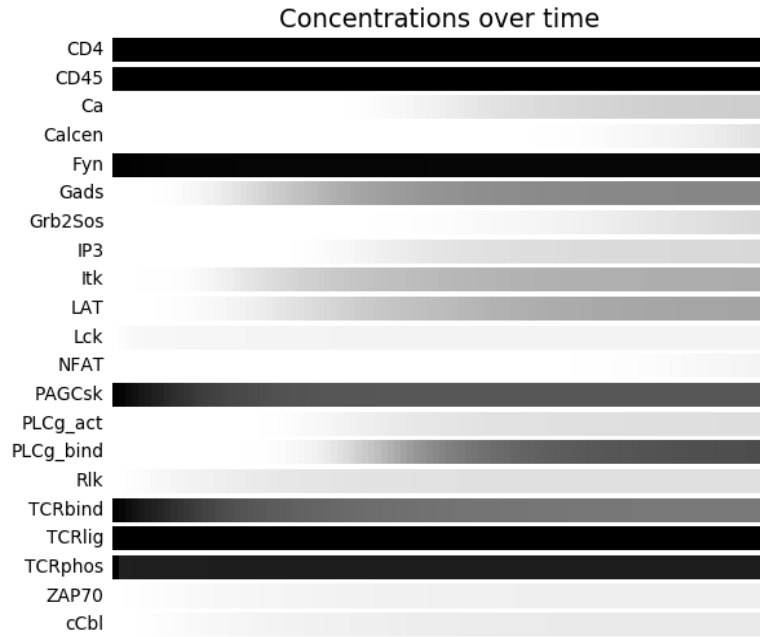


Figure 9: Components which are fixed in the trap space with $s = 0$ simulated until $T = 10$.

is depicted in Tab. 7. The reduced network has roughly half of the amount of components than the original one (19 components).

We compared the original system and the reduced system and measured the difference of the two solutions with the L^2 -norm and L^∞ -norm. The result is depicted in Tab. 8. We see that for a larger value of t the L^2 -norm decreases and seems to converge to zero. We also observe a big drop in the L^2 -norm between $t = 0$ in the first row and $t = 1$ in the second row. A similar observation can be made using the L^∞ -norm. This agrees with our observation that for $t = 0$ the trap space is not preserved, but only for higher t it is. This example suggests that in general for networks with relatively sparse interaction graphs a low Hill coefficient can suffice to allow a network reduction based on trap spaces.

Species	Boolean update function
CRE	CREB
PKCth	DAG
Fos	ERK
Rsk	ERK
SLP76	0
Ras	RasGRPI
NFkB	!IkB
IkB	!IKKbeta
Jun	JNK
JNK	SEK
API	Jun & Fos
ERK	MEK
RasGRPI	PKCth & DAG
IKKbeta	PKCth
SEK	PKCth
DAG	0
MEK	Raf
Raf	Ras
CREB	Rsk

Table 7: Boolean function restricted to the trap space.

t	L^2 -norm	L^∞ -norm
0	42.39366320006479	0.6143910698641019
1	$6.415065690624532e - 11$	$1.7056744591181783e - 06$
10	$1.1664356807309132e - 18$	$6.281553055487166e - 10$

Table 8: L^2 -norms and L^∞ -norms comparing the reduced system with the original one.