Piecewise linear models of chemical reaction networks

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Abstract

We show that certain non-linear dynamical systems with non-linearities in the form of Hill functions, can be approximated by piecewise linear dynamical systems. The resulting piecewise systems have closed form solutions that can be used to understand the behavior of the fully nonlinear system. We justify the reduction using geometric singular perturbation theory, and illustrate the results in networks modeling a genetic switch and a genetic oscillator.

1 Introduction

Accurately describing the behavior of interacting enzymes, proteins, and genes requires spatially extended stochastic models. However, such models are difficult to implement and fit to data, hence modelers frequently use tractable reduced models. In most popular models of biological networks, the dynamics of each node is described by a single ODE, and sigmoidal functions are used to model interactions between the network elements. The resulting ODEs are generally not analytically tractable. This can hinder the study of large networks, where the number of parameters and the potential dynamical complexity make it difficult to analyze the behavior of the system using purely numerical methods.

Analytical treatments are possible in certain limits. For instance, the approaches that have been developed to analyze models of gene interaction networks can be broadly classified into three categories [Polynikis et al. (2009)]: Quasi Steady State Approximations (QSSA), Piecewise Linear Approximations (PLA), and discretization of continuous time ODEs.

Here, we aim to develop the theory of PLAs. In certain limits interactions between network elements become switch-like [Kauffman (1969); Alon (2006); Davidich and Bornholdt (2008)]. For instance, the Hill function, \( f(x) = x^n / (x^n + J^n) \), approaches the Heaviside function, \( H(x - J) \), in the limit of large \( n \). In this limit the domain on which the network is modeled is also

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naturally broken into subdomains. For Hill functions, the thresholds, defined by $J$, divides the domain into two subdomains within which the Heaviside function is constant. Thus within each subdomain a node is either fully expressed, or not expressed at all. The original Hill function, $f(x)$, is approximately constant in each of the subdomains, and boundary layers occur when $x$ is close to threshold [Ironi et al. (2011)].

This general approach has a long and rich history, and piecewise linear functions of the form proposed in [Glass and Kauffman (1973)] have been shown to be well suited for the modeling of genetic regulatory networks (for a brief review see [De Jong (2002)]). In certain cases the results can be justified rigorously. In particular, singular perturbation theory can be used to obtain reduced equations within each subdomain and the boundary layers, and global approximations within the entire domain [Ironi et al. (2011)].

Here we take a similar approach, but work in a different limit. We again start with the Hill function, $x^n/(x^n + J^n)$, but assume that $J$ is small. Although the subsequent results hold for any fixed $n$, for simplicity we assume $n = 1$. Equations involving this special class of Hill functions are known as Michaelis-Menten equations, and $J$ is known as the Michaelis-Menten constant [Michaelis and Menten (1913); Goldbeter and Koshland (1981); Ciliberto et al. (2007); Ma et al. (2009); Davidich and Bornholdt (2008); Goldbeter (1991); Novak and Tyson (1993); Novak et al. (2001); Tyson et al. (2003)]. We note that the models of chemical reactions we consider can be rigorously derived from the Chemical Master Equation only in the case of a single reaction [Kumar and Josić (2011)]. The models of networks of chemical reactions that we take as the starting point of our reduction should therefore be regarded as phenomenological.

We will examine the case when the Michaelis-Menten constant, $J$, is small. This case has a simple physical interpretation: Consider the Hill function that occurs in the Michaelis-Menten scheme, where an enzyme is catalyzing the conversion of the inactive form of some protein to its active form. When $J$ is small the total enzyme concentration is much smaller than the total protein concentration. The asymptotic limit $J \to 0$ was recently considered to obtain heuristically a Boolean approximation of a protein interaction network [Davidich and Bornholdt (2008)]. Here we consider a rigorous justification underlying such reductions, as well as how the reduction could be used to understand the dynamics of gene networks.

The main idea behind the reduction we propose can be summarized as follows: Given the non-linear term $f(x) = x/(x + J)$, when $x \gg J$ then $f(x) \approx 1$, and when $x \approx 0$ then we do the analysis by introducing a new variable like $\tilde{x} := J/x$. This new variable $\tilde{x}$ serves as a microscope to observe the boundary regions. As we will show, the domain is naturally decomposed into a nested sequence of hypercubes such that for each level of nesting we get a separate linear equation.

We proceed as follows: In Section 2 we illustrate our approach using simple examples and provide numerical evidence for the validity of our claim. In Section 3 we describe a general class of differential equations which subsumes these examples. Furthermore, in this section we justify our approach mathematically using Geometric Singular Perturbation Theory (GSPT). We will conclude with a discussion on limitations of these reductions.

## 2 Example problems

We start by demonstrating the main idea of our approach in the cases of two and three mutually repressing biological elements. For instance, these elements could be genes that mutually inhibit each other’s production [Gardner et al. (2000); Elowitz and Leibler (2000)]. However, as the theory we develop is general, we do not constrain it to a particular interpretation. We first provide an intuitive illustration of the approach along with a heuristic justification of the different steps in the reduction. A mathematical justification follows.
Fig. 1: (a) Nodes $u_1$, $u_2$ inhibiting each others activity. End result is like a switch. The node which was stronger in the beginning will stay stronger and will completely suppress the other. (b) Nodes $u_1$, $u_2$, and $u_3$ suppressing each other in a cyclic fashion. Not surprisingly, the end result is oscillatory behavior.

2.1 A network of two mutually inhibiting elements

First we consider two mutually repressing elements within a biological network. This toggle switch motif (see Figure 1a) is common in biological networks [Tyson et al. (2003); Gardner et al. (2000)]. Let $u_1, u_2 \in [0,1]$ represent the normalized levels of activity of the first and second element, respectively. Therefore, when $u_i = 1$ the $i$th network element is maximally active (expressed). The system be modeled by

$$
\frac{du_1}{dt} = 0.5 \frac{1 - u_1}{J + 1 - u_1} - u_2 \frac{u_1}{J + u_1},
$$

$$
\frac{du_2}{dt} = 0.5 \frac{1 - u_2}{J + 1 - u_2} - u_1 \frac{u_2}{J + u_2},
$$

(1)

where $J$ is some positive constant. The structure of Eq. (1) implies that the cube $[0,1]^2 = \{ (u_1, u_2) \mid 0 \leq u_1, u_2 \leq 1 \}$ is invariant (see Proposition 1).

In the limit of small $J$, Eq. (1) can be approximated by a piecewise linear differential equation as follows: If $u_i$ is not too close to zero the expression $u_i/(J + u_i)$ is approximately unity. More precisely, we fix a small $\delta > 0$, which will be chosen to depend on $J$. When $u_i > \delta$ and $J$ is small then $u_i/(J + u_i) \approx 1$. Similarly, when $u_i > 1 - \delta$ then $(1 - u_i)/(J + 1 - u_i) \approx 1$.

With this convention in mind we break the cube $[0,1]^2$ into several subdomains, and define a different reduction of Eq. (1) within each. For example, the interior of the domain $[0,1]^2$ is defined by

$$
R_0^0 := \{ (u_1, u_2) \in [0,1]^2 \mid \delta \leq u_1 \leq 1 - \delta \text{ and } \delta \leq u_2 \leq 1 - \delta \}. 
$$

(2)

Eq. (1), restricted to $R_0^0$ is approximated by the linear differential equation

$$
\frac{du_1}{dt} = 0.5 - u_2, \quad \frac{du_2}{dt} = 0.5 - u_1.
$$

(3)

On the other hand, if one of the coordinate is near the boundary, while the other is in the interior, the approximation is different. For instance, the region

$$
R_1^0 := \{ (u_1, u_2) \in [0,1]^2 \mid u_1 < \delta \text{ and } \delta \leq u_2 \leq 1 - \delta \},
$$

(4)

forms a boundary layer where $u_1$ is of the same order as $J$. Therefore the term $u_1/(J + u_1)$ can
not be approximated by unity. Instead the approximation takes the form

\[
\frac{du_1}{dt} = 0.5 - u_2 \frac{u_1}{J + u_1},
\]

\[
\frac{du_2}{dt} = 0.5 - u_1.
\]  

(5a)

(5b)

This equation can be simplified further. Since the boundary defined by \(u_1 = 0\) is invariant, \(\frac{du_1}{dt}\) must be small inside the boundary layer \(R_0^0\). We therefore use the approximations \(\frac{du_1}{dt} \approx 0\) in Eq. (5a) and \(u_1 \approx 0\) in Eq. (5b) to obtain

\[
0 = 0.5 - u_2 \frac{u_1}{J + u_1},
\]  

\[
\frac{du_2}{dt} = 0.5.
\]  

(6a)

(6b)

Note that Eq. (6b) is linear and decoupled from Eq. (6a), while Eq. (6a) is an algebraic system which can be solved to obtain \(u_1 \approx J/(2u_2 - 1)\). Within \(R_0^0\) we thus obtain the approximation \(u_2(t) \approx 0.5t + u_2(0)\) and \(u_1(t) \approx J/(t + 2u_2(0) - 1)\).

Note that here we have the freedom of only specifying the initial condition \(u_2(0)\), while \(u_1(0)\) is determined from the solution of the algebraic equation (6a). As we explain below, this algebraic equation defines a slow manifold within the subdomain \(R_1^0\). The reduction assumes that solutions are instantaneously attracted to this manifold.

Table 1 shows how these ideas can be extended to all of \([0, 1]^2\). In each of the 9 listed subdomain one or both variables are close to either \(0\) or \(1\). Therefore each subdomain corresponds to either the interior, edge, or corner of the unit square. Following the preceding arguments, we assume that variable(s) that are close to \(0\) or \(1\) are in steady state and lead to an algebraic equation. Similarly, the evolution of the interior variables is described by linear differential equations. The resulting algebraic-differential systems are given in the last column of Table 1.

Each approximate solution has the potential of exiting the subdomain within which it is defined, and entering another. The global approximate solution of Eq. (1) is obtained by using the exit point from one subdomain as the initial condition for the approximation in the next. In subdomains other than \(R_0^0\) some of the initial conditions will be prescribed by the algebraic part of the reduced system. The global approximation may therefore be discontinuous, as solutions entering a new subdomain are assumed to instantaneously jump to the slow manifold defined by the algebraic part of the reduced system. Fig. 2 shows that when \(J\) is small, this approach provides a good approximation.

### 2.2 A network of three mutually inhibiting elements

The same reduction can be applied to systems of arbitrary dimension. As an example consider the repressilator [Tyson et al. (2003); Elowitz and Leibler (2000)] described by

\[
\frac{du_1}{dt} = 0.6 \frac{1 - u_1}{J + 1 - u_1} - u_3 \frac{u_1}{J + u_1},
\]

\[
\frac{du_2}{dt} = 0.4 \frac{1 - u_2}{J + 1 - u_2} - u_1 \frac{u_2}{J + u_2},
\]

\[
\frac{du_3}{dt} = 0.3 \frac{1 - u_3}{J + 1 - u_3} - u_2 \frac{u_3}{J + u_3}.
\]  

(7)
The cyclic repression of the three elements in this network leads to oscillatory solutions over a large range of values of $J$. The domain of this system, $[0,1]^3$, can be divided into 27 subdomains: 1 interior, 6 faces, 12 edges, and 8 vertices. We can again approximate Eq. (7) with solvable differential–algebraic equation within each subdomain, to obtain a global approximate solution. We demonstrate the validity of this approximation in Fig. 2. Note that both the numerically obtained solution to Eq. (7), and its approximation exhibit oscillations, and that the approximation is discontinuous.

3 General setup

The approximations described in the previous section can be extended to more general models. Suppose we describe the evolution of $n$ interacting elements, $u_1, u_2, ..., u_n$, by

$$\frac{du_i}{dt} = A_i \frac{u_i}{J_i^A + 1} - I_i \frac{u_i}{J_i^I + u_i}, \quad \text{(8)}$$

where $J_i^A, J_i^I$ are some positive constants. Here $A_i$ and $I_i$ are activation/inhibition functions that capture the impact of other variables on the evolution of $u_i$. The initial conditions are assumed to satisfy $u_i(0) \in [0,1]$ for all $i$.

We assume that the activation and inhibition functions are both affine [De Jong (2002)],

$$A_i := \sum_{j=1}^n w_{ij}^+ u_j + b_i^+, \quad I_i := \sum_{j=1}^n w_{ij}^- u_j + b_i^-, \quad \text{(9)}$$

where we use the convention $x^+ = \max\{x,0\}$ and $x^- = \max\{-x,0\}$. The $n \times n$ matrix, $W = [w_{ij}]$ and the $n \times 1$ vector $b = [b_1 b_2 ... b_n]^t$ capture the connectivity and external input to the network, respectively. In particular, $w_{ij}$ gives the contribution of the $j$th variable to the growth rate of the $i$th variable. If $w_{ij} > 0$, then $w_{ij}$ appears in the activation function for $u_i$; and if $w_{ij} < 0$ then $-w_{ij}$ appears in the inhibition function for $u_i$. The intensity of the external input to the $i$th element is $|b_i|$, and it contributes to the activation or the inhibition function, depending on whether $b_i > 0$ or $b_i < 0$, respectively.
Figure 3: Comparison of the numerical solution of Eq. (7) (dashed black) and the solution of the approximate linear system (not explicitly provided) for two different sets of $J$ and $\delta$. For (a)-(c) $J = 10^{-2}, \delta = 0.06$; for (c)-(f) $J = 10^{-4}, \delta = 0.01$. The approximate solution changes color when switching between different subdomains. Note that the approximate solution is discontinuous in general. The reason is that as soon as the solution enters a new subdomain, the solution jumps (see inset) to the manifold defined by the algebraic part of the linear differential algebraic system corresponding to the new subdomain.

**Proposition 1.** If $A_i$ and $I_i$ are positive, then the cube $[0,1]^n$ is invariant for the dynamical system given by Eq. (8).

**Proof.** It will be enough to show that the vector field at any point on the boundary is directed inward. Since, $A_i$ and $I_i$ are positive, for any $i$,

$$\left.\frac{du_i}{dt}\right|_{u_i=0} = A_i \frac{1}{J_i^A + 1} \geq 0, \quad \text{and} \quad \left.\frac{du_i}{dt}\right|_{u_i=1} = -I_i \frac{1}{J_i^I + 1} \leq 0.$$  

\[ \square \]

### 4 General reduction of the model system

To obtain a solvable reduction of Eq. (8) we follow the procedure outlined in Section 2. We present the result here, and provide the mathematical justification in the next section. For notational convenience we consider the case $J_i^A = J_i^I = J$, with $J$ small and positive. The general case is equivalent. Let $\delta$ be some positive number which will be used to define the thickness of the boundary layers, and which will depend on $J$ in general. We start with the subdivision of the $n$-dimensional cube, $[0,1]^n$.

Let $T$ and $S$ be two disjoint subsets of $\{1,2,...,n\}$, and let

$$R_{S,T}^n := \{(u_1,u_2,...,u_n) \in [0,1]^n \mid u_s < \delta \text{ for all } s \in S; \quad u_t > 1 - \delta \text{ for all } t \in T; \quad \text{and } \delta \leq u_k \leq 1 - \delta \text{ for all } k \notin S \cup T\}.$$
We extend the convention used in Table 1, and in Eqs. (2) and (4) so that \( \mathcal{R}_T^0 := \mathcal{R}_S^T \) when \( S \) is empty; \( \mathcal{R}_S^T := \mathcal{R}_T^S \) when \( T \) is empty; and \( \mathcal{R}_T^0 := \mathcal{R}_S^T \) when \( T, S \) are both empty.

Within each subdomain \( \mathcal{R}_S^T \) Eq. (8) can be approximated by a different linear differential–algebraic system. Following the reduction from Eq. (1) to Eq. (5), for \( i \notin S \cup T \) we obtain the linear system

\[
\frac{du_i}{dt} = \sum_{j=1}^{n} a_{ij} u_j + b_i. \tag{10a}
\]

For \( s \in S \) one of the nonlinear terms remains and we obtain

\[
\frac{du_s}{dt} = \left( \sum_{j=1}^{n} a_{sj}^+ u_j + b_s^+ \right) - \left( \sum_{j=1}^{n} a_{sj}^- u_j + b_s^- \right) \frac{u_s}{J + u_s}, \tag{10b}
\]

while for \( t \in T \) we will have

\[
\frac{du_t}{dt} = \left( \sum_{j=1}^{n} a_{tj}^+ u_j + b_t^+ \right) \frac{1 - u_t}{J + 1 - u_t} - \left( \sum_{j=1}^{n} a_{tj}^- u_j + b_t^- \right). \tag{10c}
\]

Eq. (10) is simpler than Eq. (8), but it is not solvable yet. Following the reduction from Eq. (5) to Eq. (6), we now further reduce Eqs. (10b–10c). First we use the approximations \( u_s \approx 0 \) and \( u_t \approx 1 \) in the activation and inhibition functions appearing in Eq. (10). Second, we assume that \( u_s \) for \( s \in S \) and \( u_t \) for \( t \in T \) are in steady state.

Under these assumptions we obtain the reduction of Eq. (8) within any subdomain \( \mathcal{R}_S^T \)

\[
\frac{du_i}{dt} = \sum_{j \notin S \cup T} a_{ij} u_j + \sum_{j \in T} a_{ij} + b_i \quad \text{for} \ i \notin S \cup T; \tag{11a}
\]

\[
0 = \sum_{j \notin S \cup T} a_{sj}^+ u_j + \sum_{t \in T} a_{st}^+ + b_s^+ - \left( \sum_{j \notin S \cup T} a_{sj}^- u_j + \sum_{t \in T} a_{st}^- + b_s^- \right) \frac{u_s}{J + u_s}; \quad \text{for} \ s \in S, \tag{11b}
\]

\[
0 = - \left( \sum_{j \notin S \cup T} a_{tj}^+ u_j + \sum_{j \in T} a_{tj}^- + b_t^+ \right) \frac{1 - u_t}{J + 1 - u_t} + \sum_{j \notin S \cup T} a_{tj}^- u_j + \sum_{j \in T} a_{tj}^- + b_t^-; \quad \text{for} \ t \in T. \tag{11c}
\]

Eq. (11) is solvable since Eq. (11a) is decoupled from the rest, and Eqs. (11b) and (11c) are solvable for \( u_s \) and \( u_t \), respectively, as functions of the solution of Eq. (11a).

### 5 Mathematical justification

We next justify our claim that the variables close to the boundary can be assumed to be in steady state. We define the following new variables to “magnify” the boundary region.

\[
\tilde{u}_s := \frac{u_s}{J} \quad \text{for} \ s \in S, \quad \text{and} \quad \tilde{u}_t := \frac{1 - u_t}{J} \quad \text{for} \ t \in T. \tag{12}
\]

Using Eq. (12) in Eq. (10) we get for \( i \notin S \cup T \)

\[
\frac{du_i}{dt} = \sum_{j \notin S \cup T} a_{ij} u_j + \sum_{j \in T} a_{ij} + J \left( \sum_{s \in S} a_{is} \tilde{u}_s - \sum_{t \in T} a_{it} \tilde{u}_t \right) + b_i, \tag{13a}
\]
and for \( s \in S \),
\[
J \frac{d\tilde{u}_s}{dt} = \sum_{j \notin S \cup T} a_{sj}^+ u_j + \sum_{t \in T} a_{st}^+ + J \left( \sum_{j \in S} a_{sj}^+ \tilde{u}_j - \sum_{t \in T} a_{st}^+ \tilde{u}_t \right) + b_s^+ \\
- \left( \sum_{j \notin S \cup T} a_{sj}^- u_j + \sum_{t \in T} a_{st}^- + b_s^- \right) \frac{\tilde{u}_s}{1 + \tilde{u}_s} - J \left( \sum_{j \in S} a_{sj}^- \tilde{u}_j - \sum_{t \in T} a_{st}^- \tilde{u}_t \right) \frac{\tilde{u}_s}{1 + \tilde{u}_s}.
\]
(13b)

and similarly, for \( t \in T \),
\[
J \frac{d\tilde{u}_t}{dt} = - \left( \sum_{j \notin S \cup T} a_{tj}^+ u_j + \sum_{j \in S} a_{tj}^+ + b_t^+ \right) \frac{\tilde{u}_t}{1 + \tilde{u}_t} - J \left( \sum_{j \in S} a_{tj}^+ \tilde{u}_j - \sum_{t \in T} a_{tj}^+ \tilde{u}_t \right) \frac{\tilde{u}_t}{1 + \tilde{u}_t} + \sum_{j \notin S \cup T} a_{tj}^- u_j + \sum_{j \in S} a_{tj}^- + b_t^- + J \left( \sum_{j \in S} a_{tj}^- \tilde{u}_j - \sum_{j \notin S \cup T} a_{tj}^- \tilde{u}_t \right).
\]
(13c)

When \( J \) is small, we can apply Geometric Singular Perturbation Theory (GSPT) to Eq. (13) [Hek (2010); Kaper (1998)]. The GSPT posits that, under a normal hyperbolicity condition which we will prove below, Eq. (13) can be further simplified by assuming that \( J = 0 \). This yields a differential-algebraic system
\[
\frac{du_i}{dt} = \sum_{j \notin S \cup T} a_{ij} u_j + \sum_{j \in S} a_{ij} + b_i, \quad i \notin S \cup T;
\]
(14a)
\[
0 = \sum_{j \notin S \cup T} a_{sj}^+ u_j + \sum_{t \in T} a_{st}^+ + b_s^+ - \left( \sum_{j \notin S \cup T} a_{sj}^- u_j + \sum_{t \in T} a_{st}^- + b_s^- \right) \frac{\tilde{u}_s}{1 + \tilde{u}_s}, \quad s \in S;
\]
(14b)
\[
0 = - \left( \sum_{j \notin S \cup T} a_{tj}^+ u_j + \sum_{j \in S} a_{tj}^+ + b_t^+ \right) \frac{\tilde{u}_t}{1 + \tilde{u}_t} + \sum_{j \notin S \cup T} a_{tj}^- u_j + \sum_{j \in S} a_{tj}^- + b_t^- \quad t \in T.
\]
(14c)

which is equivalent to Eq. (11) after rescaling. This conclusion will be justified if the manifold defined by Eqs. (14b) and (14c) is normally hyperbolic and stable [Fenichel (1979); Kaper (1998); Hek (2010)]. We verify this condition next.

Let \( \tilde{u} = \{u_{i_1}, ..., u_{i_m}\} \) where \( \{i_1, ..., i_m\} = \{1, 2, ..., n\} \setminus (S \cup T) \), be the coordinates of \( u \) which are away from the boundary, and denote the right hand side of Eq. (14a) by \( F_s(\tilde{u}, \tilde{u}_{i_s}) \), for all \( s \in S \), so that
\[
F_s(\tilde{u}, \tilde{u}_{i_s}) := \sum_{j \notin S \cup T} a_{sj}^+ u_j + \sum_{t \in T} a_{st}^+ + b_s^+ - \left( \sum_{j \notin S \cup T} a_{sj}^- u_j + \sum_{t \in T} a_{st}^- + b_s^- \right) \frac{\tilde{u}_s}{1 + \tilde{u}_s},
\]
and
\[
\frac{\partial F_s}{\partial \tilde{u}_s} = - \left( \sum_{j \notin S \cup T} a_{sj}^+ u_j + \sum_{t \in T} a_{st}^- + b_s^- \right) \left( \frac{1}{1 + \tilde{u}_s} \right)^2 < 0
\]
for all \( s \in S \). Similarly, by denoting the right hand side of Eq. (14c) by \( G_t(\tilde{u}, \tilde{u}_{i_t}) \), for all \( t \in T \), i.e.
\[
G_t(\tilde{u}, \tilde{u}_{i_t}) := - \left( \sum_{j \notin S \cup T} a_{tj}^+ u_j + \sum_{j \in S} a_{tj}^+ + b_t^+ \right) \frac{\tilde{u}_t}{1 + \tilde{u}_t} + \sum_{j \notin S \cup T} a_{tj}^- u_j + \sum_{j \in S} a_{tj}^- + b_t^-,
\]

8
we see that

\[
\frac{\partial G_t}{\partial \tilde{u}_i} = - \left( \sum_{j \notin S \cup T} a_{ij}^t u_j + \sum_{j \in T} a_{ij}^t + b_i^t \right) \left( \frac{\tilde{u}_i}{1 + \tilde{u}_i} \right)^2 < 0.
\]

Hence, the manifold defined by Eqs. (14b) and (14c) is normally hyperbolic and stable. This completes the proof that the reduction of the non-linear system (8) to a solvable system (11) is justified for small \( J \).

6 Discussion

A special class of non-linear differential equation was studied with non-linear interaction terms given by Hill functions. We showed that when the Michaelis-Menten constants are sufficiently small, the behavior of the system is captured by an approximate piecewise linear systems. This induces a natural decomposition of the domain into a nested sequence of hypercubes, with a separate linear-algebraic system giving an approximation in each subdomain. We have illustrated the theory in examples, and justified the conclusions using GSPT.

A potential limitation in our arguments is that we have an approximation valid only in an asymptotic limit. It is unknown when and how the approximation breaks down. Another major limitation of our analysis is that we have not provided a systematic relationship between the thickness of the boundary, \( \delta \), and the Michaelis-Menten constant, \( J \). Numerical tests suggest that \( J = O(\delta^2) \).

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### Table 1: List of differential–algebraic systems that approximate Eq. (1) in different parts of the domain.

The subdomains are named so that the superscript (subscript) lists the coordinates that are close to 1 (close to 0), with 0 denoting the empty set. For example, \( R^2_{12} \) denotes that subdomain with \( u_1 \approx 1 \) and \( u_2 \approx 0 \), and \( R^2_0 \) the subdomain where \( u_2 \) is near 1, but \( u_1 \) is away from the boundary. The middle column define the subdomain explicitly. The right column gives the differential-algebraic system that approximates Eq. (1) within the given subdomain.

| Subdomain’s name | \( u_1 \) | \( u_2 \) | Approximating linear system |
|------------------|---------|---------|----------------------------|
| \( R^0_{0} \)    | \( \delta \leq u_1 \leq 1 - \delta \)  | \( \delta \leq u_2 \leq 1 - \delta \)  | \( u'_1 = 0.5 - u_2, \) \( u'_2 = 0.5 - u_1 \) |
| \( R^1_{0} \)    | \( u_1 > 1 - \delta \)  | \( \delta \leq u_2 \leq 1 - \delta \)  | \( 0 = 0.5 - \frac{1 - u_1}{J + 1 - u_1} - u_2, \) \( u'_2 = -0.5 \) |
| \( R^2_{0} \)    | \( \delta \leq u_1 \leq 1 - \delta \)  | \( u_2 > 1 - \delta \)  | \( u'_1 = -0.5, \) \( 0 = 0.5 - \frac{1 - u_2}{J + 1 - u_1} - u_1 \) |
| \( R^0_{1} \)    | \( u_1 < \delta \)  | \( \delta \leq u_2 \leq 1 - \delta \)  | \( 0 = 0.5 - u_2 \frac{1}{J + u_1}, \) \( u'_2 = 0.5 \) |
| \( R^2_{1} \)    | \( \delta \leq u_1 \leq 1 - \delta \)  | \( u_2 < \delta \)  | \( u'_1 = 0.5, \) \( 0 = 0.5 - u_1 \frac{u_2}{J + u_2} \) |
| \( R^1_{02} \)   | \( u_1 > 1 - \delta \)  | \( u_2 > 1 - \delta \)  | \( 0 = 0.5 - \frac{1 - u_1}{J + 1 - u_1} - 1, \) \( 0 = 0.5 - \frac{1 - u_2}{J + 1 - u_2} - 1 \) |
| \( R^0_{12} \)   | \( u_1 < \delta \)  | \( u_2 < \delta \)  | \( 0 = 0.5 - J \frac{u_1}{J + u_1}, \) \( 0 = 0.5 - J \frac{u_2}{J + u_2} \) |
| \( R^1_{2} \)    | \( u_1 > 1 - \delta \)  | \( u_2 < \delta \)  | \( 0 = 0.5 - \frac{1 - u_1}{J + 1 - u_1}, \) \( 0 = 0.5 - \frac{1 - u_2}{J + u_2} \) |
| \( R^0_{2} \)    | \( u_1 < \delta \)  | \( u_2 > 1 - \delta \)  | \( 0 = 0.5 - J \frac{u_1}{J + u_1}, \) \( 0 = 0.5 - J \frac{u_2}{J + 1 - u_2} \) |