Revealing Bistability in Neurological Disorder Models By Solving Parametric Polynomial Systems Geometrically

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Abstract. Understanding the mechanisms of the brain is a common theme for both computational neuroscience and artificial intelligence. Machine learning technique, like artificial neural network, has been benefiting from a better understanding of the neuronal network in human brains. In the study of neurons, mathematical modeling plays a vital role. In this paper, we analyze the important phenomenon of bistability in neurological disorders modeled by ordinary differential equations in virtue of our recently developed method for solving bi-parametric polynomial systems. Unlike the algebraic symbolic approach, our numeric method solves parametric systems geometrically. With respect to the classical bifurcation analysis approach, our method naturally has good initial points thanks to the critical point technique in real algebraic geometry.

Special heuristic strategies are proposed for addressing the multi-scale problem of parameters and variables occurring in biological models, as well as taking into account the fact that the variables representing concentrations are non-negative. Comparing with its symbolic algebraic counterparts, one merit of this geometrical method is that it may compute smaller boundaries.

1 Introduction

Due to the tremendous increase in computing power, a machine learning approach named artificial neural network is enjoying a renaissance. Design of artificial neural network has been being inspired by advances in neuroscience and it is believed that a better understanding of the mechanisms of human brain and nervous system will play a vital role for the advent of more powerful artificial intelligence technology [13]. The study of human brain and nervous system is also the main subject of computational neuroscience [1,2,11,21]. Different from the "black-box" approach in machine learning, explicit mathematical models were built and analyzed in this discipline.

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Historically, different models were proposed for studying neurons [11]. In this paper, we are particularly interested in neurological disorder models [21]. A study of the underlying mechanism is important for understanding various modalities of learning, such as long-term memory [20,23].

In general, dynamical system defined by ordinary different equations (ODEs) is a powerful tool for modeling biochemical networks [10]. The dominant approach for solving these systems is numerical simulation [24], which can handle large systems of equations. For small size problems, bifurcation analysis [12,16] is a very useful tool for understanding the role that parameters play.

The study of equilibria and their stability can be cast to an algebraic problem [19,26], which creates opportunities for symbolic tools for solving parametric polynomial systems, such as cylindrical algebraic decomposition [6,8], the border polynomial approach [29], the discriminant variety approach [17], real comprehensive triangular decomposition [7], and so on. Symbolic methods for handling special biological systems also exist, for instance in [3,15]. In [5], we proposed a numerical approach for solving bi-parametric polynomial systems. This approach is essentially geometrical, which is based on curve tracing and projection of points rather than elimination. This approach is further generalized to computing stability boundary of dynamical systems defined by ODEs and applied directly to analyzing stability of biological systems [4].

Two important characteristics peculiar to biological models were not exploited in [4], namely the multiscale problem and non-negative requirement of variables and parameters. In this paper, we introduced heuristics such as variable rescaling and restricted curve tracing to address them. We re-examine two neurological disorder models studied in [9,20] but provide improved or new results by analyzing the bistability phenomenon in the models. To overcome the difficulty of traditional bifurcation analysis method for finding initial starting points, we reply on critical point techniques [14,22,28] in real algebraic geometry and homotopy continuation methods in numerical algebraic geometry [18,25] to find at least one witness point for each connected component of fold and Hopf bifurcation curves. As illustrated by the two models in Sect. 3, with respect to symbolic methods, our method has the advantage of producing smaller boundary since it only traces positive branches of the bifurcation in real space rather than computing the Zariski closure of the projection of the bifurcation curve in complex space.

2 Methodology

In this section, we first briefly review the theory introduced in [4,5] for computing the fold and Hopf bifurcation boundaries of dynamical systems. Then we present new strategies tuned for biological systems to enhance the algorithm in [4].

2.1 Basic Theory

Throughout this section, we consider continuous dynamical systems defined by autonomous ODEs of the form $\dot{x} = F(x, u)$, where $x = (x_1, \ldots, x_m)$

are unknowns, $u = (u_1, u_2)$ are parameters independent of time t, and $F = (F_1, \ldots, F_m)$ are rational functions of $\mathbb{R}(u, x)$, called the *vector field* of the system.

Let $\mathcal{J}$ be the Jacobian matrix of F with respect to x. The following system defines the fold bifurcation [16], which is a bifurcation where the equilibrium has zero eigenvalue:

$$\{F = 0, \mathcal{J}v = 0, \alpha v - 1 = 0\}, \tag{1}$$

where $v = v_1, \ldots, v_m$ is a vector of auxiliary variables and α is a random vector of $\mathbb{R}^m$ to avoid $v = 0$. This system has $2m + 1$ equations and $2m + 2$ variables. "Generically" it defines a one-dimensional curve, called *fold bifurcation curve*. To avoid v approaching to infinity or a large number, sometimes it is better to replace $\alpha v - 1 = 0$ by $vv - 1 = 0$ in Eq. (1).

Another defining system for fold bifurcation is $\{F = 0, \det(\mathcal{J}(F)) = 0\}$, which is suitable for symbolic solvers. But for our method, Eq. (1) is usually preferred for better numerical stability and taking advantage of sparsity.

Let $P(x, u)$ be the vector of the numerators of $F(x, u)$. Assume that the denominators of F never vanish (which is usually automatically satisfied for biological systems due to the natural requirement that all the variables should take non-negative values). It is shown in [4] that one can safely replace F by P in the above two systems.

Next we derive the defining system for Hopf bifurcation [16], which is a bifurcation where the equilibrium has a pair of purely imaginary eigenvalues. Suppose that $\mathcal{J}$ has a pair of purely imaginary eigenvalues $\lambda = \pm\omega i$. Let $(\mu + i\nu)$ be the corresponding eigenvectors. Then we have $\mathcal{J}(\mu + i\nu) = (\omega i)(\mu + i\nu)$, which implies that $\mathcal{J}\mu = -\omega\nu$ and $\mathcal{J}\nu = \omega\mu$ hold. Thus a defining system for Hopf bifurcation can be defined as below

$$\begin{cases} F = 0 \\ \mathcal{J}\mu = -\omega\nu \\ \mathcal{J}\nu = \omega\mu \\ \alpha\mu - \beta\nu = 1 \\ \beta\mu + \alpha\nu = 0, \end{cases} \tag{2}$$

where both μ and ν are additional vectors of m variables, ω is an additional scalar variable, and α and β are random real vectors of $\mathbb{R}^m$ to avoid $\mu + i\nu = 0$. This system has $3m+2$ equations and $3m+3$ variables. "Generically", it defines a one-dimensional curve, called *Hopf bifurcation curve*. Note that in Eq. (2), when $\omega \neq 0$, it defines exactly the Hopf bifurcation. When $\omega = 0$, it defines exactly the fold bifurcation [4]. Another typical defining system for Hopf bifurcation is: $\{F = 0, \Delta_{m-1}(F) = 0\}$, where $\Delta_{m-1}(F)$ is the $(m-1)$-th Hurwitz determinant of $\mathcal{J}(F)$. This defining system is usually used for symbolic solvers as it does not introduce extra variables. Note that this defining system may contain points where $\mathcal{J}(F)$ has eigenvalues of opposite signs.

Let $\pi : \mathbb{R}^{m+2} \to \mathbb{R}^2$ be the projection defined by $\pi(x_1, \ldots, x_m, u_1, u_2) = (u_1, u_2)$. Let R be a bounding box of the parametric space (u_1, u_2). Let P_F be the vector of numerators of F. Let F_H be the right hand side of Eq. (2),

which defines Hopf bifurcation. Let P_H be the vector of numerators of F_H. Let $B_H := \pi(V_{\mathbb{R}}(P_H))$. Then B_H is the fold and Hopf bifurcation boundaries of the vector field F. Note that when parameters take values crossing B_H, the sign of the real part of some eigenvalue of an equilibrium may change. So is stability of the equilibrium. We call B_H the *stability boundary of* F.

Assuming that P_F, P_H and R satisfy the following assumptions:

- (A_1) The set $V_{\mathbb{R}}(P_F) \cap \pi^{-1}(R)$ is compact.
- (A_2) We have $\dim V_{\mathbb{R}}(P_H) = 1$.
- (A_3) At each regular point of $V_{\mathbb{R}}(P_H)$, the Jacobian of P_H has full rank.

Then the following property holds.

Proposition 1 [4]**.** *Let B_H be the stability boundary of the vector field $F(x, u)$ restricted to some bounding box R. Then $R \setminus B_H$ is divided into finitely many connected components, called cells, such that in each cell, the number of equilibria of $F(x, u)$ does not change. Moreover, in every given cell, each equilibrium is a smooth function of u with stability unchanged.*

Remark 1. *As argued in bifurcation analysis, "generically", the assumptions A_2 and A_3 are satisfied. It is argued in [4] that we can force A_1 to be satisfied for biological systems modeled by dynamical system $\dot{x} = F(x, u)$, since the variables x usually denote concentrations of biological substances, which are non-negative and bounded by conservation laws. More precisely, in addition to B_H, one should also computes boundaries corresponding to constraints $0 \leq x_i \leq b_i$, namely $B_i := \pi(V_{\mathbb{R}}(P_F, x_i))$, $i = 1, \ldots, m$ and $B_{i+m} := \pi(V_{\mathbb{R}}(P_F, x_i - b_i))$, $i = 1, \ldots, m$.*

2.2 Computing Stability Boundary of Biological Systems

Next we present a numeric algorithm for computing the stability boundary of biological systems modeled by the dynamical system $F(x, u)$. It is specially tuned for biological systems and improves the algorithm in our earlier work [4]. See Remark 2 for details.

Let RealWitnessPoint be the routine introduced in [27] for computing a set of witness points W of a real variety $V_{\mathbb{R}}(P_H)$ satisfying Assumption (A_3). Recall that a set of witness points W of a real variety V is a finite subset of V such that W has non-empty intersection with every connected component of V. The basic idea of this routine is to introduce a random hyperplane L. Then "roughly speaking" the witness points of $V_{\mathbb{R}}(P_H)$ either belong to $V_{\mathbb{R}}(P_H) \cap L$ or are the critical points (points attaining local minima) of the distance from the connected components of $V_{\mathbb{R}}(P_H)$ to L.

Algorithm StabilityBoundary
Input: a bi-parametric biological system defined by $\dot{x} = F(x_1, \ldots, x_m, u_1, u_2)$, where F is a vector of m rational functions with real coefficients; a bounding box R in the first quadrant of the (u_1, u_2)-plane.
Output: an approximation of the stability boundary of the vector field F restricted to R.

Steps:

1. Let F_H be the left hand side of Eq. (2) and let P_H be the vector of numerators of F_H.
2. Choose a random point u in R and compute $S := P_H(u)^{-1}(0) \cap \mathbb{R}^m$ by homotopy continuation method [18].
3. Based on solutions in S, rescale each x_i and each u_i to the range $[0, \ell]$, where ℓ is a small integer between 1 and 10.
4. Rescale R accordingly to R'. Choose a big integer $K \gg \ell$ and set $R_2 := R' \times [0, K]^m$.
5. Set $W := \emptyset$.
6. Compute the intersection of $V_{\mathbb{R}}(P_H)$ with ∂R_2 by a homotopy continuation method and add the points into W.
7. Compute $\mathsf{RealWitnessPoint}(P_H)$ and add the points into W.
8. For $p \in W$, starting from p, follow both directions of the tangent line of $V_{\mathbb{R}}(P_H)$ at p, trace the curve P_H by a prediction-projection method, until a closed curve is found or a boundary of R_2 is met.
9. Return the projections of the traced points in R.

Remark 2. Comparing with our algorithm in [4] for general dynamical systems, this algorithm is specially tuned for biological systems. In particular, in Steps 2 and 3, we apply a rescaling strategy considering the factor that variables and parameters in biological systems usually have different scales. In Step 4, we take into account the fact that the variables of biological systems are non-negative. Introducing the box R_2 has two advantages. First it will force the following curve tracing to be restricted in a positive box and thus avoid computing projections of bifurcation points with negative coordinates, which has no biological meanings. Secondly it will compute an approximation of the projection of positive infinity points. This is one key reason why our numeric geometrical method produces smaller boundaries than symbolic algebraic methods, which first computes Zariski closure of bifurcation boundaries in complex space. Another key reason is we use a defining system encoding exactly the fold and Hopf bifurcation curve and trace the curve in real space. It is usually infeasible for symbolic method to use this defining system due to the fact that almost twice more auxiliary variables are introduced.

Remark 3. *If only one parameter effectively appears in $F(x, u)$. Then computing the stability boundary boils down to computing zero-dimensional systems defined by Eq. (2) and $\{F, \partial R_2\}$.*

3 Two Examples

In this section, we analyze the bistability of two neurological disorder models in detail by means of the algorithm presented in last section. In particular, the strategies of rescaling and tracing only positive branches are illustrated.

3.1 Alzheimer's Disease Model

In [9], the authors proposed a model for studying Alzheimer's disease. Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by progressive and irreversible cognitive decline. The pathogenesis of AD is only partially understood and there is no cure. The bistability is the property of the coexistence between a stable steady-state characterized by low levels of Ca^{2+} and $A\beta$ (corresponding to a healthy situation) and another stable steady-state where the levels of both compounds are high (corresponding to a pathological situation). The study would like to reveal the fact that appropriate perturbations of various kinetic parameters can lead to a switch from the healthy to the pathological state.

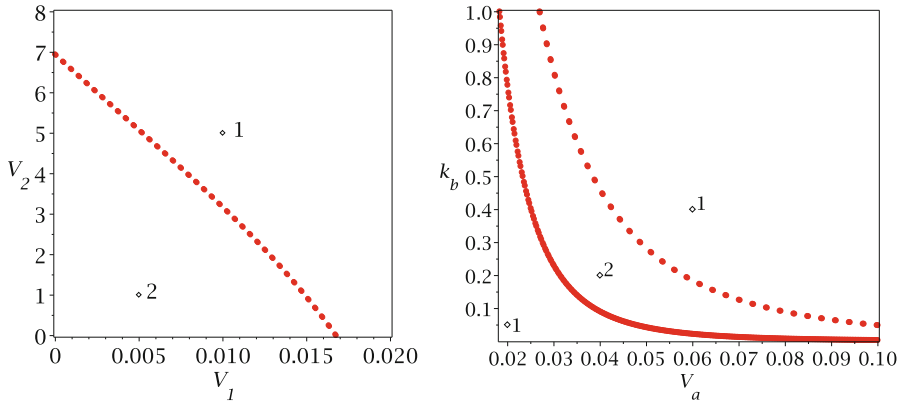
The model is described by the following ODEs:

$$\begin{array}{l} \frac{da}{dt} = V_1 + \frac{V_a\, c^n}{{K_a}^n + c^n} - k_1\, a \\ \frac{dc}{dt} = V_2 + k_b\, a^m - k_2\, c, \end{array} \tag{3}$$

where the suggested values of the parameters in [9] is $V_1 = \frac{13}{2000}$, $V_2 = 4$, $V_a = 1/20$, $K_a = 120$, $k_b = 1/5$, $k_1 = \frac{1}{100}$, $k_2 = 1/10$, $m = 4$, $n = 2$. Let F be the right hand-side of the above ODE. We notice that it is impossible for the above system to have Hopf bifurcation since the trace of the Jacobian matrix $\mathcal{J}_F$ is negative no matter what values the parameters take. Thus to compute the stability boundary, it is enough to compute the fold bifurcation boundary.

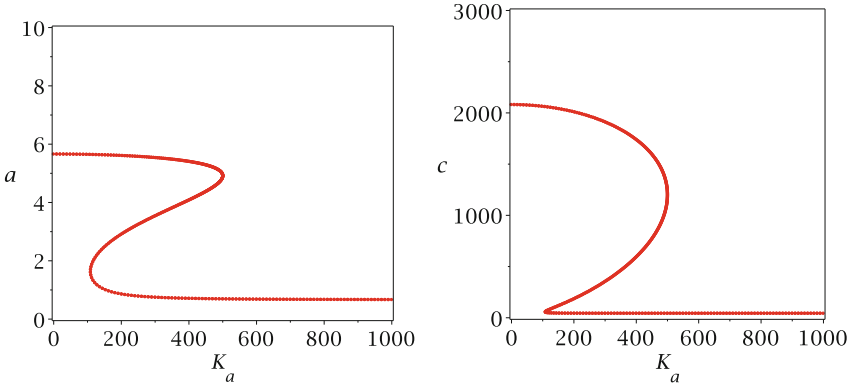
First we free two parameters V_1 and V_2 while the other parameters take the suggested values. Now Eq. (1) defines a one-dimensional fold curve. Before solving Eq. (1), we first randomly set $V_1 = 0.7926710114, V_2 = 0.5581108504$. Solving F, we get one solution $a = 5.778935983, c = 2286.410222$. Since the value of c is pretty high, we rescale $c = 1000c'$. Similarly we rescale $V_1 = V_1'/100$ and $V_2 = 10V_2'$. To take into account the infinity boundary and non-negative boundary, we plot the curve defined by Eq. (1) in the box $(V_1', V_2', a, c') \in [0, 2] \times [0, 2] \times [0, K] \times [0, K]$, where K is a big number, say 10^4. Finally, we rescale the values back and obtain the following fold boundary depicted in left subfigure of Fig. 1, which is also the border curve of F in parameter space (V_1, V_2). The number of (asymptotically) stable equilibria is also displayed. Similarly, we obtain stability boundary in parameter space (V_a, k_b), depicted by the right subfigure of Fig. 1.

Finally, we free one parameter K_a while using default values for other parameters, then Eq. (1) is a zero-dimensional system. After rescaling the variable c as before, we solve Eq. (1) by homotopy continuation method restricted to the box $[0, \infty] \times [0, 10000]^2$, we get two boundary points $K_a = 109.6069757, 501.1488977$ and the system is bistable if K_a is between them, which corrects the value $K_a \in (105, 520)$ given in [9]. Indeed, there is only one (non-negative) equilibrium in $(105, 109.6069757)$ or $(501.1488977, 520)$. Bifurcation diagrams depending on K_a is illustrated in Fig. 2.



Stability boundary in (V_1, V_2). Stability boundary in (V_a, k_b).

Fig. 1. Stability analysis of system (3).



Bifurcation diagram in (K_a, a). Bifurcation diagram in (K_a, c).

Fig. 2. Bifurcation diagrams of system 3.

3.2 The Protein Kinase $M\zeta$ Network

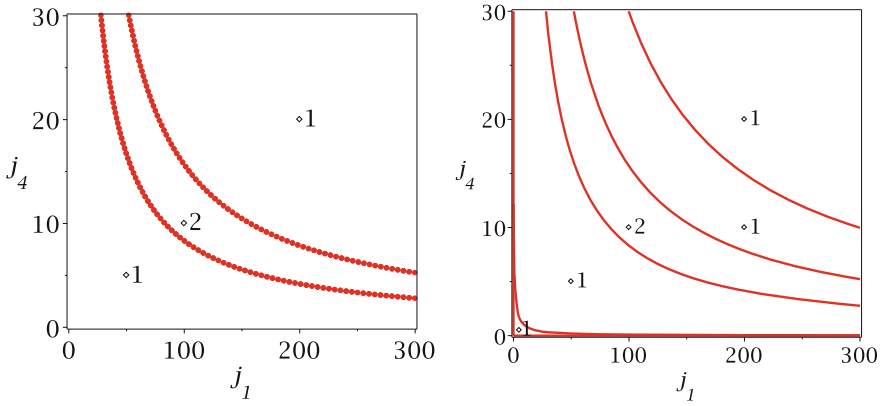
In [20], the author proposed a model for the protein kinase $M\zeta$ network. Protein kinase $M\zeta$ has drawn increasing attention as a molecule maintaining neuronal memory for an extremely long period of time. It can enhance excitatory postsynaptic currents and lead to the long-term potention of synapses. It is crucial for various modalities of learning, including spatial memory and fear conditioning. Bistable positive feedback loops of enzymatic reactions may provide a basis for cellular memory [9,20].

The model is described by the following ODEs:

$$\begin{array}{l} \frac{dP}{dt} = \frac{j_1\, R(1-P)-P}{T_1} \\ \frac{dF}{dt} = \frac{(Pj_3+j_2)(1-F)-F}{T_2} \\ \frac{dR}{dt} = \frac{j_4\, F(P+s)(1-R)-R}{T_3}, \end{array} \tag{4}$$

where the default values of the parameters are: $T_1 = 1500, T_2 = 0.5, T_3 = 60, j_1 = 80, j_2 = 0.05, j3 = 0.5, j4 = 0.16, s = 0.003$.

First we free two parameters j_2 and j_3 while the other parameters take the suggested values. Now Eq. (2) defines a one-dimensional fold curve. First we rescale $j_1 = 100j_1'$ and $j_4 = j_4/10$. Since solving the right hand of Eq. (4) at random parameter values does not reveal equilibria with large coordinates, it is unnecessary to rescale the variables. To take into account the infinity boundary and non-negative boundary, we plot the curve defined by Eq. (2) in the box $(j_1', j_4, P, F, R) \in [0, 3] \times [0, 3] \times [0, K]^3$, where where K is a big number, say 10^4. Finally, we rescale the values back and obtain the following stability boundary depicted in left subfigure of Fig. 3. The number of (asymptotically) stable equilibria is also displayed. The right subfigure plots the stability boundary obtained by a symbolic approach by computing the discriminant variety [17] of the parametric system $\{F = 0, \Delta_{m-1}(F) \neq 0\}$, where the two redundant boundaries are projections of equilibria with negative coordinates. Similarly, we obtain stability boundary in parameter space (j_2, j_3), which is exactly the same as Fig. 4C in [20].



True (biological) stability boundary in (j_1, j_4). Stability boundary got by symbolic solver.

Fig. 3. Stability analysis of system 3.

Finally, we free one parameter s while using default values for other parameters, then Eq. (2) is a zero-dimensional system. After rescaling the variable c as before, we solve Eq. (2) by homotopy continuation method restricted to the

box $[0, \infty] \times [0, 10000]^2$, we get one bifurcation point $s = 0.00984547072$ and the system is bistable if $s \in (0, 0.00984547072)$. Note that a direct use of symbolic approaches [17,29] by solving the parametric system $\{F = 0, \Delta_{m-1}(F) \neq 0\}$ returns four points $0.009845470722, 0.4396431008, 2.100000000, 2.197170170$, while that last three does not have biological meanings as they are projections of equilibria with negative coordinates. A bifurcation diagram depending on s is illustrated in Fig. 4. It is interesting to see that initially the system is bistable for $s < 0.00984547072$, where a stable equilibrium with high concentrations coexists with another stable one with low concentrations. As the stimulation s increases, the system finally turns monotone and only one equilibrium with high concentrations is left and its concentration will never turn low even one reduces the value of s. This phenomenon is called irreversibility and the system behaves like maintaining memory.

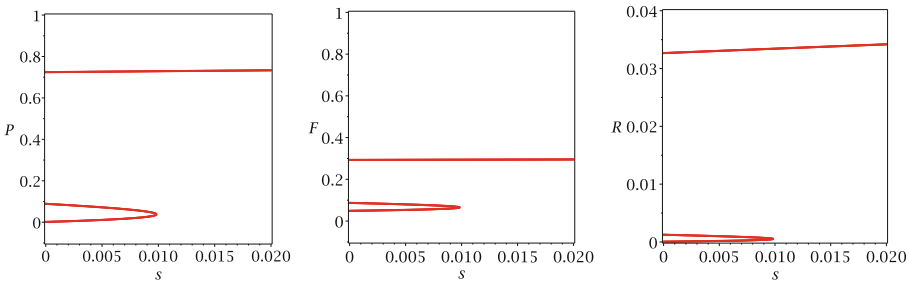


Fig. 4. Bifurcation diagrams of system 4.

4 Conclusion

In this paper, we presented a geometrical method for computing the stability boundary of biological systems, which may produce less redundant boundaries than symbolic methods. Its effectiveness was illustrated by revealing the bistability property of two neurological disorder models, which could be useful for a better understanding of molecular mechanisms of Alzheimer's disease and neuronal memory.

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