

Special Algorithm for Stability Analysis of Multistable Biological Regulatory Systems*

Hoon Hong

Department of Mathematics, North Carolina State University, Raleigh NC 27695, USA

Xiaoxian Tang[†] Bican Xia

LMAM & School of Mathematical Sciences, Peking University, Beijing 100871, China

Abstract

We consider the problem of counting (stable) equilibria of an important family of algebraic differential equations modeling multistable biological regulatory systems. The problem can be solved, in principle, using real quantifier elimination algorithms, in particular real root classification algorithms. However, it is well known that they can handle only very small cases due to the enormous computing time requirements. In this paper, we present a special algorithm which is much more efficient than the general methods. Its efficiency comes from the exploitation of certain interesting structures of the family of differential equations.

Key words: quantifier elimination, root classification, biological regulation system, stability

1 Introduction

Modeling biological networks mathematically as dynamical systems and analyzing the local and global behaviors of such systems is an important method of computational biology. The most concerned behaviors of such biological systems are equilibrium, stability, bifurcations, chaos and so on.

Consider the stability analysis of biological networks modeled by autonomous systems of differential equations of the form $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{u}, \mathbf{x})$ where $\mathbf{x} = (x_1, \dots, x_n)$,

$$\mathbf{f}(\mathbf{u}, \mathbf{x}) = (f_1(\mathbf{u}, x_1, \dots, x_n), \dots, f_n(\mathbf{u}, x_1, \dots, x_n))$$

and each $f_k(\mathbf{u}, x_1, \dots, x_n)$ is a rational function in x_1, \dots, x_n with real coefficients and real parameter(s) \mathbf{u} . We would like to compute a partition of the parametric space of \mathbf{u} such that, inside every open cell of the partition, the number of (stable) equilibria of the system is uniform. Furthermore, for each open cell, we would like to determine the number of (stable) equilibria.

Such a problem can be easily formulated as a real quantifier elimination problem. It is well known that the real quantifier elimination problem can be carried out algorithmically. [61, 18, 3, 46, 47, 48, 31, 33, 34, 20, 50, 51, 52, 7, 8, 9, 11, 12, 26, 16, 57, 58, 14, 42, 10, 15]. There are several software systems such as QEPcad [20, 35, 11, 13], Redlog [28], Reduce (in Mathematica) [55, 56] and SyNRAC [1]. Hence, in principle, the stability analysis of regulation system the above system can be carried out automatically using those software systems. However, it is also

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[†]Corresponding author

well known that the complexity [25, 7] of those algorithms are way beyond current computing capabilities since those algorithms are for general quantifier elimination problems.

The stability analysis is a special type of quantifier elimination problem, in particular, real root classification. Hence, it would be advisable to use real root classification algorithms [69, 70]. In fact, [62, 63], [65] and [66] tackled the stability analysis problem using DISCOVERER [67]¹. They were able to tackle a specialized simultaneous decision problem ($n = 6$ and $c = 2$) [22] in 55,000 secs [66]. However, the real root classification software could not go beyond these, due to enormous computing time/memory requirements.

In this paper, we consider the problem of counting (stable) equilibriums of an important family of algebraic differential equations modeling multistable biological regulation systems, called MSRS (see Definition 1). In fact, the family is a straightforward generalization of several interesting classes of systems in the literature [22, 23, 24]. The family of differential equations has the form $\dot{\mathbf{x}} = \mathbf{f}(\sigma, \mathbf{x})$ where \mathbf{f} is a real function determined by certain real functions $l(z)$, $g(z)$, $h(z)$ and $P(\mathbf{x})$ and parameterized by a real parameter σ .

We present a special algorithm which is much more efficient than the general root classification algorithm. The efficiency of the special algorithm comes from the exploitation of certain interesting structures of the differential equation under investigation such as

- (1) the eigenvalues of the Jacobian at every equilibrium are all real, see Theorem 1;
- (2) every equilibrium of the system is made up of at most two components, see Theorem 2;
- (3) the eigenvalues of the Jacobian at every equilibrium have certain structures (see Theorems 3 and 4), aiding the determination of stability of an equilibrium (see Corollary 1).

The special algorithm can handle much larger system than the general root classification algorithm. For example, it can handle a specialized simultaneous decision problem ($n = 11$ and $c = 8$) in several seconds.

We remark that our work can be viewed as following the numerous efforts in applying quantifier elimination to tackle problems from various other disciplines [44, 45, 30, 29, 43, 64, 39, 40, 71, 2, 62, 63, 17, 32, 65, 68, 54, 59, 66, 53].

The paper is organized as follows. Section 2 provides a precise statement of the problem. Section 3 reviews a general algorithm based on real root classification. Section 4 proves several interesting structures of the problem. Section 5 gives a special algorithm that exploits the structure proved in Section 4. Section 6 presents the experimental timings and compares them to those of a general algorithm.

2 Problem

In this section, we give a precise and self-contained description of the problem. First we introduce a family of differential equations that we will be considering.

Definition 1 (MultiStable Regulatory System). *A system of ordinary differential equations*

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(\sigma, x_1, \dots, x_n) \\ &\vdots \\ \frac{dx_n}{dt} &= f_n(\sigma, x_1, \dots, x_n) \end{aligned}$$

is called a multistable regulatory system (MSRS) if f_k has the following form

$$f_k(\sigma, x_1, \dots, x_n) = -l(x_k) + \sigma \frac{g(x_k)}{P(x_1, \dots, x_n) + h(x_k)}$$

where

¹DISCOVERER was integrated later in the RegularChains package in Maple. Since then, there are several improvements on the package from both mathematical and programming aspects [21]. One can see the command RegularChains[ParametricSystemTools][RealRootClassification] in any version of Maple that is newer than Maple 13.

1. σ is a positive parameter;
2. The function P is symmetric, that is,

$$P(x_1, \dots, x_i, \dots, x_j, \dots, x_n) = P(x_1, \dots, x_j, \dots, x_i, \dots, x_n)$$

for every i, j ;

3. $\forall k \forall (x_1, \dots, x_n) \in \mathbb{R}_{>0}^n \quad P(x_1, \dots, x_n) + h(x_k) > 0$;
4. $l(z) \neq 0$ and for every $\sigma \in \mathbb{R}_{>0}$, the function

$$\sigma \frac{g(z)}{l(z)} - h(z)$$

has at most one extreme point on the intended domain of z .

Example 1. We present several examples of MSRS from cellular differentiation [22, 23, 24]. In fact, the above definition of MSRS is a straightforward generalization of those differential equations.

1. Simultaneous decision [22].

$$\frac{dx_k}{dt} = -x_k + \sigma \frac{1}{1 + \sum_{m=1}^n x_m^c - x_k^c}$$

where the quantities $x_1, \dots, x_n \in \mathbb{R}_{>0}$ denote the concentrations of n proteins, $c \in \mathbb{R}_{>0}$ the cooperativity, and $\sigma \in \mathbb{R}_{>0}$ the strength of unrepressed protein expression, relative to the exponential decay. It is easy to verify that it is a MSRS with

$$l(z) = z, \quad g(z) = 1, \quad h(z) = -z^c,$$

$$P(x_1, \dots, x_n) = 1 + \sum_{m=1}^n x_m^c.$$

The first graph in Figure 1 shows the graph of $\sigma \frac{g(z)}{l(z)} - h(z)$ for $c = 4$ and $\sigma = 1$.

2. Mutual inhibition with autocatalysis [23].

$$\frac{dx_k}{dt} = -x_k + \alpha + \sigma \frac{x_k^c}{1 + \sum_{m=1}^n x_m^c}$$

where the quantities $x_1, \dots, x_n \in \mathbb{R}_{>0}$ denote the concentrations of n proteins, $c \in \mathbb{R}_{>0}$ the cooperativity, $\sigma \in \mathbb{R}_{>0}$ the relative speed for transcription/translation, and $\alpha \in \mathbb{R}_{\geq 0}$ the leak expression. It is easy to verify that it is a MSRS with

$$l(z) = z - \alpha, \quad g(z) = z^c, \quad h(z) = 0,$$

$$P(x_1, \dots, x_n) = 1 + \sum_{m=1}^n x_m^c.$$

The second graph in Figure 1 shows the graph of $\sigma \frac{g(z)}{l(z)} - h(z)$ for $\alpha = 1$, $c = 2$ and $\sigma = 1$.

3. bHLH dimerisation [23, 24].

$$\frac{dx_k}{dt} = -x_k + \sigma \frac{x_k^2}{\frac{K_2}{a_t^2} (1 + \sum_{m=1}^n x_m)^2 + x_k^2}$$

where the quantities $x_1, \dots, x_n \in \mathbb{R}_{>0}$ denote the concentrations of n proteins, $\sigma \in \mathbb{R}_{>0}$ the relative speed for transcription/translation, $K_2 \in \mathbb{R}_{>0}$ the binding constant, and $a_t \in \mathbb{R}_{>0}$ the total quantity of activator. It is easy to verify that it is a MSRS with

$$l(z) = z, \quad g(z) = z^2, \quad h(z) = z^2,$$

$$P(x_1, \dots, x_n) = \frac{K_2}{a_t^2} (1 + \sum_{m=1}^n x_m)^2.$$

The third graph in Figure 1 shows the graph of $\sigma \frac{g(z)}{l(z)} - h(z)$ for $\sigma = 1$.

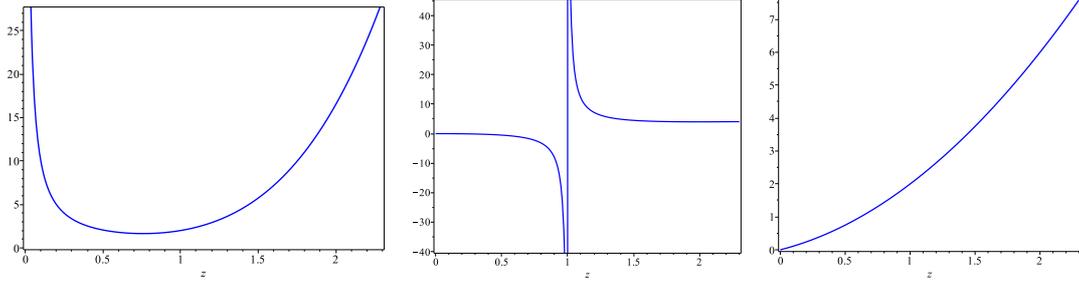


Figure 1: Graphs of $\sigma \frac{g(z)}{l(z)} - h(z)$ for the models in Example 1

Definition 2 (Equilibrium). For given σ , an $\mathbf{r} \in \mathbb{R}_{>0}^n$ is called an equilibrium if

$$f_1(\mathbf{r}) = \dots = f_n(\mathbf{r}) = 0.$$

Notation 1 (Jacobian). The Jacobian of \mathbf{f} is denoted by

$$J_{\mathbf{f}} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \dots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \dots & \frac{\partial f_n}{\partial x_n} \end{bmatrix}.$$

Definition 3 (Stable). An equilibrium \mathbf{r} is called stable (more precisely, locally asymptotically stable) if all eigenvalues of $J_{\mathbf{f}}(\mathbf{r})$ have strictly negative real parts.

We are ready to state the problem that will be tackled in this paper. Informally, the problem is as follows. For given polynomials l, g, h and P , we have a family of MSRS parameterized by σ . We would like to find a partition of σ values into several intervals so that for all σ in each interval the number of (stable) equilibria is uniform. Furthermore, for each interval, we would like to determine the number of (stable) equilibria. Now let us state the problem precisely.

Problem. Devise an algorithm with the following specification.

Input: $\mathbf{f} = (f_1, \dots, f_n) \in (\mathbb{Q}(\sigma, \mathbf{x}))^n$ such that $\dot{\mathbf{x}} = \mathbf{f}$ is a MSRS

Output:

$B \in \mathbb{Z}[\sigma]$,

$I_1, \dots, I_{w-1} \in \mathbb{I}\mathbb{Q}_{>0}$ (that is, closed intervals with positive rational endpoints) and

$(e_1, s_1), \dots, (e_w, s_w) \in \mathbb{Z}_{\geq 0}^2$

such that

$$\forall j \in \{1, \dots, w-1\}, B \text{ has one and only one real root, say } \sigma_j, \text{ in } I_j,$$

$$\sigma_1 < \dots < \sigma_{w-1}, \text{ and}$$

$$\forall j \in \{1, \dots, w\} \quad \forall v \in (\sigma_{j-1}, \sigma_j) \quad E_v = e_j \wedge S_v = s_j$$

where

$$\sigma_0 = 0, \sigma_w = \infty,$$

$$E_v (S_v) \text{ denotes the number of (stable) equilibria of } \dot{\mathbf{x}} = \mathbf{f}(v, \mathbf{x})$$

Example 2. We illustrate the above input and output specification by an example, which is a specific simultaneous decision model ($n = 4$ and $c = 4$) as shown in Example 1.

Input: f_1, f_2, f_3, f_4

where $f_k = -x_k + \frac{\sigma}{1+x_1^4+x_2^4+x_3^4+x_4^4-x_k^4}$, $k = 1, \dots, 4$

Output:

$$B = (42755090541778564453125\sigma^{24} + \dots - 140737488355328)(\sigma - 4)^2,$$

$$I_1 = [\frac{5}{4}, \frac{21}{16}], \quad I_2 = [4, 4],$$

$$(e_1, s_1) = (1, 1), \quad (e_2, s_2) = (9, 5), \quad (e_3, s_3) = (15, 4)$$

By Definition 1, the input system is

$$\frac{dx_k}{dt} = -x_k + \frac{\sigma}{1 + x_1^4 + x_2^4 + x_3^4 + x_4^4 - x_k^4}.$$

The meaning of the output is as follows. Let $\sigma_1 (\approx 1.303331342)$ be the unique positive root of $B(\sigma) = 0$ in I_1 and $\sigma_2 (= 4)$ be the unique positive root of $B(\sigma) = 0$ in I_2 . Then the system has the following properties:

- (1) if $0 < \sigma < \sigma_1$, then the system has exactly 1 equilibrium and the equilibrium is stable;
- (2) if $\sigma_1 < \sigma < \sigma_2$, then the system has exactly 9 distinct equilibriums, 5 of which are stable;
- (3) if $\sigma_2 < \sigma < \infty$, then the system has exactly 15 distinct equilibriums, 4 of which are stable.

3 Review of General Algorithm

In this section, we briefly review a general algorithm [62, 63, 65, 66] for stability analysis based on real root classification. As stated in Section 1, the general algorithm works for systems with rational functions and thus can be applied to solve the Problem posted in last section for MSRS if all the involved functions, *i.e.*, l, g, h, P , are polynomials.

Suppose we are given a system $\dot{\mathbf{x}} = \mathbf{f}(\sigma, \mathbf{x})$ where

$$\mathbf{f}(\sigma, \mathbf{x}) = (f_1(\sigma, x_1, \dots, x_n), \dots, f_n(\sigma, x_1, \dots, x_n))$$

and each $f_k(\sigma, x_1, \dots, x_n)$ is a rational function. A sketch description of the general algorithm may be as follows.

1. Equate the numerators of all $f_k(\sigma, x_1, \dots, x_n)$ to 0, yielding a system of polynomial equations. To simplify the notations, we still use $\{f_1 = 0, \dots, f_n = 0\}$ to denote the equations. Note that there may be some constraints on the system. For example, the denominators of all f_k should be nonzero, σ and some variables should be positive, and so on. Therefore, we actually obtain a semi-algebraic system. Let us denote it by \mathcal{S} .
2. Compute the Hurwitz determinants $\Delta_1, \dots, \Delta_n$ of the Jacobian matrix $J_{\mathbf{f}}(\sigma, \mathbf{x})$. Let $\det(\lambda I - J_{\mathbf{f}}(\sigma, \mathbf{x})) = b_n \lambda^n + b_{n-1} \lambda^{n-1} + \dots + b_0$ ($b_n > 0$), then $\Delta_1, \dots, \Delta_n$ are defined as the leading principal minors of

$$\begin{bmatrix} b_{n-1} & b_{n-3} & b_{n-5} & \dots & b_{n-(2n-1)} \\ b_n & b_{n-2} & b_{n-4} & \dots & b_{n-(2n-2)} \\ 0 & b_{n-1} & b_{n-3} & \dots & b_{n-(2n-3)} \\ 0 & b_n & b_{n-2} & \dots & b_{n-(2n-4)} \\ 0 & 0 & b_{n-1} & \dots & b_{n-(2n-5)} \\ \vdots & \vdots & \vdots & \vdots & \vdots \end{bmatrix}_{n \times n}.$$

By the Routh-Hurwitz Criterion, an equilibrium \mathbf{r} is stable if and only if

$$\Delta_1(\mathbf{r}) > 0 \wedge \dots \wedge \Delta_n(\mathbf{r}) > 0.$$

Therefore, add the constraints $\Delta_1 > 0, \dots, \Delta_n > 0$ to \mathcal{S} and obtain a new system \mathcal{T} .

3. Compute the so-called *border polynomial* $B(\sigma)$ of the system \mathcal{T} . Simply speaking, $B(\sigma)$ is a polynomial in σ satisfying

$$\left[\exists \mathbf{x} \left(\mathbf{f}(\sigma, \mathbf{x}) = 0 \wedge \det(J_{\mathbf{f}}(\sigma, \mathbf{x})) \cdot \prod_{k=1}^n \Delta_k(\sigma, \mathbf{x}) = 0 \right) \right] \implies B(\sigma) = 0.$$

For more details on border polynomials, please refer to [69, 62].

4. Because there is only a single parameter σ , we can take a rational sample point v_j in the open interval (σ_j, σ_{j+1}) for all j ($0 \leq j \leq w-1$) by isolating the distinct positive roots $\sigma_1, \dots, \sigma_{w-1}$ of $B(\sigma) = 0$, where $\sigma_0 = 0$ and $\sigma_w = +\infty$.
5. For each sample point v_j , substitute v_j for σ in \mathcal{S} and \mathcal{T} , respectively, yielding two new constant systems $\mathcal{S}(v_j)$ and $\mathcal{T}(v_j)$. By real solution counting (or isolating) of $\mathcal{S}(v_j)$ and $\mathcal{T}(v_j)$, respectively, we obtain the number of equilibriums and the number of stable equilibriums of the original system at v_j , respectively. By the property of $B(\sigma)$, the number of (stable) equilibriums of the original system at v_j equals the number of (stable) equilibriums of the original system at any $\sigma \in (\sigma_j, \sigma_{j+1})$.

In general, the Hurwitz determinants may be huge and thus computing them is very time-consuming. Furthermore, huge Hurwitz determinants may cause it infeasible in practice to compute the border polynomial of system \mathcal{T} .

4 Structure

In this section, we describe certain special structures of the multi-stable regulatory system that we will exploit in order to develop an efficient special algorithm. Before we plunge into the details, we first provide an overview of the special structures:

- (1) the eigenvalues of the Jacobian at every equilibrium are all real, see Theorem 1;
- (2) every equilibrium of the system is made up of at most two components, see Theorem 2;
- (3) the eigenvalues of the Jacobian at every equilibrium have certain nice structures, simplifying the stability analysis, see Theorems 3 and 4 and Corollary 1.

Now, we plunge into the technical details. In the discussion below, when we say “(stable) equilibrium”, we mean (stable) equilibrium of a MSRS $\dot{\mathbf{x}} = \mathbf{f}(\sigma, \mathbf{x})$. We will use the following notations throughout this section:

$$a(\sigma, z) = \sigma \frac{g(z)}{l(z)} - h(z),$$

$$D_k(\mathbf{x}) = -\frac{P(\mathbf{x}) + h(x_k)}{l(x_k)}.$$

It is easy to see that

$$f_k(\mathbf{x}) = \frac{P(\mathbf{x}) - a(\sigma, x_k)}{D_k(\mathbf{x})}.$$

Theorem 1 (Real eigenvalues). *If \mathbf{r} is an equilibrium, then every eigenvalue of $J_{\mathbf{f}}(\mathbf{r})$ is real.*

Proof. Let \mathbf{r} be an equilibrium and $A = J_{\mathbf{f}}(\mathbf{r})$. For every k , let

$$N_k(\mathbf{x}) = P(\mathbf{x}) - a(\sigma, x_k).$$

Then for any i, j ,

$$A_{i,j} = \begin{cases} \frac{\partial f_i}{\partial x_i}(\mathbf{r}) & i = j \\ \frac{\frac{\partial N_i}{\partial x_j}(\mathbf{r}) D_i(\mathbf{r}) - N_i(\mathbf{r}) \frac{\partial D_i}{\partial x_j}(\mathbf{r})}{D_i(\mathbf{r})^2} & i \neq j \end{cases}.$$

Since \mathbf{r} is an equilibrium, we have $N_i(\mathbf{r}) = 0$ for any i . Hence,

$$A_{i,j} = \begin{cases} \frac{\partial f_i}{\partial x_i}(\mathbf{r}) & i = j \\ \frac{\partial N_i}{\partial x_j}(\mathbf{r}) \\ D_i(\mathbf{r}) & i \neq j \end{cases} = \begin{cases} \frac{\partial f_i}{\partial x_i}(\mathbf{r}) & i = j \\ \frac{\partial P}{\partial x_j}(\mathbf{r}) \\ D_i(\mathbf{r}) & i \neq j \end{cases}.$$

Let E be the $n \times n$ diagonal matrix such that

$$E_{i,i} = \frac{\frac{\partial P}{\partial x_i}(\mathbf{r})}{\prod_{k \neq i} D_k(\mathbf{r})}.$$

Let $C = EA$. Then for any i, j such that $i \neq j$, we have

$$C_{i,j} = E_{i,i} A_{i,j} = \frac{\frac{\partial P}{\partial x_i}(\mathbf{r})}{\prod_{k \neq i} D_k(\mathbf{r})} \cdot \frac{\frac{\partial P}{\partial x_j}(\mathbf{r})}{D_i(\mathbf{r})} = \frac{\frac{\partial P}{\partial x_i}(\mathbf{r}) \frac{\partial P}{\partial x_j}(\mathbf{r})}{\prod_{k=1}^n D_k(\mathbf{r})},$$

$$C_{j,i} = E_{j,j} A_{j,i} = \frac{\frac{\partial P}{\partial x_j}(\mathbf{r})}{\prod_{k \neq j} D_k(\mathbf{r})} \cdot \frac{\frac{\partial P}{\partial x_i}(\mathbf{r})}{D_j(\mathbf{r})} = \frac{\frac{\partial P}{\partial x_j}(\mathbf{r}) \frac{\partial P}{\partial x_i}(\mathbf{r})}{\prod_{k=1}^n D_k(\mathbf{r})}.$$

Thus $C_{i,j} = C_{j,i}$. Hence C is a real symmetric matrix.

Let λ be an eigenvalue of A and α a corresponding eigenvector, namely $A\alpha = \lambda\alpha$. Then $C\alpha = EA\alpha = \lambda E\alpha$. By taking conjugate transpose, we have

$$\alpha^* C^* = \lambda^* \alpha^* E^*.$$

Since both E and C are real symmetric, we have $\overline{\alpha^* C} = \lambda^* \alpha^* E$. Therefore, $\alpha^* C \alpha = \lambda^* \alpha^* E \alpha$ and hence

$$\lambda \alpha^* E \alpha = \lambda^* \alpha^* E \alpha.$$

Since $\alpha^* E \alpha$ is non-zero, we have $\lambda = \lambda^*$. In other words, λ is real. \square

Theorem 2 (Structure of equilibrium). *Let $\mathbf{r} = (r_1, \dots, r_n)$ be an equilibrium. The components of \mathbf{r} consist of at most two different numbers.*

Proof. For every k , we have

$$f_k(\mathbf{r}) = \frac{P(\mathbf{r}) - a(\sigma, r_k)}{D_k(\mathbf{r})} = 0.$$

Thus

$$a(\sigma, r_1) = \dots = a(\sigma, r_n) = P(\mathbf{r}).$$

Note that, for every σ , the function $a(\sigma, z)$ has at most one extreme point for z over $\mathbb{R}_{>0}$ by Definition 1. Thus for every real number ϱ , the equation $a(\sigma, z) = \varrho$ has at most two different positive solutions in z . Hence r_1, \dots, r_n consist of at most two different positive numbers. \square

From now on, we will say that an equilibrium \mathbf{r} is *diagonal* if $r_1 = \dots = r_n$.

Theorem 3 (Characteristic polynomial for diagonal equilibrium). *Let \mathbf{r} be a diagonal equilibrium (q, \dots, q) . Then*

$$\det(\lambda I - \mathbf{J}_{\mathbf{f}}(\mathbf{r})) = (\lambda - G_1)^{n-1} (\lambda - G_2).$$

where

$$G_1 = \tau - \xi,$$

$$G_2 = \tau + (n-1)\xi.$$

where again

$$\tau = \frac{\partial f_n}{\partial x_n}(\mathbf{r}), \quad \xi = \frac{\frac{\partial P}{\partial x_{n-1}}(\mathbf{r})}{D_n}(\mathbf{r}).$$

Proof. Note for any i, j ,

$$\begin{aligned} f_i(x_1, \dots, x_i, \dots, x_j, \dots, x_n) &= f_j(x_1, \dots, x_j, \dots, x_i, \dots, x_n), \\ P(x_1, \dots, x_i, \dots, x_j, \dots, x_n) &= P(x_1, \dots, x_j, \dots, x_i, \dots, x_n). \end{aligned}$$

Thus,

$$\begin{aligned} \frac{\partial f_i}{\partial x_i}(x_1, \dots, x_i, \dots, x_j, \dots, x_n) &= \frac{\partial f_j}{\partial x_j}(x_1, \dots, x_j, \dots, x_i, \dots, x_n), \\ \frac{\partial P}{\partial x_i}(x_1, \dots, x_i, \dots, x_j, \dots, x_n) &= \frac{\partial P}{\partial x_j}(x_1, \dots, x_j, \dots, x_i, \dots, x_n). \end{aligned}$$

Hence,

$$\begin{aligned} \frac{\partial f_i}{\partial x_i}(\mathbf{r}) &= \frac{\partial f_i}{\partial x_i}(q, \dots, q) = \frac{\partial f_j}{\partial x_j}(q, \dots, q) = \frac{\partial f_j}{\partial x_j}(\mathbf{r}), \\ \frac{\partial P}{\partial x_i}(\mathbf{r}) &= \frac{\partial P}{\partial x_i}(q, \dots, q) = \frac{\partial P}{\partial x_j}(q, \dots, q) = \frac{\partial P}{\partial x_j}(\mathbf{r}). \end{aligned}$$

Note also for any i, j ,

$$D_i(\mathbf{r}) = D_i(q, \dots, q) = D_j(q, \dots, q) = D_j(\mathbf{r}).$$

Therefore

$$J_{\mathbf{f}}(\mathbf{r}) = \begin{bmatrix} \tau & \xi & \dots & \xi \\ \xi & \tau & \dots & \xi \\ \vdots & \vdots & \ddots & \vdots \\ \xi & \xi & \dots & \tau \end{bmatrix}_{n \times n}.$$

Note

$$J_{\mathbf{f}}(\mathbf{r}) = (\tau - \xi)I + \xi u^T u.$$

where $u = [1 \ \dots \ 1]$. Hence,

$$\begin{aligned} \det(\lambda I - J_{\mathbf{f}}(\mathbf{r})) &= \det(\lambda I - (\tau - \xi)I - \xi u^T u) \\ &= \det((\lambda - (\tau - \xi))I - \xi u^T u) \\ &= (\lambda - (\tau - \xi))^n \det\left(I - \frac{\xi}{\lambda - (\tau - \xi)} u^T u\right) \\ &= (\lambda - (\tau - \xi))^n \left(1 - \frac{\xi}{\lambda - (\tau - \xi)} uu^T\right) \text{ (Sylvester's determinant theorem)} \\ &= (\lambda - (\tau - \xi))^n \left(1 - \frac{\xi}{\lambda - (\tau - \xi)} n\right) \\ &= (\lambda - (\tau - \xi))^{n-1} (\lambda - (\tau + (n-1)\xi)) \\ &= (\lambda - G_1)^{n-1} (\lambda - G_2). \end{aligned}$$

□

Theorem 4 (Characteristic polynomial for non-diagonal equilibrium). *Let \mathbf{r} be a non-diagonal equilibrium. Let p and q appear in \mathbf{r} respectively i times and $n - i$ times, where $1 \leq i \leq \lfloor \frac{n}{2} \rfloor$. Then*

$$\det(\lambda I - J_{\mathbf{f}}(\mathbf{r})) = (\lambda - G_1)^{n-i-1} (\lambda - G_2)^{i-1} (\lambda^2 - G_3\lambda + G_4),$$

where

$$G_1 = \tau - \xi,$$

$$G_2 = \beta - \gamma,$$

$$G_3 = \beta + \tau + (i-1)\gamma + (n-i-1)\xi,$$

$$G_4 = (\beta + (i-1)\gamma)(\tau + (n-i-1)\xi) - i(n-i)\mu\nu,$$

where again

$$\beta = \frac{\partial f_1}{\partial x_1}(\mathbf{r}), \quad \tau = \frac{\partial f_n}{\partial x_n}(\mathbf{r}), \quad \gamma = \frac{\partial P}{\partial x_2}(\mathbf{r}), \quad \xi = \frac{\partial P}{\partial x_{n-1}}(\mathbf{r}), \quad \mu = \frac{\partial P}{\partial x_n}(\mathbf{r}), \quad \nu = \frac{\partial P}{\partial x_1}(\mathbf{r}).$$

Proof. Without loss of generality, suppose that $r_1 = \dots = r_i = p$ and $r_{i+1} = \dots = r_n = q$. By symmetry, we have

$$J_{\mathbf{f}}(\mathbf{r}) = \begin{bmatrix} E & S \\ T & F \end{bmatrix}_{n \times n},$$

where

$$E = \begin{bmatrix} \beta & \gamma & \dots & \gamma \\ \gamma & \beta & \dots & \gamma \\ \vdots & \vdots & \ddots & \vdots \\ \gamma & \gamma & \dots & \beta \end{bmatrix}_{i \times i}, \quad F = \begin{bmatrix} \tau & \xi & \dots & \xi \\ \xi & \tau & \dots & \xi \\ \vdots & \vdots & \ddots & \vdots \\ \xi & \xi & \dots & \tau \end{bmatrix}_{(n-i) \times (n-i)},$$

$$S = \mu \begin{bmatrix} 1 & 1 & \dots & 1 \\ 1 & 1 & \dots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \dots & 1 \end{bmatrix}_{i \times (n-i)}, \quad T = \nu \begin{bmatrix} 1 & 1 & \dots & 1 \\ 1 & 1 & \dots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \dots & 1 \end{bmatrix}_{(n-i) \times i}.$$

From Laplace's Theorem, we have

$$\det(\lambda I - J_{\mathbf{f}}(\mathbf{r})) = (-1)^{2(1+2+\dots+i)} \det(\lambda I - E) \det(\lambda I - F) + \sum_{k=1}^i \sum_{\omega=1}^{n-i} M_{k,\omega} A_{k,\omega},$$

where $M_{k,\omega}$ is the minor of $\lambda I - J_{\mathbf{f}}(\mathbf{r})$ consisting of the first i rows and the columns indexed by

$$1, 2, \dots, k-1, k+1, \dots, i, i+\omega$$

and $A_{k,\omega}$ is the cofactor of $M_{k,\omega}$. By the same reasoning as that in the proof of Theorem 3, we have

$$\det(\lambda I - E) = (\lambda - (\beta + (i-1)\gamma))(\lambda - G_2)^{i-1}$$

and

$$\det(\lambda I - F) = (\lambda - (\tau + (n-i-1)\xi))(\lambda - G_1)^{n-i-1}.$$

It is not difficult to check that

$$M_{k,\omega} = (-1)^{i-k+1} \mu (\lambda - G_2)^{i-1},$$

$$A_{k,\omega} = (-1)^{2(1+2+\dots+i)-k+2\omega+i} \nu (\lambda - G_1)^{n-i-1}.$$

Hence

$$\det(\lambda I - J_{\mathbf{f}}(\mathbf{r})) = (\lambda - G_1)^{n-i-1} (\lambda - G_2)^{i-1} (\lambda^2 - G_3\lambda + G_4).$$

□

Corollary 1 (Stability of equilibrium). *Let \mathbf{r} be an equilibrium. Then*

(1) *Case: \mathbf{r} is diagonal (q, \dots, q) . Then \mathbf{r} is stable if and only if*

$$G_1 < 0 \wedge G_2 < 0,$$

where G_1 and G_2 are defined as in Theorem 3.

(2) *Case: \mathbf{r} is non-diagonal such that p appears once and q appears $n-1$ times. Then*

(2a) *if $n=2$, then \mathbf{r} is stable if and only if*

$$G_3 < 0 \wedge G_4 > 0;$$

(2b) if $n > 2$, then \mathbf{r} is stable if and only if

$$G_1 < 0 \wedge G_3 < 0 \wedge G_4 > 0,$$

where G_1, G_3, G_4 are defined as in Theorem 4.

(3) Case: \mathbf{r} is non-diagonal such that p appears i times and q appears $n - i$ times where $2 \leq i \leq \lfloor \frac{n}{2} \rfloor$. Then \mathbf{r} is stable if and only if

$$G_1 < 0 \wedge G_2 < 0 \wedge G_3 < 0 \wedge G_4 > 0,$$

where G_1, G_2, G_3, G_4 are defined as in Theorem 4.

Proof.

(1) Case: \mathbf{r} is diagonal (q, \dots, q) . From Theorem 3, the eigenvalues of $J_{\mathbf{f}}(\mathbf{r})$ are

$$\begin{aligned} \lambda_1 &= \dots = \lambda_{n-1} = G_1, \\ \lambda_n &= G_2. \end{aligned}$$

From Definition 3, the conclusion follows immediately.

(2) Case: \mathbf{r} is non-diagonal such that p appears once and q appears $n - 1$ times.

(2a) If $n = 2$, from Theorem 4, λ_1 and λ_2 , the eigenvalues of $J_{\mathbf{f}}(\mathbf{r})$, are the two solutions of $\lambda^2 - G_3\lambda + G_4 = 0$. Note

$$\begin{aligned} \lambda_1 + \lambda_2 &= G_3, \\ \lambda_1\lambda_2 &= G_4. \end{aligned}$$

By Theorem 1, both λ_1 and λ_2 are real. Hence, $\lambda_1 < 0$ and $\lambda_2 < 0$ if and only if $\lambda_1 + \lambda_2 < 0$ and $\lambda_1\lambda_2 > 0$. From Definition 3, the conclusion follows immediately.

(2b) If $n > 2$, from Theorem 4, the eigenvalues of $J_{\mathbf{f}}(\mathbf{r})$ are

$$\lambda_1 = \dots = \lambda_{n-2} = G_1$$

and

$$\lambda_{n-1} \text{ and } \lambda_n \text{ are the two solutions of } \lambda^2 - G_3\lambda + G_4 = 0.$$

Note

$$\begin{aligned} \lambda_{n-1} + \lambda_n &= G_3, \\ \lambda_{n-1}\lambda_n &= G_4. \end{aligned}$$

By Theorem 1, both λ_{n-1} and λ_n are real. Hence, $\lambda_{n-1} < 0$ and $\lambda_n < 0$ if and only if $\lambda_n + \lambda_{n-1} < 0$ and $\lambda_{n-1}\lambda_n > 0$. From Definition 3, the conclusion follows immediately.

(3) Case: \mathbf{r} is non-diagonal such that p appears i times and q appears $n - i$ times where $2 \leq i \leq \lfloor \frac{n}{2} \rfloor$. From Theorem 4, the eigenvalues of $J_{\mathbf{f}}(\mathbf{r})$ are

$$\begin{aligned} \lambda_1 &= \dots = \lambda_{n-i-1} = G_1, \\ \lambda_{n-i} &= \dots = \lambda_{n-2} = G_2 \end{aligned}$$

and

$$\lambda_{n-1} \text{ and } \lambda_n \text{ are the two solutions of } \lambda^2 - G_3\lambda + G_4 = 0.$$

Note

$$\begin{aligned} \lambda_{n-1} + \lambda_n &= G_3, \\ \lambda_{n-1}\lambda_n &= G_4. \end{aligned}$$

By Theorem 1, both λ_{n-1} and λ_n are real. Hence, $\lambda_n < 0$ and $\lambda_{n-1} < 0$ if and only if $\lambda_n + \lambda_{n-1} < 0$ and $\lambda_{n-1}\lambda_n > 0$. From Definition 3, the conclusion follows immediately.

□

5 Special Algorithm

In this section, we present algorithms for the problem posed in Section 2, that exploits several special structures proved in Section 4. The description of the main algorithm is given in Algorithm 1. It is high-level in that it does not specify implemental details. Below we will explain the main ideas underlying the sub-algorithms and the main algorithm.

- **Algorithm 5 (NonDiagonalEquilibrium)**: The correctness of the algorithm follows from the symmetry of $\dot{\mathbf{x}} = \mathbf{f}$ and Theorem 4.
- **Algorithm 4 (DiagonalEquilibrium)**: The correctness of the algorithm follows from the symmetry of $\dot{\mathbf{x}} = \mathbf{f}$ and Theorem 3.
- **Algorithm 3 (EquilibriumCounting)**: Given \mathbf{f} satisfying the conditions in Definition 1, and a real number v , we compute $E_v(S_v)$, the number of (stable) equilibriums of $\dot{\mathbf{x}} = \mathbf{f}(v, \mathbf{x})$. To this purpose, we transform the n -dimensional system $\dot{\mathbf{x}} = \mathbf{f}$ into several 2-dimensional systems by Algorithms 4 and 5, determine the stability easily by Corollary 1 and count the number of (stable) equilibriums by symmetry. See more details below.
 - **Lines 1–3**: We count the number of diagonal equilibriums and determine the stability of the diagonal equilibriums by Corollary 1-(1).
 - **Lines 5–13**: We are preparing to count the number of non-diagonal equilibriums. If $i = 1$ and $n = 2$, we determine the stability of a non-diagonal equilibrium by Corollary 1-(2a). If $i = 1$ and $n > 2$, we determine the stability of a non-diagonal equilibrium by Corollary 1-(2b). If $i \neq 1$, we determine the stability of a non-diagonal equilibrium by Corollary 1-(3).
 - **Lines 14–17**: We compute the number of (stable) equilibriums by combining the results computed by **Lines 5–13** together. In fact, by the symmetry of $\dot{\mathbf{x}} = \mathbf{f}$, for every i ($i = 1, \dots, \lfloor \frac{n}{2} \rfloor$), if the system $\sigma = v \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q$ has \tilde{e}_i positive solutions, then
 - (a) if $i = \frac{n}{2}$, the system $\sigma = v \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q$ is symmetric and thus \tilde{e}_i is even and the system $\dot{\mathbf{x}} = \mathbf{f}$ has $\frac{\tilde{e}_i}{2} \cdot \binom{n}{i}$ non-diagonal equilibriums.
 - (b) if $i \neq \frac{n}{2}$, the system $\dot{\mathbf{x}} = \mathbf{f}$ has $\tilde{e}_i \cdot \binom{n}{i}$ non-diagonal equilibriums.
 Similarly, we count the number of stable equilibriums.
- **Algorithm 2 (CriticalPolynomial)**: Given \mathbf{f} satisfying the conditions in Definition 1, we compute a polynomial $B(\sigma)$ such that every “critical” σ value of the system $\dot{\mathbf{x}} = \mathbf{f}$ is a root of $B(\sigma) = 0$. By the “critical” values, we mean that the number of the (stable) equilibriums of the system changes only when σ passes through those values. Note that the number of the (stable) equilibriums changes only when an eigenvalue of the Jacobian vanishes. In diagonal case, by Algorithm 4, an eigenvalue vanishes if and only if $G_1G_2 = 0$, see **Lines 1–2**. In non-diagonal case, by Algorithm 5, if an eigenvalue vanishes then $G_1G_2G_3G_4 = 0$, see **Lines 4–5**.
- **Algorithm 1 (EquilibriumClassification (Special algorithm for MSRS))**:
 - **Lines 1–3**: By Algorithm 2, we compute $B(\sigma)$ and isolate the real roots of $B(\sigma) = 0$. Note that for all σ in each open interval determined by $B(\sigma) \neq 0$, the number of (stable) equilibriums is uniform. Thus we sample one rational number v_i from each open interval.
 - **Lines 5–14**: In this loop, we compute $e_j(s_j)$, the number of (stable) equilibriums for $\sigma = v_j$ by Algorithm 3. We also collect all root isolation intervals containing the “critical” σ values. Recall that a root of B may not be critical, although B vanishes at every critical σ value. So we check whether a root of $B(\sigma) = 0$ is critical or not by **Lines 7–13**.

Example 3. *We will illustrate the algorithm on Example 2.*

Algorithm 1: EquilibriumClassification (Special algorithm for MSRS)

Input:

$\mathbf{f} = (f_1, \dots, f_n) \in (\mathbb{Q}(\sigma, \mathbf{x}))^n$ such that $\dot{\mathbf{x}} = \mathbf{f}$ is a MSRS

Output:

$B \in \mathbb{Z}[\sigma]$,

$I_1, \dots, I_{w-1} \in \mathbb{I}\mathbb{Q}_{>0}$, (that is, closed intervals with positive rational endpoints) and

$(e_1, s_1), \dots, (e_w, s_w) \in \mathbb{Z}_{\geq 0}^2$

such that

$\forall j \in \{1, \dots, w-1\}$, B has one and only one real root, say σ_j , in I_j ,

$\sigma_1 < \dots < \sigma_{w-1}$, and

$\forall j \in \{1, \dots, w\} \quad \forall v \in (\sigma_{j-1}, \sigma_j) \quad E_v = e_j \wedge S_v = s_j$

where

$\sigma_0 = 0, \sigma_w = \infty$,

$E_v (S_v)$ denotes the number of (stable) equilibriums of $\dot{\mathbf{x}} = \mathbf{f}(v, \mathbf{x})$.

```
1  $B \leftarrow \text{CriticalPolynomial}(\mathbf{f});$ 
2  $I_1, \dots, I_m \leftarrow$  real root isolation of  $B(\sigma) = 0 \wedge \sigma > 0;$ 
3  $v_1, \dots, v_{m+1} \leftarrow$  rational points in each open interval of  $B(\sigma) \neq 0 \wedge \sigma > 0;$ 
4  $Intervals \leftarrow$  empty list,  $Numbers \leftarrow$  empty list;
5 for  $j$  from 1 to  $m+1$  do
6    $(e_j, s_j) \leftarrow \text{EquilibriumCounting}(\mathbf{f}, v_j);$ 
7   if  $j > 1$  then
8     if  $e_j = e_{j-1}$  and  $s_j = s_{j-1}$  then
9        $e \leftarrow$  number of the equilibriums when  $B(\sigma) = 0$  and  $\sigma \in I_j;$ 
10       $s \leftarrow$  number of the stable equilibriums when  $B(\sigma) = 0$  and  $\sigma \in I_j;$ 
11      if  $e = e_j$  and  $s = s_j$  then
12        next;
13       $Intervals \leftarrow$  Append  $I_{j-1}$  to  $Intervals;$ 
14       $Numbers \leftarrow$  Append  $(e_j, s_j)$  to  $Numbers;$ 
15 return  $B, Intervals, Numbers;$ 
```

In **Algorithm 1. Line 1**, we compute $B(\sigma)$ by *Algorithm 2*.

In **Algorithm 2. Line 1**, we call $\text{DiagonalEquilibrium}(f_1, f_2, f_3, f_4)$, where

$$f_k = -x_k + \frac{\sigma}{1 + x_1^4 + x_2^4 + x_3^4 + x_4^4 - x_k^4}, \quad k = 1, \dots, 4,$$

and get

$$\begin{cases} F(\sigma, q) = -q + \frac{\sigma}{1+3q^4} \\ G_1(\sigma, q) = -1 + \frac{4q^4}{1+3q^4} \\ G_2(\sigma, q) = -1 - \frac{12q^4}{1+3q^4}. \end{cases}$$

In **Algorithm 2. Line 2**, we compute the projection of $F = 0 \wedge G_1 G_2 = 0$ on σ axis and obtain $B_0(\sigma) = \sigma - 4$.

In **Algorithm 2. Line 3**, we start loop. Note that $\lfloor \frac{n}{2} \rfloor = 2$, so $i = 1, 2$.

For $i = 1$, in **Algorithm 2. Line 4**, we call

$$\text{NonDiagonalEquilibrium}(f_1, f_2, f_3, f_4, 1)$$

and get

$$\begin{cases} F_1(\sigma, p, q) = -p + \frac{\sigma}{1+3q^4} \\ F_2(\sigma, p, q) = -q + \frac{\sigma}{1+p^4+2q^4} \\ G_1(\sigma, p, q) = -1 + \frac{4q^4}{1+p^4+2q^4} \\ G_2(\sigma, p, q) = -1 + \frac{4q^3 p}{1+3q^4} \\ G_3(\sigma, p, q) = -2 - \frac{8q^4}{1+p^4+2q^4} \\ G_4(\sigma, p, q) = 1 + \frac{8q^4}{1+p^4+2q^4} - \frac{48q^4 p^4}{(1+3q^4)(1+p^4+2q^4)} \end{cases}$$

Then in **Algorithm 2. Line 5**, we compute the projection of $F_1 = 0 \wedge F_2 = 0 \wedge G_1 G_2 G_3 G_4 = 0$ on σ axis and obtain

$$B_1 = (\sigma - 4)(42755090541778564453125\sigma^{24} + \dots - 140737488355328).$$

For $i = 2$, in **Algorithm 2. Line 4**, we call

$$\text{NonDiagonalEquilibrium}(f_1, f_2, f_3, f_4, 2)$$

Algorithm 2: CriticalPolynomial

Input:

$$\mathbf{f} = (f_1, \dots, f_n) \in (\mathbb{Q}(\sigma, \mathbf{x}))^n \text{ such that } \dot{\mathbf{x}} = \mathbf{f} \text{ is a MSRS}$$

Output:

$$B \in \mathbb{Z}[\sigma] \text{ such that if } v \text{ is critical for } \text{MSRS}(l, g, h, p, \sigma), \text{ then } B(v) = 0$$

- 1 $F, G_1, G_2 \leftarrow \text{DiagonalEquilibrium}(\mathbf{f});$
 - 2 Compute B_0 such that $[\exists q(F = 0 \wedge G_1 G_2 = 0)] \Rightarrow B_0(\sigma) = 0;$
 - 3 **for** i **from** 1 **to** $\lfloor \frac{n}{2} \rfloor$ **do**
 - 4 $F_1, F_2, G_1, G_2, G_3, G_4 \leftarrow \text{NonDiagonalEquilibrium}(\mathbf{f}, i);$
 - 5 Compute B_i such that $[\exists p, q(F_1 = 0 \wedge F_2 = 0 \wedge G_1 G_2 G_3 G_4 = 0)] \Rightarrow B_i(\sigma) = 0;$
 - 6 $B \leftarrow \prod_{i=0}^{\lfloor \frac{n}{2} \rfloor} B_i;$
 - 7 **return** $B;$
-

Algorithm 3: EquilibriumCounting

Input:

$\mathbf{f} = (f_1, \dots, f_n) \in (\mathbb{Q}(\sigma, \mathbf{x}))^n$ such that $\dot{\mathbf{x}} = \mathbf{f}$ is a MSRS

v , a positive real number

Output:

(e, s) such that $E_v = e \wedge S_v = s$, where E_v (S_v) denotes the number of (stable) equilibrium of $\dot{\mathbf{x}} = \mathbf{f}(v, \mathbf{x})$.

```
1  $F, G_1, G_2 \leftarrow \text{DiagonalEquilibrium}(\mathbf{f});$ 
2  $e \leftarrow$  number of positive roots of  $\sigma = v \wedge F = 0;$ 
3  $s \leftarrow$  number of positive roots of  $\sigma = v \wedge F = 0 \wedge G_1 < 0 \wedge G_2 < 0;$ 
4 for  $i$  from 1 to  $\lfloor \frac{n}{2} \rfloor$  do
5    $F_1, F_2, G_1, G_2, G_3, G_4 \leftarrow \text{NonDiagonalEquilibrium}(\mathbf{f}, i);$ 
6    $\tilde{e} \leftarrow$  number of positive solutions of  $\sigma = v \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q;$ 
7   if  $i = 1$  then
8     if  $n = 2$  then
9        $\tilde{s} \leftarrow$  number of positive solutions of
10       $\sigma = v \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q \wedge G_3 < 0 \wedge G_4 > 0$ 
11    else
12       $\tilde{s} \leftarrow$  number of positive solutions of
13       $\sigma = v \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q \wedge G_1 < 0 \wedge G_3 < 0 \wedge G_4 > 0;$ 
14    if  $i = \frac{n}{2}$  then
15       $e \leftarrow e + \frac{\tilde{e}}{2} \cdot \binom{n}{i}, s \leftarrow s + \frac{\tilde{s}}{2} \cdot \binom{n}{i};$ 
16    else
17       $e \leftarrow e + \tilde{e} \cdot \binom{n}{i}, s \leftarrow s + \tilde{s} \cdot \binom{n}{i};$ 
18 return  $(e, s);$ 
```

Algorithm 4: DiagonalEquilibrium

Input:

$\mathbf{f} = (f_1, \dots, f_n) \in (\mathbb{Q}(\sigma, \mathbf{x}))^n$ such that $\dot{\mathbf{x}} = \mathbf{f}$ is a MSRS

Output:

$F, G_1, G_2 \in \mathbb{Q}(\sigma, q)$ such that for every $\sigma \in \mathbb{R}_{>0}$,

(1) $\mathbf{r} = (q, \dots, q)$ is an equilibrium if and only if $F = 0$

(2) if $\mathbf{r} = (q, \dots, q)$ is an equilibrium then the eigenvalues of $J_{\mathbf{f}}(\mathbf{r})$ are

$$\lambda_1 = \dots = \lambda_{n-1} = G_1, \lambda_n = G_2$$

```
1 Let  $l, g, h, P$  be the functions such that  $f_k = -l(x_k) + \sigma \frac{g(x_k)}{P(x_1, \dots, x_n) + h(x_k)};$ 
2  $D_n \leftarrow -\frac{P(x_1, \dots, x_n) + h(x_n)}{l(x_n)};$ 
3  $\tau \leftarrow \frac{\partial f_n}{\partial x_n}, \quad \xi \leftarrow \frac{\frac{\partial P}{\partial x_{n-1}}}{D_n}, \quad F \leftarrow f_1;$ 
4  $G_1 \leftarrow \tau - \xi, \quad G_2 \leftarrow \tau + (n-1)\xi;$ 
5 Replace  $x_1, \dots, x_n$  with  $q$  in  $F, G_1, G_2;$ 
6 return  $F, G_1, G_2;$ 
```

Algorithm 5: NonDiagonalEquilibrium

Input:

$\mathbf{f} = (f_1, \dots, f_n) \in (\mathbb{Q}(\sigma, \mathbf{x}))^n$ such that $\dot{\mathbf{x}} = \mathbf{f}$ is a MSRS

i , an positive integer such that $1 \leq i \leq \lfloor \frac{n}{2} \rfloor$

Output:

$F_1, F_2, G_1, G_2, G_3, G_4 \in \mathbb{Q}(\sigma, p, q)$ such that for every $\sigma \in \mathbb{R}_{>0}$,

(1) $\mathbf{r} = (p, \dots, p, q, \dots, q)$ is an equilibrium and p appears i times if and only if $F_1 = 0 \wedge F_2 = 0$

(2) If $\mathbf{r} = (p, \dots, p, q, \dots, q)$ is an equilibrium and p appears i times then the eigenvalues of $J_{\mathbf{f}}(\mathbf{r})$ are as follows.

(a) if $i = 1$, then

$$\lambda_1 = \dots = \lambda_{n-2} = G_1, \lambda_{n-1} + \lambda_n = G_3, \lambda_{n-1}\lambda_n = G_4$$

(b) if $i > 1$, then

$$\lambda_1 = \dots = \lambda_{n-i-1} = G_1, \lambda_{n-i} = \dots = \lambda_{n-2} = G_2, \\ \lambda_{n-1} + \lambda_n = G_3, \lambda_{n-1}\lambda_n = G_4$$

- 1 Let l, g, h, P be the functions such that $f_k = -l(x_k) + \sigma \frac{g(x_k)}{P(x_1, \dots, x_n) + h(x_k)}$;
 - 2 $D_k \leftarrow \frac{P(x_1, \dots, x_n) + h(x_k)}{l(x_k)}$ for $k = 1, n$;
 - 3 $\beta \leftarrow \frac{\partial f_1}{\partial x_1}, \quad \tau \leftarrow \frac{\partial f_n}{\partial x_n}, \quad \gamma \leftarrow \frac{\partial P}{\partial x_2}, \quad \xi \leftarrow \frac{\partial P}{\partial x_{n-1}}, \quad \mu \leftarrow \frac{\partial P}{\partial x_1}, \quad \nu \leftarrow \frac{\partial P}{\partial x_n}$;
 - 4 $F_1 \leftarrow f_1, \quad F_2 \leftarrow f_n, \quad G_1 \leftarrow \tau - \xi, \quad G_2 \leftarrow \beta - \gamma$;
 - 5 $G_3 \leftarrow \beta + \tau + (i-1)\gamma + (n-i-1)\xi$;
 - 6 $G_4 \leftarrow (\beta + (i-1)\gamma)(\tau + (n-i-1)\xi) - i(n-i)\mu\nu$;
 - 7 Replace x_1, \dots, x_i with p and x_{i+1}, \dots, x_n with q in $F_1, F_2, G_1, G_2, G_3, G_4$;
 - 8 **return** $F_1, F_2, G_1, G_2, G_3, G_4$;
-

and get

$$\begin{cases} F_1(\sigma, p, q) = -p + \frac{\sigma}{1+p^4+2q^4} \\ F_2(\sigma, p, q) = -q + \frac{\sigma}{1+2p^4+q^4} \\ G_1(\sigma, p, q) = -1 + \frac{4q^4}{1+2p^4+q^4} \\ G_2(\sigma, p, q) = -1 + \frac{4p^4}{1+p^4+2q^4} \\ G_3(\sigma, p, q) = -2 - \frac{4p^4}{1+p^4+2q^4} - \frac{4q^4}{1+2p^4+q^4} \\ G_4(\sigma, p, q) = \left(-1 - \frac{4p^4}{1+p^4+2q^4}\right) \left(-1 - \frac{4q^4}{1+2p^4+q^4}\right) - \frac{64q^4p^4}{(1+p^4+2q^4)(1+2p^4+q^4)} \end{cases}$$

Then in **Algorithm 2. Line 5**, we compute the projection of $F_1 = 0 \wedge F_2 = 0 \wedge G_1 G_2 G_3 G_4 = 0$ on σ axis and obtain

$$B_2 = \sigma - 4.$$

In **Algorithm 2. Line 6**, let $B = B_0 B_1 B_2$.

In **Algorithm 1. Line 2**, we isolate the positive roots of $B(\sigma) = 0$, obtaining

$$I_1 = \left[\frac{5}{4}, \frac{21}{16}\right], I_2 = [4, 4].$$

In **Algorithm 1. Line 3**, sample rational points from $(0, \frac{5}{4})$, $(\frac{21}{16}, 4)$, and $(4, \infty)$, obtaining

$$v_1 = 1, v_2 = 2, v_3 = 5.$$

In **Algorithm 1. Line 5**, we start the loop and compute the number of (stable) equilibriums for very sample point.

For $j = 1$, in **Algorithm 1. Line 6**, call `EquilibriumCounting`($f_1, f_2, f_3, f_4, 1$).

In **Algorithm 3. Lines 1–3**, compute the number of (stable) diagonal equilibriums and initialize $e_1 = 1$ ($s_1 = 1$).

In **Algorithm 3. Line 4**, we enter the loop.

For $i = 1$, in **Algorithm 3. Lines 5–6**, compute the number of positive solutions of

$$\sigma = 1 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q,$$

obtaining 0.

For $i = 2$, in **Algorithm 3. Lines 5–Line 6**, compute the number of positive solutions of

$$\sigma = 1 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q,$$

obtaining 0.

So when $\sigma = 1$, there is only 1 equilibrium, that is the diagonal one, and it is stable.

Note we do not pass through **Algorithm 1. Lines 8–13**.

In **Algorithm 1. Line 14**, let $Numbers = [(1, 1)]$.

For $j = 2$, call `EquilibriumCounting`($f_1, f_2, f_3, f_4, 2$).

In **Algorithm 3. Lines 1–3**, compute the number of (stable) diagonal equilibriums and initialize $e_2 = 1$ ($s_2 = 1$).

In **Algorithm 3. Line 4**, we enter the loop.

For $i = 1$, in **Algorithm 3. Lines 5–6**, compute the number of positive solutions of

$$\sigma = 2 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q,$$

obtaining 2. Then in **Algorithm 3. Lines 13**, compute the number of distinct positive solutions of

$$\sigma = 2 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q \wedge G_1 < 0 \wedge G_3 < 0 \wedge G_4 > 0,$$

obtaining 1.

For $i = 2$, in **Algorithm 3. Lines 5–6**, compute the number of positive solutions of

$$\sigma = 2 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q,$$

obtaining 0.

In **Algorithm 3. Lines 14–17**, let $e_2 = 1 + 2 \cdot \binom{4}{1} = 9$ and $s_2 = 1 + \binom{4}{1} = 5$.

So when $\sigma = 2$, there are 9 equilibriums and 5 stable equilibriums.

Since $e_1 \neq e_2$, in **Algorithm 1. Lines 8, 13 and 14**, let $Intervals = [I_1]$ and let $Numbers = [(1, 1), (9, 5)]$.

For $j = 3$, call `EquilibriumCounting`($f_1, f_2, f_3, f_4, 5$).

In **Algorithm 3. Lines 1–3**, compute the number of (stable) diagonal equilibriums and initialize $e_3 = 1$ ($s_3 = 0$).

In **Algorithm 3. Line 4**, we enter the loop.

For $i = 1$, in **Algorithm 3. Lines 5–6**, compute the number of positive solutions of

$$\sigma = 5 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q,$$

obtaining 2. Then in **Algorithm 3. Lines 13**, compute the number of distinct positive solutions of

$$\sigma = 5 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q \wedge G_1 < 0 \wedge G_3 < 0 \wedge G_4 > 0,$$

obtaining 1.

For $i = 2$, in **Algorithm 3. Lines 5–6**, compute the number of positive solutions of

$$\sigma = 5 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q,$$

obtaining 2. Then in **Algorithm 3. Lines 11**, compute the number of distinct positive solutions of

$$\sigma = 5 \wedge F_1 = 0 \wedge F_2 = 0 \wedge p \neq q \wedge G_1 < 0 \wedge G_2 < 0 \wedge G_3 < 0 \wedge G_4 > 0,$$

obtaining 0.

In **Algorithm 3. Lines 14–17**, let $e_3 = 1 + 2 \cdot \binom{4}{1} + \frac{2 \cdot \binom{4}{2}}{2} = 15$ and $s_3 = \binom{4}{1} = 4$.

So when $\sigma = 5$, there are 15 equilibriums and 4 stable equilibriums.

Since $e_2 \neq e_3$, in **Algorithm 1. Lines 8, 13 and 14**, let $Intervals = [I_1, I_2]$ and let $Numbers = [(1, 1), (9, 5), (15, 4)]$.

Finally, the main algorithm outputs shown in *Example 2*.

6 Performance

In this section, we measure how much improvement is provided by the special algorithm over the general algorithm. We use the model for simultaneous decision in *Example 1* as a benchmark. In order to measure the performance, we first need to fix the implemental details of several steps. We have made the following choices.

- (1) In **Algorithm 2. Lines 2 and 5**, we use the command `BorderPolynomial` in `DISCOVERER` [67] to compute the projection of parametric polynomial equations, which is based on triangular decomposition method.
- (2) In **Algorithm 3. Lines 2, 3, 6, 9, 11 and 13**, we first cancel the denominators. It is safe due to the condition (3) in Definition 1. Then we use `RootFinding[Isolate]` in `Maple16` to compute the real solutions of polynomial equations and inequations.

$n \backslash c$	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
2	0.0 0.0	0.0 0.0	0.1 0.0	0.1 0.0	0.1 0.1	0.2 0.1	0.2 0.1	0.4 0.2	0.7 0.3	1.4 0.7	2.2 1.1	3.6 1.6	5.8 2.6	9.1 4.2	13.8 5.9
3	0.0 0.1	0.0 1.7	0.1 96.9	0.1 ∞	0.2 ∞	0.3 ∞	0.5 ∞	0.9 ∞	1.9 ∞	3.2 ∞	6.3 ∞	10.4 ∞	19.4 ∞	29.3 ∞	53.9 ∞
4	0.0 0.1	0.1 3.1	0.1 ∞	0.2 ∞	0.3 ∞	0.7 ∞	1.3 ∞	2.4 ∞	4.7 ∞	9.1 ∞	16.7 ∞	28.6 ∞	51.4 ∞	85.5 ∞	129.7 ∞
5	0.0 0.2	0.1 0.1	0.1 ∞	0.2 ∞	0.4 ∞	0.7 ∞	1.6 ∞	2.9 ∞	6.2 ∞	11.5 ∞	22.5 ∞	36.7 ∞	67.8 ∞	110.6 ∞	192.4 ∞
6	0.1 0.3	0.1 16.7	0.1 ∞	0.2 ∞	0.6 ∞	1.3 ∞	2.6 ∞	5.0 ∞	10.1 ∞	18.8 ∞	36.2 ∞	65.6 ∞	111.9 ∞	192.1 ∞	289.2 ∞
7	0.1 0.1	0.1 177.7	0.1 ∞	0.3 ∞	0.6 ∞	1.3 ∞	3.1 ∞	5.7 ∞	11.6 ∞	22.0 ∞	42.4 ∞	70.9 ∞	134.6 ∞	220.4 ∞	354.3 ∞
8	0.1 ∞	0.1 ∞	0.2 ∞	0.3 ∞	0.7 ∞	1.7 ∞	3.7 ∞	8.3 ∞	16.7 ∞	31.9 ∞	59.7 ∞	107.2 ∞	185.1 ∞	296.9 ∞	510.4 ∞
9	0.1 ∞	0.1 ∞	0.2 ∞	0.3 ∞	0.9 ∞	1.8 ∞	4.2 ∞	8.2 ∞	18.8 ∞	34.8 ∞	67.0 ∞	114.8 ∞	213.6 ∞	340.5 ∞	590.3 ∞
10	0.1 ∞	0.2 ∞	0.2 ∞	0.3 ∞	0.9 ∞	0.9 ∞	1.8 ∞	11.0 ∞	21.6 ∞	47.6 ∞	88.8 ∞	149.4 ∞	266.8 ∞	453.5 ∞	703.0 ∞
11	0.1 ∞	0.2 ∞	0.2 ∞	0.4 ∞	0.8 ∞	2.1 ∞	5.5 ∞	10.8 ∞	23.9 ∞	43.9 ∞	94.2 ∞	161.8 ∞	293.6 ∞	482.8 ∞	768.1 ∞
12	0.1 ∞	0.2 ∞	0.3 ∞	0.4 ∞	1.0 ∞	2.3 ∞	6.7 ∞	13.6 ∞	29.1 ∞	58.2 ∞	102.0 ∞	204.7 ∞	359.5 ∞	604.9 ∞	1029.0 ∞
13	0.1 ∞	0.2 ∞	0.4 ∞	0.4 ∞	1.0 ∞	2.5 ∞	6.7 ∞	15.1 ∞	33.5 ∞	67.6 ∞	133.6 ∞	207.0 ∞	414.7 ∞	662.5 ∞	1078.1 ∞
14	0.1 ∞	0.2 ∞	0.3 ∞	0.6 ∞	1.1 ∞	2.6 ∞	7.0 ∞	15.9 ∞	37.1 ∞	74.8 ∞	143.4 ∞	259.6 ∞	415.7 ∞	812.0 ∞	1319.1 ∞
15	0.1 ∞	0.2 ∞	0.3 ∞	0.6 ∞	1.1 ∞	2.7 ∞	7.0 ∞	16.4 ∞	39.4 ∞	78.3 ∞	151.1 ∞	274.8 ∞	501.3 ∞	731.3 ∞	1427.3 ∞

Figure 2: Timings of the special algorithm (Algorithm 1) and the general algorithm

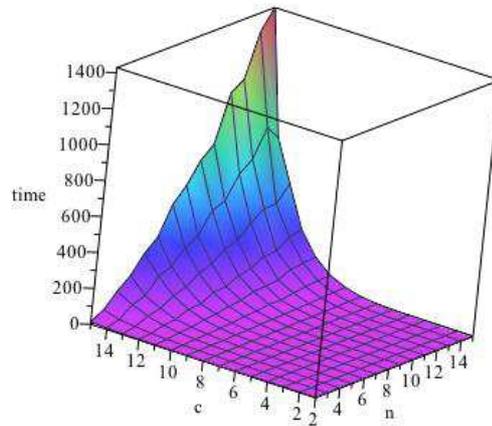


Figure 3: $time - (n, c)$ of Algorithm 1

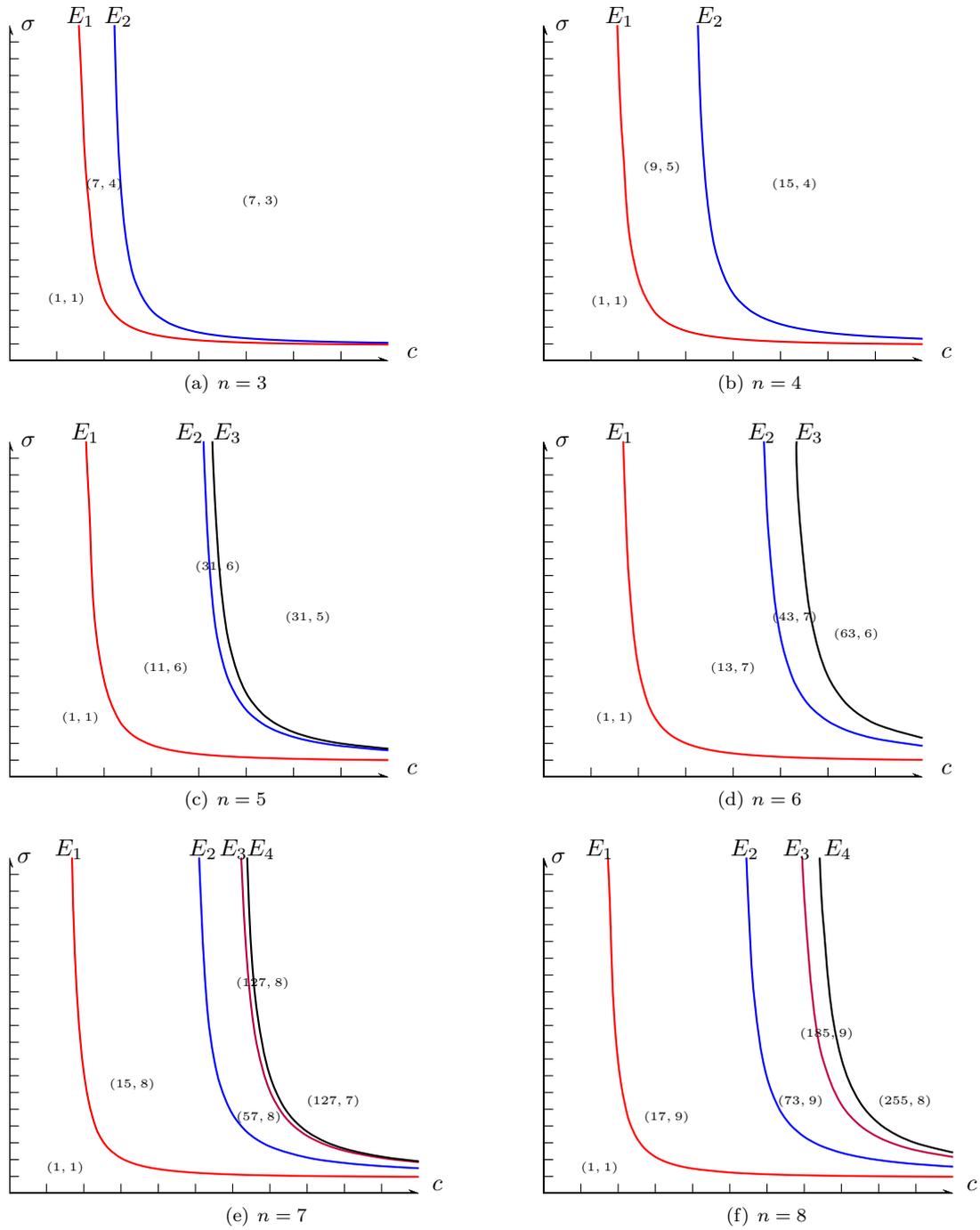


Figure 4: c - σ graphs for $n = 3, 4, 5, 6, 7, 8$

In the following, we provide the experimental results in three figures: Figure 2, Figure 3 and Figure 4.

- Figure 2 provides the timing comparison of Algorithm 1 (Section 5) and the general algorithm (Section 3) for $n = 2, \dots, 15$ and $c = 1, \dots, 15$. The top entries are the timings in seconds for Algorithm 1 and the bottom entries are for the general algorithm. The symbol ∞ means the computational time is greater than 1500 seconds (aborted). Both programs were written in Maple and were executed on an Intel Core i7 processor (2.3GHz CPU, 4 Cores and 8GB total memory).

Observe that Algorithm 1 performs much faster than the general algorithm for $n \geq 3$. As is pointed out by [66], when $n > 5$, it becomes expensive for the general algorithm to compute the Hurwitz determinants and the sizes of these determinants are usually huge, which leads to much difficulties of the subsequent computations. Moreover, when c is relatively large, the real solution isolation of the general algorithm performs quite slowly, even needs thousands of seconds for one sample point.

Note also that the special algorithm is a bit slower than the general algorithm when $n = 2$. The main reasons are that the special algorithm benefit little from exploiting the special structure and that the special algorithm pays the overhead cost for analyzing the structure.

- Figure 3 provides the timings of Algorithm 1 as a graph over *time* and (n, c) . By fitting, we find that it is very close to the graph of

$$time \approx 0.012(n-2)e^{0.6c}.$$

Observe that the computational time is approximately linear with respect to n (the number of proteins) and exponential with respect to c (the cooperativity).

- Figure 4 provides, for $n = 3, \dots, 8$, the partition of the c - σ plane into several cells by several curves $E_i(c, \sigma) = 0$. In each cell, the number of (stable) equilibria is uniform (presented in each cell). Note that Algorithm 1 can be applied to rational c values. For each n , we computed all the critical σ values for different rational c values, obtaining sufficiently many (c, σ) points. Then we obtained E_i by curve fitting.

Note that we are showing a complete answer to the multistability problem of the system for the given n values. We also remark that the curve $E_{\lceil \frac{n}{2} \rceil}(c, \sigma) = 0$ matches $c - n + 1 - \left(\frac{c}{\sigma}\right)^{\frac{c}{c+1}} = 0$. Note that only when (c, σ) is beyond the curve, the number of stable equilibria is n . Thus we have verified the following conjecture in [22] for $n = 3, \dots, 8$: the system has exactly n stable equilibria if and only if $c - n + 1 - \left(\frac{c}{\sigma}\right)^{\frac{c}{c+1}} > 0$.

From the computational results, one sees immediately that the equilibrium classifications of MSRS also have certain special structures, with interesting biological implications. A detailed analysis of the structures and their biological implications will be reported in a forthcoming article.

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