

Approximation of Dynamical Systems using S-Systems Theory: Application to Biological Systems*

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ABSTRACT

In this article we propose a new symbolic-numeric algorithm to find positive equilibria of a n -dimensional dynamical system. This algorithm uses a symbolic manipulation of ODE in order to give a local approximation of differential equations with power-law dynamics (S-systems). A numerical calculus is then performed to converge towards an equilibrium, giving at the same time a S-system approximating the initial system around this equilibrium. This algorithm has been applied to a real biological example in 14 dimensions which is a subsystem of a metabolic pathway in *Arabidopsis Thaliana*.

Categories and Subject Descriptors:

I.1.2 [Computing Methodologies]: Symbolic and algebraic manipulation - *Algorithms*

G.1.5 [Mathematics of Computing]: Numerical Analysis
Roots of Nonlinear Equations - *Iterative Methods*

General Terms: Algorithms.

Keywords: Power-law, S-systems, Dynamical Systems, Positive Equilibria, Stability.

1. INTRODUCTION

The modelling and study of biological or biochemical systems has become an exciting challenge in applied mathematics. The complexity of real biological dynamical systems lies essentially in the non-linearities of the dynamics as well as in the huge dimension of systems, often leading to a numerical approach. However, as the understanding of cellular mechanisms grows, it has become obvious that the modelling step strongly needs symbolic tools in order to manipulate more and more information and data, and to improve computational tools. Therefore a new area emerged, called "systems

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biology". It involves different fields of applied mathematics, from computer algebra (see for instance [10]) to numerical computation ([7]).

In the past decades, a lot of different frameworks have been developed to study behaviors of complex biochemical processes. Let us cite here three of them: discrete networks (see the work of R. Thomas [16]), piecewise linear systems (the so-called Glass networks [6], see also [5]) and sigmoidal switch systems ([13]). The main goal of all these approaches is to propose a (more or less) generic class of dynamical systems, either discrete or differential, that model some behaviors of complex interaction systems. Once this class is clearly defined, its mathematical relevance generally allows both theoretical and numerical analysis.

We use in this paper the class of *S-systems* (see [1], [17], [18]). The basic idea of this model is to represent interactions between biochemical species with power-law dynamics. Their mathematical expression is quite general, but sufficiently simple to allow theoretical and practical investigations. We propose in this article a symbolic-numeric algorithm that is based upon S-systems theory. Its goal is to compute iteratively the positive equilibria of a n -dimensional system of ordinary differential equations (ODE). As it converges towards a steady state, it provides a S-system that approaches the original dynamics around this steady state. As we will see, the local approximation of some dynamics with power-laws can be made symbolically at any point of the phase space. It can also include treatment of symbolic parameters. However, iterating this process in order to converge towards equilibria needs a numerical computation, which prevents the use of pure symbolic tools to the end. In the following, we give a definition of the S-system class as it can be found in the literature (see for instance [17]). We then propose a symbolic-numeric algorithm that computes an iteration leading to the positive equilibria of a dynamical system. We will see an application of this algorithm on a biological example in dimension 14. We finally conclude with some remarks on our algorithm and some future works.

2. S-SYSTEMS

2.1 Definition

In this paragraph, we give a definition of the class of *S-systems* (see for instance [1]).

DEFINITION 2.1. A n -dimensional S-system $S(\alpha, \beta, G, H)$

is a dynamical system defined by the n differential equations:

$$\dot{x}_i = \alpha_i \prod_{j=1}^n x_j^{g_{ij}} - \beta_i \prod_{j=1}^n x_j^{h_{ij}}, \quad i = 1 \dots n$$

with $\alpha = (\alpha_1, \dots, \alpha_n) \in (\mathbb{R}_+^*)^n$, $\beta = (\beta_1, \dots, \beta_n) \in (\mathbb{R}_+^*)^n$ and $G = (g_{ij})_{i,j=1 \dots n}$, $H = (h_{ij})_{i,j=1 \dots n} \in \mathcal{M}_n(\mathbb{R})$.

\mathbb{R}_+^* denotes the set of strictly positive real numbers, $\mathcal{M}_n(\mathbb{R})$ denotes the set of real square matrices of order n .

Let us introduce the vector field F defined on $\Omega = (\mathbb{R}_+^*)^n$:

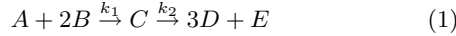
$$F(x) = \begin{pmatrix} f_1(x_1, \dots, x_n) \\ \vdots \\ f_n(x_1, \dots, x_n) \end{pmatrix}$$

with:

$$f_i(x_1, \dots, x_n) = \alpha_i \prod_{j=1}^n x_j^{g_{ij}} - \beta_i \prod_{j=1}^n x_j^{h_{ij}}, \quad i = 1 \dots n$$

F is C^1 and therefore locally lipschitz on the open Ω . Cauchy-Lipschitz theorem ensures the existence and unicity of a maximal solution of $S(\alpha, \beta, G, H)$ in Ω , given any initial condition $x(0) = x^0 \in \Omega$.

This definition of S-systems with power-law differential equations is strongly linked with equations of chemical kinetics. As an example, if we consider the following chemical pathway:



then the mass-action law applied to species C gives the equation:

$$\frac{dc}{dt} = k_1 ab^2 - k_2 d^3 e$$

(capital letters designate species and small letters designate concentrations).

Therefore in definition 2.1, coefficients α_i and β_i are sometimes called *kinetic rates* while g_{ij} and h_{ij} are called *kinetic orders*.

S-systems are part of a broader formalism known as quasi-monomial (QM) systems (see [2]). An interesting result shows that QM systems can be expressed in the form of Lotka-Volterra quadratic systems (see [2] for details).

2.2 Equilibrium points

The study of the phase portrait of a S-system $S(\alpha, \beta, G, H)$ begins with the search for equilibrium points in Ω . To find them, we have to solve the system:

$$\alpha_i \prod_{j=1}^n x_j^{g_{ij}} = \beta_i \prod_{j=1}^n x_j^{h_{ij}}, \quad i = 1 \dots n \quad (2)$$

In this paper we will use the following notation: Given a vector $x \in (\mathbb{R}_+^*)^n$ and a real square matrix $A = (a_{ij})_{i,j=1 \dots n}$, we define the vector $x^A \in (\mathbb{R}_+^*)^n$ by:

$$(x^A)_i = \prod_{j=1}^n x_j^{a_{ij}}, \quad i = 1 \dots n$$

With this notation, we can express equation (2) as follows:

$$x^{G-H} = b$$

where b is the vector $(\beta_1/\alpha_1, \dots, \beta_n/\alpha_n)$. Taking the neperian logarithm, this equation leads to:

$$(G - H) \ln x = \ln b$$

(the logarithm is applied to all components of vector, i.e. $\ln x$ is the n -dimensional vector $(\ln x_1, \dots, \ln x_n)$). Posing $y = \ln x$, we are brought back to the resolution of a n -dimensional linear system in y .

We have therefore the following proposition:

PROPOSITION 2.1. *A S-system $S(\alpha, \beta, G, H)$ has a unique equilibrium \tilde{x} in Ω (i.e. a positive equilibrium) if and only if the matrix $(G - H)$ is invertible. \tilde{x} can be calculated by the formula:*

$$\tilde{x} = b^{(G-H)^{-1}} \quad (3)$$

2.3 Stability analysis of the equilibrium

The stability analysis of the equilibrium \tilde{x} uses the study of the spectrum of $J_F(\tilde{x})$ (the jacobian of F in \tilde{x}). The question we tackle here is to find some relationship between the stability of \tilde{x} and some properties of the matrix $G - H$.

As a motivating example, let us consider the one-dimensional case. A one-dimensional S-system is expressed by a single differential equation:

$$S(\alpha, \beta, g, h) : \quad \dot{x} = f(x) = \alpha x^g - \beta x^h$$

where $\alpha, \beta > 0$ and $g, h \in \mathbb{R}$. The positive equilibrium \tilde{x} of (S) exists and is unique if and only if $g - h \neq 0$. In this case, an obvious calculation leads to:

$$\frac{\partial f}{\partial x}(\tilde{x}) = \alpha \tilde{x}^{g-1} (g - h)$$

so the stability of \tilde{x} depends directly on the sign of $g - h$: it is asymptotically stable if $g - h < 0$ and unstable if $g - h > 0$, regardless of parameters α and β .

In the n -dimensional case, the stability depends on the sign of the real parts of the jacobian's eigenvalues. Differentiating the functions $f_i(x_1, \dots, x_n)$, we obtain, for $i, j = 1 \dots n$:

$$\frac{\partial f_i}{\partial x_j}(\tilde{x}) = \frac{\alpha_i}{\tilde{x}_j} \prod_{k=1}^n \tilde{x}_k^{g_{ik}} \cdot (g_{ij} - h_{ij}) \quad (4)$$

We thus obtain a formula that links the jacobian of F in \tilde{x} with the matrix $G - H$. However, it is not trivial to link the spectrum of $J_F(\tilde{x})$ with the spectrum of $G - H$.

Let us recall here the definition of stability of matrices:

DEFINITION 2.2. *A real square matrix A of order n is said to be stable (resp. semi-stable) if all its eigenvalues λ_i , $i = 1 \dots n$, have a negative (resp. non positive) real part.*

We could hope that the stability of matrix $G - H$ was sufficient to deduce the stability of \tilde{x} . However this is not true, as we can see in the following example.

For $n = 2$, consider the S-system:

$$(S1) : \begin{cases} \dot{x} &= 3xy^2 - 2x^4 \\ \dot{y} &= 4x^3y^4 - x^5y^3 \end{cases}$$

we have:

$$\alpha = \begin{pmatrix} 3 \\ 4 \end{pmatrix}, \beta = \begin{pmatrix} 2 \\ 1 \end{pmatrix}, G = \begin{pmatrix} 1 & 2 \\ 3 & 4 \end{pmatrix}, H = \begin{pmatrix} 4 & 0 \\ 5 & 3 \end{pmatrix}$$

The matrix $G - H$ is equal to:

$$G - H = \begin{pmatrix} -3 & 2 \\ -2 & 1 \end{pmatrix}$$

Its characteristic polynomial is $\chi(\lambda) = (\lambda+1)^2$ so the matrix is stable.

Since $G - H$ is invertible, there is a unique equilibrium: $\tilde{x} = (\frac{32}{3}, \frac{256}{9})$. We can calculate the two eigenvalues λ_1 and λ_2 of $J_F(\tilde{x})$. We find that $\lambda_1, \lambda_2 > 0$, implying that \tilde{x} is an unstable node. As a result, in spite of the stability of matrix $G - H$, the equilibrium \tilde{x} is unstable.

The stability of $G - H$ is therefore insufficient to deduce the stability of \tilde{x} .

We need a stronger property known as sign stability (see [9],[11]).

DEFINITION 2.3. *Two real square matrices of order n , $A = (a_{ij})_{i,j=1\dots n}$ and $B = (b_{ij})_{i,j=1\dots n}$, have the same sign pattern if:*

$$\forall i, j = 1 \dots n, \text{sgn}(a_{ij}) = \text{sgn}(b_{ij})$$

The function sgn is the classical signum function:

$$\forall x \in \mathbb{R}, \text{sgn}(x) = \begin{cases} +1 & \text{if } x > 0 \\ 0 & \text{if } x = 0 \\ -1 & \text{if } x < 0 \end{cases}$$

DEFINITION 2.4. *A real square matrix A of order n is said to be sign stable (resp. sign semi-stable) if all the matrices that have the same sign pattern are stable (resp. semi-stable) in the sense of definition 2.2.*

In [9] we find a characterization of the sign semi-stability:

THEOREM 2.1 (QUIRK-RUPPERT-MAYBEE).

A real square matrix $A = (a_{ij})_{i,j=1\dots n}$ is sign semi-stable if and only if it satisfies the following three conditions:

- (i) $\forall i = 1 \dots n, a_{ii} \leq 0$
- (ii) $\forall i \neq j, a_{ij}a_{ji} \leq 0$
- (iii) for each sequence of $k \geq 3$ distinct indices i_1, \dots, i_k , we have: $a_{i_1 i_2} \dots a_{i_{k-1} i_k} a_{i_k i_1} = 0$

(The third condition is equivalent to the fact that the directed graph associated to A admits no k -cycle for $k \geq 3$)

With this notion, we can formulate the following proposition, which links the stability of the equilibrium \tilde{x} of a S-system with the sign semi-stability of matrix $G - H$:

PROPOSITION 2.2. *Let consider a n -dimensional S-system $S(\alpha, \beta, G, H)$. We assume that $G - H$ is invertible and we note \tilde{x} the unique positive equilibrium of (S) . We also assume that \tilde{x} is hyperbolic (i.e. none of the eigenvalues of the*

Jacobian of F in \tilde{x} have zero real part).

If the matrix $G - H$ is sign semi-stable (i.e. if it verifies the three conditions of theorem 2.1) then, regardless of parameters α and β , the equilibrium \tilde{x} is asymptotically stable.

PROOF. Let us note J the Jacobian of F in \tilde{x} and P the matrix $G - H$. The equation 4 yields:

$$\frac{\partial f_i}{\partial x_j}(\tilde{x}) = \frac{\gamma_i}{\tilde{x}_j} p_{ij}$$

with $\gamma_i = \alpha_i \prod_{k=1}^n \tilde{x}_k^{g_{ik}}$. As $\gamma_i > 0$ and $\tilde{x}_j > 0$ for all i and j , matrices J and P have the same sign pattern. We can thus deduce that J is semi-stable and as \tilde{x} is supposed hyperbolic, it is asymptotically stable. \square

We can easily verify in the previous example that $G - H$ is stable but not sign semi-stable ($g_{22} - h_{22} = 1 > 0$).

Let us remark that the latter equation gives, in matricial notation:

$$J = \Gamma P D^{-1}$$

where Γ and D are diagonal matrices:

$$\Gamma = \begin{pmatrix} \gamma_1 & & \\ & \ddots & \\ & & \gamma_n \end{pmatrix}, \quad D = \begin{pmatrix} \tilde{x}_1 & & \\ & \ddots & \\ & & \tilde{x}_n \end{pmatrix}$$

so $\text{sgn}(\det(J)) = \text{sgn}(\det(P))$. As we have supposed that P is invertible, we deduce that J is also invertible and does not have null eigenvalues. It could nevertheless have imaginary eigenvalues, which would make \tilde{x} unstable. The hyperbolicity of \tilde{x} is therefore an essential assumption in the latter proposition.

3. LOCAL APPROXIMATION OF DYNAMICAL SYSTEM USING S-SYSTEMS

In this part, we propose an algorithm for approximating the equilibria of a dynamical system using S-systems. Simultaneously, we obtain a S-system that approximates the initial system around the equilibrium.

3.1 Monomial approximation of a positive vector field

(see [18],[15],[17]).

Let's consider the positive vector field $F : (\mathbb{R}_+^*)^n \rightarrow (\mathbb{R}_+^*)^n$.

$$F(x) = \begin{pmatrix} f_1(x_1, \dots, x_n) \\ \vdots \\ f_n(x_1, \dots, x_n) \end{pmatrix}$$

We will suppose F sufficiently smooth on $(\mathbb{R}_+^*)^n$.

Let us define the following change of variables: $y = \ln x$, and express the logarithm of $F(x)$ as a function G of the new variable y :

$$\ln F(x) = \ln F(e^y) = G(y)$$

The function G is sufficiently smooth on \mathbb{R}^n . Given any arbitrary point $y^0 \in \mathbb{R}^n$, let us write the Taylor expansion

of g_i (for $i = 1 \dots n$) in the neighborhood of y^0 at the first order:

$$\forall i = 1 \dots n, g_i(y) = g_i(y^0) + \sum_{j=1}^n (y_j - y_j^0) \frac{\partial g_i}{\partial y_j}(y^0) + o(\|y - y^0\|)$$

We introduce the functions $\tilde{g}_i(y)$ for $i = 1 \dots n$:

$$\forall i = 1 \dots n, \tilde{g}_i(y) = g_i(y^0) + \sum_{j=1}^n (y_j - y_j^0) \frac{\partial g_i}{\partial y_j}(y^0)$$

and the functions $\tilde{f}_i = \exp(\tilde{g}_i(y))$:

$$\begin{aligned} \tilde{f}_i(x) &\stackrel{def}{=} e^{\tilde{g}_i(y)} \\ &= e^{g_i(y^0)} \exp\left(\sum_{j=1}^n (y_j - y_j^0) \frac{\partial g_i}{\partial y_j}(y^0)\right) \\ &= e^{g_i(y^0)} \prod_{j=1}^n \exp\left((y_j - y_j^0) \frac{\partial g_i}{\partial y_j}(y^0)\right) \end{aligned}$$

As $y = \ln x$ and $g_i(y) = \ln f_i(x)$, we have:

$$\tilde{f}_i(x) = f_i(x^0) \prod_{j=1}^n \left(\frac{x_j}{x_j^0}\right)^{\frac{\partial g_i}{\partial y_j}(y^0)}$$

and:

$$\begin{aligned} \frac{\partial g_i}{\partial y_j}(y) &= \frac{\partial}{\partial y_j} (\ln(f_i(e^y))) \\ &= \frac{1}{f_i(e^y)} \frac{\partial}{\partial y_j} (f_i(e^y)) \\ &= \frac{1}{f_i(x)} e^{y_j} \frac{\partial f_i}{\partial x_j}(e^y) \\ &= \frac{x_j}{f_i(x)} \frac{\partial f_i}{\partial x_j}(x) \end{aligned}$$

Therefore, we have defined a vector field $\tilde{F} = (\tilde{f}_i)_{i=1 \dots n}$

$$\tilde{F}(x) = \left(\alpha_i \prod_{j=1}^n x_j^{g_{ij}} \right)_{i=1 \dots n} \quad (5)$$

$$\text{with: } \begin{cases} \alpha_i(x^0) &= f_i(x^0) \prod_{j=1}^n (x_j^0)^{-g_{ij}} \\ g_{ij}(x^0) &= \frac{x_j^0}{f_i(x^0)} \frac{\partial f_i}{\partial x_j}(x^0) \end{cases} \quad (6)$$

The basic idea is to use the monomial vector field \tilde{F} as an approximation of F in a neighborhood of x^0 .

DEFINITION 3.1. Let F be a smooth n -dimensional vector field, $F : (\mathbb{R}_+^*)^n \rightarrow (\mathbb{R}_+^*)^n$ and x^0 any vector of $(\mathbb{R}_+^*)^n$. We call S -approximation of F in x^0 the vector field \tilde{F} defined by equations (5) and (6).

The following proposition is basic for what follows:

PROPOSITION 3.1. Let F be a positive vector field and \tilde{F} its S -approximation in x^0 . The following equalities hold:

- $\tilde{F}(x^0) = F(x^0)$

- $\forall i, j = 1 \dots n, \frac{\partial \tilde{f}_i}{\partial x_j}(x^0) = \frac{\partial f_i}{\partial x_j}(x^0)$
(or, which is equivalent: $J_F(x^0) = J_{\tilde{F}}(x^0)$)

The proof is easy and left to the reader.

3.2 Finding equilibria of a dynamical system

We consider a n -dimensional dynamical system of the form:

$$(S) \quad \dot{x} = V^+(x) - V^-(x)$$

where x lies in $(\mathbb{R}_+^*)^n$ and V^+, V^- are positive vector fields. $V^+, V^- : (\mathbb{R}_+^*)^n \rightarrow (\mathbb{R}_+^*)^n$. For $i = 1 \dots n$, the term $v_i^+(x)$ is the *production term* of the variable x_i and $v_i^-(x)$ the *decay term* of x_i . We propose an algorithm for finding an equilibrium point of (S) that lies in $(\mathbb{R}_+^*)^n$. Meanwhile, we get a S-system that approximates the system (S) around this equilibrium.

Given a point x^0 in $(\mathbb{R}_+^*)^n$, we introduce the fields \tilde{V}^+ and \tilde{V}^- which are the S-approximations of the fields V^+ and V^- in x^0 . Let us consider the n -dimensional S-system:

$$(S_{x^0}) \quad \dot{x} = \tilde{V}^+(x) - \tilde{V}^-(x)$$

Using (5) and (6), we obtain:

$$(S_{x^0}) : \quad \dot{x}_i = \alpha_i \prod_{j=1}^n x_j^{g_{ij}} - \beta_i \prod_{j=1}^n x_j^{h_{ij}}, \quad i = 1 \dots n$$

where:

$$\begin{cases} \alpha_i &= v_i^+(x^0) \prod_{j=1}^n (x_j^0)^{-g_{ij}} \\ \beta_i &= v_i^-(x^0) \prod_{j=1}^n (x_j^0)^{-h_{ij}} \end{cases} \quad (7)$$

and:

$$\begin{cases} g_{ij} &= \frac{x_j^0}{v_i^+(x^0)} \frac{\partial v_i^+}{\partial x_j}(x^0) \\ h_{ij} &= \frac{x_j^0}{v_i^-(x^0)} \frac{\partial v_i^-}{\partial x_j}(x^0) \end{cases} \quad (8)$$

If the matrix $G - H$ is invertible, the system (S_{x^0}) admits a unique equilibrium $x_{eq} \in (\mathbb{R}_+^*)^n$:

$$x_{eq} = b^{(G-H)^{-1}}$$

with $b = (\beta_1/\alpha_1, \dots, \beta_n/\alpha_n)$. This point x_{eq} depends on the initial point x^0 where we made our approximation. Let $x^1 = x_{eq}$ be the new initial point where we make our next S-approximation. Iterating this process produces a sequence of points x^0, x^1, \dots that converges towards a positive equilibrium of (S). A proof of the convergence is given in section 5. The main steps of this algorithm are summarized here:

4. AN EXAMPLE WITH MULTIPLE POSITIVE EQUILIBRIA

We present here the application of our algorithm for a dynamical system having multiple positive equilibrium points. It is a system known as *biological switch* (see [3]).

Algorithm 1 Search of an equilibrium point of system (S)**Require:**

- $X = x^0 \in (\mathbb{R}_+^*)^n$ (initial condition)
- V^+, V^- : positive vector fields defined over $(\mathbb{R}_+^*)^n$
- $\epsilon > 0$: precision

Ensure: unless we fall in a degenerate case, we find a point y close to a positive equilibrium of (S) with the precision ϵ . Meanwhile, we obtain the S-system (S_y) that approximate system (S) around this equilibrium.

repeat $Y := X$ **for** $i = 1$ to n **do****for** $j = 1$ to n **do**

$$g_{ij} := \frac{X_j}{v_i^+(X)} \frac{\partial v_i^+}{\partial X_j}; h_{ij} := \frac{X_j}{v_i^-(X)} \frac{\partial v_i^-}{\partial X_j}$$

end for

$$\alpha_i := v_i^+(X) \prod_{j=1}^n (X_j)^{-g_{ij}}; \beta_i := v_i^-(X) \prod_{j=1}^n (X_j)^{-h_{ij}}$$

$$b_i := \beta_i / \alpha_i$$

end for**if** $\det(G - H) \neq 0$ **then**

$$X := b^{(G-H)^{-1}}$$

else

degenerate case: algorithm terminated \rightarrow restart the algorithm with a new initial condition

end if**until** $\|X - Y\| < \epsilon$ **Result** := X

Let's consider the two dimensional dynamical system:

$$\begin{cases} \dot{x} = f_1(x, y) = \frac{3}{1+y^2} - x \\ \dot{y} = f_2(x, y) = \frac{6.75}{3.375+x^3} - y \end{cases} \quad (9)$$

It represents the temporal evolution of two positive quantities x and y with linear decay and sigmoidal production (we use here the Hill function $H^-(z) = \frac{K^n}{K^n + z^n}$ often used by biologists to model sigmoidal interactions). As we can see on figure 1, this system has three equilibrium points. The values of these points can be calculated:

$$P1 \approx \begin{pmatrix} 0.697 \\ 1.818 \end{pmatrix} \quad P2 = \begin{pmatrix} 1.5 \\ 1.0 \end{pmatrix} \quad P3 \approx \begin{pmatrix} 2.802 \\ 0.266 \end{pmatrix}$$

We can show that $P2$ is unstable whereas $P1$ and $P3$ are stable (cf. [3]).

Applying our program in **Maple**, we found three different initial conditions, each of which tending towards one of the three equilibrium points (see figure 1 and numerical results below). The convergence appears to be fast since we need only 4 iterations to approach the equilibria with a precision of 10^{-5} . We will discuss about the convergence speed in part 5.3.

- With initial condition $x^0 = (2, 2)$, algorithm finished in 4 iterations and found $P2$ with a precision of 10^{-5} .

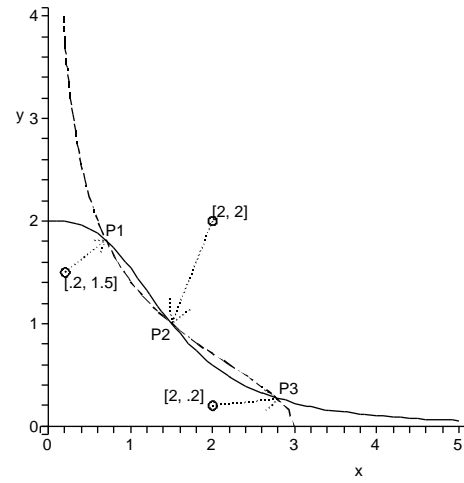


Figure 1: The two curves represents the nullclines of system (9), i.e. the curves $f_1(x, y) = 0$ (dashed line) and $f_2(x, y) = 0$ (solid line). The central equilibrium $P2$ can be shown to be unstable while the two others, $P1$ and $P3$ are stable. The arrows represent the three experimentations described in the text.

The numerical S-system obtained is given by:

$$\begin{cases} \dot{x} = 1.500 y^{-1} - x \\ \dot{y} = 1.837 x^{-1.5} - y \end{cases}$$

- With initial condition $x^0 = (0.2, 1.5)$, algorithm finished in 4 iterations and found $P1$ with a precision of 10^{-5} . The numerical S-system obtained is given by:

$$\begin{cases} \dot{x} = 1.745 y^{-1.535} - x \\ \dot{y} = 1.647 x^{-0.274} - y \end{cases}$$

- With initial condition $x^0 = (2, 0.2)$, algorithm finished in 4 iterations and found $P3$ with a precision of 10^{-5} . The numerical S-system obtained is given by:

$$\begin{cases} \dot{x} = 2.352 y^{-0.132} - x \\ \dot{y} = 3.879 x^{-2.6} - y \end{cases}$$

5. ANALYSIS OF THE ALGORITHM

5.1 Correctness

Let's describe the first iteration of our algorithm. Let $x^0 \in (\mathbb{R}_+^*)^n$. With formulae (7) and (8), we define the quantities $\alpha_i(x^0)$, $\beta_i(x^0)$, $g_{ij}(x^0)$ and $h_{ij}(x^0)$. Let us assume that matrices $G(x^0)$ and $H(x^0)$ verify the condition: $\det(G-H) \neq 0$. Thanks to this assumption, there exists a unique equilibrium point of the system (S_{x^0}). We denote it x^1 , and we define the function $\Psi : (\mathbb{R}_+^*)^n \rightarrow (\mathbb{R}_+^*)^n$ that, to each $x^0 \in (\mathbb{R}_+^*)^n$ associates the point x^1 .

Our algorithm computes the recurrent sequence:

$$(I) \begin{cases} x^0 \in (\mathbb{R}_+^*)^n \\ x^{n+1} = \Psi(x^n) \end{cases}$$

This iterative process converges towards fixed points of Ψ . However we do not *a priori* know if all fixed points of Ψ are

indeed limits of (I). In other words, we must find which fixed points are attracting.

The correctness of the algorithm (1) is a consequence of the two following lemmas:

LEMMA 5.1. *The equilibria of initial system (S) are the fixed points of the function Ψ*

LEMMA 5.2. *Given a fixed point \bar{x} of Ψ , there exists some initial points x^0 that lead to \bar{x} by the iteration (I). In other words, the positive equilibria of (S) are the attracting fixed points of Ψ .*

PROOF. (First lemma) Let $\bar{x} \in (\mathbb{R}_+^*)^n$ such that the determinant of $G(\bar{x}) - H(\bar{x})$ is different from zero. (for convenience, we will omit the dependency in \bar{x} , and note G in place of $G(\bar{x})$). Using equation (3), we have:

$$\Psi(\bar{x}) = b^{(G-H)^{-1}} \quad (10)$$

where b is the vector $(\beta_i/\alpha_i)_{i=1\dots n}$. Therefore:

$$\begin{aligned} \Psi(\bar{x}) = \bar{x} &\iff b^{(G-H)^{-1}} = \bar{x} \\ &\iff b = \bar{x}^{(G-H)} \\ &\iff \forall i = 1 \dots n, \frac{\beta_i}{\alpha_i} = \prod_{j=1}^n \bar{x}_j^{g_{ij} - h_{ij}} \\ &\iff \forall i = 1 \dots n, \beta_i \prod_{j=1}^n \bar{x}_j^{h_{ij}} = \alpha_i \prod_{j=1}^n \bar{x}_j^{g_{ij}} \end{aligned}$$

By definition, $\alpha_i \prod_{j=1}^n \bar{x}_j^{g_{ij}}$ (resp. $\beta_i \prod_{j=1}^n \bar{x}_j^{h_{ij}}$) is the S-approximation of V^+ (resp. V^-) in \bar{x} . Proposition 3.1 implies then:

$$\Psi(\bar{x}) = \bar{x} \iff V^+(\bar{x}) = V^-(\bar{x})$$

Thus, the equilibria of (S) are the fixed points of the function Ψ . \square

In order to prove the second lemma, we will use the following fixed point criterion (known as Ostrowski's theorem, see e.g. [12]):

If the function Ψ is a contraction on the open set W and if $\bar{x} \in W$ is a fixed point of Ψ , then \bar{x} is the unique fixed point of Ψ in W and it is attracting, that is to say, for all $x^0 \in W$, the iteration (I) converges towards \bar{x} .

PROOF. (Second lemma) Let \bar{x} be a fixed point of Ψ . We assume that $\det(G(\bar{x}) - H(\bar{x})) \neq 0$. The continuity of the determinant implies that there exists a neighborhood W of \bar{x} in which $\det(G - H) \neq 0$. To prove that \bar{x} is attracting, we have to show that there exists an open neighbourhood of \bar{x} in which Ψ is contracting, i.e. the spectral radius of the jacobian of Ψ is strictly less than one.

Using (7) and (8) and posing:

$$\begin{cases} U^+ &= \log(V^+) \\ U^- &= \log(V^-) \\ U &= U^+ - U^- = \log\left(\frac{V^+}{V^-}\right) \\ P &= G - H \end{cases}$$

we obtain, for all $x \in W$:

$$\Psi_i(x) = x_i \prod_{j=1}^n \left(\frac{v_j^-(x)}{v_j^+(x)} \right)^{p_{ij}^{(-1)}(x)}$$

where $(p_{ij}^{(-1)})_{i,j=1\dots n}$ is the inverse of the matrix $P = G - H$. Let's calculate p_{ij} :

$$\begin{aligned} p_{ij} &= g_{ij} - h_{ij} \\ &= x_j \left(\frac{1}{v_i^+} \frac{\partial v_i^+}{\partial x_j} - \frac{1}{v_i^-} \frac{\partial v_i^-}{\partial x_j} \right) \\ &= x_j \left(\frac{\partial u_i^+}{\partial x_j} - \frac{\partial u_i^-}{\partial x_j} \right) \\ &= x_j \frac{\partial u_i}{\partial x_j} \end{aligned}$$

in matricial notation: $P = J_u(x)\Delta$ where $J_u(x)$ is the jacobian of the function U evaluated in x and Δ is the diagonal matrix:

$$\Delta = \begin{pmatrix} x_1 & & \\ & \ddots & \\ & & x_n \end{pmatrix}$$

Therefore $P^{-1} = \Delta^{-1}(J_u(x))^{-1} = \Delta^{-1}(J_{u^{-1}}(x))$ (u^{-1} is the reciprocal function of u) and so:

$$\forall i, j = 1 \dots n, \quad p_{ij}^{(-1)} = \frac{1}{x_i} \frac{\partial u_i^{-1}}{\partial x_j}$$

With (10) we have, for $i = 1 \dots n$ and $x \in W$:

$$\begin{aligned} \Psi_i(x) &= x_i \prod_{j=1}^n \exp\left(-\frac{1}{x_i} u_j(x) \frac{\partial u_i^{-1}}{\partial x_j}(x)\right) \\ &= x_i \exp\left(-\sum_{j=1}^n \frac{u_j(x)}{x_i} \frac{\partial u_i^{-1}}{\partial x_j}(x)\right) \end{aligned}$$

Differentiating this (and omitting the dependency in x), we get, for $k \neq i$:

$$\frac{\partial \Psi_i}{\partial x_k} = \left[\sum_{j=1}^n u_j \frac{\partial^2 u_i^{-1}}{\partial x_j \partial x_k} \right] \exp\left(-\sum_{j=1}^n \frac{u_j(x)}{x_i} \frac{\partial u_i^{-1}}{\partial x_j}\right)$$

and

$$\begin{aligned} \frac{\partial \Psi_i}{\partial x_i} &= \left[\sum_{j=1}^n u_j \frac{\partial^2 u_i^{-1}}{\partial x_j \partial x_k} - \frac{1}{x_i} \sum_{j=1}^n u_j \frac{\partial u_i^{-1}}{\partial x_j} \right] \times \\ &\quad \exp\left(-\sum_{j=1}^n \frac{u_j(x)}{x_i} \frac{\partial u_i^{-1}}{\partial x_j}\right) \end{aligned}$$

As we have shown that the fixed points of Ψ are the equilibria of (S), we deduce that $\forall k = 1 \dots n, u_k(\bar{x}) = 0$, therefore:

$$J_\Psi(\bar{x}) = 0$$

This implies that the spectral radius of $J_\Psi(\bar{x})$ is strictly less than one. Consequently, Ψ is a contraction on an open neighbourhood of \bar{x} . According to the aforementioned fixed point criterion, we can deduce that \bar{x} is attracting. This concludes the proof of the second lemma and the correctness of the algorithm. \square

5.2 Stability analysis of approximate S-system

We have proven that our algorithm is correct, i.e. that it converges towards an equilibrium point of our initial system. At the same time, it provides a sequence of S-systems that locally approximate the initial system. We show here that this sequence of systems is useful because it facilitates the study of the stability of the equilibrium.

Consider the n -dimensional dynamical system:

$$\begin{cases} \frac{dx}{dt} = F(x) = V^+(x) - V^-(x) \\ x \in (\mathbb{R}_+^*)^n \end{cases} \quad (11)$$

Algorithm 1 ensures that, given any initial condition x^0 in $(\mathbb{R}_+^*)^n$, unless we fall in a degenerate case, we produce a sequence $(x^q)_{q \in \mathbb{N}}$ (with $x^q \in (\mathbb{R}_+^*)^n$) that tends towards a limit point $\tilde{x} \in (\mathbb{R}_+^*)^n$ which is an equilibrium of (11). More precisely, $x^q = \Psi^{(q)}(x^0)$.

Meanwhile, at each step, it provides us with a S-system $S_q(\alpha_q, \beta_q, G_q, H_q)$ which comes from the S-approximations of functions V^+ and V^- in x^q . Thus, we have:

$$\begin{cases} \alpha_q = \alpha(x^q) \\ \beta_q = \beta(x^q) \\ G_q = (g_{ij}^q)_{i,j=1 \dots n} \text{ with: } g_{ij}^q = g_{ij}(x^q) \\ H_q = (h_{ij}^q)_{i,j=1 \dots n} \text{ with: } h_{ij}^q = h_{ij}(x^q) \end{cases}$$

where α , β , g_{ij} and h_{ij} are the functions defined in (6). If we assume that V^+ and V^- are at least \mathcal{C}^1 , we deduce that these sequences converge, as q tends to ∞ , towards:

$$\begin{cases} \alpha_q \rightarrow \alpha(\tilde{x}) \stackrel{def}{=} \tilde{\alpha} \\ \beta_q \rightarrow \beta(\tilde{x}) \stackrel{def}{=} \tilde{\beta} \\ G_q \rightarrow G(\tilde{x}) \stackrel{def}{=} \tilde{G} \\ H_q \rightarrow H(\tilde{x}) \stackrel{def}{=} \tilde{H} \end{cases}$$

Let (\tilde{S}) be the following S-system:

$$(\tilde{S}) : \dot{x}_i = \tilde{\alpha}_i \prod_{j=1}^n x_j^{\tilde{g}_{ij}} - \tilde{\beta}_i \prod_{j=1}^n x_j^{\tilde{h}_{ij}}, \quad i = 1 \dots n \quad (12)$$

We want to know in which sense the system (12) approximates the system (11). An answer is given by the following proposition:

PROPOSITION 5.1. *F is supposed \mathcal{C}^r ($r \geq 1$). The equilibrium \tilde{x} of (11) is an equilibrium of (12). Moreover, if \tilde{x} is hyperbolic, then the flow generated by (12) is topologically conjugate to the flow generated by (11) in a neighborhood of \tilde{x} .*

PROOF. The first assertion is obvious with proposition 3.1. Let us prove the second assertion: it is a direct consequence of the Hartman-Grobman theorem (see e.g. [19]). According to Hartman-Grobman theorem, a dynamical system is topologically conjugate to its linearized system. Proposition 3.1 shows that systems (11) and (12) have the same linearized dynamical systems in \tilde{x} . By transitivity of the topological conjugation, (11) and (12) are so topologically conjugate around \tilde{x} . \square

This proposition implies that the stability of \tilde{x} for system (12) is the same that the stability of \tilde{x} for system (11). As

an exemple, let us consider the following 2-dimensional dynamical system:

$$(Ex) \begin{cases} \dot{x} = \frac{x}{2+y} - \frac{x^2 y^4}{(3+x)(4+y^3)} \\ \dot{y} = \frac{5x}{3+x} - \frac{2xy^3}{(x+1)(y+2)} \end{cases}$$

We find the equilibrium point $\tilde{x} \approx (1.2301, 1.6950)$ and the matrix $\tilde{G} - \tilde{H}$:

$$\tilde{G} - \tilde{H} = \begin{pmatrix} -0.709 & -2.812 \\ 0.261 & -2.541 \end{pmatrix}$$

Thanks to theorem 2.1, we see that $\tilde{G} - \tilde{H}$ is sign semi-stable. According to proposition 5.1, the point \tilde{x} , as equilibrium of (Ex) is hence stable.

5.3 Discussion about convergence

The algorithm described above computes the iterations of a vectorial function Ψ on an initial point $x^0 \in (\mathbb{R}_+^*)^n$, in order to converge towards a fixed point of Ψ . As the jacobian of Ψ is the null matrix in those fixed points, we know that the convergence is very fast (up to four or five iterations in all the examples presented, for a precision of 10^{-4} or 10^{-5}). As a matter of fact, we are in a case where the speed of convergence is the best possible. Indeed, if the function Ψ is K -contractant, one can easily verify that the convergence of the iteration is in K^n (where n is the number of iterations). Since $J_\Psi(\tilde{x}) = 0$, then we can find a neighborhood of \tilde{x} wherein Ψ is K -contractant for any $0 < K < 1$.

However, even if the speed of convergence is very fast, the algorithm's behaviour is strongly dependent on the choice of initial point x^0 . Indeed, if initial system has multiple positive equilibria, each of them has distinct basins of attraction. We cannot *a priori* know in which of these basins the point x^0 is. We even cannot ensure that x^0 actually lies in one of them. In fact, the study of basins of attractions of such iterations is a complex issue. The boundaries of such basins can be quite complicated, even fractals [8]. As an exemple, we launched our algorithm for the switch system (9) with initial conditions taken on a grid of $]0, 4]^2$. To visualize the three basins, we associated a color to each equilibrium. Then we colored the points of our grid with respect to the equilibrium towards which they lead (see fig 2).

6. APPLICATION TO BIOLOGY

As we said in section 2.1, S-systems are particularly appropriate to model biochemical pathways. Indeed, in a biochemical pathway, each ODE represents the evolution of the concentration of a chemical species. It is composed of the difference of two positive terms (production and decay of the species). In the exemple given above (equation (1)), we saw that the mass-action law gives, for a simple reaction, monomial terms. The structure of S-systems seems therefore particularly relevant in the modeling of biochemical systems. Nevertheless, in most biochemical pathways, systems are obviously more complicated. Most of biochemical reactions depend on the concentration of appropriate enzymes that catalyse the reaction. The dynamics of simple substrate-product enzymatic reaction: $S \xrightarrow{E} P$ is given by the Michaelis law:

$$\dot{S} = -\frac{kES}{K_M + S}$$

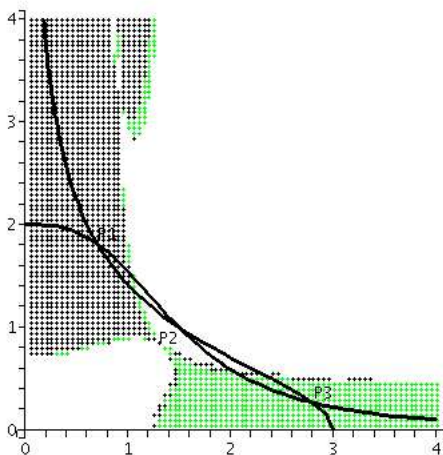


Figure 2: Basins of attraction of points $P1$ (dark), $P2$ (white) and $P3$ (grey). We obtained these graphs by applying algorithm 1 for system (9) with initial conditions taken in a regular grid of $]0, 4[$.

where k and K_M are specific constants. The presence of such expressions implies rational functions in the equations. Actually, biological enzymes may exhibit even more complex behaviours like cooperativity or allostery, that introduce terms such as Hill functions or composition of Hill functions. Because of these terms, it is not possible to give a global representation of such a system with a S-system. The idea of S-approximation is therefore to propose a local approximation of the dynamics of a complex biochemical pathway in the shape of a S-system.

We are currently working in collaboration with G. Curien (see [4]) on a specific example. The goal of this work is to understand the metabolic system responsible for the synthesis of aminoacids in Arabidopsis Thaliana. So far, we have focused our study on a subsystem of 14 variables, with 9 symbolic parameters. *In vivo*, this system exhibits a stationary behaviour. Giving realistic values of parameters and initial conditions, we managed, thanks to our algorithm, to find this positive equilibrium. We now have to study the S-approximation of the system near this equilibrium, with different realistic sets of parameters. This work is in progress.

7. CONCLUSION AND PERSPECTIVES

As we said in the introduction, a large part of research concerning the analysis of biological phenomena uses both symbolic and numerical techniques. The S-systems as we described represent a large class of systems, yet their simple mathematical expression allows symbolic manipulations, providing a practical framework of study. Algorithm 1, as presented here, needs numerical estimations of symbolic parameters. Nevertheless the technique of S-approximation (def 3.1) consists of symbolic manipulations (in particular, we use symbolic computation of partial derivatives). It can be calculated in any point of the phase space and can include symbolic parameters.

S-approximation gives a computable and rather good approximation of ODE systems (see [18] for a comparison between power-law approximation and linearization). A very interesting idea is therefore to use the context information (given for instance by biologists) of a particular system in order to create a piecewise S-approximation of this system. This should provide a global approximation interpolating the system in some critical points in the phase space (see [14]).

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