Journal of Symbolic Computation 70 (2015) 112–135

Contents lists available at ScienceDirect

Journal of Symbolic Computation

www.elsevier.com/locate/jsc

Special algorithm for stability analysis of multistable biological regulatory systems ☆

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ARTICLE INFO

Article history:
Received 25 December 2013
Accepted 21 September 2014
Available online 2 October 2014

Keywords:
Quantifier elimination
Root classification
Biological regulation system
Stability

ABSTRACT

We consider the problem of counting (stable) equilibriums 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.

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 $\mathbf{x} = (x_1, \ldots, x_n)$,

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

☆ This research was partly supported by US National Science Foundation Grant 1319632, China Scholarship Council (201206010094), National Science Foundation of China Grants 11290141 and 11271034 and 2014 NIMS Thematic Program on Applied Algebraic Geometry.

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http://dx.doi.org/10.1016/j.jsc.2014.09.039

and each $f_k(\mathbf{u}, x_1, \ldots, x_n)$ is a rational function in $x_1, \ldots, x_n$ 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) equilibriums of the system is uniform. Furthermore, for each open cell, we would like to determine the number of (stable) equilibriums.

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 (Tarski, 1951; Collins, 1975; Arnon et al., 1988; McCallum, 1988, 1999, 2001; Grigoriev, 1988; Hong, 1990a, 1990b; Collins and Hong, 1991; Renegar, 1992a, 1992b, 1992c; Basu et al., 1996, 1999, 2006; Brown, 2001a, 2001b; Dolzmann et al., 2004; Brown and McCallum, 2005 Strzeboński, 2006, 2011; Brown, 2012; Hong and Safey El Din, 2012; Bradford et al., 2013; Brown, 2013). There are several software systems such as `QEPCAD` (Collins and Hong, 1991; Hong, 1992; Brown, 2001a, 2003), `Redlog` (Dolzmann and Sturm, 1997), `Reduce` (in Mathematica) (Strzeboński, 2000, 2005) and `SyNRAC` (Anai and Yanami, 2003). Hence, in principle, the stability analysis of the above system can be carried out automatically using those software systems. However, it is also well known that the complexity (Davenport and Heintz, 1988; Basu et al., 1996) of those algorithms is 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 (Yang et al., 2001; Yang and Xia, 2008). In fact, Wang and Xia (2005a, 2005b), Niu and Wang (2008) and Niu (2012) tackled the stability analysis problem using `DISCOVERER` (Xia, 2007).[1] They were able to tackle a specialized simultaneous decision problem ($n = 6$ and $c = 2$) (Cinquin and Demongeot, 2002) in 55,000 seconds (Niu, 2012). 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 (Cinquin and Demongeot, 2002, 2005; Cinquin and Page, 2007). The family of differential equations has the form $\dot{\mathbf{x}} = \mathbf{f}(\sigma, \mathbf{x})$ where $\mathbf{f}$ is a rational 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 (Lazard, 1988; Liska and Steinberg, 1993; González-Vega, 1996; Dorato et al., 1997; Jirstrand, 1997; Weispfenning, 1997; Hong et al., 1997a, 1997b; Ying et al., 1999; Anai and Weispfenning, 2001; Wang and Xia, 2005a, 2005b; Brown et al., 2006; Größlinger et al., 2006; Niu and Wang, 2008; Xia et al., 2008; She et al., 2009; Sturm et al., 2009; Niu, 2012; She et al., 2013).

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

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[1] `DISCOVERER` was integrated later in the `RegularChains` package in Maple. Since then, there are several improvements on the package from both mathematical and programming aspects (Chen et al., 2013). One can see the command `RegularChains[ParametricSystemTools][RealRootClassification]` in any version of Maple that is newer than Maple 13.