Alicia Dickenstein

Informe de la licencia por año sabático durante 2017

Durante el año 2017, en uso del Año Sabático que me fue concedido por Resolución CS-2017 No. 6446, cumplí con creces con el Plan de Trabajo presentado con mi solicitud.

Durante los meses de febrero, marzo y abril, ejercí un cargo de Profesora Invitada en el Royal Institute of Technology (KTH), Estocolmo, Suecia, por medio de un subsidio de la prestigiosa fundación sueca Kurt and Alice Wallenberg. En este marco dicté la primer parte de una materia para alumnos graduados tanto del KTH como de la Universidad de Estocolmo sobre "Topics in Applied Algebraic Geometry".

En octubre/noviembre visité por un mes el International Center for Theoretical Physics (ICTP), Trieste, Italia, en mi carácter de Simons Senior Research Associate.

Por otra parte, participé de diversos encuentros matemáticos internacionales, que detallo a continuación, en los que dicté conferencias de investigación invitadas:

- Conferencia Rey Pastor II, Reunión Conjunta UMA-RSME, Argentina, Diciembre 2017.
- ICTP Basic Notions Seminar, Trieste, Italia, Noviembre 2017.
- ICTP Math Seminar, Trieste, Italia, Noviembre 2017.
- Max Planck Institute for Mathematics and the Sciences, Leipzig, Alemania, Noviembre 2017.
- Tercera Escuela Latinoamericana de Geometría Algebraica (ELGA III), México, Agosto 2017.
- SIAM AG 17, Atlanta, EEUU, Agosto 2017.
- IMCARA, Conferencia Plenaria, Brasil, Julio 2017.
- MCA 2017, Session on Foliations and Singularities, Canada, Julio 2017.
- Workshop on Reaction Networks and Population Dynamics, MFO, Alemania, Junio 2017.
- MEGA 2017, Niza, Francia, Junio 2017.
- BIRS Workshop on Mathematical Analysis of Biological Interaction Networks, Canada, Junio 2017.
- VI MACI, Conferencia plenaria, C. Rivadavia, Argentina, Mayo 2017.
- Colloquium, Stockholm Mathematics Center, Suecia, Abril 2017.
- Commutative Algebra Seminar, U. Stockholm. Suecia, March 2017.
- Algebraic Algorithms and Applications, U. Pisa, Italia, Marzo 2017.
- Polar Geometry, U. Oslo, Noruega, Enero 2017.

Asimismo, dicté una conferencia de divulgación en el Espacio Avanza, ANTEL, Montevideo, organizada por docentes de la Facultad de Ingeniería de la Universidad de la República, Uruguay, Diciembre de 2017.

Durante todo el año continué con mis tareas de dirección de mi alumna de doctorado Magalí Giaroli, con la dirección de los posdoctorandos Juliana García Galofre y Javier Gargiulo, así como la dirección de tres Investigadores Asistentes del CONICET: Mercedes Pérez Millán, M. Isabel Herrero y Nicolás Botbol.

En este período avancé en la mayoría de los puntos de mi plan de trabajo. Por un lado, en el libro que estoy escribiendo con la Prof. Elisenda Feliu, de la Universidad de Copenhaguen, sobre *"Algebraic Methods for the Study of Biochemical Reaction Networks"*, que esperamos terminar en 2018. Por otro lado, realizamos las correcciones requeridas por los editores del paper *The structure of MESSI biological systems,* con M. Pérez Millán, que está próximo a ser aceptado en el SIAM Journal on Applied Dynamical Systems. Con la doctoranda Magalí Giaroli y el Prof. Frédéric Bihan, de la U. Savoie Mont Blanc, Francia, estamos terminando la redacción de dos trabajos, titulados: "Lower bounds for positive roots and regions of multistationarity in chemical reaction networks" and "Regions of multistationarity in cascades of Goldbeter-Koshland loops". Con la postdoctoranda Juliana Pérez Galofre, la Dra. M. Pérez Millán (UBA-CONICET) y el Prof. Reinhard Laubenbacher (Department of Cell Biology, University of Connecticut, USA) estamos terminando un trabajo cuyo título tentativo es "Beyond Boolean Networks". Con la Dra. Pérez Millán y las Prof. Anne Shiu y Xiaoxiao Tang (TAMU, EEUU), estamos terminando un trabajo titulado "Investigating multistationarity in structured reaction networks". Con la Dra. M. Isabel Herrero y el Dr. Bernard Mourrain (INRIA Mediterranée, Francia) estamos terminando un trabajo con título provisorio "An elementary tropical approach to the implicitization of generic rational varieties". Con la Prof. Sandra Di Rocco (KTH, Suecia) y el Prof. Ralph Morrison (Williams College, USA) tenemos un trabajo en realización titulado "Iterated multivariate discriminants and mixed discriminants", que también esperamos terminar en los próximos meses. He iniciado además otros tres trabajos de investigación, que se encuentran en etapas más incipientes.

Terminé los siguientes artículos invitados:

- *Algebraic tips in the study of biochemical reaction networks,* por aparecer: Oberwolfach Reports, European Math. Society Publishing House, 2018.
- *Algebraic geometry in the interface of pure and applied mathematics*, por aparecer: Mathematical Intelligencer, 2018.

Los siguientes trabajos fueron publicados a lo largo del 2017:

- *Higher selfdual toric varieties,* con R. Piene, Annali Mat. Pur. Appl. (2017), Vol. 195, n.5, 1759-1777.
- *Arithmetics and combinatorics of tropical Severi varieties of univariate polynomials*, con M. Isabel Herrero y Luis F. Tabera, Israel J. Math., September 2017, Volume 221, Issue 2, 741–777.
- *Descartes' Rule of Signs for Polynomial Systems supported on Circuits, con F. Bihan, International Mathematics Research Notices*, Volume 2017, Issue 22, 1 November 2017, 6867–6893.

Continué asimismo con mis tareas como Vice-Presidenta de la Unión Matemática Internacional (IMU), que se desarrollan durante todo el año por via electrónica. Además, asistí a la Reunión Anual del Comité Ejecutivo de la IMU que se realizó en marzo en Londres, Inglaterra y a la Reunión Anual del Comité Ejecutivo de la Commission for Mathematical Instruction (ICMI), dependiente de la IMU, que se realizó en junio en Ginebra, Suiza.

Como miembro del Council de la American Mathematical Society (AMS) participé de la reunión del Consejo que se realizó en Atlanta, EEUU, en enero de 2017 y de la reunión del Committee for the Profession, que se realizó en Chicago, EEUU, en octubre de 2017.

Realicé las siguientes tareas editoriales:

- Editora del *Journal of Symbolic Computation.*
- Editora de la *Revista de la Unión Matemática Argentina.*
- Editora Correspondiente del SIAM Journal on Applied Algebra and Geometry.
- Editora del Vietnam Mathematical Journal.
- Referatos para diversas revistas de circulación internacional, incluyendo Advances in Mathematics, Foundations of Computational Mathematics, Journal of Mathematical Biology, etc.

Por otro lado, durante 2017 realicé las siguientes tareas profesionales de asesoramiento, evaluación y organización:

- Miembro del I Scientific Program Committee del MCA2021, Argentina, 2021.
- Miembro del Program Committee del ICME14, a realizarse en Shangai, China, 2020.
- Miembro del Comité Científico del Workshop Nonlinear Algebra in Applications, ICERM, Providence, EEUU, 2019.
- Miembro del Comité Científico del ELGA IV, Chile, 2019.
- Miembro del Comité Científico del ELGA III, México, 2017.
- Miembro del Comité Científico de SIAM AG17, EEUU, 2017.
- Coorganización de Sesión, MCA 2017, Canada, 2017.
- Miembro del Comité Científico de IMCARA, Brasil, 2017.
- Miembro del Comité Científico del Pan African Congress of Mathematicians, Marruecos, 2017.
- Miembro del Comité Asesor de la Red ARCADES, subvencionada por la Unión Europea en el marco de las Marie Sklodowska-Curie Actions — Innovative Training Networks (ITN).
- Miembro del Comité Científico del CIMAT, Guanajuato, México.
- Jurado del Premio Ramanujan, 2017-2018, otorgado por la IMU y el ICTP, Trieste.
- Miembro del Comité Evaluador del Heidelberg Laureate Forum, Alemania.

- Miembro del Equipo Argentino del proyecto SAGA (STEM and Gender Advancement), UNESCO.
- Evaluación de proyecto para el Instituto Fields, Canada.
- Evaluación de proyecto para ANR, Francia.
- Evaluación de proyecto para la Austrian Science Fund (FWF), Austria.
- Evaluación de proyecto para el FondeCyT, Chile.
- Jurado de la Tesis Doctoral de Nardo Giménez, FCEN, UBA.
- Jurado de la Tesis de Maestría de Lisa Niklasson, Universidad de Estocolmo, Suecia.
- Miembro de la Subcomisión de Doctorado, Departamento de Matemática, FCEN, UBA,
- Miembro del Consejo Asesor Departamental, Departamento de Matemática, FCEN, UBA.

En 2017 recibí el Premio "Consagración en Matemática", otorgado por la Academia Nacional de Ciencias Exactas, Físicas y Naturales (ANCEFN), Argentina.

Dra. Alicia Dickenstein
Leg. 45.267

BEYOND BOOLEAN NETWORKS

J. GARCÍA GALOFRE*,**, M. PÉREZ MILLÁN*,**, R. LAUBENBACHER***, A. DICKENSTEIN*,**

ABSTRACT. We introduce discrete multivalued networks with arbitrary finitely many states for each node and we model the dynamics of networks (for instance, gene regulatory networks) via operations in multivalued logic [1], which can be seen as tropical operations. We are able to generalize several good properties of Boolean networks. Inspired by [6, 7], we show how to transform any input into a multivalued version of AND/NOT networks, followed by a reduction of variables. We give an algorithm to compute the steady states of the system that in most instances has a complexity which does not essentially increase with the number of states.

1. INTRODUCTION (*DRAFT VERSION*)

This paper is an invitation to model biological networks with any (fixed) finite number of states for every node, in particular to predict the qualitative behavior of gene regulatory networks. We fix a natural number m and we consider networks with $m+1$ states

$$X = \{0, \frac{1}{m}, \frac{2}{m}, \dots, \frac{m-1}{m}, 1\}. \tag{1}$$

In particular, we have a Boolean network when $m = 1$. Our aim is to study the dynamics of the iteration of a function $f : X^n \to X^n$, with $n \in \mathbb{N}$, with syncronous updates.

Any function f defined over a finite set of cardinality a power of a prime number can be thought as a function over a finite field $\mathbb{F}$, moreover it can be expressed as a polynomial function and this opens the use of tools for computational algebraic geometry as in [?]. However, we propose to use in the multivariate setting the operations $\odot$, $\oplus$ introduced in Section 1 that come from multivalued logic [1, 2], which are more intuitive and closer to biological interpretations than the usual operations in $\mathbb{F}$ (and there is no restriction on the number of values).

We show that via these operations of multivalued logic, which are indeed expressed in terms of linear inequalities, we can recover most of the good properties of Boolean networks. Moreover, we show that the computation of steady states can be done algorithmically for any m using tools to find lattice points in rational polytopes and that in most cases, the complexity to compute the steady states is essentially the same as in the Boolean setting. This is opposed to the standard way of translating a multivalued model into a Boolean one, but with $(m+1)n$ nodes (see for instance [5] and the references therein).

Furthermore, even if we work with a syncronous update of the nodes, we exemplify with a small network extracted from the foundational book [4] how the syncronous multivalued setting can model the features of an asyncronous model, as the networks become more *expressive*.

In section 1 we introduce the logic operations $\oplus, \odot, neg$ together with their main properties and we give in Theorem 7 a constructive way of turning data from a table into an expression of the function in terms of $\odot, neg$ and constant functions. In section 2, we further show how to algorithmically translate any network into a $\odot - neg$ network similarly to the AND/NOT networks in the Boolean case, together with further possible reductions of the number of variables as in [6, 7] (see Theorem 6 for the increase in the number of variables). We present in Example 8 the translation to our setting of an interesting network extracted from www.cellcolective.org, where the number of nodes eventually decreases. One crucial algorithmic fact for $\odot - neg$ networks is Lemma 10, that allows us to automatize the computations without simulations, which would be too costly in general.

Section 5 addresses the computation of steady states for $\odot - neg$ networks, which in turn compute the steady states of any network function $F : X^n \to X^n$ by Lemma 15. Our approach is applied in Example 20 Finally, section 6 features a preliminary version into the multivalued syncronous setting of asyncronous Boolean networks.

G.G., PM and D. were partially supported by UBACYT 20020100100242, CONICET PIP 20110100580, and ANPCyT PICT 2013-1110, Argentina; L. etc.

ACKNOWLEDGEMENTS

We are grateful to Alejandro Petrovich and to Patricio Díaz Varela for the references and explanations about MV-algebras in logic.

REFERENCES

[1] Cignoli, Roberto L. O. and D'Ottaviano, Itala M. L. and Mundici, Daniele, Algebraic foundations of many-valued reasoning, Trends in Logic—Studia Logica Library, Vol. 7, Kluwer Academic Publishers, Dordrecht, 2000.

[2] Epstein, G.: *The lattice theory of Post algebras*. Transactions of the American Mathematical Society Vol. 95, No. 2 (May, 1960), 300–317.

[3] Free software Latte, by J. de Loera and collaborators, available at: https://www.math.ucdavis.edu/latte/.

[4] Thomas, R. and d'Ari, R.: Biological feedback, CRC press, 1990.

[5] Tonello, E.: *On the conversion of multivalued gene regulatory networks to Boolean dynamics*, arXiv:1703.06746.

[6] Veliz-Cuba A, Buschur K, Hamershock R, Kniss A, Wolff E, Laubenbacher R.: *AND-NOT logic framework for steady state analysis of Boolean network models*, Appl Math and Inform Sci. 7(4) (2013):1263.

[7] Veliz-Cuba A, Laubenbacher R, Aguilar B.:*Dimension reduction of AND-NOT network model.* Electronic Notes in Theoretical Computer Science 316 (2015), 83–95.

[8] Weinstein, N., Ortiz-Gutiérrez, E., Muoz, S., Rosenblueth, D., Alvarez-Buylla, E. and Mendoza, L.: *A model of theregulatory network involved in the control of the cell cycle and cell differentiation in the Caenorhabditis elegans vulva*, BMC Bioinformatics 16 (2015): 81.

* DTO. DE MATEMÁTICA, FCEN, UNIVERSIDAD DE BUENOS AIRES, CIUDAD UNIVERSITARIA, PAB. I, C1428EGA BUENOS AIRES, ARGENTINA.

** IMAS (UBA-CONICET), CIUDAD UNIVERSITARIA, PAB. I, C1428EGA BUENOS AIRES, ARGENTINA.

*** UCHC, ETC

E-mail address: jgarciag@dm.uba.ar, mpmillan@dm.uba.ar, laubenbacher@uchc.edu, alidick@dm.uba.ar

LOWER BOUNDS FOR POSITIVE ROOTS AND REGIONS OF MULTISTATIONARITY IN CHEMICAL REACTION NETWORKS

FRÉDÉRIC BIHAN, ALICIA DICKENSTEIN, AND MAGALÍ GIAROLI

ABSTRACT. Given a real sparse polynomial system, we present a general framework to find explicit coefficients for which the system has more than one positive solution, based on the recent article by Bihan and Spaenlehauer [3]. We apply this approach to find explicit *reaction rate constants* and *total conservation constants* in biochemical reaction networks for which the associated dynamical system is multistationary.

1. INTRODUCTION

Multistationarity is a key property of biochemical reaction networks, because it provides a mechanism for switching between different response states. This enables multiple outcomes for cellular-decision making in cell signaling systems. Questions about steady states in biochemical reaction networks under *mass-action kinetics* are fundamentally questions about nonnegative real solutions to parametrized polynomial ideals. In particular, multistationarity corresponds to the existence of more than one positive steady state with fixed conserved quantities. We refer the reader to [10] for an expansion of this point of view and further references.

In this work, we develop tools from real algebraic geometry based on the paper [3] by Bihan and Spaenlehauer, to analyze systems biology models (see the basic terminology in Section 1.1 and a simple meaningful example in Section 1.2). We present a general framework to find "explicit" parameters for which multistationarity occurs and we exemplify our theoretical results in different biochemical networks of interest of arbitrary size and number of variables. For this, we need to adapt the theoretical results to make them amenable to effective computations in a variety of specific instances in the modeling of biochemical systems. Our developments are also based on the existence of explicit parametrizations of the corresponding steady state varieties, as described in Theorem 4.1 in [25].

We give two complementary approaches. On one side, we show how to deform a given choice of reaction rate constants and total concentration constants in order to produce multistationarity. On the other side, we describe open sets where multistationarity occurs in the space of all these constants. We derive inequalities in the reaction constants and in the total conservation constants whose validity implies the presence of multistationarity.

We show the practicality of our methods in our companion article [16], where we apply the theoretical tools develped in the paper to enzymatic cascades of Goldbeter-Koshland loops [20] with any number n of layers, with a repeated phosphatase. In this case, the associated polynomial systems have positive dimensions growing linearly with n and the number of conservation relations (and then of total conservation constants) also grows linearly with n, and it is at least four if $n \geq 2$ (the first case in which multistationarity occurs [12]).

1.1. Basics on chemical reaction networks and multistationarity.

Given a set of s chemical species, a *chemical reaction network* on this set of species is a finite directed graph whose vertices are labeled by complexes and whose edges $\mathcal{R}$ represent the reactions and are labeled by parameters $\kappa \in \mathbb{R}^{|\mathcal{R}|}_{>0}$, which are called *reaction rate constants*. Complexes

AD and MG are partially supported by UBACYT 20020100100242, CONICET PIP 11220150100473, and ANPCyT PICT 2013-1110, Argentina.

determine vectors in $\mathbb{Z}^s_{\geq 0}$ according to the species they consist of. We identify a complex with its corresponding vector and also with the formal linear combination of species specified by its coordinates. Under mass-action kinetics, the concentrations $x_1, x_2, \ldots, x_s$ of the species are functions *functions of time* t which evolve according to the following autonomous system of ordinary differential equations:

$$f(x) = \dot{x} = \left(\frac{dx_1}{dt}, \frac{dx_2}{dt}, \ldots, \frac{dx_s}{dt}\right) = \sum_{y \to y' \in \mathcal{R}} \kappa_{yy'} x^y (y' - y), \tag{1.1}$$

where $x = (x_1, \ldots, x_s)$, $x^y = x_1^{y_1} \ldots x_s^{y_s}$ and $y \to y'$ indicates that $(y, y') \in \mathcal{R}$; that is, the complex y reacts to the complex y'. The right-hand side of each differential equation $\frac{dx_i}{dt}$ is a polynomial f_i in $x_1, \ldots, x_s$ with real coefficients. A concentration vector $\bar{x} \in \mathbb{R}^s_{\geq 0}$ is a *steady state* of the system if $f(\bar{x}) = 0$, and $\bar{x}$ is a *positive* steady state if moreover $\bar{x} \in \mathbb{R}^s_{>0}$.

We observe that the vector $\dot{x}(t)$ lies for all time t in the so called *stoichiometric subspace* S which is the linear subspace spanned by the reaction vectors $\{y' - y : y \to y' \in \mathcal{R}\}$. In fact, a trajectory $x(t)$ beginning at a positive vector $x(0) = x^0 \in \mathbb{R}^s_{>0}$ remains in the intersection $(x^0 + S) \cap \mathbb{R}^s_{>0}$ of a parallel translate of S with the positive orthant, for all $t \geq 0$. If the subspace S is cut out by linear equations $S = \{\ell_1(x) = \ldots, \ell_m(x) = 0\}$ each ℓ_i defines a *conservation law* for the dynamics; the constant terms $T_1, \ldots, T_m$ of the linear equations of $x^0 + S = \{\ell_1(x) = T_1, \ldots, \ell_m(x) = T_m\}$ are called *total concentration constants.*

We say that the network *has the capacity for multistationarity* if there exists a choice of reaction rate constants κ such that there are two or more steady states in a same stoichiometric compatibility class for some initial state x^0, that is, for an appropriate choice of total conservation constants. Starting with [7, 8], several articles studied the capacity for multistationarity from the structure of the digraph [1, 12, 14, 21, 24, 25]. Once the capacity for multistationarity is determined, the following difficult question is to find values of multistationary parameters as exhaustively and explicitly as possible. This problem is in principle effectively computable but the inherent high complexity does not allow to treat interesting networks with standard general tools. Several articles addressed this task, providing different answers based on ad-hoc computations, injectivity results based on signs of minors, and degree theory [4, 5, 6, 18, 22, 30].

1.2. **Our results for a two-component system.** We showcase our results in a simple meaningful example . The following chemical reaction network is a *two-component system* [26] with *hybrid* histidine kinase (hybrid HK) whose multistationarity was studied in [4, 22]. Two-component signal transduction systems enable bacteria to sense, respond, and adapt to a wide range of environments, stressors, and growth conditions. This network has six species $X_1, \ldots, X_6$, ten complexes (e.g. X_1 or $X_1 + X_6$, also identified with the vectors e_1 and $e_1 + e_6$ in $\mathbb{Z}^6_{\geq 0}$) and six reactions (directed edges), with labels given by positive reaction rate constants $k_1, \ldots, k_6$:

$$\begin{aligned} X_1 &\xrightarrow{k_1} X_2 \xrightarrow{k_2} X_3 \xrightarrow{k_3} X_4 \\ X_3 + X_5 &\xrightarrow{k_4} X_1 + X_6 \\ X_4 + X_5 &\xrightarrow{k_5} X_2 + X_6 \\ X_6 &\xrightarrow{k_6} X_5 \end{aligned} \tag{1.2}$$

This labeled digraph represent the following biological mechanism. Two component signaling relies on phosphotransfer reactions between histidine and aspartate residues on histidine kinases (HKs) and response regulator (RR) proteins. The hybrid HK consists of two phosphorylable domains. We denote the phosphorylation state of each site by p if the site is phosphorylated and 0 if it is not; the four possible states of HK are denoted

by HK_{00}, HK_{p0}, HK_{0p}, and HK_{pp}. We let RR be the unphosphorylated response regulator protein, and RR_p the phosphorylated form. Upon receiving a signal, the HK can auto-phosphorylate. Whenever the second phosphorylation site is occupied, the phosphate group can be transferred to RR.

We denote by $X_1, \ldots, X_6$ the chemical species $HK_{00}, HK_{p0}, HK_{0p}, HK_{pp}, RR, RR_p$, respectively. The concentration of the chemical species $X_1, \ldots, X_6$ are denoted by lowercase letters $x_1, \ldots, x_6$. These concentrations are assumed to be functions which evolve in time t, according to the following polynomial autonomous dynamical system:

$$\frac{dx_1}{dt} = f_1(k,x) = -k_1x_1 + k_4x_3x_5, \qquad \frac{dx_2}{dt} = f_2(k,x) = k_1x_1 - k_2x_2 + k_5x_4x_5,$$
$$\frac{dx_3}{dt} = f_3(k,x) = k_2x_2 - k_3x_3 - k_4x_3x_5, \qquad \frac{dx_4}{dt} = f_4(k,x) = k_3x_3 - k_5x_4x_5,$$
$$\frac{dx_5}{dt} = f_5(k,x) = -k_4x_3x_5 - k_5x_4x_5 + k_6x_6, \quad \frac{dx_6}{dt} = f_6(k,x) = k_4x_3x_5 + k_5x_4x_5 - k_6x_6.$$

It is straightforward to check that there are two linearly independent relations: $f_1 + f_2 + f_3 + f_4 = f_5 + f_6 = 0$, which imply the existence of two constants T_1, T_2 such that for any value of t:

$$\ell_1 = x_1 + x_2 + x_3 + x_4 = T_1, \qquad \ell_2 = x_5 + x_6 = T_2. \tag{1.3}$$

Indeed, the stoichiometric subspace equals $S = \{\ell_1(x) = \ell_2(x) = 0\}$. We assume that there is a positive point in the translate of S defined by the total conservation constants T_1, T_2, so they are positive real numbers.

We now explain our strategy. Our problem is to determine values of $(k_1, \ldots, k_6, T_1, T_2)$ in $\mathbb{R}^8_{>0}$ for which the polynomial system

$$f_1(k,x) = \cdots = f_6(k,x) = \ell_1(x) - T_1 = \ell_2(x) - T_2 = 0, \tag{1.4}$$

has *more than one positive solution* $x \in \mathbb{R}^6_{>0}$. We have, using the framework of the main Theorems ?? and ??:

Theorem 1.1. *With the notation of (1.2) and (1.3), assume that a fixed choice of reaction rate constants and total concentration constants verifies the inequalities*

$$k_6\left(\frac{1}{k_2} + \frac{1}{k_3}\right) < \frac{T_1}{T_2} < k_6\left(\frac{1}{k_1} + \frac{1}{k_2}\right). \tag{1.5}$$

Then, there exist positive constants N_1, N_2 such that for any values of β_4 and β_5 veryfying $\beta_4 > N_1$ and $\frac{\beta_5}{\beta_4} > N_2$, the system (1.4) has at least three positive steady states after modifying only the parameters k_4, k_5 via the rescaling $\overline{k_4} = \beta_4\, k_4$, $\overline{k_5} = \beta_5\, k_5$.

In [4], the authors present necessary and sufficient conditions for the multistationarity of the network. They prove that the region of reaction rate constant space for which multistationarity exists is completely characterized by the inequality $k_3 > k_1$, but they do not describe the particular stoichiometric compatibility classes for which there are multistationarity. Note that our inequalities (1.5) imply in particular that $k_1 < k_3$ as in [4], but also involve the total concentrations. In [22] are provided necessary and sufficient conditions on all the parameters of the system for bistability, with a treatment ad hoc using Sturm's Theorem.

1.3. **The contents of the paper.** The basic idea we develop in this paper is to detect in the convex hull of the support of the monomials that define the equations of the steady states, (at least two) simplices *positively decorated* (see Definition ??) that form part of a regular subdivision. This ensures the extension of the positive real solutions of the corresponding subsystems to the total system. In Sections ?? and ?? we state and explain the theoretical setting which is of general interest for the search of positive solutions of sparse real polynomial systems beyond the applications we consider. In Section ?? we

work with the same support for all the polynomials of the system. Our main results are Theorems ??, ??. In Section ?? we present a mixed approach to the results of Section ??, considering different supports for each polynomial, summarized in Theorems ?? and ??. We refer the reader to [2, 3, 11, ?, 19, ?, 27] for the definitions and main properties of the mathematical objects we deal with.

In Section ?? we present a class of biological systems which contains many important mechanisms, called MESSI systems [25]. We focus on a particular class of MESSI systems called s-toric MESSI systems, for which explicit monomial parametrizations of the steady states are given in [25]. We present two examples of s-toric MESSI systems: the known case of sequential distributive multisite phosphorylation systems (with any number n of phosphorylation sites) and the case of enzymatic cascades with a single phospo/dephosphorylation cycle in each layer. We show a parametrization of the steady states following the algorithm given in [25]. We apply our method using this parametrization and a complete description of the conservation laws. This application is not straightforward. We need to develop special results, that we state and prove in general, beyond the particular enzymatic networks of interest that we study explicitly in Sections ?? and ??.

In Section ??, we study the sequential distributive multisite phosphorylation systems. Such systems were studied by many authors, starting with Wang and Sontag [30], who gave bounds and conditions for monostationarity and multistationarity in the parameters, with an interesting treatment ad hoc which also allowed them to find improved lower bounds (see also [18]). In [6], Conradi and Mincheva showed using degree theory and computations with the aid of a computer algebra system, that catalytic constants determine the capacity for multistationarity in the dual phosphorylation mechanism. They also indicate in the case $n = 2$ how to find values of the total concentrations such that multistationarity occurs. The more general interesting approach in [4] is also based on degree theory. The authors show how to find conditions on the reaction rates to guarantee mono or multistationarity, but they do not describe the particular total concentration constants for which there are multiple equilibria. With our approach, we obtain a system of three polynomial equations in three variables that describes the steady states (independently of n), that are in the framework of [3]. We give conditions on all the parameters (both on the reaction constants and on the total concentration constants) so that there are at least two positively decorated simplices in the triangulation of the convex hull of our support and by rescaling the rest of the parameters, we guarantee the existence of at least two non-degenerate positive steady states.

REFERENCES

[1] M. Banaji, C. Pantea. *The inheritance of nondegenerate multistationarity in chemical reaction networks.* Preprint, available at: arXiv:1608.08400 (2016).

[2] D. N. Bernstein. *The number of roots of a system of equations.* Funkcional. Anal. i Prilozen., 9(3) (1975), 1–4.

[3] F. Bihan, P-J. Spaenlehauer. *Sparse polynomial systems with many positive solutions from bipartite simplicial complexes.* Preprint, available at: arXiv:1510.05622 (2015).

[4] C. Conradi, E. Feliu, M. Mincheva, C. Wiuf. *Identifying parameter regions for multistationarity.* PLoS Comput Biol 13(10) (2017): e1005751.

[5] C. Conradi, D. Flockerzi, J. Raisch. *Multistationarity in the activation of a MAPK: Parametrizing the relevant region in parameter space.* Mathematical biosciences 211 (1) (2012), 105-131

[6] C. Conradi, M. Mincheva. *Catalytic constants enable the emergence of bistability in dual phosphorylation.* J. R. Soc. Interface (2014), rsif20110664.

[7] G. Craciun, M. Feinberg. *Multiple equilibria in complex chemical reaction networks: I. The injectivity property.* SIAM J. Appl. Math. 65 (2005), 1526–1546.

[8] G. Craciun, M. Feinberg. *Multiple equilibria in complex chemical reaction networks: II. The Species-Reactions Graph.* SIAM J. Appl. Math. 66(4) (2006), 1321–1338.

[9] J. de Loera, J.A. Rambau, F. Santos. Triangulations: Structures for Algorithms and Applications, vol. 25. Springer-Verlag (2010).

[10] A. Dickenstein. *Biochemical reaction networks: an invitation for algebraic geometers.* MCA 2013, Contemporary Mathematics 656 (2016), 65–83.

[11] A. Dickenstein, E. Feichtner, B. Sturmfels. *Tropical discriminants.* J. Amer. Math. Soc. 20 (2007), no. 4, 1111–1133.
[12] E. Feliu, C. Wiuf. *Enzyme-sharing as a cause of multi-stationarity in signaling systems* J. R. Soc. Interface 9 (2012), 1224–1232.
[13] E. Feliu, C. Wiuf *Simplifying biochemical models with intermediate species.* J. R. Soc. Interface (2013) 10: 20130484.
[14] D. Flockerzi, C. Conradi. *Subnetwork analysis for multistationarity in mass action kinetics.* J. of Physics: Conference Series 138 (2008), 012006.
[15] E. Gawrilow, M. Joswig. polymake: a framework for analyzing convex polytopes. Polytopescombinatorics and computation (Oberwolfach, 1997), 4373, DMV Sem., 29, Birkhuser, Basel, 2000.
[16] M. Giaroli, F. Bihan, A. Dickenstein. *Regions of multistationarity in cascades of Goldbeter-Koshland loops*, preprint, 2018.
[17] A. Goldbeter, D. E. Koshland. *An amplified sensitivity arising from covalent modification in biological systems.* Proceedings of the National Academy of Sciences, 78(11), (1981) 6840-6844.
[18] K. Holstein, D. Flockerzi, C. Conradi. *Multistationarity in Sequential Distributed Multisite Phosphorylation Networks.* Bull. Math. Biol. 75 (11) (2013), 2028–2058.
[19] I. M. Gelfand, M. M. Kapranov, A. V. Zelevinsky. Discriminants, resultants, and multidimensional determinants. Mathematics: Theory & Applications. Birkhauser Boston Inc., Boston, MA, 1994.
[20] A. Goldbeter, D. E. Koshland. *An amplified sensitivity arising from covalent modification in biological systems.* Proceedings of the National Academy of Sciences, 78(11), (1981) 6840-6844.
[21] B. Joshi, A. Shiu. *Atoms of multistationarity in chemical reaction networks.* J. Math. Chem. 51(1) (2013), 153–178.
[22] V. B. Kothamachu, E. Feliu, L. Cardelli, O. S. Soyer. *Unlimited multistability and Boolean logic in microbial signaling.* J. R. Soc. Interface (2015), 12 20150234 .
[23] I. Mirzaev, J. Gunawardena. *Laplacian dynamics on general graphs.* Bull. Math. Biol., 75 (2013), 2118–2149.
[24] S. Mueller, E. Feliu, G. Regensburger, C. Conradi, A. Shiu, A. Dickenstein. *Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry.* FoCM Journal 16 (1) (2016), 69–97.
[25] M. Pérez Millán, A. Dickenstein. *The structure of MESSI biochemical networks.* Preprint, available at: arXiv:1612.08763 (2017).
[26] A. M. Stock, V. L. Robinson, P. N. Goudreau. *Two-component signal transduction*, Annual review of biochemistry, 69(1) (2000), 183–215.
[27] B. Sturmfels. *On the Newton polytope of the resultant.* Journal of Algebraic Combinatorics 3 (1994), 207–236.
[28] T. Suwanmajo, J. Krishnan. *Mixed mechanisms of multi-site phosphorylation.* Journal of the Royal Society Interface (2015), 12 20141405.
[29] W. T. Tutte, *The dissection of equilateral triangles into equilateral triangles.* Proc. Cambridge Philos. Soc., 44 (1948), 463–482.
[30] L. Wang, E. Sontag. *On the number of steady states in a multiple futile cycle.* J. Math. Biol. 57(1) (2008), 29–52.

Laboratoire de Mathématiques, Université Savoie Mont Blanc, 73376 Le Bourget-du-Lac Cedex, France
E-mail address: Frederic.Bihan@univ-savoie.fr
URL: http://www.lama.univ-savoie.fr/~bihan/

Dto. de Matemática, FCEN, Universidad de Buenos Aires, and IMAS (UBA-CONICET), Ciudad Universitaria, Pab. I, C1428EGA Buenos Aires, Argentina
E-mail address: alidick@dm.uba.ar
URL: http://mate.dm.uba.ar/~alidick

Dto. de Matemática, FCEN, Universidad de Buenos Aires, and IMAS (UBA-CONICET), Ciudad Universitaria, Pab. I, C1428EGA Buenos Aires, Argentina
E-mail address: mgiaroli@dm.uba.ar

REGIONS OF MULTISTATIONARITY IN CASCADES OF GOLDBETER-KOSHLAND LOOPS

MAGALÍ GIAROLI, FRÉDÉRIC BIHAN, AND ALICIA DICKENSTEIN

We consider cascades of enzymatic Goldbeter-Koshland loops [17] with any number n of tiers, for which there exist two layers involving the same phosphatase. Even if the number of variables and the number of conservation laws tend to infinity as n goes to infinity, we find explicit regions in *reaction rate constant* and *total conservation constant* space for which the associated mass-action kinetics dynamical system is multistationary.

Our computations are based on the theoretical results of our companion paper [4], which are inspired by results in real algebraic geometry by Bihan and Spaenlehauer [3]. In the case of enzymatic cascades of Goldbeter-Koshland loops with any number n of layers, the associated polynomial systems have positive dimensions growing linearly with n and the number of conservation relations (and then of total conservation constants) also grows linearly with n, and it is at least four if $n \geq 2$. Such systems were studied in [5, 25] when all the enzymes are different, in which case there cannot be more than one positive steady state. In the case of two layers, it was shown in [13] that in the case $n = 2$ (see Figure 1), if the same phosphatase is acting at both tiers, then the network has the capacity for multistationarity. It can be deduced from the results in [1], that if there are any number of tiers, and the last two share a phosphatase, multistationarity parameters for the case $n = 2$ can be extended to produce multistationarity parameters in the general case. Our approach allows us to describe open sets in the rate constant and total concentration parameters which ensure multistationarity as long as at any pair of tiers in the cascade there is a shared phosphatase.

To clarify our results, we postpone some computations and technical proofs to an Appendix.

REFERENCES

[1] M. Banaji, C. Pantea. *The inheritance of nondegenerate multistationarity in chemical reaction networks.* Preprint, available at: arXiv:1608.08400 (2016).

[2] D. N. Bernstein. *The number of roots of a system of equations.* Funkcional. Anal. i Prilozen., 9(3) (1975), 1–4.

[3] F. Bihan, P-J. Spaenlehauer. *Sparse polynomial systems with many positive solutions from bipartite simplicial complexes.* Preprint, available at: arXiv:1510.05622 (2015).

[4] F. Bihan, A. Dickenstein, M. Giaroli, . *Lower bounds for positive roots and regions of multistationarity in chemical reaction networks*, preprint, 2018.

[5] S. Catozzi, J. P. Di-Bella, A. C. Ventura, J. A. Sepulchre. *Signaling cascades transmit information downstream and upstream but unlikely simultaneously.* BMC Systems Biology, 10(1), 84, (2016).

AD and MG are partially supported by UBACYT 20020100100242, CONICET PIP 11220150100473, and ANPCyT PICT 2013-1110, Argentina.

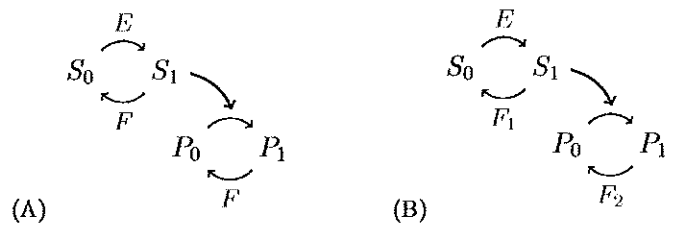

FIGURE 1. Same and different phosphatases in a 2-tier cascade of GK-loops.

[6] C. Conradi, E. Feliu, M. Mincheva, C. Wiuf. *Identifying parameter regions for multistationarity.* PLoS Comput Biol 13(10) (2017): e1005751.
[7] C. Conradi, D. Flockerzi, J. Raisch. *Multistationarity in the activation of a MAPK: Parametrizing the relevant region in parameter space.* Mathematical biosciences 211 (1) (2012), 105-131
[8] C. Conradi, M. Mincheva. *Catalytic constants enable the emergence of bistability in dual phosphorylation.* J. R. Soc. Interface (2014), rsif20110664.
[9] G. Craciun, M. Feinberg. *Multiple equilibria in complex chemical reaction networks: I. The injectivity property.* SIAM J. Appl. Math. 65 (2005), 1526–1546.
[10] G. Craciun, M. Feinberg. *Multiple equilibria in complex chemical reaction networks: II. The Species-Reactions Graph.* SIAM J. Appl. Math. 66(4) (2006), 1321–1338.
[11] J. de Loera, J.A. Rambau, F. Santos. Triangulations: Structures for Algorithms and Applications, vol. 25. Springer-Verlag (2010).
[12] A. Dickenstein. *Biochemical reaction networks: an invitation for algebraic geometers.* MCA 2013, Contemporary Mathematics 656 (2016), 65–83.
[13] E. Feliu, C. Wiuf. *Enzyme-sharing as a cause of multi-stationarity in signaling systems* J. R. Soc. Interface 9 (2012), 1224–1232.
[14] E. Feliu, C. Wiuf *Simplifying biochemical models with intermediate species.* J. R. Soc. Interface (2013) 10: 20130484.
[15] D. Flockerzi, C. Conradi. *Subnetwork analysis for multistationarity in mass action kinetics.* J. of Physics: Conference Series 138 (2008), 012006.
[16] E. Gawrilow, M. Joswig. polymake: a framework for analyzing convex polytopes. Polytopescombinatorics and computation (Oberwolfach, 1997), 4373, DMV Sem., 29, Birkhuser, Basel, 2000.
[17] A. Goldbeter, D. E. Koshland. *An amplified sensitivity arising from covalent modification in biological systems.* Proceedings of the National Academy of Sciences, 78(11), (1981) 6840-6844.
[18] K. Holstein, D. Flockerzi, C. Conradi. *Multistationarity in Sequential Distributed Multisite Phosphorylation Networks.* Bull. Math. Biol. 75 (11) (2013), 2028–2058.
[19] I. M. Gelfand, M. M. Kapranov, A. V. Zelevinsky. Discriminants, resultants, and multidimensional determinants. Mathematics: Theory & Applications. Birkhauser Boston Inc., Boston, MA, 1994.
[20] B. Joshi, A. Shiu. *Atoms of multistationarity in chemical reaction networks.* J. Math. Chem. 51(1) (2013), 153–178.
[21] V. B. Kothamanchu, E. Feliu, L. Cardelli, O. S. Soyer. *Unlimited multistability and Boolean logic in microbial signaling.* J. R. Soc. Interface (2015), 12 20150234 .
[22] I. Mirzaev, J. Gunawardena. *Laplacian dynamics on general graphs.* Bull. Math. Biol., 75 (2013), 2118–2149.
[23] S. Mueller, E. Feliu, G. Regensburger, C. Conradi, A. Shiu, A. Dickenstein. *Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry.* FoCM Journal 16 (1) (2016), 69–97.
[24] M. Pérez Millán, A. Dickenstein. *The structure of MESSI biochemical networks.* Preprint, available at: arXiv:1612.08763 (2017).
[25] J. A. Sepulchre, A. C. Ventura. *Intrinsic Feedbacks in MAPK Signaling Cascades Lead to Bistability and Oscillations.* Acta biotheoretica, 61(1) (2013), 59–78.
[26] T. Suwanmajo, J. Krishnan. *Mixed mechanisms of multi-site phosphorylation.* Journal of the Royal Society Interface (2015), 12 20141405.

Dto. de Matemática, FCEN, Universidad de Buenos Aires, and IMAS (UBA-CONICET), Ciudad Universitaria, Pab. I, C1428EGA Buenos Aires, Argentina
E-mail address: mgiaroli@dm.uba.ar

Laboratoire de Mathématiques, Université Savoie Mont Blanc, 73376 Le Bourget-du-Lac Cedex, France
E-mail address: Frederic.Bihan@univ-savoie.fr
URL: http://www.lama.univ-savoie.fr/~bihan/

Dto. de Matemática, FCEN, Universidad de Buenos Aires, and IMAS (UBA-CONICET), Ciudad Universitaria, Pab. I, C1428EGA Buenos Aires, Argentina
E-mail address: alidick@dm.uba.ar
URL: http://mate.dm.uba.ar/~alidick

Algebraic Methods for Biochemical Reaction Networks

Alicia Dickenstein, Elisenda Feliu

26/11/2017

Contents

Preface

In the recent years the number of applications of algebraic geometry to the life sciences, and to the sciences in general, has dramatically increased. In this book we address one such application, namely the use of algebraic techniques and approaches to study the solutions to polynomial systems that naturally arise when modeling biochemical reaction networks. The techniques we develop are also applicable in many other applied questions.

This book is intended to advanced undergraduates in mathematics, graduate students, and anyone interested in discovering the field. It can be used for personal reading, or as a textbook of a course in this topic. Standard courses in basic linear algebra and calculus are required, and knowledge on ordinary differential equations is advantageous. It is also recommended to have access to symbolic software to do the exercises. Extra background in algebra or dynamical systems is provided in the book, either in the main text, or in appendices.

We have tried to avoid technicalities whenever possible and illustrated definitions, results and proofs with numerous examples. Our wish is that the book is written such that the advanced mathematician is able to enjoy reading it on the bus, while the young mathematician, with not much experience in algebra nor in the topics of this book, can follow the text and do the exercises, no need to say, with the appropriate effort.

Chapters 2-6, rely on the foundational Chapter 1, but the dependencies among them have been kept to a minimum. Therefore, the reader can jump directly to a chapter of interest.

The current version (as of November 30, 2017) contains complete versions of Chapters 1 and 4, plus the first part of Chapter 2 (still in draft form). We also included motivations and lists of subjects to be expanded, together with some very preliminary parts of text. Of course, as we complete the book, we will also polish the current chapters.

We hope you enjoy reading the book and find the topic as interesting and challenging as we do. There are definitely many open questions to address. Comments and suggestions are welcome.

Alicia Dickenstein and Elisenda Feliu

Bibliography

[1] *Differential Equations, Dynamical Systems, and an Introduction to Chaos.* Elsevier, second edition, 2004.

[2] T. Ahsendorf, F. Wong, R. Eils, and J. Gunawardena. A framework for modelling gene regulation which accommodates non-equilibrium mechanisms. *BMC Biol*, 12(1):102, 23 pages, (2014).

[3] D. Angeli, P. De Leenheer, and E. Sontag. A petri net approach to the study of persistence in chemical reaction networks. *Math. Biosci.*, 210(2):598–618, 2007.

[4] M. Banaji and G. Craciun. Graph-theoretic approaches to injectivity and multiple equilibria in systems of interacting elements. *Commun. Math. Sci.*, 7(4):867–900, 2009.

[5] M. Banaji and G. Craciun. Graph-theoretic criteria for injectivity and unique equilibria in general chemical reaction systems. *Adv. Appl. Math.*, 44:168–184, 2010.

[6] M. Banaji and C. Pantea. The inheritance of nondegenerate multistationarity in chemical reaction networks, 2016.

[7] H. Bass, E.H. Connell, and D. Wright. The Jacobian conjecture: reduction of degree and formal expansion of the inverse. *Bull. Amer. Math. Soc.*, 7(2):287–330, 1982.

[8] A Ben-Israel. Notes on linear inequalities, 1: The intersection of the nonnegative orthant with complementary orthogonal subspaces. *J. Math. Anal. Appl.*, (9):303314, 1964.

[9] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, and P. E. Bourne. The Protein Data Bank (http://www.rcsb.org/pdb/). *Nucleic Acids Res.*, 28(1):235–242, 2000.

[10] V. I. Bykov and G. S. Yablonskii. Steady-state multiplicity in heterogeneous catalytic reactions. *Int. Chem. Engng.*, 21:142–155, 1981.

[11] W. Carver. Systems of linear inequalities. *Annals of Mathematics, Second Series*, 23, No. 3:212–220, (1922).

[12] S. Chaiken and D. Kleitman. Matrix tree theorems. *Journal of Combinatorial Theory, Series A*, 24:377–381, 1978.

[13] B. L. Clarke. Theorems on chemical network stability. *The Journal of Chemical Physics*, 62(3):773, 1975.

[14] B. L. Clarke. *Stability of Complex Reaction Networks*, volume 43 of *Advances in Chemical Physics*. John Wiley & Sons, Inc., Hoboken, NJ, USA, 1980.

[15] P. Cohen. The regulation of protein function by multisite phosphorylation–a 25 year update. *Trends Biochem. Sci.*, 25(12):596–601, Dec 2000.

[16] C. Conradi, E. Feliu, M. Mincheva, and C. Wiuf. Identifying parameter regions for multistationarity, 2016.

[17] G. M. Cooper and R. E. Hausman. *The cell.* ASM Press, Washington, fifth edition, 2009.

[18] A. Cornish-Bowden. *Fundamentals of Enzyme Kinetics.* Portland Press, London, third edition, 2004.

[19] D. Cox, J. Little, and D. O'Shea.. *Ideals, varieties, and algorithms.* Undergraduate Texts in Mathematics. Springer, New York, third edition, 2007. An introduction to computational algebraic geometry and commutative algebra.

[20] G. Craciun, A. Dickenstein, A. Shiu, and B. Sturmfels. Toric dynamical systems. *J. Symbolic Comput.*, 44(11):1551–1565, 2009.

[21] G. Craciun and M. Feinberg. Multiple equilibria in complex chemical reaction networks. I. The injectivity property. *SIAM J. Appl. Math.*, 65(5):1526–1546, 2005.

[22] G. Craciun and M. Feinberg. Multiple equilibria in complex chemical reaction networks: extensions to entrapped species models. *Syst. Biol. (Stevenage)*, 153:179–186, 2006.

[23] Gheorghe Craciun and Casian Pantea. Identifiability of chemical reaction networks. *Journal of Mathematical Chemistry*, 44(1):244–259, 2008.

[24] A. Deshpande and M. Gopalkrishnan. Autocatalysis in reaction networks. *Bull. Math. Biol.*, 76:2570–2595, 2014.

[25] A. Dickenstein. Biochemical reaction networks: an invitation for algebraic geometers. mca 2013. *Contemp. Math.*, 656:65–83, (2016).

[26] P. Érdi and J. Tóth. *Mathematical models of chemical reactions.* Nonlinear Science: Theory and Applications. Princeton University Press, Princeton, NJ. Theory and applications of deterministic and stochastic models.

[27] V. Kh. Fedotov, B. V. Alekseev, N. I. Koltsov, and S. L. Kiperman. On the multiplicity criterion for steady states in catalytic reactions. *Reaction Kinetics and Catalysis Letters*, 26(1-2):25–29, March 1984.

[28] M. Feinberg. Lectures on chemical reaction networks. http://www.chbmeng.ohio-state.edu/ feinberg/LecturesOnReactionNetworks/, 1980.

[29] M. Feinberg. Chemical reaction network structure and the stability of complex isothermal reactors I. The deficiency zero and deficiency one theorems. *Chem. Eng. Sci.*, 42(10):2229–68, 1987.

[30] M. Feinberg. Chemical reaction network structure and the stability of complex isothermal reactors–II. Multiple steady states for networks of deficiency one. *Chem. Eng. Sci.*, 43(1):1–25, 1988.

[31] M. Feinberg. The existence and uniqueness of steady states for a class of chemical reaction networks. *Arch. Rational Mech. Anal.*, 132(4):311–370, 1995.

[32] M. Feinberg and F.J.M. Horn. Chemical mechanism structure and the coincidence of the stoichiometric and kinetic subspaces. *Arch. Rational. Mech. Anal.*, 66(1):83–97, 1977.

[33] E. Feliu and C. Wiuf. Variable elimination in chemical reaction networks with mass-action kinetics. *SIAM J. Appl. Math.*, 72, 2012.

[34] E. Feliu and C. Wiuf. A computational method to preclude multistationarity in networks of interacting species. *Bioinformatics*, 29:2327–2334, 2013.

[35] E. Feliu and C. Wiuf. Simplifying biochemical models with intermediate species. *J. R. S. Interface*, 10:20130484, 2013.

[36] D. Flockerzi, K. Holstein, and C. Conradi. N-site Phosphorylation Systems with 2N-1 Steady States. *Bulletin of Mathematical Biology*, 76(8):1892–1916, 2014.

[37] Shinar G., Milo R., Martínez M. R., and Alon U. Input-output robustness in simple bacterial signaling systems. *Proc. Natl. Acad. Sci. USA*, 104:19931–19935, (2007).

[38] A. N. Gorban, V. I. Bykov, and G. S. Yabloskii. Thermodynamic function analogue for reactions proceeding without interaction of various substances. *Chemical Engineering Science*, 41(11):2739–2745, 1986.

[39] J. L. Gouze. Positive and negative circuits in dynamical systems. *J. Biol. Syst.*, 6:11–15, 1998.

[40] E. Gross, H. A. Harrington, Z. Rosen, and B. Sturmfels. Algebraic Systems Biology: A Case Study for the Wnt Pathway. *Bulletin of Mathematical Biology*, 78(1):21–51, 2015.

[41] J. Guckenheimer, M. Myers, and B. Sturmfels. Computing hopf bifurcations i. *SIAM J. Numer. Anal.*, 34:1–21, 2006.

[42] J. Gunawardena. Distributivity and processivity in multisite phosphorylation can be distinguished through steady-state invariants. *Biophys. J.*, 93:3828–3834, 2007.

[43] J. Gunawardena. Some lessons about models from michaelis and menten. *Molecular Biology of the Cell*, 23(4):517–519, 2012.

[44] J. Gunawardena. Biology is more theoretical than physics. *Molecular Biology of the Cell*, 24(12):1827–1829, 2013.

[45] J. Gunawardena. Time-scale separation michaelis and mentens old idea, still bearing fruit. *FEBS Journal*, 281(2):473–488, 2013.

[46] Jeremy Gunawardena. A linear framework for time-scale separation in nonlinear biochemical systems. *PLoS ONE*, 7(5):e36321, 2012.

[47] V. Hárs and J. Tóth. On the inverse problem of reaction kinetics. *Colloquia Mathematica Societatis János Bolyai 30. Qualitative Theory of Differential Equations, Szeged (Hungary)*, pages 363–379, 1979.

[48] F.J.M. Horn. Necessary and sufficient conditions for complex balance in chemical kinetics. *Arch. Rational Mech. Anal.*, 49:172–186, 1972.

[49] F.J.M. Horn and R. Jackson. General mass action kinetics. *Arch. Rational Mech. Anal.*, 47:81–116, 1972.

[50] B.P. Ingalls. *Mathematical Modeling in Systems Biology: An Introduction.* The MIT Press, 2013.

[51] A.N. Ivanova. Conditions for uniqueness of stationary state of kinetic systems related to structural scheme of reactions. *Kinet. Katal.*, 20:1019–1023, 1979.

[52] F. Jacob and J. Monod. Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.*, 3:318–356, 1961.

[53] B. Joshi and A. Shiu. Atoms of multistationarity in chemical reaction networks. *J. Math. Chem.*, 51:DOI:10.1007/s10910–012–0072–0, 2011.

[54] R.L. Karp, M. Pérez Millán, T. Dasgupta, A. Dickenstein, and J. Gunawardena. Complex-linear invariants of biochemical networks. *Journal of Theoretical Biology*, 311:130–138, 2012.

[55] E. L. King and C. Altman. A schematic method of deriving the rate laws for enzyme- catalyzed reactions. *?*, ?:?, 1956.

[56] G. Kirchhoff. Ueber die auflösung der gleichungen, auf welche man bei der untersuchung der linearen vertheilung galvanischer ströme geführt wird. *Annalen der Physik und Chemie*, 148:497–508, 1847.

[57] V. B. Kothamachu, E. Feliu, L. Cardelli, and O. S. Soyer. Unlimited multistability and boolean logic in microbial signalling. *J. R. S. Interface*, (DOI: 10.1098/rsif.2015.0234), 2015.

[58] J. P. Kruse and W. Gu. SnapShot: p53 posttranslational modifications. *Cell*, 133(5):930–930, May 2008.

[59] Pérez Millán M. and Dickenstein A. Implicit dose-response curves. *J. Math. Biol.*, 70:1669–1684, (2015).

[60] A. K. Manrai and J. Gunawardena. The geometry of multisite phosphorylation. *Biophys. J.*, 95:5533–5543, 2008.

[61] N. I. Markevich, J. B. Hoek, and B. N. Kholodenko. Signaling switches and bistability arising from multisite phosphorylation in protein kinase cascades. *J. Cell Biol.*, 164:353–359, 2004.

[62] T. W. McKeithan. Kinetic proofreading in T-cell receptor signal transduction. *Proceedings of the National Academy of Sciences*, 92(8):5042–5046, 1995.

[63] L Michaelis and M L Menten. Die kinetik der invertinwirkung. *Biochem z*, 1913.

[64] M. Milln Prez and A. Dickenstein. The structure of MESSI biological systems. *arXiv.org*, 2016.

[65] D. M. Mirzaev, I.and Bortz. Analytical equilibrium solutions of biochemical systems with synthesis and degradation. *Bull. Math. Biol.*, 77:1013–1045, 2015.

[66] I. Mirzaev and J. Gunawardena. Laplacian dynamics on general graphs. *Bull. Math. Biol.*, 75 (11):2118–2149, (2013).

[67] S. Müller, E. Feliu, G. Regensburger, C. Conradi, A. Shiu, and A. Dickenstein. Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry. *Found. Comput. Math.*, 16:69–97, 2016.

[68] J. D. Murray. *Mathematical Biology: I. An introduction*, volume 17 of *Interdisciplinary Applied Mathematics*. Springer, third edition, 2002.

[69] Mitio Nagumo. über die Lage der Integralkurven gewöhnlicher Differentialgleichungen. *Proc. Phys.-Math. Soc. Japan (3)*, 24:551–559, 1942.

[70] Casian Pantea, Heinz Koeppl, and Gheorghe Craciun. Global injectivity and multiple equilibria in uni- and bi-molecular reaction networks. *Discrete Contin. Dyn. Syst. Ser. B*, 17(6):2153–2170, 2012.

[71] M. Pérez Millán and A. Dickenstein. How far is complex balancing from detailed balancing? *Bull. Math. Biol*, 73 (4):811–828, (2011).

[72] M. Pérez Millán, A. Dickenstein, A. Shiu, and C. Conradi. Chemical reaction systems with toric steady states. *Bull. Math. Biol.*, 74:1027–1065, 2012.

[73] L. Perko. *Differential equations and dynamical systems*, volume 7 of *Texts in Applied Mathematics*. Springer-Verlag, New York, third edition, 2001.

[74] Sergey Pinchuk. A counterexample to the strong real Jacobian conjecture. *Math. Z.*, 217(1):1–4, 1994.

[75] Grayson D. R. and Stillman M. E. Macaulay2, a software system for research in algebraic geometry.

[76] R. T. Rockafellar. The elementary vectors of a subspace of $\mathbb{R}^n$. In R. C. Bose and T. A. Dowling, editors, *Combinatorial Mathematics and its Applications (Proc. Conf., Univ. North Carolina, Chapel Hill, N.C., 1967)*, chapter 7, pages 104–127. Univ. North Carolina Press, Chapel Hill, N.C., 1969.

[77] S. D. Santos, R. Wollman, T. Meyer, and Ferrell J. E. Jr. Spatial positive feedback at the onset of mitosis. *Cell*, 149(7):1500–1513, 2012.

[78] G. Shinar and M. Feinberg. Structural sources of robustness in biochemical reaction networks. *Science*, 327(5971):1389–91, 2010.

[79] G. Shinar and M. Feinberg. Concordant Chemical Reaction Networks and the Species-Reaction Graph. *Math. Biosci.*, In press:http://dx.doi.org/10.1016/j.mbs.2012.08.002, 2012.

[80] A. Shiu and B. Sturmfels. Siphons in chemical reaction networks. *Bull. Math. Biol.*, 72:1448–1463.

[81] E. D. Sontag. Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction. *Institute of Electrical and Electronics Engineers. Transactions on Automatic Control*, 46(7):1028–1047, 2001.

[82] E. D. Sontag. Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction. *IEEE. Transactions on Automatic Control*, 46(7):1028–1047, 2001.

[83] C. Soulé. Graphical requirements for multistationarity. *ComplexUs*, 1:123–133, 2003.

[84] R. P. Stanley. *Enumerative combinatorics. Vol. 2*, volume 62 of *Cambridge Studies in Advanced Mathematics*. Cambridge University Press, Cambridge, 1999.

[85] Gbor Szederknyi. Comment on 'identifiability of chemical reaction networks' by g. craciun and c. pantea. *Journal of Mathematical Chemistry*, 45(4):1172–1174, 2009.

[86] Dasgupta T., Croll D. H., Owen J.A., Vander Heiden M. G., Locasale J. W., Alon U., Cantley L. C., and Gunawardena J. A fundamental trade off in covalent switching and its circumvention in glucose homeostasis. *J Biol Chem.*, 289(19):13010–25, 2014.

[87] R. Thomas. On the relation between the logical structure of systems and their ability to generate multiple steady states or sustained oscillations. *Springer series in Synergetics*, 9:180–183, 1981.

[88] W. T. Tutte. The dissection of equilateral triangles into equilateral triangles. *Proc. Cambridge Philos. Soc.*, 44:463–482, 1948.

[89] A. I. Vol'pert. Differential equations on graphs. *Math. USSR-Sb*, 17:571582, 1972.

[90] A. I. Vol'pert and S. I. Hudjaev. *Analysis in classes of discontinuous functions and equations of mathematical physics*, volume 8 of *Mechanics: Analysis*. Martinus Nijhoff Publishers, Dordrecht, 1985.

[91] Decker W., Greuel G.-M., Pfister G., and Schönemann H. SINGULAR 3-1-3 — A computer algebra system for polynomial computations. 2011.

[92] L. Wang and E. D. Sontag. On the number of steady states in a multiple futile cycle. *J. Math. Biol.*, 57(1):29–52, 2008.

[93] R. Wegscheider. über simultane gleichgewichte und die beziehungen zwischen thermodynamik und reactionskinetik homogener systeme. *Monatshefte fr Chemie / Chemical Monthly*, 32(8):849–906, (1901).

Investigating multistationarity in structured reaction networks

Alicia Dickenstein[1], Mercedes Pérez Millán[1],
Anne Shiu[2], and Xiaoxian Tang[2]

[1]*Dto. de Matemática, FCEN, Universidad de Buenos Aires*
[2]*Texas A&M University*

February 14, 2018

Abstract

Many dynamical systems arising in applications exhibit multistationarity (two or more positive steady states), but it is often difficult to determine whether a given system is multistationary, and if so to identify a witness to multistationarity, that is, specific parameter values for which the system exhibits multiple steady states. Here we investigate both problems. We prove two sufficient conditions for multistationarity in reaction networks: (1) when the steady states admit a parametrization and a certain *critical function* changes sign, and (2) when the steady-state equations can be replaced by equivalent triangular-form equations. We also investigate the mathematical structure of this critical function, and give conditions that guarantee that triangular-form equations exist. Finally, we present methods for finding witnesses to multistationarity, which we show work well for certain structured reaction networks, including those common to biological signaling pathways and those for which the steady states are defined by binomial equations. Our work relies on results from degree theory and on the specialization of Gröbner bases.

Keywords: reaction network, mass-action kinetics, multistationarity, parametrization, binomial ideal, Brouwer degree, Gröbner basis.

1 Introduction

An important problem in applications is to determine whether a given dynamical system is multistationary, and if so to find a witness to multistationarity (parameter values for which the system exhibits two or more steady states). Here we resolve this problem for dynamical systems arising from reaction networks with certain structure. Specifically, our main results are criteria for multistationarity and procedures for obtaining witnesses for certain networks:

(A) networks that admit a parametrization of the steady states and where the resulting *critical function* changes sign (Theorem 3.4), and

(B) networks for which the steady-state equations are equivalent to binomial equations (Theorem 4.6) or triangular-form equations (Theorem 5.5).

The critical function in (A) refers to the composition of the steady-state parametrization with the determinant of the Jacobian matrix. Theorem 3.4 therefore generalizes recent results, which rely on degree theory, due to Conradi, Feliu, Mincheva, and Wiuf [2]. Also, we show by example that our critical functions can be simpler to analyze than theirs.

Additionally, we explain how critical functions are related to discriminants (Proposition 3.9), investigate the mathematical structure of critical functions arising from "binomial networks" (Lemma 4.4), and give conditions that guarantee that triangular-form equations, as in (B) above, exist. This last result relies on prior work on the specialization of Gröbner bases. Finally, we illustrate our results on a number of reaction networks arising in biology.

Our results fit in the context of recent progress on the problems of deciding multistationarity (reviewed in [20]; see also [1, 9]), obtaining witnesses for multistationarity (e.g., [23, 25]), and characterizing parameter regions for multistationarity (e.g., [2, 17, 28, 31]). Indeed, here we give new criteria for multistationarity and methods for witnesses, and also show for some networks that the multistationary parameter regions arising from degree theory are open sets and thus full-dimensional (Theorem 4.10).

As mentioned above, one of our criteria for multistationarity involves examining the determinant of the Jacobian matrix. The first such criterion (without composing with a steady-state parametrization) was given by Craciun and Feinberg [6], and then was extended by many researchers (e.g., [1, 7, 24, 27, 32]). One version of such a result, a so-called *injectivity criterion*, says: If every term in the determinant of the Jacobian matrix has the same sign, then the network is not multistationary. Also, under some hypotheses, the converse holds [1, 2, 6, 11]. Here we prove analogous results, after using steady-state parametrizations.

Steady-state parametrizations have already been shown to be useful in analyzing reaction networks [2, 3, 23, 25, 30], and we build on those prior works. Similarly, like many before us, we use degree theory to decide multistationarity (see e.g. [2, 8, 10]) and develop theory attuned to networks with certain structure [12, 15, 23], including binomials [18, 24, 25].

Given that our work harnesses several techniques that have already been used for analyzing reaction networks – steady-state parametrizations, degree theory, and structured reaction networks – we emphasize that our final results rely on a new technique. Specifically, we use results on specialization of Gröbner bases [22]. To our knowledge we are the first to use such methods for analyzing multistationarity in reaction networks.

Finally, our work is related to the following open question: If a network G admits a positive steady state that is degenerate, does this guarantee that G admits multiple positive steady states? (This question is similar to the Nondegeneracy Conjecture [21].) One might hope that perturbing the parameters, i.e., rate constants and conservation-law values, would break apart the degenerate steady state into two or more steady states.

Several prior results answered the above question, under some hypotheses, in the affirmative [2, 6, 12, 14, 29]. Some of these results also yield a procedure for generating a witness

to multistationarity. Here, we add new results to this list, in the settings listed earlier: when the critical function changes sign, and when the steady-state equations can be replaced by equivalent triangular-form equations.

The outline of our work is as follows. In Section 2, we introduce mass-action kinetics systems and recall a well-known result about Newton polytopes. In Sections 3 and 4, we consider networks that admit steady-state parametrizations. We prove that multistationarity is guaranteed (by degree theory) when the critical function changes sign. We also explain how these critical functions are related to discriminants, and prove that, for networks whose steady-states are defined by binomials, the regions of multistationarity guaranteed by degree theory are full-dimensional. In Section 5, we consider the networks whose steady-state equations can be replaced by equivalent triangular-form equations. We give conditions for such a network that guarantee that a degenerate steady state breaks into two steady states. We also show that triangular-form equations exist under general conditions. Finally, we end with a Discussion in Section 6.

2 Background

In this section, we introduce reaction networks and their mass-action kinetics systems (Section 2.1), and then recall a useful result pertaining to Newton polytopes (Section 2.2).

2.1 Reaction networks

Here we largely follow the notation of Conradi, Feliu, Mincheva, and Wiuf [2]. A *reaction network* G consists of a set of s species $\{X_1, \ldots, X_s\}$ and a set of m reactions:

$$\sum_{i=1}^{s} \alpha_{ij} X_i \to \sum_{i=1}^{s} \beta_{ij} X_i, \quad j = 1, \ldots, m \,,$$

where α_{ij} and β_{ij} are non-negative integers. The *stoichiometric matrix* of G, denoted by N, is the $s \times m$ matrix with (i,j)-entry equal to $\beta_{ij} - \alpha_{ij}$. Let $im(N)^\perp$ denote the orthogonal complement of the image of the stoichiometric matrix N, and let $d = s - \text{rank}(N)$. A *conservation-law matrix* of G, denoted by W, is any row-reduced $d \times s$-matrix whose rows form a basis of $im(N)^\perp$. When every column of W contains at least one nonzero entry, that is, every species takes part in some conservation law, then G is *conservative*.

The concentrations of the species $X_1, \ldots, X_s$ are denoted by $x_1, \ldots, x_s$, respectively. The evolution of the concentrations with respect to time is given by a system of ordinary differential equations:

$$\dot{x} \;=\; f(x) \;:=\; N \cdot v(x) \,, \tag{1}$$

where $x = (x_1, \ldots, x_s)$ and $v : \mathbb{R}^s_{\geq 0} \to \mathbb{R}^m_{\geq 0}$ is a *reaction rate function*. This function, in the case of *mass-action kinetics*, is given by:

$$v_j(x) = \kappa_j x_1^{\alpha_{1j}} \cdots x_s^{\alpha_{sj}}, \quad j = 1, \ldots, m,$$

assume $\mathrm{lpp}_x(g) = x_s^{a_s} \cdots x_j^{a_j} x_{j-1}^{a_{j-1}}$. If $a_{j-1} = 0$, then $g \in G_m \cap \mathbb{C}[b_1, \ldots, b_n, x_j, \ldots, x_s]$ and by the induction hypothesis, $g \in \{g_j, \ldots, g_s\}$. If $a_{j-1} > 0$, then $\mathrm{lpp}_x(g_{j-1}) | \mathrm{lpp}_x(g)$ since $\mathrm{lpp}_x(g_{j-1}) = x_{j-1}$. By the definition of noncomparable subset, $g = g_{j-1}$. □

Remark 6.6. If the polynomial system $F \subset \mathbb{Q}[b_1, \ldots, b_n, x_1, \ldots, x_s]$, by the Buchberger's algorithm [5], we know a Gröbner basis G of $\mathcal{I}(F)$ is also a subset of $\mathbb{Q}[b_1, \ldots, b_n, x_1, \ldots, x_s]$ and hence the polynomials $g_1, \ldots, g_s$ stated in Theorem 5.8 will all have rational coefficients.

References

[1] Murad Banaji and Casian Pantea. Some results on injectivity and multistationarity in chemical reaction networks. *preprint,* `http://arXiv.org/abs/1309.6771`, 2013.

[2] Carsten Conradi, Elisenda Feliu, Maya Mincheva, and Carsten Wiuf. Identifying parameter regions for multistationarity. *PLoS Comput. Biol.*, 13(10):e1005751, 2017.

[3] Carsten Conradi and Anne Shiu. Dynamics of post-translational modification systems: recent progress and future challenges. *Biophys. J.*, 114(3):507–515, 2018.

[4] D. A. Cox, J. Little, and D. O'Shea. *Using Algebraic Geometry,* volume 185. Springer Science & Business Media, 2005.

[5] David Cox, Jon Little, and Donal O'Shea. *Ideals, varieties, and algorithms: an introduction to computational algebraic geometry and commutative algebra.* Springer-Verlag, 2007.

[6] Gheorghe Craciun and Martin Feinberg. Multiple equilibria in complex chemical reaction networks. I. The injectivity property. *SIAM J. Appl. Math.*, 65(5):1526–1546, 2005.

[7] Gheorghe Craciun and Martin Feinberg. Multiple equilibria in complex chemical reaction networks: Semiopen mass action systems. *SIAM J. Appl. Math.*, 70(6):1859–1877, 2010.

[8] Gheorghe Craciun, J. William Helton, and Ruth J. Williams. Homotopy methods for counting reaction network equilibria. *Math. Biosci.*, 216(2):140–149, 2008.

[9] Alicia Dickenstein. Biochemical reaction networks: An invitation for algebraic geometers. In *Mathematical Congress of the Americas,* volume 656, pages 65–83. American Mathematical Soc., 2016.

[10] German Enciso. Fixed points and convergence in monotone systems under positive or negative feedback. *Int. J. Control,* 87(2):301–311, 2014.

[11] Elisenda Feliu. Injectivity, multiple zeros and multistationarity in reaction networks. *Proc. Roy. Soc. Lond. Ser. A,* 471(2173), 2014.

[12] Elisenda Feliu. Injectivity, multiple zeros and multistationarity in reaction networks. *P. Roy. Soc. Lond. A Mat.*, 471(2173):18 pages, 2014.

[13] Elisenda Feliu and Wiuf. Carsten. Enzyme-sharing as a cause of multi-stationarity in signalling systems. *J. R. Soc. Interface*, 9(71):1224–1232, 2012.

[14] Bryan Félix, Anne Shiu, and Zev Woodstock. Analyzing multistationarity in chemical reaction networks using the determinant optimization method. *Appl. Math. Comput.*, 287–288:60–73, 2016.

[15] Gilles Gnacadja. Reachability, persistence, and constructive chemical reaction networks (part iii): a mathematical formalism for binary enzymatic networks and application to persistence. *J. Math. Chem.*, 49(10):2158–2176, 2011.

[16] S. Grimbs, A. Arnold, A. Koseska, J. Kurths, Selbig J., and Nikoloski Z. Spatiotemporal dynamics of the calvin cycle: Multistationarity and symmetry breaking instabilities. *BioSystems*, 103:212–223, 2011.

[17] Katharina Holstein, Dietrich Flockerzi, and Carsten Conradi. Multistationarity in sequential distributed multisite phosphorylation networks. *Bull. Math. Biol.*, 75(11):2028–2058, 2013.

[18] Matthew D. Johnston. Translated chemical reaction networks. *Bull. Math. Biol.*, 76(6):1081–1116, 2014.

[19] Badal Joshi. Complete characterization by multistationarity of fully open networks with one non-flow reaction. *Appl. Math. Comput.*, 219:6931–6945, 2013.

[20] Badal Joshi and Anne Shiu. A survey of methods for deciding whether a reaction network is multistationary. *Math. Model. Nat. Phenom., special issue on "Chemical dynamics"*, 10(5):47–67, 2015.

[21] Badal Joshi and Anne Shiu. Which small reaction networks are multistationary? *SIAM J. Appl. Dyn. Syst.*, 16(2):802–833, 2017.

[22] D. Kapur, Y. Sun, and D. Wang. A new algorithm for computing comprehensive Gröbner systems. In *ISSAC'10 Proceedings of the 35th International Symposium on Symbolic and Algebraic Computation*, pages 29–36, 2010.

[23] Mercedes Pérez Millán and Alicia Dickenstein. The structure of MESSI biological systems. *preprint*, `arXiv:1612.08763`, 2016.

[24] Stefan Müller, Elisenda Feliu, Georg Regensburger, Carsten Conradi, Anne Shiu, and Alicia Dickenstein. Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry. *Found. Comput. Math.*, 16(1):69–97, 2016.

[25] Mercedes Pérez Millán, Alicia Dickenstein, Anne Shiu, and Carsten Conradi. Chemical reaction systems with toric steady states. *Bull. Math. Biol.*, 74(5):1027–1065, 2012.

[26] Boris Y. Rubinstein, Henry H. Mattingly, Alexander M. Berezhkovskii, and Stanislav Y. Shvartsman. Long-term dynamics of multisite phosphorylation. *Mol. Biol. Cell*, 27(14):2331–2340, 2016.

[27] G. Shinar and M. Feinberg. Concordant chemical reaction networks. *Math. Biosci.*, 240(2):92–113, 2012.

[28] Anne Shiu. The smallest multistationary mass-preserving chemical reaction network. *Lect. Notes Comput. Sc.*, 5147:172–184, 2008.

[29] Anne Shiu and Timo de Wolff. Nondegenerate multistationarity in small reaction networks. *Preprint,* `arXiv:1802.00306`, 2018.

[30] Matthew Thomson and Jeremy Gunawardena. The rational parameterisation theorem for multisite post-translational modification systems. *J. Theoret. Biol.*, 261(4):626–636, 2009.

[31] Liming Wang and Eduardo D. Sontag. On the number of steady states in a multiple futile cycle. *J. Math. Biol.*, 57(1):29–52, 2008.

[32] C. Wiuf and E. Feliu. Power-law kinetics and determinant criteria for the preclusion of multistationarity in networks of interacting species. *SIAM J. Appl. Dyn. Syst.*, 12:1685–1721, 2013.

EXACTAS UBA

Ref.: Exp. (FCEN) Nº 494.054

Ciudad de Buenos Aires, 26 FEB 2018

VISTO lo dispuesto en el artículo 50º del Estatuto Universitario que instituye el Año Sabático para profesores regulares de la Universidad,

CONSIDERANDO:

Que por Resolución CD Nº 2488/16 se solicitó al Consejo Superior se autorice a la Dra. Alicia Marcela Dickenstein, Profesora Titular Plenaria con dedicación exclusiva del Departamento de Matemática a hacer uso del Año Sabático,

Que por Resolución CS Nº 6446/17 se aprobó dicha solicitud otorgando licencia entre el 1 de enero de 2017 y hasta el 31 de diciembre de 2017,

Que en cumplimiento con el Art. 12º de la Resolución CS Nº 4518/93 la Dra. Alicia Marcela Dickenstein presentó su informe de actividades,

Que es necesario cumplir con lo establecido por los Art. 13º y 14º de la citada resolución,

Lo aconsejado por la Comisión de Enseñanza, Programas y Planes de Estudio,

Lo actuado por este cuerpo en la sesión realizada en el día de la fecha,

En uso de las atribuciones que le confiere el art. 113º del Estatuto Universitario,

EL CONSEJO DIRECTIVO DE LA FACULTAD DE CIENCIAS EXACTAS Y NATURALES
RESUELVE:

Artículo 1º: Aprobar el informe correspondiente a las actividades desempeñadas por la Dra. Alicia Marcela Dickenstein durante su Año Sabático.

Artículo 2º: Enviar un ejemplar del informe a la Biblioteca de esta Facultad.

Artículo 3º: Regístrese, notifíquese a quienes corresponda, elévese al Consejo Superior y cumplido, archívese.

0014

RESOLUCIÓN CD Nº

Dr. JORGE ZILBER
SECRETARIO ACADEMICO ADJUNTO

Dr. JUAN CARLOS REBOREDA
DECANO