# MINISYMPOSIUM

# ALGEBRAIC, ANALYTIC, AND ALGORITHMIC APPROACHES TO STEADY STATES OF REACTION NETWORKS

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**Minisymposium Keywords**: existence and uniqueness of steady states, complex balance, generalized mass-action, weak reversibility, multistationarity

Systems of ordinary differential equations are often used to model the evolution of the concentrations of the species in a chemical reaction network. Realistic systems in molecular biology, like signaling networks, typically involve unknown parameters and a high number of variables. Therefore, the mathematical analysis of the system poses big challenges. The field of “Chemical Reaction Network Theory” has focused originally on getting insight in the solutions of the system from structural characteristics of the network, mainly under the assumption of mass-action kinetics.

Recently, this field has made a huge step forward by incorporating advanced mathematical techniques from algebra, analysis, and computation. With these tools in hand, new theorems and algorithms have been derived with the aim of extracting relevant properties of interest to the biological community. Examples are the determination of multistationarity, oscillations, or stability properties of steady states. In this new era, the goal is to understand the solutions of the system *qualitatively* and delimit regions in *parameter space* where different behaviours arise. In particular, this should be done avoiding the use of numerical simulations or parameter sampling.

In this minisymposium, we focus on recent results in the study of the *steady states* of a reaction network. Results concerning steady states for networks with mass-action kinetics have existed for some time, with key works by Horn, Jackson, and Feinberg dating back to the 1970s, and have been further developed afterwards [6, 7, 10]. For example, there exist two well-described classes of steady states, complex- and detailed-balanced steady states, which are unique and asymptotically stable relative to the linear invariant subspace they belong to.

However, important questions regarding existence, number, and stability of steady states remain only partially understood. For example, are there other classes of steady states behaving like complex-balanced steady states? What can one say beyond mass-action? Are results that hold for mass-action kinetics extendable to generalized mass-action kinetics? What networks admit positive steady states? Are complex-balanced steady states global attractors (this is known as the *Global attractor conjecture* [2])? Provided there is multistationarity, for what parameter values this happens and how many steady states can the network at most have? What about the stability of steady states?

The five talks in this minisymposium will present recent progress in these questions by combining tools from algebra, analysis, and computation. The talks focus mainly on steady states of weakly reversible networks.

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# NODE BALANCED STEADY STATES: UNIFYING AND GENERALIZING COMPLEX AND DETAILED BALANCED STEADY STATES

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*Keywords*: Reaction network, Mass-action kinetics, Reaction graph, Deficiency, Asymptotically stable steady state.

In this talk I will start by introducing the minisymposium and outlining open questions regarding steady states.

Afterwards, I will introduce a unifying and generalizing framework for complex and detailed balanced steady states. In [5], we generalize the graph commonly used to represent a reaction network and introduce reaction graphs. A special class of steady states, called *node balanced steady states*, is naturally associated with such a reaction graph. We show that complex and detailed balanced steady states are special cases of node balanced steady states by choosing appropriate reaction graphs. Further, we show that node balanced steady states have properties analogous to complex balanced steady states, such as uniqueness and asymptotical stability in each stoichiometric compatibility class.

By means of an integer, called *deficiency*, and a partial order on the set of reaction graphs (modulo isomorphism), we find independent relations in the reaction rate constants that need to be satisfied for a positive node balanced steady state to exist and show that any node balanced steady state is also complex balanced.

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# CHARACTERIZING GENERALIZED MASS-ACTION SYSTEMS WITH A UNIQUE COMPLEX-BALANCING EQUILIBRIUM

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*Keywords*: Chemical reaction network theory, Generalized mass-action kinetics, Complex balancing, Generalized Birch's theorem, Oriented matroids.

In the setting of generalized mass-action systems, uniqueness and existence of complex-balancing equilibria (in every compatibility class and for all rate constants) are equivalent to injectivity and surjectivity of a certain exponential map (the Birch map). In previous work, we have shown that injectivity can be characterized in terms of sign-vectors of the stoichiometric and kinetic-order subspaces [11]. The negation of this sign-vector condition is equivalent to the existence of multiple complex-balancing equilibria (for some compatibility class and some rate constant). In this work, we characterize the existence of a unique complex-balancing equilibrium, that is, the bijectivity of the exponential map [9]. Surprisingly, the conditions for bijectivity do not only involve sign vectors, but also the subspaces themselves.

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# COMPUTING SIGN-VECTOR CONDITIONS FOR BOUNDING THE NUMBER OF COMPLEX-BALANCING EQUILIBRIA

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We discuss how sign-vector conditions for bounding the number of complex-balancing equilibria in generalized mass-action systems (see also the talk by Stefan Müller) can be computed efficiently. The approach is based on equivalent conditions involving only sign vectors with maximal support, which can be enumerated even for high-dimensional subspaces [8]. In particular, we describe sufficient sign-vector conditions for the existence of a unique complex-balancing equilibrium (in every compatibility class and for all rate constants). It turns out that these conditions are also stable with respect to small perturbations in the kinetic orders, which are often not known exactly in applications.

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# WEAK REVERSIBILITY IMPLIES EXISTENCE OF A POSITIVE STEADY STATE

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*Keywords*: Mass-action systems, Weak reversibility, Positive steady states, Birch's Theorem, Brouwer's Fixed Point Theorem.

For each weakly reversible (in particular, reversible) mass-action system, there exists a positive steady state in each positive stoichiometric class. Thus, a property of the underlying Feinberg-Horn-Jackson graph enables one to conclude the existence of a positive steady state of a mass-action system. A proposal for the proof of this statement was suggested by Deng, Feinberg, Jones, and Nachman [4]. Based on that, we recently provided a complete proof [1]. In this talk, we give an overview of its main ingredients. Further, we briefly discuss other results and related open questions on the existence of positive steady states for (generalized) mass-action systems.

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# POLYNOMIAL DYNAMICAL SYSTEMS AND REACTION NETWORKS: PERSISTENCE, PERMANENCE AND GLOBAL STABILITY

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*Keywords*: Reaction networks, Polynomial dynamical systems, Persistence, Permanence, Global stability.

The set of trajectories of polynomial dynamical systems on the positive orthant can be generated by reaction networks. If these networks are weakly reversible then the Persistence Conjecture says that the dynamical system must be persistent (i.e., in the long run no variable can “go extinct”); moreover, the Permanence Conjecture says that the dynamical system must be permanent (i.e., in the long run solutions enter a compact subset of the positive orthant).

On the other hand, the Global Attractor Conjecture says that if a polynomial dynamical system has a vertex balanced equilibrium, then this equilibrium is a global attractor. We will describe how our recent proof of the Global Attractor Conjecture [3] also sheds some light of the Persistence and Permanence Conjectures.

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