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CoNtRol: an open source framework for the analysis of chemical reaction networks

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ABSTRACT

Summary: We introduce CoNtRol, a web based framework for analysis of chemical reaction networks (CRNs). It is designed to be both extensible and simple to use, complementing existing CRN-related tools. CoNtRol currently implements a number of necessary and/or sufficient structural tests for multiple equilibria, stable periodic orbits, convergence to equilibria and persistence, with the potential for incorporation of further tests.

Availability: Reference implementation: `reaction-networks.net/control/`. Source code and binaries, released under the GPLv3: `reaction-networks.net/control/download/`. Documentation: `reaction-networks.net/wiki/CoNtRol`.

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1 INTRODUCTION

Differential equation models of chemical reaction networks (CRNs), encompassing many ecological, epidemiological and related nonnegative systems, are almost universally complicated by parameter uncertainty. However, dynamical properties of large classes of CRN models are remarkably robust to changes in parameter values, leading to a range of results relating network structure to dynamical behaviour. Such parameter-free approaches to the analysis of CRNs fall into the scope of *chemical reaction network theory* (Horn and Jackson, 1972; Feinberg, 1972, 1979). Fuelled in part by its implications to systems biology (Bailey, 2001; Shinar and Feinberg, 2010), chemical reaction network theory has seen a surge of interest in recent years, attacking questions about multistationarity (Craciun *et al.*, 2006; Conradi *et al.*, 2007; Banaji *et al.*, 2007; Banaji and Craciun, 2009; Shinar and Feinberg, 2012), global stability (Craciun *et al.*, 2009; Angeli *et al.*, 2010; Anderson, 2011; Donnell and Banaji, 2013), oscillatory behavior (Angeli *et al.*, 2013) and persistence (Angeli *et al.*, 2007; Pantea, 2012).

Many of the results in chemical reaction network theory lend themselves to algorithmic implementation, which is useful for large networks. In this note we introduce CoNtRol (CRN tool), a new, fully open source platform, currently coded in C, Java, Octave and PHP, to perform computations on CRNs without the need for any proprietary software. CoNtRol has a web based front end interfacing with a suite of modular tests, to which users may add new tests in any language. With its array of features, CoNtRol complements existing software tools. The Chemical Reaction Network Toolbox (Ellison *et al.*, 2011) is a proprietary Windows program which implements the results of deficiency theory (Feinberg, 1979), as well as checking for concordance (Shinar and Feinberg, 2012), equivalent to network injectivity. It applies to various types of kinetics, including mass action, and generates detailed information about network properties, multiple and degenerate steady states, and their stability. ERNEST (Soranzo and Altafini, 2009) and CRNreals (Szederkényi *et al.*, 2012) are MATLAB toolboxes aimed at testing multistationarity, and respectively, distinguishability and identifiability of CRNs. Tests for multistationarity of CRNs are also implemented in Maple (Feliu and Wiuf, 2013). While not all criteria included in these tools are currently tested in CoNtRol, its extensible nature allows for their future inclusion.

2 FEATURES AND FUNCTIONALITY

CoNtRol has an intuitive user interface where a list of reactions can be input manually or uploaded in a variety of formats. While the focus so far has been on developing the framework for extensible functionality, a number of tools for the analysis of CRNs have also been implemented and tested.

2.1 Network Analysis

The current functionality of CoNtRol includes a number of necessary and/or sufficient structural tests for multiple equilibria, stable oscillation, convergence to equilibria, and persistence, assuming mass action or more general kinetics. In particular the following are checked: sufficient conditions for convergence to equilibria based on the theory of monotone dynamical systems (Angeli *et al.*, 2010; Donnell and Banaji, 2013); conditions of the deficiency zero and deficiency one theorems (Feinberg, 1987), resulting in claims about local stability of equilibria, absence of multiple positive equilibria, and absence of periodic orbits, primarily for mass action kinetics; structural conditions for persistence (Angeli *et al.*, 2007; Donnell and Banaji, 2013) based on examining the siphons of the system; and a large number of sufficient/necessary conditions for injectivity and absence of multistationarity gathered from the literature and developed in

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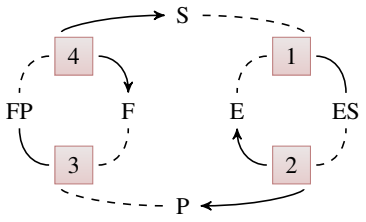

Fig. 1. Futile cycle DSR graph $\begin{cases} E+S & \rightleftharpoons & ES & \rightarrow & E+P \\ F+P & \rightleftharpoons & FP & \rightarrow & F+S \end{cases}$

(Banaji and Pantea, 2013). The outputs are cross-referenced to the documentation of CoNtRol, where each conclusion and its implications are described in detail. We note that some of the multistationarity results of CoNtRol are similar to those of The Chemical Reaction Network Toolbox (Ellison *et al.*, 2011).

2.2 DSR graph generation

A useful tool in the parameter-free study of CRNs is the DSR graph: a bipartite graph with signed, labelled, and sometimes directed edges. CoNtRol includes a Java Web Start application for drawing DSR graphs. The graph layout is highly customisable, and the "export to LaTeX" feature generates TikZ code for the resulting DSR diagram. An example is illustrated in Figure 1. Easily checked structural conditions on the DSR graph can imply, or contribute towards, powerful conclusions regarding multistationarity, asymptotic stability, or oscillatory behavior in a CRN (Craciun *et al.*, 2006; Banaji and Craciun, 2009; Angeli *et al.*, 2010, 2013; Shinar and Feinberg, 2013). Several of these are implemented or lend themselves naturally to future implementation.

2.3 Batch processing

This feature allows users to analyse a number of networks in a single run, thus generating statistics about the occurrence of certain behaviours. An archive containing individual files describing each network is uploaded, and the user is emailed a link to the output once it is complete. For example, the table below summarises the results of some injectivity tests implemented in CoNtRol, applied to the database of all 4082 nonisomorphic bimolecular CRNs with three species and three reactions (Deckard *et al.*, 2009).

GKα	GKβ	MAα	MAβ
44%	45%	45%	47%

GK: general kinetics. MA: mass action kinetics. α: the system is injective on the relative interior of each nontrivial stoichiometry class. β: the fully open system is injective on the nonnegative orthant. For example, with mass action kinetics, 45% (MAα) of the networks were injective on the relative interior on each nontrivial stoichiometric class, only slightly more than with general kinetics (GKα). See (Banaji and Pantea, 2013) for more details.

2.4 Miscellaneous

A number of features that further improve usability have been implemented. These include multiple input formats, the option to receive the output via email, and automatic generation of LaTeX code (e.g., list of reactions, stoichiometric matrix).

3 CONCLUSION

We have written CoNtRol aiming for a user friendly tool with maximal functionality, implementing state of the art theory on CRNs. We expect future inclusion of further results from the rich theory of CRNs, with contributions from the research community.

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