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Applications Note

Systems biology

BioSwitch: a tool for the detection of bistability and multi-steady state behaviour in signalling and gene regulatory networks

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Abstract

Motivation: Multi-steady state behaviour, and in particular multi-stability, provides biological systems with the capacity to take reliable decisions (such as cell fate determination). A problem arising frequently in systems biology is to elucidate whether a signal transduction mechanism or a gene regulatory network has the capacity for multi-steady state behaviour, and consequently for a switch-like response to stimuli. Bifurcation diagrams are a powerful instrument in non-linear analysis to study the qualitative and quantitative behaviour of equilibria including bifurcation into different equilibrium branches and bistability. However, in the context of signalling pathways, the inherent large parametric uncertainty hampers the (direct) use of standard bifurcation tools.

Results: We present BioSwitch, a toolbox to detect multi-steady state behaviour in signalling pathways and gene regulatory networks. The tool combines results from chemical reaction network theory with global optimization to efficiently detect whether a signalling pathway has the capacity to undergo a saddle node bifurcation, and in case of multi-stationarity, provides the exact coordinates of the bifurcation where to start a numerical continuation analysis with standard bifurcation tools, leading to two different branches of equilibria. Bistability detection in the G1/S transition pathway of *Saccharomyces cerevisiae* is included as an illustrative example.

Availability and implementation: BioSwitch runs under the popular MATLAB computational environment, and is available at https://sites.google.com/view/bioswitch.

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1 Introduction

Evaluating the capacity of gene regulatory networks and signal transduction mechanisms to function as biochemical switches is a recurrent and challenging problem in the context of systems biology. Here, we present a tool that allows to detect bistability (and multi-steady state behaviour in general) in biochemical networks starting from the network graph. Information such as parameter values and steady state concentration ranges, although not needed for the analysis, can be easily incorporated to constrain the analysis to the conditions of interest. In this way, the tool can be used to elucidate under which circumstances (induction strength, environmental conditions, protein levels, internal kinetic rates, etc.) multi-steady state behaviour might arise.

The first software tool testing chemical reaction networks for their capacity to undergo multi-steady state behaviour, the CRNToolbox, was developed in the nineties by Martin Feinberg and incorporates in updated versions (Ellison *et al.*, 2018) advanced-deficiency as well as injectivity-oriented results from Chemical Reaction Network Theory (CRNT). Classical CRNT results (Feinberg, 2019) provide various criteria to preclude multi-stationarity but might not be conclusive when the aim is to detect the capacity for multiple steady states. The ERNEST toolbox by Soranzo and Altafini (2009) is an open-source Matlab implementation of CRNT-based methods. Other tools capable to preclude multi-stationarity based on structural properties of the network alone have been developed by Feliu and Wiuf (2013) (based on injectivity) and Donnell *et al.* (2014) (the open source framework CoNtRol based on DSR graphs). GraTeLPy (Walther *et al.*, 2014) is a Python package that inspects the bipartite digraph of reaction networks for a preliminary analysis of potential instabilities including Turing, multi-stability and oscillations.

In another vein, continuation tools based on bifurcation theory (Dhooge *et al.*, 2008; Govaerts *et al.*, 2003, 2012) are very useful to

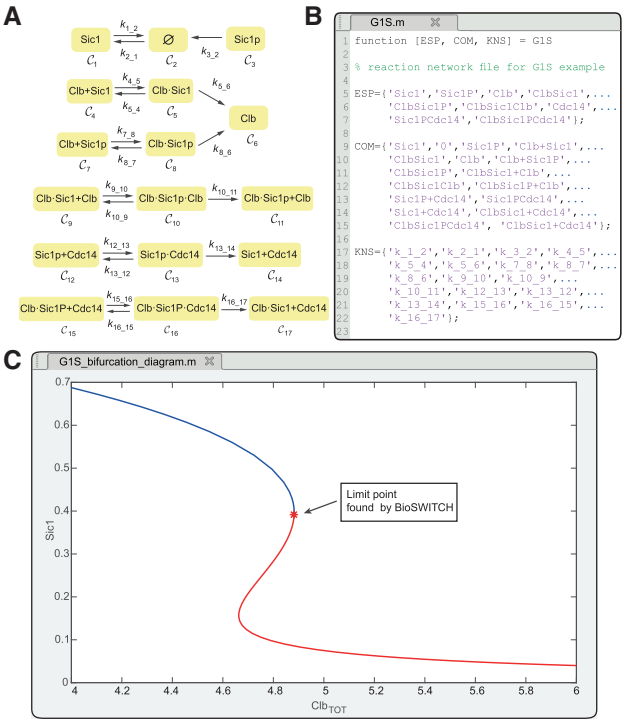

Fig. 1. Detection of bistability with BioSwitch: (**A**) C-graph of the G1/S transition network, (**B**) reaction network input file and (**C**) output: bifurcation diagram from the limit point detected. The continuation is performed by Cl-Matcont (Govaerts *et al.*, 2012)

study the behaviour of equilibria when appropriate parameter and steady state values to start the continuation are provided. However, standard continuation methods are not suitable in practice if (as it is usually the case in systems biology problems) adequate *a priori* information about the parameters is not available.

BioSwitch implements the methods introduced by Otero-Muras *et al.* (2012, 2017) and combines insights from CRNT, bifurcation analysis and optimization to detect multi-steady state behaviour and bistability in biochemical reaction networks with mass action kinetics. If a network is multi-stable, the tool will detect it efficiently from the network structure alone. In contrast to other bifurcation detection methods (Chickarmane *et al.*, 2005), BioSwitch exploits the inherent structural properties of biochemical systems, which makes it particularly suited for gene regulatory and signalling networks.

2 Summary of features

BioSwitch is a Matlab-based multi-platform (Windows, Linux and Mac OS) software toolbox for automated detection of multi-stability in signalling pathways and gene regulatory networks. The function `BioSWITCH_Evaluate` takes as input the network C-graph (Otero-Muras *et al.*, 2012, 2017) and computes the mass conservation laws, the deficiency of the network and other relevant information for further analysis. Starting from the C-graph, `BioSWITCH_Lpsearch` searches for limit points and, in case a limit point is found, `BioSWITCH_Ncontin` invokes the continuation algorithm (Govaerts *et al.*, 2012) to compute the bifurcation diagram. If the system is bistable, the bifurcation diagram indicates the region of bistability. Depending on user requirements and data availability, information about parameters might be omitted or included during the search. The toolbox offers (i) *generality*: a broad range of biochemical networks can be analyzed with BioSwitch since methods for networks both with and without mass conservation are implemented; (ii) *high computational efficiency*: the search for a limit point is formulated as an optimization problem, very efficiently solved by global optimization. Using the recommended solver eSS (Egea *et al.*, 2014), if the network is multi-stationary, a limit point is found in the order of seconds; (iii) *high flexibility*: although the only strictly required input is the C-graph of the network, the user can introduce all the information available/desired regarding parameters, solver options etc. (iv) *ease of use*: the files for optimization with the global solver eSS and continuation with Cl-Matcont (Govaerts *et al.*, 2012) are automatically generated on the basis of the C-graph and user's specifications.

Example. A number of examples are provided with the toolbox, including the G1/S transition in the cell cycle of the budding yeast *S. cerevisiae*, which has been originally reported as multi-stable in Conradi *et al.*, (2007). Figure 1A and B represent, respectively, the C-graph (with 9 species, 17 complexes and 18 reactions) and the corresponding BioSwitch input file. The bifurcation diagram obtained is depicted in Figure 1C. The bistability region is enclosed by two limit point bifurcation points.

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Conflict of Interest: none declared.

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