BIOINFORMATICS APPLICATIONS NOTE Vol. 29 no. 11 2013, pages 1469–1470
doi:10.1093/bioinformatics/btt165

Systems biology

Advance Access publication April 5, 2013

MonaLisa—visualization and analysis of functional modules in biochemical networks

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Associate Editor: Olga Troyanskaya

ABSTRACT

Summary: Structural modeling of biochemical networks enables qualitative as well as quantitative analysis of those networks. Automated network decomposition into functional modules is a crucial point in network analysis. Although there exist approaches for the analysis of networks, there is no open source tool available that combines editing, visualization and the computation of steady-state functional modules. We introduce a new tool called MonaLisa, which combines computation and visualization of functional modules as well as an editor for biochemical Petri nets. The analysis techniques allow for network decomposition into functional modules, for example t-invariants (elementary modes), maximal common transition sets, minimal cut sets and t-clusters. The graphical user interface provides various functionalities to construct and modify networks as well as to visualize the results of the analysis.

Availability and implementation: MonaLisa is licensed under the Artistic License 2.0. It is freely available at http://www.bioinformatik.uni-frankfurt.de/software.html. MonaLisa requires at least Java 6 and runs under Linux, Microsoft Windows and Mac OS.

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Received on June 27, 2012; revised on February 20, 2013; accepted on April 3, 2013

1 INTRODUCTION

The development of powerful experimental high-throughput technologies supports the development of large-scale biochemical network models with hundreds to several thousands of reactions. However, because detailed kinetic data are often incomplete, structural and stoichiometric properties become critically important for the analysis and validation of these networks.

Various visualization and/or analysis tools for biochemical hypergraphs as well as bipartite graphs have been developed, such as CellDesigner (Funahashi *et al.*, 2003), COPASI (Hoops *et al.*, 2006), Vanted (Junker *et al.*, 2006), Cytoscape (Cline *et al.*, 2007), CellIllustrator (Nagasaki *et al.*, 2011) and Snoopy (Fieber, 2004).

The Petri net (PN) formalism (Reisig, 1986) implements bipartite, directed graphs and provides a rich variety of rigorous analysis methods. In the past decades, PN has been applied to various biochemical systems, for example to signal transduction pathways, gene regulatory networks and metabolic models; for an overview see Koch *et al.* (2011).

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Functional modules at steady state have been defined in several concepts, such as transition and place invariants (t-invariants and p-invariants) (Lautenbach, 1973), elementary modes, (Schuster and Hilgetag, 1994), minimal cut sets (MCS; Klamt and Gilles, 2004), enzyme subsets (Pfeiffer *et al.*, 1999), maximal common transition sets (MCT-sets; Sackmann *et al.*, 2006) and transition clusters (t-clusters; Grafahrend-Belau *et al.*, 2008). Because the number of invariants exponentially grows up to millions, the computation and evaluation of all invariants is still a challenging task.

There exist tools for the automated detection of functional modules, but none of them comprises so many concepts and provides a suitable visualization combined with a graphical editor. We want to fill this gap by providing an open source tool for functional analysis without prior knowledge of detailed kinetic data.

MonaLisa is partly based on earlier implementations in PInA (Grafahrend-Belau *et al.*, 2008) and TInA (Thormann *et al.*, 2009).

2 FEATURES

MonaLisa implements a PN editor with numerous functions for creating, removing, moving, zooming, coloring and labeling of objects as well as several network decomposition techniques, including the graphical visualization of the resulting functional modules (Fig. 1). We also provide a knockout analysis (single, double, and multi knockout), i.e. the set of reactions that are inactive in the case of a knockout of a particular reaction (Grunwald *et al.*, 2008), and furthermore the computation of general topological features, e.g. the distribution of vertex degrees and cluster coefficients.

MonaLisa implements the following network decomposition techniques: (i) t- and p-invariants, i.e. the minimal sets of reactions at steady state and the minimal sets of places whose substance sum is always constant; (ii) MCSs, i.e. the sets of reactions whose inactivation inhibits a certain function; (iii) MCT-sets, i.e. the sets of reactions that exclusively occur in the same t-invariants; and (4) t-clusters, i.e. the sets of reactions that describe a specific biological function.

MonaLisa supports the PN-based file formats PNML (Petri Net Markup Language; Billington *et al.*, 2003), PNT (Petri Net Technology; Starke, 1997), SPPED (Fieber, 2004), the biological file formats SBML (Systems Biology Markup Language; Finney and Hucka, 2003), KGML (KEGG Markup Language), DAT (Metatool format; Kamp and Schuster, 2006)

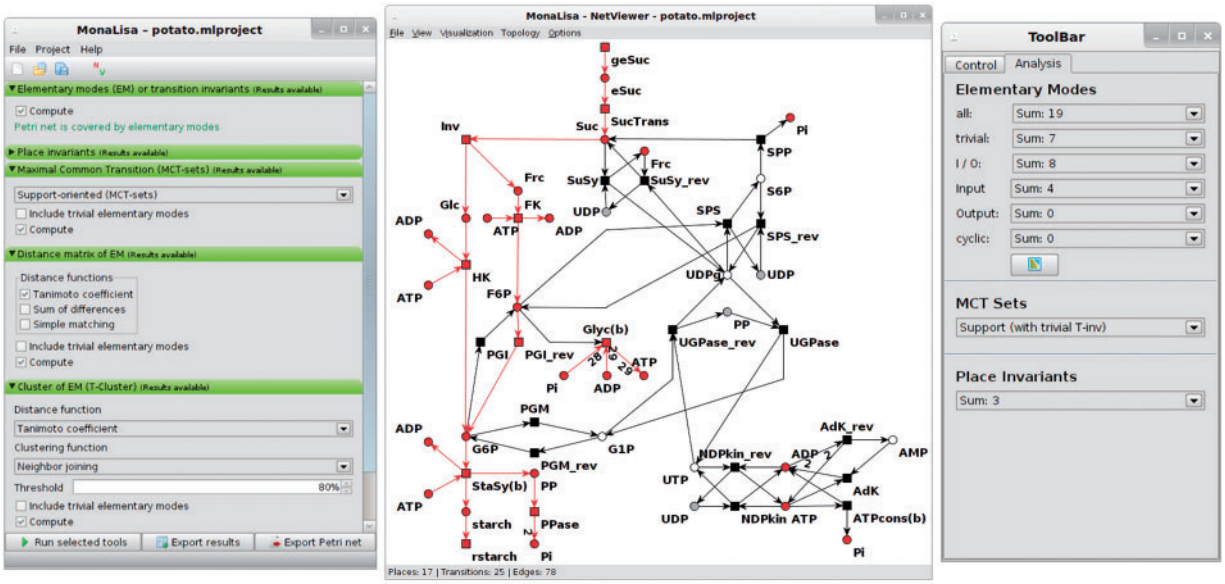

Fig. 1. The graphical user interface (GUI) of MonaLisa. In the left part, the user can select the analysis tool, define the settings, export the results and/or the PN model in different formats. The NetViewer (middle part) depicts the PN model of the carbon metabolism of the sucrose breakdown pathway in potato tubers (Koch *et al.*, 2005). The metabolites (places) are drawn as circles and the reactions (transitions) as rectangles. The gray-filled circles indicate logical places, e.g. PP or UDP. The red color highlights a functional module defined by the reactions of a t-invariant, including their pre- and post-places and the edges in between. The right part shows results of t-invariant analysis

and the image file formats Portable Network Graphics (PNG) and Scalable Vector Graphics (SVG).

3 SUMMARY

MonaLisa is an open-source tool for modeling biochemical networks without any knowledge of kinetic parameters. It is based on the PN formalism and focuses on decomposition methods to identify functional modules at steady state. As t-invariants correspond to elementary modes, the tool can also be applied to elementary mode analysis. Besides network visualization and editing, it enables a visual inspection of the analysis results. Furthermore, MonaLisa implements interfaces to many tools in systems biology, PN world and graph-theory.

ACKNOWLEDGMENTS

We gratefully thank Tim Schäfer, Jenia Schlegel and Frank Stämmler for testing and many suggestions. We would like also to thank the reviewers for the valuable comments.

Conflict of Interest: none declared.

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