Logical modelling of cellular decision processes with GINsim

Claudine Chaouiya, Aurélien Naldi, Lionel Spinelli, Pedro Monteiro, Duncan Berenguier, Luca Grieco, Abibatou Mbodj, Samuel Collombet, Anna Niarakis, Laurent Tichit, et al.

Logical modelling of cellular decision processes with GINsim

Claudine CHAOUIYA[1,2], Aurélien NALDI[3], Lionel SPINELLI[1,4,], Pedro MONTEIRO[2], Duncan BERENGUIER[1,4,5], Luca GRIECO[1,4,6], Abibatou MBODJ[1,4], Samuel COLLOMBET[6], Anna NIARAKIS[6], Laurent TICHIT[4,5], Elisabeth REMY[4] and Denis THIEFFRY1[1,6,7]

[1]TAGC (INSERM U1090), Marseille, France

[2]Institute Gulbenkian of Science, Oeiras, Portugal

chaouiya@igc.gulbenkian.pt

[3]University of Lausanne, Switzerland

[4]Institut de Mathématiques de Luminy, Marseille, France

[5]Université de la Méditerranée, Marseille, France

[6]Institut de Biologie de l'Ecole Normale Supérieure, Paris, France

thieffry@ens.fr

[7]CONTRAINTES, INRIA Paris-Rocquencourt, Le Chesney, France

Systems biologists are facing the difficult challenge of modelling and analysing regulatory networks encompassing numerous and diverse components and interactions. Furthermore, available data sets are often qualitative, which complicates the definition of quantitative computational models.

Logical modelling constitutes a flexible framework to build qualitative predictive models, which can be readily analysed or simulated as such, and potentially used as scaffolds to build more quantitative (continuous or stochastic) models. The dynamics of such models can be represented as State Transition Graphs (STG). It is then particularly relevant to identify subgraphs corresponding to dynamical attractors (i.e. terminal strongly connected components in STGs), as well as their reachability properties. For complex networks, however, the explicit construction of state transition graphs can be cumbersome or even intractable. This led us to develop several complementary computational strategies, which are implemented in our logical modelling software suite, GINsim [2, 8].

A first strategy consists in deducing properties directly from the model, defined as a regulatory graph (i.e. a set regulatory components or nodes, connected by signed arcs representing regulatory interactions). Using Multi-valued Decision Diagrams to represent (multi-level) logical updating rules enabled the development of efficient algorithms for the identification of all the stable states of a model, or yet to relate specific (positive or negative) regulatory circuits with specific dynamical properties (e.g., multiple attractors or sustained oscillations) [7, 11]. The rationale consists in deducing the structure of the state transition graph directly from the regulation graph. We are currently working on the identification of complex attractors, using recent mathematical results connecting the presence of positive or negative regulatory circuits in the regulatory graph with the occurrence of multiple attractors or dynamical cycles in the state transition graph.

A second strategy leads to the reduction of state spaces, either by reducing the model (the regulatory graph) or directly by working on the STG. More specifically, GINsim encompasses a reduction method that essentially preserves the dynamical properties of the model, although some reachability properties could be lost [10].

More recently, we have developed an algorithm to compact state transition graphs on the fly. The result of a simulation is compressed into a hierarchical graph, where the nodes represent connected sets of states or components, each symbolically represented by a decision diagram. Each component is labelled as either stable state (terminal nodes in the state transition graphs), cyclic attractor (terminal strongly connected components), transient cycle(s) (non-terminal strongly connected components) or basins of attraction (subsets of transient states), depending on the topology of the underlying transition sub-graph.

Finally, we are currently considering the application of formal methods, in particular model-checking techniques. To that end, GINsim has recently been equipped with an export facility, which enables the use of NuSMV to query logical models [6].

Beside these recent developments, we are developing means for incremental, compositional verification, to analyse large logical models defined as compositions of simpler regulatory modules.

All methodological developments are motivated by and used to tackle the analysis of regulatory networks involved in the control of cell fate, including of cell proliferation, differentiation and programmed death [1, 3, 4, 5, 8, 9, 12, 13]. In this talk, we will refer to ongoing applications to the modelling of MAPK signalling pathways or of the network controlling hematopoietic cell specification in mammals, or yet of the network controlling the specification of mesoderm in drosophila embryo. These applications are described in more details in the contributions of Grieco et al., Collombet et al., Niarakis et al., and Mbodj et al. in these proceedings.

Acknowledgements

This work has been supported grants from ANR (grant ANR-08-SYSC-003), FCT (grant PTDC/EIA-CCO/099229/2008), BELSPO (IAP BioMaGnet), and EU FP7 (Project APO-SYS).

References

[1] L. Calzone, L. Tournier, S. Fourquet, D. Thieffry, B. Zhivotovsky, E. Barillot, A. Zinovyev (2010). Mathematical Modelling of Cell-Fate Decision in Response to Death Receptor Engagement. *PLoS Computational Biology* 6: e1000702.

[2] C. Chaouiya, A. Naldi, D. Thieffry (2012). Logical modelling of gene regulatory networks with GINsim. *Methods in Molecular Biology* 804: 463-79.

[3] A. Fauré, A. Naldi, C. Chaouiya, D. Thieffry (2006). Dynamical analysis of a generic Boolean model for the control of the mammalian cell cycle. *Bioinformatics* 22: e124-31.

[4] A. Fauré, A. Naldi, F. Lopez, C. Chaouiya, A. Ciliberto, D. Thieffry (2009). Modular logical modelling of the budding Yeast cell cycle. *Molecular Biosystems* 5: 1787–96.

[5] A.G. González, C. Chaouiya, D. Thieffry (2008). Qualitative dynamical modelling of the formation of the anterior-posterior compartment boundary in the Drosophila wing imaginal disc. *Bioinformatics* 24: i234-40.

[6] P.T. Monteiro, C. Chaouiya (2012). Efficient verification for logical models of regulatory networks. Advances in Intelligent and Soft Computing 154: 259-267.

[7] A. Naldi, Thieffry D, Chaouiya C (2007). Decision diagrams for the representation and analysis of logical models of genetic networks. *Lecture Notes in Bioinformatics* 4695: 233-47.

[8] A. Naldi, D. Bérenguier, A. Fauré, F. Lopez, D. Thieffry, C. Chaouiya (2009). Logical modelling of regulatory networks with GINsim 2.3. *BioSystems* 97: 134-9.

[9] A. Naldi, J. Carneiro, C. Chaouiya, D. Thieffry (2010). Diversity and plasticity of Th cell types predicted from regulatory network modelling. *PLoS Computational Biology* 6: e1000912.

[10] A. Naldi, E. Remy, D. Thieffry, C. Chaouiya (2011). Dynamically consistent reduction of logical regulatory graphs. *Theoretical Computer Science* 412: 2207-18.

[11] E. Remy, P. Ruet, D. Thieffry (2006). Positive or negative regulatory circuit inference from multilevel dynamics. *Lecture Notes in Control and Information Sciences* 341: 263-70.

[12] O. Sahin, H. Fröhlich, C. Löbke, U. Korf, S. Burmester, M. Majety, J. Mattern, I. Schupp, C. Chaouiya, D. Thieffry, A. Poustka, S. Wiemann, T. Beissbarth, D. Arlt (2009). Modeling ERBB receptor-regulated G1/S transition to find targets for de novo trastuzumab resistance. *BMC Systems Biology* 3: 1.

[13] L. Sánchez, C. Chaouiya, D. Thieffry (2008). Segmenting the fly embryo: logical analysis of the role of the Segment Polarity cross-regulatory module. *International Journal of Developmental Biology* 52: 1059-75.