# MINISYMPOSIUM

## LOGICAL MODELLING OF (MULTI)CELLULAR NETWORKS

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**Minisymposium Keywords**: Boolean regulatory networks, Logical models, regulatory circuits, discrete dynamics

Boolean and multilevel logical approaches are increasingly used to study the behaviours of biological regulatory networks, which govern essential cellular processes. Moreover, modellers can rely on a broad array of model definitions, simulation methods, computational algorithms and software tools.

This mini-symposium aims at introducing these modelling approaches as well as discussing recent advances on both formal aspects and applications. It is organized in connection with the Consortium for Logical Modelling and Tools (CoLoMoTo, http://colomoto.org), which has been launched to promote the logical modelling framework and to provide scientists with dedicated standards, repositories and tools.

First, an overview of the field will be presented, covering different model classes, current challenges and application ranges. Four speakers will then present their recent achievements. These will first concern the assessment of the dynamics relying on topological features – namely regulatory circuits – of the modelled regulatory networks. Appropriate abstractions of large asynchronous dynamics will be then discussed, as well as the concept of model sets. Finally, definition of multicellular logical models by specifying cell-cell communication rules will be illustrated through the dorsal-ventral axis specification during sea urchin embryogenesis.

*Minisymposium: Logical modelling of (multi)cellular networks*

# LOGICAL MODELLING OF CELLULAR NETWORKS, INTRODUCTION AND METHODOLOGICAL CHALLENGES

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*Keywords*: Regulatory networks, Logical modelling, Discrete dynamics.

This introductory talk will provide the basics on the logical modelling formalism, covering some distinct variants. Logical models define discrete dynamics whose properties of interest will be introduced, including their counterparts for the biological networks under study. Distinctive features of signalling and regulatory networks amenable to such a qualitative approach will be discussed.

For large regulatory networks, model definition and analysis are often hampered due to diverse sources of complexity. We will conclude by discussing how to tackle these issues, through methods that have been developed relying on diverse mathematical and computational approaches.

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# LOCAL NEGATIVE CIRCUITS AND CYCLIC ATTRACTORS: A BOOLEAN SATISFIABILITY APPROACH

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*Keywords*: Boolean networks, Negative regulatory circuits, Cyclic attractors, Boolean satisfiability problem.

Negative circuits in Boolean networks are necessary for the system to display sustained oscillations. In dimension greater than 6, the negative circuits are not necessarily local. In this work we investigate the existence of Boolean maps with desired properties using Boolean satisfiability problems. We translate the absence of local negative circuits into an expression on $n2^n$ variables. We then implement a necessary condition for the existence of a cyclic attractor. We verify with a satisfiability solver that, for networks of dimension less or equal to 5, a local negative circuit is required for sustained oscillations, and find new counterexamples for $n \geq 6$.

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# BOOLEAN DYNAMICS OF COMPOUND REGULATORY CIRCUITS

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*Keywords*: Boolean networks, Regulatory circuits, Synchronous/asynchronous dynamics, Asymptotic behaviours.

In biological regulatory networks represented in terms of signed, directed graphs, topological motifs such as circuits are known to play key dynamical roles. After reviewing established results on the roles of simple motifs, we present recent results on the impact of the addition of a short-cut in a regulatory circuit. More precisely, based on Boolean formalisation of regulatory graphs, we provide complete descriptions of the discrete dynamics of particular motifs, under the synchronous and asynchronous updating schemes. These motifs are made of a circuit of arbitrary length, combining positive and negative interactions in any sequence, and are including a short-cut, and hence a smaller embedded circuit. The asymptotical behavior of such motifs strongly depends on the coherence of the signs of the two involved circuits. Such results on the functionality of motifs allow to improve the dynamical analysis of large regulatory biological networks.

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# APPROXIMATING THE BEHAVIOR OF BOOLEAN NETWORKS

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*Keywords*: Boolean networks, Asynchronous dynamics, Invariant sets, Boolean model sets.

One of the key advantages of Boolean models is their low complexity that allows for a more comprehensive analysis of the state space comparative to, e.g., ordinary differential equation (ODE) models. However, scalability is still an issue, in particular, when considering asynchronous update schemes that are often better suited for capturing the behaviour of biological systems and more comparable to ODE models. To tackle this issue, instead of considering the full state transition graph the model dynamics can be analysed on a coarser level. Rather than computing one trajectory step by step, sets of trajectories can be described by sequences of invariant sets finally leading to an attractor. In this talk, we will discuss some applications of this idea both in the context of single model analysis as well as for model sets.

# LOGICAL MODELLING OF THE REGULATORY NETWORK GOVERNING DORSAL-VENTRAL AXIS SPECIFICATION IN THE SEA URCHIN P. LIVIDUS

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*Keywords*: Developmental patterning, Logical modelling, Multicellular system.

Located at the basis of the deuterostome branch, echinoderms occupy a unique position to study the regulatory networks governing embryo morphogenesis. The dorsal-ventral (D-V) axis specification in the sea urchin Paracentrotus lividus is controlled by various transcription factors, including two TGF-$\beta$s: Nodal and BMP2/4. However, the signalling network downstream of these key morphogens is not yet fully understood. To identify Nodal and BMP2/4 target genes, we have performed a systematic functional analysis using RNA sequencing and in situ hybridization screens. The analysis of these data enables to delineate novel interactions. To gain further insights into this developmental process, we have developed a predictive dynamical model of the corresponding signalling/regulatory network. More specifically, using a logical modelling framework, we account for the specification of three main ectodermal regions along the D-V axis (ventral, ciliary and dorsal ectoderm) in terms of specific marker gene expression patterns. In our model analysis, we first focused on the computation of stable states and on their reachability in single representative cells, depending on signalling inputs. Next, taking advantage of the software EpiLog (http://epilog-tool.org), we have simulated grids of cells connected through signalling molecules. These model simulations correctly reproduces the wild-type pattern, as well as various reported embryo mutant phenotypes, including double Nodal mRNA injections.