GINsim, current status and future developments

Claudine Chaouiya

Instituto Gulbenkian de Ciência (IGC)
Oeiras PORTUGAL

2^{nd} CoLoMoTo Meeting - March 27-29, 2012

FUNDAÇÃO CALOUSTE GULBENKIAN
Instituto Gulbenkian de Ciência

Network Modelling

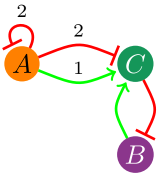
Outline

- modelling framework supported by GINsim
- GINsim main features currently available
- Next release
- Future developments: SAT and abstraction techniques

Logical formalism as supported by GINsim

Logical Regulatory Graph

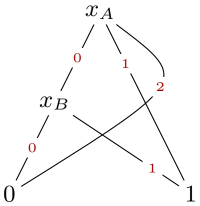
$\mathcal{R} = (\mathcal{G}, \mathcal{I}, \mathcal{K})$



$\mathcal{K}_C$: C is activated by A (at its medium level) of by B, or by both

x_a	x_b	x_c
0	0	0
0	1	1
1	0	1
1	1	1
2	0	0
2	1	0

OMDD representation

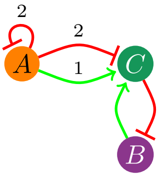


- Nodes : components (genes, proteins, ...), $i \in \mathcal{G}$, $x_i \in \{0, \dots max_i\}$
- Edges : interactions (activations/inhibitions), $\mathcal{I} \subset \mathcal{G} \times \mathcal{G}$, interaction (i, j) is *effective* iff $x_i \geq \theta_{i,j}$
- (Logical) regulatory function defining the component evolution

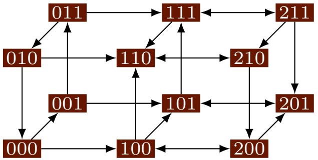
$$\mathcal{K}_i : \Pi_{j \in \mathcal{G}}\{0, \dots max_j\} \rightarrow \{0, \dots max_i\}$$

Logical formalism as supported by GINsim

Logical Regulatory Graph
$\mathcal{R} = (\mathcal{G}, \mathcal{I}, \mathcal{K})$



State Transition Graph (STG) $\mathcal{E} = (\mathcal{S}, \mathcal{T})$



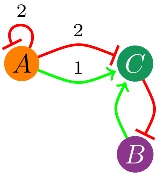
- Nodes : states $x \in \mathcal{S} = \Pi_{j \in \mathcal{G}}\{0 \ldots max_j\}$
- Edges : transitions $(x, y) \in \mathcal{T}$ iff

(asynchronous) $$\begin{cases} \exists i \in \mathcal{G} \text{ s.t. } \mathcal{K}_i(x) \neq x_i, & y_i = x_i + \frac{|\mathcal{K}_i(x) - x_i|}{\mathcal{K}_i(x) - x_i} \\ \forall j \neq i \quad y_j = x_j \end{cases}$$

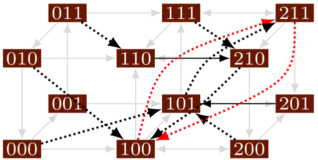
As many successors as the number of components updating their values

Logical formalism as supported by GINsim

Logical Regulatory Graph
$\mathcal{R} = (\mathcal{G}, \mathcal{I}, \mathcal{K})$



State Transition Graph (STG) $\mathcal{E} = (\mathcal{S}, \mathcal{T})$



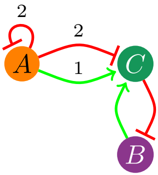
- Nodes : states $x \in \mathcal{S} = \Pi_{j \in \mathcal{G}}\{0 \dots max_j\}$
- Edges : transitions $(x, y) \in \mathcal{T}$ iff

(synchronous)
$$\begin{cases} \forall i \in \mathcal{G} \text{ s.t. } \mathcal{K}_i(x) \neq x_i, & y_i = x_i + \frac{|\mathcal{K}_i(x) - x_i|}{\mathcal{K}_i(x) - x_i} \\ \forall j \in \mathcal{G} \text{ s.t. } \mathcal{K}_j(x) = x_j, & y_j = x_j \end{cases}$$

At most one successor

Logical formalism as supported by GINsim

Logical Regulatory Graph
$\mathcal{R} = (\mathcal{G}, \mathcal{I}, \mathcal{K})$



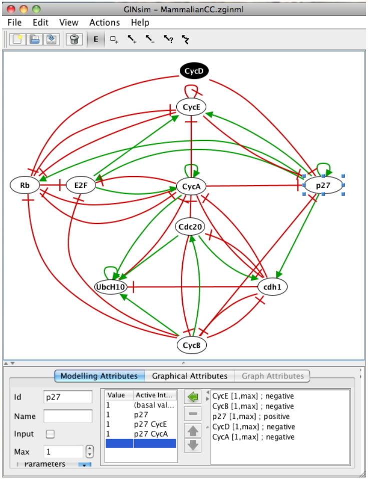
State Transition Graph (STG) $\mathcal{E} = (\mathcal{S}, \mathcal{T})$ with priority classes:

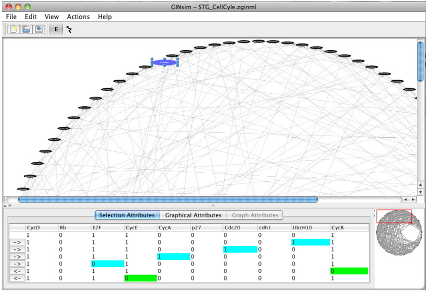
1. class C_i associated with a rank $r(C_i)$ and with an updating policy (synchronous or asynchronous);
2. several classes may have the same rank: concurrent transitions from distinct classes with identical rank triggered asynchronously;
3. at state s, trigger transitions involving components of the classes with the highest rank;
4. concurrent transitions of a class triggered accordingly to the policy associated to that class;
5. increasing and decreasing transitions can be distinguished and associated to different classes

GINsim

A dedicated tool for the qualitative modelling and analysis of regulatory networks

A. Naldi *et al* (2009) *Biosystems* 97(2):134-9, 2009





GINsim

Current functionalities

- From the model
  - Regulatory circuit analysis
  - Stable states determination
  - Model reduction
  - Mutant specification
  - Export facilities: Petri nets, Documentation
- From the dynamics
  - Construction of STG under synchronous, asynchronous and mixed priority classes
  - SCC graph
- Other export facilities: Graphviz (.dot), BioLayout, Cytoscape, SVG, PNG

- From the model
  - Import facilities: SBML qual, truth table (synchronous dynamics)
  - Export facilities: SBML qual, GNA, NuSVM, SAT
- From the dynamics
  - Hierarchical Transition Graphs: compact view of the dynamics

    ($\rightarrow$ D. Thieffry's talk)

Role and analysis of regulatory circuits

Thomas R (1988). Springer Series in Synergics 9: 180-93.

Regulatory circuits play a fundamental role in the dynamics:

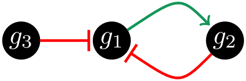
- A positive circuit is necessary for multistability
- A negative circuit is necessary for stable oscillations

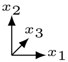
Thomas R (1988). Springer Series in Synergics 9: 180-93.

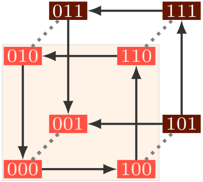
Regulatory circuits play a fundamental role in the dynamics:

- A positive circuit is necessary for multistability
- A negative circuit is necessary for stable oscillations

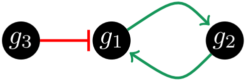
Conditions ensuring that a circuit is functional?

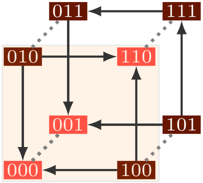






negative circuit **functional** when $x_3 = 0$





positive circuit **functional** when $x_3 = 0$

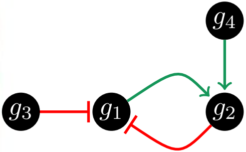
Role and analysis of regulatory circuits

Thomas R (1988). Springer Series in Synergics 9: 180-93.

Regulatory circuits play a fundamental role in the dynamics:

- A positive circuit is necessary for multistability
- A negative circuit is necessary for stable oscillations

Functionality context of $\mathcal{C} = [g_1, \ldots g_n]$: $X_{\mathcal{C}} = \bigcap_{i=1\ldots n} X_{i,i+1}$ with $X_{i,i+1} = \{s \in \mathcal{S}, \mathcal{K}_j(s) \neq \mathcal{K}_j(\bar{s}^i)\}$ functionality context of $(i, i+1)$



- $g_1 \rightarrow g_2$: $\mathcal{X}_{1,2} = \{s \in \mathcal{S},\ s_3 = 0\}$
- $g_2 \rightarrow g_1$: $\mathcal{X}_{2,1} = \{s \in \mathcal{S},\ s_4 = 1\}$
- $\mathcal{C} = [g_1, g_2]$: $X_{\mathcal{C}} = \{s \in \mathcal{S},\ s_3 = 0,\ s_4 = 1\}$

A. Naldi et al. (2007) LNCS/LNBI 4695:233-247

An efficient algorithm, based on OMMDs manipulations, to determine the functionality context of regulatory circuits

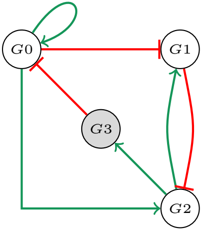
Model reduction

Reducing the STG, yet controlling the impact on its properties

A. Naldi *et al* (2011) *Theor Comp Sc* 412(21):2207-18

Define a *complete* model and reduce it by iteratively masking components (non auto-regulated)

$G3$ selected for reduction



$\mathbf{K_{G0}(x) = (x_{G1} = 1) \vee (x_{G3} = 0)}$
$K_{G1}(x) = (x_{G2} = 1)$
$K_{G2}(x) = (x_{G0} = 1) \wedge (x_{G1} = 0)$

$K_{G3}(x) = (x_{G2} = 1)$

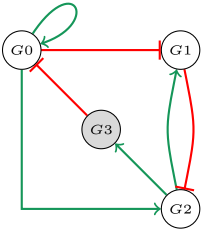
Model reduction

Reducing the STG, yet controlling the impact on its properties

A. Naldi *et al* (2011) *Theor Comp Sc* 412(21):2207-18

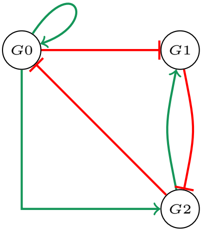
Define a *complete* model and reduce it by iteratively masking components (non auto-regulated)

$G3$ selected for reduction



$$\mathbf{K_{G0}(x) = (x_{G1} = 1) \vee (x_{G3} = 0)}$$
$$K_{G1}(x) = (x_{G2} = 1)$$
$$K_{G2}(x) = (x_{G0} = 1) \wedge (x_{G1} = 0)$$
$$K_{G3}(x) = (x_{G2} = 1)$$

$G0$ function revised



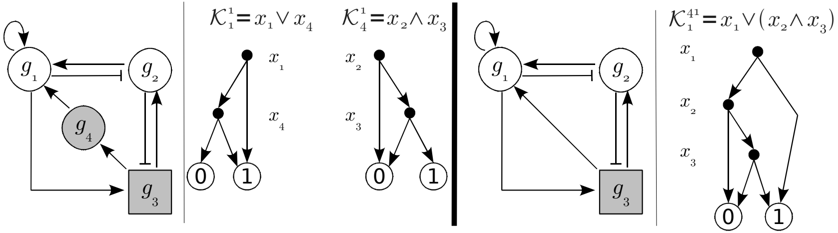
$$\mathbf{K_{G0}^{G3}(x) = (x_{G2} = 0) \vee (x_{G1} = 1)}$$

Model reduction

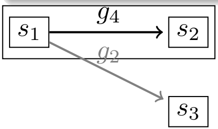
Reducing the STG, yet controlling the impact on its properties

A. Naldi *et al* (2011) *Theor Comp Sc* 412(21):2207-18

Computing the MDD representing $\mathcal{K}_i^r$ from those of the original model



Reduction amounts to consider that the component is faster



Model reduction

Reducing the STG, yet controlling the impact on its properties

A. Naldi *et al* (2011) *Theor Comp Sc* 412(21):2207-18

Impact of the reduction on dynamical properties

- Terminal SCC in the STG (*i.e.* attractors) are conserved:
  - exactly the same stable states
  - the elementary cycles are conserved, new ones might appear
  - the complex attractors might be split, new ones might appear
- Loss of trajectories
- New (non-trivial) attractors proceed from SCCs of the original STG

Reachability in reduced STG implies reachability in original STG

Model-checking to investigate logical models

P. Monteiro et al (2012) PACC'12, Adv Intel and Soft Comp, Vol. 154

- Symbolic encoding of LRG (using SMV)
- Support for different updating policies
- Reduction of the state space, considering free input variations
- Implementation in the form of an export facility in GINsim
- Property specifications encoded in CTL

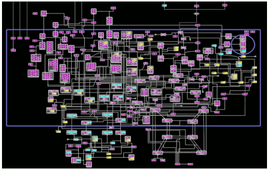
Compositional modelling framework

To tackle realistic processes, a compositional modelling framework is required

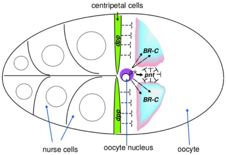
The goal is to deduce properties of the whole from the properties of the constitutive modules

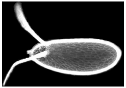
Network modularity still needs to be properly identified. Multi-cellular processes provide relevant/meaningful modules

Control of proliferation

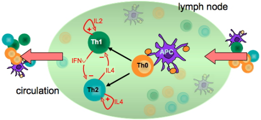


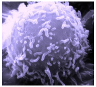
Drosophila oogenesis





T cells differentiation





Take advantage of the intrinsic modularity of inter-cellular regulatory networks

Compositional modelling framework

To tackle realistic processes, a compositional modelling framework is required

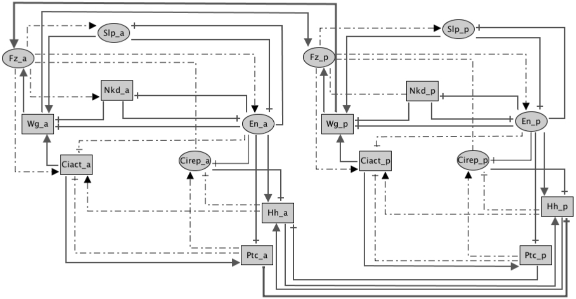
The goal is to deduce properties of the whole from the properties of the constitutive modules

Network modularity still needs to be properly identified. Multi-cellular processes provide relevant/meaningful modules

- *Open logical module*, with proper and input components
- *Integration function*, to convey input behaviours
- Processes specified in LOTOS NT
- Synchronisation rules
- Hidden components $\rightarrow \tau$ transitions
- Reductions (branching equivalence, partial orders)
- Check *e.g.* stable states reachability

Use of CADP, collaboration with VASY, INRIA Grenoble

Compositional modelling framework



	STG (GINsim)	LTS (CADP)
time	–	760 sec
size (states)	2,599,749	77
memory pic	–	1,627,348 KB

Composition of two LRMs encompassing the segment-polarity module, accounting for two cells flanking the segmental border.
Each module contains 9 components, 4 Boolean (oval nodes) and 5 ternary (rectangle nodes).
Only Wg and En are kept visible, use of safety equivalence: $\rightarrow$ elimination of all τ transitions and preservation of stable state reachability.

(paper submitted)

Conclusions

Formal methods to handle larger models:

- SAT to assess attractors (stable states and complex cyclic attractors)
- Model-checking approaches to assess attractor reachability, properties along trajectories
- Model revision: use of the counter-examples, notion of minimal revision

Ever more important to exchange models and methods

- SBML qual
- CoLoMoTo initiative

Acknowledgements

A. Naldi (CIG, Lausanne)
L. Spinelli & D. Berenguier (TAGC, IML, Marseille)
D. Thieffry(ENS, Paris)

P. Monteiro (IGC)

N. Mendes (IGC)

H. Klaudel & F. Pommereau (IBISC, Evry)
G. Batt (INRIA, Rocquecourt)
R. Mateescu &F. Lang (INRIA, Grenoble)

AGENCE NATIONALE DE LA RECHERCHE ANR

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

FUNDAÇÃO CALOUSTE GULBENKIAN
Instituto Gulbenkian de Ciência