Logical modelling of regulatory networks
ITQB PhD programs (MolBioS & Plants for Life)

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9 February 2017
Outline

1. Motivation - Context
2. Brief introduction to the logical formalism
3. Application: Core regulatory network of the lambda phage switch
4. Application: T cell differentiation
5. Application: Patterning of the Drosophila eggshell
6. Conclusions
1 Motivation - Context

2 Brief introduction to the logical formalism

3 Application: Core regulatory network of the lambda phage switch

4 Application: T cell differentiation

5 Application: Patterning of the Drosophila eggshell

6 Conclusions
Cellular processes (proliferation, differentiation, apoptosis,...) are controlled by underlying heterogeneous, complex interaction networks

→ understand, predict, intervene

“And that’s why we need a computer.”
Cellular processes (proliferation, differentiation, apoptosis,...) are controlled by underlying heterogeneous, complex interaction networks.

A wide variety of regulatory mechanisms

Transcriptional regulation

Protein phosphorylation

Cell cycle regulation (B. Novak)
Motivation - Context

A wide variety of regulatory mechanisms

- Transcriptional regulation
- Protein phosphorylation

Different mathematical/computational frameworks to decipher network dynamics

- Graph theory
- Logical networks
- Bayesian networks
- Petri nets
- Process algebras
- Constraint-based models
- Differential equations
- Rule-based models
- Cellular automata
- Agent-based models
- and others...
Different mathematical/computational frameworks to decipher network dynamics

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- Process algebras
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N Le Novère, Nat Rev Genet 2015
Motivation - Context

Qualitative (logical) modelling of regulatory networks

- Lack of precise, quantitative data (concentrations, kinetic parameters...)
- Sigmoid regulatory functions $\rightsquigarrow$ step functions $\rightarrow$ Boolean abstraction
- Bistability as a key phenomenon

Kinetic logic - R. Thomas (1973)
- State of the system as a Boolean vector
- Boolean function describes the target state
- Asynchronous dynamics
- Extension to multi-valued variables

Does the model reproduce observed behaviour?
Which components drive this behaviour?
What are the effects of perturbations?
Motivation - Context

Qualitative (logical) modelling of regulatory networks

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6 Conclusions
Brief introduction to the logical formalism

Model definition

Regulatory graph
\[ \mathcal{R} = (\mathcal{G}, \mathcal{I}, \mathcal{K}) \]

Logical rules

\[
\begin{align*}
    f_A(x) &= \begin{cases} 
    2 & \text{if } x_A \geq 1 \& x_B = 1 \\
    1 & \text{if } (x_A \geq 1) \| (x_B = 1) \| (x_C = 1) \& \neg((x_A \geq 1) \& (x_B = 1)) \\
    0 & \text{otherwise}
    \end{cases} \\
    f_B(x) &= \begin{cases} 
    1 & \text{if } x_A = 1 \\
    0 & \text{otherwise}
    \end{cases} \\
    f_C(x) &= \begin{cases} 
    1 & \text{if } x_A = 1 \\
    0 & \text{otherwise}
    \end{cases}
\end{align*}
\]

Components (genes, proteins, ...), \( i \in \mathcal{G}, \ x_i \in \{0, \ldots \max_i\} \)

Interactions \( \mathcal{I} \subset \mathcal{G} \times \mathcal{G} \): \((i, j)\) effective iff \( x_i \geq \theta_{i,j} \)

Regulatory, logical functions defining components evolutions
\[
\begin{align*}
    \mathcal{K}_i : \Pi_{j \in \mathcal{G}} \{0, \ldots \max_j\} &\rightarrow \{0, \ldots \max_i\} \\
    \mathcal{K}_C : C \text{ is activated by } A \text{ (at its medium level) of by } B, \text{ or by both}
\end{align*}
\]
Brief introduction to the logical formalism

Model definition

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

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

Asynchronous

- States \( x \in \mathcal{S} = \prod_{j \in \mathcal{G}} \{0 \ldots \text{max}_j\} \)
- Transitions (asynchronous)
  \((x, y) \in \mathcal{T} \text{ iff } \) 
  \[ \exists i \in \mathcal{G} \text{ s.t. } \mathcal{K}_i(x) \neq x_i, \quad y_i = x_i + \frac{\left| \mathcal{K}_i(x) - x_i \right|}{\mathcal{K}_i(x) - x_i} \]
  \[ \forall j \neq i \quad y_j = x_j \]

A state has as many successors as the number of components called to update their values

Terminal strongly connected components \( \rightarrow \) attractors

stable states, cyclical attractors
Brief introduction to the logical formalism

Model definition

Regulatory graph
\[ \mathcal{R} = (\mathcal{G}, \mathcal{I}, \mathcal{K}) \]

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

States \[ x \in \mathcal{S} = \prod_{j \in \mathcal{G}} \{0 \ldots \text{max}_j\} \]

Transitions (synchronous)
\[ (x, y) \in \mathcal{T} \text{ iff } \left \{ \begin{array}{l} \forall i \in \mathcal{G} \text{ s.t. } \mathcal{K}_i(x) \neq x_i, \quad y_i = x_i + \frac{\mathcal{K}_i(x) - x_i}{\mathcal{K}_i(x) - x_i} \\ \text{otherwise} \quad y_j = x_j \end{array} \right \] 

A state has at most one successor

Terminal strongly connected components → attractors

stable states, cyclical attractors
Brief introduction to the logical formalism

Model analysis

Identify, in huge STG, asymptotical behaviours (attractors), properties along trajectories, perturbed behaviours...

⇒ combinatorial explosion ($2^n$ states)
Brief introduction to the logical formalism

Model analysis

Identify, in huge STG, asymptotical behaviours (attractors), properties along trajectories, perturbed behaviours...

⇒ combinatorial explosion ($2^n$ states)

- Definition of adequate methods
- Development of software tools: GINsim freely available at ginsim.org
Brief introduction to the logical formalism

Model analysis

Identify, in huge STG, asymptotical behaviours (attractors), properties along trajectories, perturbed behaviours...

⇒ combinatorial explosion ($2^n$ states)

- Stable state identification
- Model reduction
- Circuit analysis
- Model composition (mutli-cellular systems)
- Generation of the dynamics: (a)synchronous, priorities, state transition graph, Hierarchical transition graph
- Several export facilities: Model-checking, Petri nets, Random simulation, etc.

Import/export of SBML qual, SBML package for qualitative models
Brief introduction to the logical formalism

Exercices!!

\[
\begin{align*}
g_1 & \rightarrow g_2 \\
\{ & \quad f_1(x) = x_2 \\
& \quad f_2(x) = \neg x_1
\end{align*}
\]

STG on the 2D Boolean hypercube?

\[
\begin{array}{ccc}
00 & & 10 \\
\hline
01 & & 11
\end{array}
\]

Regulatory network?

\[
\begin{align*}
g_1 & \rightarrow g_2 \\
\{ & \quad f_1(x) = x_2 \\
& \quad f_2(x) = x_1
\end{align*}
\]

STG on the 2D Boolean hypercube?

\[
\begin{array}{ccc}
00 & & 10 \\
\hline
01 & & 11
\end{array}
\]

Logical rules?

\[
\begin{align*}
g_1 & \rightarrow g_2 \\
\{ & \quad f_1(x) = x_2 \& x_3 \\
& \quad f_2(x) = \neg x_1 \& x_3 \\
& \quad f_3(x) = x_1
\end{align*}
\]

STG on the 2D Boolean hypercube?

\[
\begin{array}{ccc}
000 & & 100 \\
\hline
010 & & 110 \\
011 & & 111 \\
001 & & 101
\end{array}
\]
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The lambda phage (λ) lysis-lysogeny decision

Life cycle of phage λ

Application: Core regulatory network of the phage λ switch
Application: Core regulatory network of the phage λ switch

The lambda phage (λ) lysis-lysogeny decision

Y Cao et al (2010) PNAS vol. 107 no. 43 18445-50

Note: This decision may be not fully random, as it may be influenced by some cell variations

Kinetic logic - R. Thomas (1973)

\[ X = B(x) \]

\[ \begin{align*} 
  X_i \text{ (logical function): } & \text{indicates if gene } i \text{ is currently transcribed} \\
  x_i \text{ (logical variable): } & \text{current level of the functional product of gene } i 
\end{align*} \]
Application: Core regulatory network of the phage λ switch

The lambda phage (λ) lysis-lysogeny decision

Y Cao et al (2010) PNAS vol. 107 no. 43 18445-50
The lambda phage ($\lambda$) lysis-lysogeny decision

Synchronous dynamics of Boolean networks (S. Kauffman)

\[
\begin{align*}
  x_{t+1} &= \overline{y_t} \\
  y_{t+1} &= \overline{x_t}
\end{align*}
\]

<table>
<thead>
<tr>
<th>($xy)_t$</th>
<th>($xy)_{t+1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>11</td>
</tr>
<tr>
<td>[01]</td>
<td>01</td>
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<tr>
<td>[10]</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>00</td>
</tr>
</tbody>
</table>

Y Cao et al (2010) PNAS vol. 107 no. 43 18445-50
The lambda phage (λ) lysis-lysogeny decision

**Synchronous** dynamics of Boolean networks (S. Kauffman)

\[
\begin{align*}
x_{t+1} &= \overline{y_t} \\
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\end{align*}
\]

| \(x_y_t\) | \(x_y_{t+1}\) \\
|-------|-------|
| 00    | 11    \\
| [01]  | 01    \\
| [10]  | 10    \\
| 11    | 00    |

**Asynchronous** dynamics of Boolean networks (R. Thomas)

\[
\begin{align*}
x & \equiv \overline{y} \\
y & \equiv \overline{x}
\end{align*}
\]

| \(xy\) | \(XY\)  \\
|-------|-------|
| 00    | 11    \\
| [01]  | 01    \\
| [10]  | 10    \\
| 11    | 00    |
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Application: T cell differentiation

This classical view of T-helper cell differentiation has been recently challenged. Recent experiments have revealed:
- Novel subsets (i.e. Th9 and Th22)
- Hybrid subsets expressing more than one master regulator
- Examples of Th cell plasticity
Application: T cell differentiation


Model accounting for Th1, Th2, Th17, Treg, Tfh, Th9, Th22

101 components (21 input nodes), 221 interactions
Application: T cell differentiation

Model accounting for Th1, Th2, Th17, Treg, Tfh, Th9, Th22

101 components (21 input nodes), 221 interactions
82 context-dependent stable states (associated with a subset of input combinations)

- Canonical 8 Th types
- Hybrid cellular types, i.e. 4 hybrids expressing 2 master regulators (reported) and another one (Tbet$^+$Gata3$^+$Foxp3$^+$) (not yet observed)

<table>
<thead>
<tr>
<th>Transcription factors</th>
<th>Secreted cytokines</th>
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<tr>
<td>TBET</td>
<td>IFNG</td>
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<tr>
<td>GATA3</td>
<td>IL4</td>
</tr>
<tr>
<td>RORGT</td>
<td>IL17</td>
</tr>
<tr>
<td>FOXP3</td>
<td>IL21</td>
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<td>BCL6</td>
<td>IL22</td>
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<td>IL5</td>
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<tr>
<td>STAT3</td>
<td>IL13</td>
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<tr>
<td></td>
<td>IL9</td>
</tr>
<tr>
<td></td>
<td>TGFβ</td>
</tr>
<tr>
<td>Th0</td>
<td></td>
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<td>Treg</td>
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<tr>
<td>Tfh</td>
<td></td>
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<tr>
<td>Th9</td>
<td></td>
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<tr>
<td>Th22</td>
<td></td>
</tr>
</tbody>
</table>

- TBET, GATA3, RORGT, FOXP3, BCL6, PU.1, STAT3, IFNG, IL4, IL17, IL21, IL22, IL5, IL13, IL9, TGFβ
Application: T cell differentiation

82 context-dependent stable states (associated with a subset of input combinations)

- Canonical 8 Th types
- Hybrid cellular types, i.e. 4 hybrids expressing 2 master regulators (reported) and another one (Tbet\(^+\)Gata3\(^+\)Foxp3\(^+\)) (not yet observed)

Selection of relevant input combinations

<table>
<thead>
<tr>
<th>Environmental conditions</th>
<th>APC</th>
<th>IL12(_e)</th>
<th>IL4(_e)</th>
<th>IL6(_e)</th>
<th>TGFB(_e)</th>
<th>IL1B(_e)</th>
<th>IL23(_e)</th>
<th>IL21(_e)</th>
<th>IL2(_e)</th>
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<tr>
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</tr>
<tr>
<td>proTreg</td>
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<tr>
<td>proTfh</td>
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<td>proTh9</td>
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<tr>
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</tbody>
</table>

Reachability analysis using model-checking techniques

SPECIFICATION

Existence of a path from a canonical Th pattern $c_1$ towards a (stable) canonical Th pattern $c_2$, under an input condition $e$. 

Application: Assessing the flexibility and plasticity of T helper cells
Application: Assessing the flexibility and plasticity of T helper cells

Reprogramming graph between Th subsets under prototypic polarizing conditions
1. Motivation - Context
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Oogenesis in Drosophila melanogaster: groups of specialised cells shape the dorsal appendages
Application: Patterning of the *Drosophila* eggshell

Oogenesis in *Drosophila melanogaster*: groups of specialised cells shape the dorsal appendages
Oogenesis in Drosophila melanogaster: groups of specialised cells shape the dorsal appendages

Model accounting for the formation of the broad domain (roof) and the rhomboid domain (floors)

- Grk and Dpp signals
- Juxtacrine signal
- Vitelline membrane formation cancelling out Grk signal

A. Fauré et al. (2014) Plos Comp Bio 10(3): e1003507

Application: Patterning of the *Drosophila* eggshell

1) **Single cell model:** a logical model of the intra-cellular network

![Network Diagram](image_url)
Application: Patterning of the *Drosophila* eggshell

1) **Single cell model:** a logical model of the intra-cellular network

![Diagram of single cell model]

2) **Epithelial model:** a grid of cells

![Diagram of epithelial model]

- **Step 1:** Mirror Rhomboid Broad
- **Step 2:** VM formation
- **Steps 3 to 10:** Further grid configurations

**Legend:**
- Mirror
- Rhomboid
- Broad

**VM formation**
Application: Patterning of the *Drosophila* eggshell

**Single cell model**

**A**

- **Dpp**
- **Grk**
- **dpERK**
- **Pnt**
- **Mirr**
- **Rho**
- **Br**
- **Aos**
- **Mid**
- **X**

**B**

<table>
<thead>
<tr>
<th>Component</th>
<th>Level</th>
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<tr>
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<td>Mid</td>
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<tr>
<td>A</td>
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<tr>
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<tr>
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<tr>
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<td>(Mirr</td>
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<tr>
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<td>dpERK:2 &amp; Mirr &amp; !Br</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>dpERK:1 &amp; Mirr &amp; !Br</td>
</tr>
</tbody>
</table>
Application: Patterning of the *Drosophila* eggshell

Single cell model

324 input combinations → 8 stable states (cell fates), 3 cyclical attractors

**Dpp**

- R4: 39% 26% 2%
- R8: 35% 1% 23%
- R4: 33% 12% 29%

**Grk**

- R3: 54% 13% 31%
- R7: 41% 2% 20%
- R2: 36% 3% 53%

**Mid**

<table>
<thead>
<tr>
<th>dpERK</th>
<th>Mirr</th>
<th>Pnt</th>
<th>Rho</th>
<th>Aos</th>
<th>Br</th>
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<td>6-8</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>10-12</td>
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<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
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**CA**

- [0-2] [0-1] [0-1] [0-2] [0-1] 0 4
- [1-2] 1 [0-1] [1-2] [0-1] 0 2-3
- [1-2] 1 [0-1] [0-2] [0-1] [0-1] 6-7
- [0-2] [0-1] [0-1] [0-2] [0-1] [0-1] 8

**Before VM formation**

- F1: undifferentiated
- F5: roof
- F8: operculum and floor (floor alone after VM formation)

**After VM formation**

- 23/31
Application: Patterning of the *Drosophila* eggshell

Single cell model

Naive cell, fixed inputs defined by the latest state of the epithelial model before / after Grk extinction, in relevant (sub)-regions

Further analysis needed for e.g. R6
In R6 (Dpp=0, Grk=2), two reachable stable states, fixing the remaining inputs e.g. Aos_ext=2, Br_adj=1 and Rho_ext=1 and starting from a naive state (all internal variables =0)

Pnt+ with a lower priority (∼ introduction of a delay in Pnt activity) to force the reachability of F5. Biologically, this may correspond to the phosphorylation and expression of 2 Pnt isoforms.
EpiLog, a tool for the logical modelling of multi-cellular networks (epithelia)

Cellular automaton → a collection of "colored" cells on a grid that evolves through a number of discrete time steps according to a set of rules based on the states of neighbouring cells (von Neumann ∼ 1950, Wolfram ∼ 1980).

- Grid of hexagonal cells
- State of cells governed by: (1) associated logical models, (2) rules of cell-cell communication
- All updates are performed synchronously
EpiLog, a tool for the logical modelling of multi-cellular networks (epithelia)

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- All updates are performed synchronously
Application: Patterning of the *Drosophila* eggshell

Simulation of the wild-type model

Before VM formation

After VM formation

Grk signal extinction

EGFR
Mirr
Rho
Pnt
Aos
Br
Grk
Dpp

Before VM formation

After VM formation

Grk
Dpp
Application: Patterning of the *Drosophila* eggshell

Simulation of the wild-type model

Variables updated synchronously, BUT
- integration variables S, A, and X are updated before all other variables
- then dpERK is updated (variations in EGF pathway much faster than changes in gene expression)
- Aos expression is delayed (expression pattern does not immediately follow changes in EGF activity)
Application: Patterning of the *Drosophila* eggshell

Simulation for Grk and Dpp mis-expressions

Images reproduced with permission from Shravage et al. (2007) Development 134(12):2261-71
Application: Patterning of the *Drosophila* eggshell

Simulation for LOF and GOF mutants and clones

- **Aos LOF** has no visible effect on the Br domain, but prevents the splitting after VM formation (J-F Boisclair Lachance *et al* 2009)
- **Aos GOF** has a minimal effect (prediction)
- **Br clones** induce Rho positive cells within the clone (EJ Ward *et al* 2006)
Outline

1 Motivation - Context

2 Brief introduction to the logical formalism

3 Application: Core regulatory network of the lambda phage switch

4 Application: T cell differentiation

5 Application: Patterning of the *Drosophila* eggshell

6 Conclusions
Conclusions

Versatility of the logical modelling framework

A growing number of published models, methods & tools:

TOPIC: (boolean network) OR (Boolean gene regulatory network) OR (logical regulatory network)

Model sizes: \(\rightarrow\) up to several dozens
Conclusions

Versatility of the logical modelling framework

A variety of applications:

- Developmental biology: *D. melanogaster, C. elegans, Arabidopsis*, etc.
- Cell cycle regulation: yeast, mammals
- T helper cell differentiation & activation, Cytotoxic T lymphocytes
- Mammalian cell fate decision (apoptosis, senescence, proliferation)
- Cancer networks:
  - Epithelial to mesenchymal transition
  - Rb/E2F network, exploring patterns of mutations in bladder tumours
- Microbiota composition: genus interactions characterized as positive (growth promoting) or negative (growth suppressing)
Conclusions

Logical modelling largely used for regulatory and signalling networks of **larger sizes**
- integration of qualitative knowledge in a formal, organised manner
- analysis of dynamical properties
- *in silico* experiments

Asynchronous dynamics
- huge state transition graphs, difficult to analyse
- include all potential behaviours

→ development of methods to assess dynamical properties (HTG, model reduction, model-checking, etc.), focus on attractors and their reachability
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