Dynamical analysis of logical models of genetic regulatory networks

Contents

- Logical modelling of regulatory networks
- Novel algorithms for dynamical analysis
- Application to T cell activation and differentiation
- Conclusions and prospects
Logical modelling of regulatory networks

- A graph describes the interactions between genes or regulatory products
- **Discrete levels** of expression associated to each gene (logical variables) and interaction

- Logical parameters define the effect of combinations of incoming interactions
  - $K_B(\emptyset)=0$
  - $K_B(\{A,1\})=1$
  - $K_B(\{A,2\})=0$

- The dynamics is represented by a State Transition Graph (here, all possible trajectories)

GINsim (Gene Interaction Networks simulation)

Available at http://gin.univ-mrs.fr/GINsim

Discrete dynamics of simple feedback circuits

Positive circuit

Negative circuit

Feedback circuits & Thomas' rules

✓ A positive feedback circuit is necessary to generate multiple stable states or attractors

✓ A negative feedback circuit is necessary to generate homeostasis or sustained oscillatory behaviour


Mathematical theorems and demonstrations:

✓ In the differential framework:

✓ In the discrete framework:
Dynamical analysis tools

- **Priorities**
  - Mixed a/synchronous simulations

- **Decision diagrams** (Aurélien NALDI)
  - Stable state identification
  - Feedback circuit analysis

- **Petri nets** (Claudine CHAOUUIYA)

- **Logical programming**
  - Attractor identification
Behaviour of $B$ given by the logical function $K_B$

\[
K_B = \begin{cases} 
1 & \text{if } (A_1 \lor C) \\
0 & \text{otherwise}
\end{cases}
\]
Logical functions as decision diagrams

Dynamics of B given by the logical function $K_B$

$K_B = \begin{cases} 
1 & \text{if} \quad (A_1 \lor C) \\
0 & \text{otherwise} 
\end{cases}$

Efficient structure

Canonical representation (for an ordering of the decision variables)
Determination of stable states

- **Stable states**: all variables are stable
- **Analytic method** to find all possible stable states
  - No simulation
  - No initial condition
- **Principle**
  - Build a stability condition for each variable
  - Combine these partial conditions
Determination of stable states

\[ \begin{align*}
 & K_A & A \\
 & K_B & A \land \neg C \\
 & K_C & \neg A \\
\end{align*} \]
Determination of stable states

2 stable states: 001 et 110
Functionality context

Example: negative circuit inducing a cyclic behaviour
C prevents A from activating B

The circuit is **functional** in a given **context**: in **absence of C**
Functionality context

**Functionality context**: set of constraints on the expression levels of regulators

Each **interaction** has its own **context**

**Context of the circuit**: combination of all interaction contexts
In a circuit \((...,A,B,C,...)\), the functionality of the interaction \((A,B)\) depends on:

- \(K_B\)
- the threshold of \((A,B)\)
- the threshold of \((B,C)\)

**Functionality**: logical function depending on the regulators of B (represented as a decision diagram)
Functionality of an interaction

A

B

C

$K_B$

A

X

Y

X

Y

X

Y

1 1 1 0

0 1 1 1

-1 0 0 +1

-1 0 0 +1
Restrictions on circuit functionality context

- Auto-regulation and (more generally) “short-circuit”
  - Circuit members appear in functionality context
  - Members of the circuit must be able to cross their threshold
Applications

- **Cell cycle** (DIAMONDS FP6 STREP)
  - Yeast (*S. cerevisiae*)
  - Generic mammalian core
  - Drosophila (embryos)

- **T cell differentiation and activation** (ACI IMPbio & ANR BioSys)
  - Differentiation: Th1/Th2, Regulatory T cells, lymphoid lineages
  - TCR signalling

- **Drosophila development** (with Lucas SANCHEZ)
  - Genetic control of segmentation
  - Compartment formation in imaginal disks
T cell activation and differentiation

Naive T helper cell

Th1 cell

Th2 cell

TCR Activation

T-bet

GATA-3

Cellular response

Humoral response

T-bet

GATA-3
Application: TCR signalling

- Circuit analysis:
  4 circuits functional among 12
  - 3 positive circuits: auto-regulations on inputs
    → 8 attractors: one for each input combination
  - 1 negative circuit: ZAP70/cCbl (functional in presence of LCK and TCRphos)
    → cyclic attractor (for 111 input)

- Stable state analysis:
  7 stable states

5 functional (positive) circuits among 22

4 stable states:
  - Th0 (naive)
  - Th1 and Th1* (cellular response)
  - Th2 (humoral response)
Attractors and feedback circuits

Th0

Tbet
IFNγ circuits
+ IFNγ or L12+IL18

Th1
Medium IFNγ

Th1*
High IFNγ

Th2
IL4+IL10

GATA3/IL4/IL4R/STAT6
+ IL4

Tbet/GATA3

Inflammation
Cellular response

Humoral response

IFNγ circuits
## Mutant simulations

<table>
<thead>
<tr>
<th>Genetic background</th>
<th>Predicted phenotypes</th>
<th>Desactivatated Circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>Th0, Th1, Th1*, Th2</td>
<td>5 functional positive circuits</td>
</tr>
<tr>
<td>Tbet KO</td>
<td>Th0, Th2</td>
<td>Tbet, GATA3/Tbet</td>
</tr>
<tr>
<td>Tbet KI (high)</td>
<td>Th1*</td>
<td>Tbet, GATA3/Tbet</td>
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<td>GATA3 KO</td>
<td>Th0, Th1, Th1*</td>
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<td>GATA3 KI</td>
<td>Th1 &amp; Th1* like, Th2</td>
<td>GATA3/Tbet, GATA3/IL4/IL4R/STAT6</td>
</tr>
<tr>
<td>GATA3+Tbet DKO</td>
<td>Th0</td>
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<td>Th1*</td>
<td>IFNγ circuits</td>
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</tbody>
</table>

Qualitative agreement with documented perturbations
Take-home messages

- **Flexibility** of logical/discrete modelling
- **Versatility** (gene regulation, cell cycle, differentiation...)
- **Analytical developments** (circuits functionality, stable state)
- Insights into **topology - dynamics relationships**
- Implementation of novel algorithms into **GINsim**
Prospects

- **Methodological developments**
  - Determination of complex attractors
  - Further elaboration of circuit analysis

- **Th model**
  - Extension to other regulatory components (IL2)
  - Other differentiative pathways (Treg and T17)
  - Model composition (Tcell activation and differentiation)
Current supports