Reduction of logical regulatory network preserving dynamical properties

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1 Introduction
   - Modelisation of gene regulatory network
   - Identification of parameters

2 Framework

3 Reduction methods
   - Method suppressing a variable (Naldi 2011)
   - Method suppressing a threshold
   - Example

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Gene regulatory network

Interactions of elements (ADN, ARN, proteins) → Biological function
Gene regulatory network

Interactions of elements (ADN, ARN, proteins) → Biological function
Modelisation of a regulatory network ...

René Thomas theory (1973)
- Discretization of concentrations
Modelisation of a regulatory network …

René Thomas theory (1973)

- Discretization of concentrations
- Abstraction of gene products to variables

Interaction graph
... driven by parameters

State of a network
Vector for which components are value of variables.
... driven by parameters

State of a network

Vector for which components are value of variables.
... driven by parameters

State of a network
Vector for which components are value of variables.

\[ \mathbf{K}_{\mathbf{v},\omega} : \text{value toward which } \mathbf{v} \text{ tends depends to the level of its predecessors} \]
... driven by parameters

State of a network
Vector for which components are value of variables.

\( K_{v,\omega} \): value toward which \( v \) tends
depends to the level of its predecessors

Example:
In the state \((0,0)\) \( K_{b,\omega} = 1 \) and \( K_{a,\omega} = 2 \)
Desynchronization and shorting transitions

- 2 variables can’t cross their thresholds at the same time.
Desynchronization and shorting transitions

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- A variable can’t cross several thresholds at the same time.
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Determining parameters

Determining by biological experimentation is very difficult

→ Systematic checking of the compatibility of all parametrizations with the biological informations (model checking)
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Number of parametrizations

\[ \#K = \prod_i n_i^{2^{\text{pred}_i}} \]

where \( n \): number of values of \( i \) / \( \text{pred}_i \): number of predecessors
Determining parameters

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**Number of parametrizations**

\[
\#K = \prod_{i} n_{i}^{2^{\text{pred}_i}}
\]

where \( n \): number of values of \( i \) / \( \text{pred}_i \): number of predecessors

⚠️ Gene network are often very large.

→ The checking of all parametrizations can be very long
An intuitive solution: reduction of networks

Biological experimentation is based on an hypothesis.

Suppressing of less important information to reduct the number of possible parametrizations

In this presentation:
- To which states tends the network?
- Suppression of non-informative states
- Preservation of final states

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In this presentation:

To which states tends the network?
- Suppression of non informative state
- Preservation of final states
Formalisation with multiplexes (Khalis 2009)

Multiplex

Symbol $m$ associated with a logical formula $\varphi_m$ representing conditions of regulation between variables.

Integration of cooperations and concurrency in the interaction graph
Formalisation with multiplexes (Khalis 2009)

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Symbol $m$ associated with a logical formula $\varphi_m$ representing conditions of regulation between variables.

Integration of cooperations and concurrency in the interaction graph

$\alpha \geq 2$

$\neg (b \geq 1) \land a \geq 2$

$\gamma \geq 1$

$\beta$
Formalisation with multiplexes

Set of resources

Predecessor multiplexes of a variable $v$ which the formula is evaluated to true, in the current state $\eta: \rho(\eta, v)$
Formalisation with multiplexes

Set of resources

Predecessor multiplexes of a variable $v$ which the formula is evaluated to true, in the current state $\eta : \rho(\eta, v)$

State $(a,b)$ | Resources
--- | ---
$(1,1)$ | $\emptyset$
$(2,1)$ | $\{\alpha\}$
$(0,0)$ | $\{\beta\}$
$(2,0)$ | $\{\alpha, \beta\}$
The immunity regulatory network of phage λ

Bacteriophage λ

Virus infecting bacteria like E. Coli
The immunity regulatory network of phage λ

Bacteriophage λ

Virus infecting bacteria like E. Coli

2 ways after infection:
- **lytic**: release of produced viruses and host destruction
- **lysogenic**: host preservation and immunity to this virus against superinfection
The immunity regulatory network of phage λ

Bacteriophage λ

Virus infecting bacteria like E. Coli

2 ways after infection:
- lytic: release of produced viruses and host destruction
- lysogenic: host preservation and immunity to this virus against superinfection

4 main genes: CI, Cro, CII, N
- CI represses other genes to maintain the lysogenic cycle
- Cro inhibits the gene CI to maintain the lytic mode
The immunity regulatory network of phage $\lambda$

2 genes considered: Cro and CI

![Diagram of the regulatory network]

Parameters (Thieffry 1995):

- $K_{CI} = 0$
- $K_{CI}, \{m_{CI}\} = 1$
- $K_{Cro} = 0$
- $K_{Cro}, \{m_{Cro}^{1}\} = 1$
- $K_{Cro}, \{m_{Cro}^{2}\} = 0$
- $K_{Cro}, \{m_{Cro}^{1}, m_{Cro}^{2}\} = 2$
The immunity regulatory network of phage λ

6 states: 3 values for Cro and 2 values for CI

Attraction basin: minimal set of terminal states
The immunity regulatory network of phage $\lambda$

6 states: 3 values for Cro and 2 values for CI

Attraction bassin: minimal set of terminal states
Suppressing of variables (Naldi 2011)

The suppressed variable is considered as very fast.

\begin{center}
\begin{tikzpicture}[scale=0.5]
  \draw[thick,->] (0,0) -- (6,0) node[right] {Cro};
  \draw[thick,->] (0,0) -- (0,6) node[above] {CI};
  \draw[thick,red] (0,0) -- (2,0) -- (2,2) -- (0,2) -- (0,0);
  \draw[thick,blue] (2,0) -- (4,0) -- (4,4) -- (2,4) -- (2,0);
  \draw[thick,green] (4,0) -- (6,0) -- (6,6) -- (4,6) -- (4,0);
  \draw[thick,->] (0,2) -- (2,2);
  \draw[thick,->] (2,4) -- (4,4);
  \draw[thick,->] (4,6) -- (6,6);
  \draw[thick,->] (0,0) -- (2,2);
  \draw[thick,->] (2,0) -- (4,4);
  \draw[thick,->] (4,2) -- (6,6);
  \draw[thick,->] (0,2) -- (2,0);
  \draw[thick,->] (2,4) -- (4,2);
  \draw[thick,->] (4,6) -- (6,4);
\end{tikzpicture}
\end{center}
Suppressing of variables (Naldi 2011)

The suppressed variable is considered as very fast.

Possible reduction if the variable is not autoregulated.

Order of successive reductions → different minimum state graphs.
Suppressing of variables (Naldi 2011)

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Possible reduction if the variable is not autoregulated

Order of successive reductions $\rightarrow$ different minimum state graphs
Suppressing of variables (Naldi 2011)

- Important reduction of number of states
- Need to know the values of parameters
- Multiplicity of edges after reduction
Suppressing of threshold

Reduction of a threshold of a variable

Similar to Naldi’s method
Suppressing of threshold

Reduction of a threshold of a variable

Similar to Naldi’s method

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Reduction of logical regulatory network

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Comparison

Reduction of a threshold of a variable

Suppressing variable method: more drastic but loss of information.
Folding of reduced network ($fold_s^v$)

Decreasing of number of values of a variable

- Folding of states ($fold_{s}^v$)
- Folding of parameters ($fold_{k}^v$)
- Folding of formulas ($fold_{f}^v$)
Formulas

- Adjacent states to suppressed threshold
  \[ \Phi_s^v \equiv \left( v \geq s - 1 \right) \land \neg \left( v \geq s + 1 \right) \]

- A set \( \omega \) is the set of resources of \( v \) in the current state
  \[ \Phi_\omega^v \equiv \left( \bigwedge_{m \in \omega} \varphi_m \right) \land \left( \bigwedge_{m \in G^{-1} \setminus \omega} \neg \varphi_m \right) \]

- A set of resources allows to \( v \) to cross its threshold \( s \)
  \[ \Phi_{\geq s}^v \equiv \bigwedge_{\omega \subset A^{-1}(v)} \left( \Phi_\omega^v \implies K_{v,\omega} \geq s \right) \]
Reduction definition

- $V^B = V^A$. $\forall u \neq v$ avec $u, v \in V^B$, $b^B_u = b^A_u$ et $b^B_v = b^A_v - 1$
- $\mathcal{K}^B = \{ K^B_{v, \omega} = \text{fold}^v_s(K^A_{v, \omega}) \}$
- $E^B = E^A$
- $M^B = M^A$. $\forall m \in M^B$, $\varphi^B_m \equiv \text{fold}^v_s((\neg \Phi^v_s \land \varphi^A_m) \lor (\Phi^v_s \land \varphi^A_m[v \geq s \leftarrow \Phi^{v\geq s}])))$
Reduction definition

- $V^B = V^A$. $\forall u \neq v$ avec $u, v \in V^B$, $b_u^B = b_u^A$ et $b_v^B = b_v^A - 1$
- $\mathcal{K}^B = \{K_{v,\omega} = fold_s^v(K_{v,\omega})\}$
- $E^B = E^A$
- $M^B = M^A$. $\forall m \in M^B$, 
  $\varphi_m^B \equiv fold_s^v((\neg \Phi_s^v \land \varphi_m^A) \lor (\Phi_s^v \land \varphi_m^A[v \geq s \leftarrow \Phi^v[s^s])))$

\[ s-3 \quad s-2 \quad s-1 \quad s \quad s+1 \quad s+2 \]
Reduction definition

\[ V^B = V^A. \quad \forall u \neq v \text{ avec } u, v \in V^B, \quad b^B_u = b^A_u \text{ et } b^B_v = b^A_v - 1 \]

\[ K^B = \{ K^B_{v, \omega} = \text{fold}_s^v(K^A_{v, \omega}) \} \]

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Reduction of the phage $\lambda$ network by Naldi: 4 variables (Thieffry 1995)

With Naldi’s method

Initial network: 48 states
Reduction of the phage λ network by Naldi: 4 variables (Thieffry 1995)

With Naldi’s method

Initial network: 48 states
Reduction of the phage λ network by Naldi: 4 variables (Thieffry 1995)

With Naldi’s method

\[ \neg CI \geq 2 \]
\[ \neg Cro \geq 3 \]
\[ \neg CI \geq 2 \land \neg Cro \geq 3 \land \neg N \geq 1 \]

Initial network: 48 states / Reduced network: 12 states
Reduction of the phage $\lambda$ network : 2 variables

Reduction by our method

\[\neg \text{CI} \geq 2 \quad \neg \text{Cro} \geq 1 \lor (\neg \text{Cro} \geq 2 \land \neg \text{CI} \geq 1)\]

Initial network : 12 states

Reduced network : 4 states
Reduction of the phage $\lambda$ network: 2 variables

Reduction by our method

Initial network: 12 states

Reduced network: 4 states
Reduction of the phage λ network : 2 variables

Reduction by our method

Initial network : 12 states / Reduced network : 4 states
Formula of $m_{CI}$ after reduction

\[ \neg Cro \geq 2 \land \neg \left\{ \begin{array}{l} \neg Cl \geq 1 \land Cro \geq 2 \\
\neg Cro \geq 2 \land Cl \geq 1 \\
\neg Cro \geq 2 \land \neg Cl \geq 1 \end{array} \right\} \land (Cro \geq 2 \lor Cl \geq 1) \Rightarrow K_{Cro} \geq 1 \]

\[ K_{Cro}, \{m_{Cro}^1\} \geq 1 \]

\[ K_{Cro}, \{m_{Cro}^2\} \geq 1 \]

\[ K_{Cro}, \{m_{Cro}^1, m_{Cro}^2\} \geq 1 \]
Conclusion

What have we doing?

- Reformulation of Naldi’s method with multiplexes.
- Definition of a method to reduct a autoregulated variable.
- Proof of preserving stable states and cycles.

What we must finish?

- Proof the preserving complex attractors and reachability of states.