Symbolic reductions of gene network models

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Introduction

- Abstraction and simplification within models
  - stochastic, differential, discrete, hybrid frameworks
  - abstraction $\equiv$ essence of modelling activity (to grasp the key elements and their roles)
  - pragmatical fact : combinatoric explosion
- Thomas' modelling frameworks
- If parameters are all known
  - Naldi's method for computing reduced networks
  - Preservation of dynamical properties
- **Reversing the problem**
  - Is it possible to infer parameters
  - from the parameters of the simplified one ?

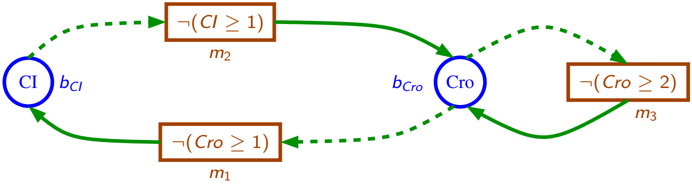
$\Rightarrow$ define **symbolic reductions**

Outline

Gene network specifications

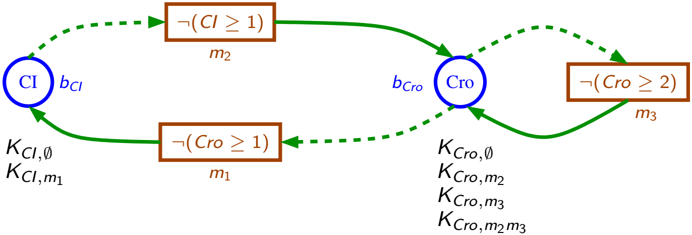
Set of Variables

Gene network specifications



Set of Variables
Set of multiplexes : each multiplex is equiped with a formula
Regulations : which variable does act on which one ?

Gene network specifications



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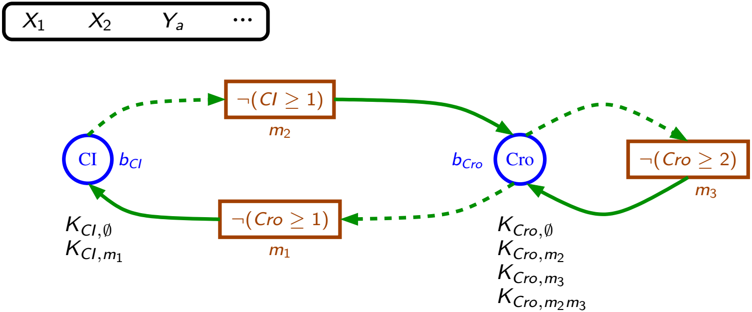
Gene network specifications



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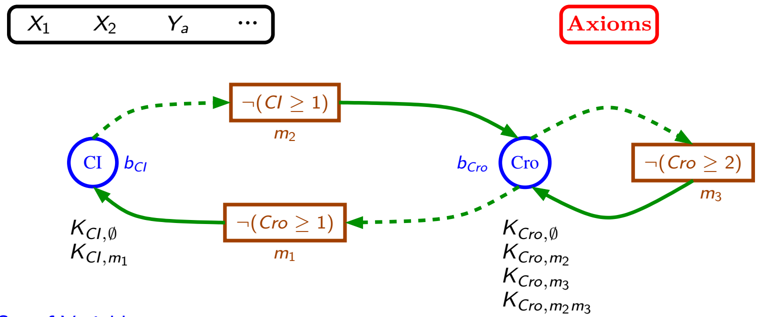


Set of Variables
Set of multiplexes : each multiplex is equiped with a formula
Regulations : which variable does act on which one ?
Set of parameters : towards which value is attracted a variable ? + environment parameters
Axioms : memorize the relationships between original model and derived models

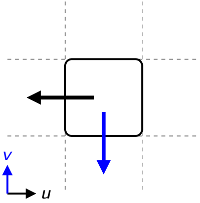
Giving a value to each parameter : a realization

- A realization $\equiv$ substitution $\sigma : X \to \mathbb{N}$ s.t.
  - $\sigma(K_{v,\omega}) \leq b_v$ for all $v \in V$ and $\omega \in S^{-}(v)$
  - $\sigma(\psi)$ is satisfied in $\mathbb{N}$ for all $\psi \in Axioms$

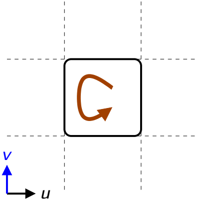
Gene network dynamics : as usual...

The transition graph (ζ, T_σ) :

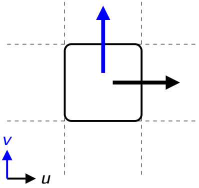
- the nodes are the states : $\eta : V \to \mathbb{N}$
- the resources $\rho_\sigma(v,\eta) \equiv$ the set of predecessors whose formulas are evaluated to true
- transitions depend on substitution σ



$\eta(u) > \sigma(K_{u,\rho_\sigma(u,\eta)})$
$\eta(v) > \sigma(K_{v,\rho_\sigma(v,\eta)})$



$\begin{cases} \eta(u) = \sigma(K_{u,\rho_\sigma(u,\eta)}) \\ \eta(v) = \sigma(K_{v,\rho_\sigma(v,\eta)}) \end{cases}$



$\eta(u) < \sigma(K_{u,\rho_\sigma(u,\eta)})$
$\eta(v) < \sigma(K_{v,\rho_\sigma(v,\eta)})$

Gene network dynamics : 3 useful formulas

1. The set of resources of v is ω :

$$\Phi_v^\omega \equiv \Big(\bigwedge_{m \in \omega} \varphi_m\Big) \wedge \Big(\bigwedge_{m \in S^-(v) \setminus \omega} \neg\varphi_m\Big)$$

2. The variable v can increase :

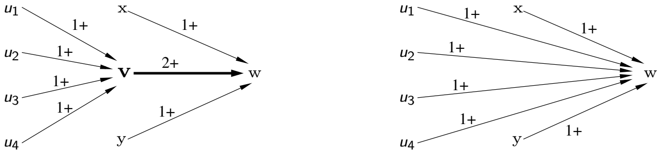
$$\Phi_v^+ \equiv \bigwedge_{\omega \subset S^-(v)} (\Phi_v^\omega \Longrightarrow K_{v,\omega} > v)$$

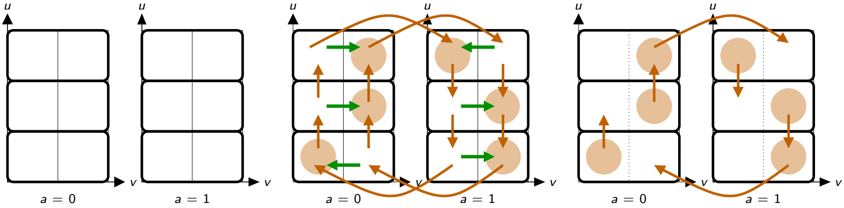
3. The variable v can decrease :

$$\Phi_v^- \equiv \bigwedge_{\omega \subset S^-(v)} (\Phi_v^\omega \Longrightarrow K_{v,\omega} < v)$$

Naldi's reductions of network specifications (intuition)

- if v is no auto-regulated :
  v is supposed to go immediately to its focal value





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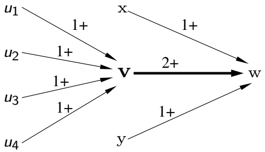
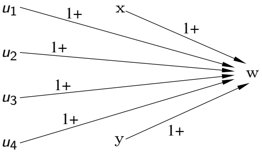
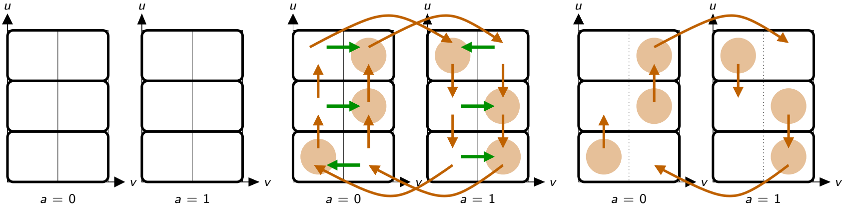




$2^3 + 2^4 = 24$

$2^6 = 64$



Suppressing a variable in specif. $S = (V, X, M, E, Ax)$

1. $\mathbf{R_v^S(V)} = V \setminus \{v\}$
2. $\mathbf{R_v^S(X)} = (X \setminus \{K_{v,\omega} | \omega \subset S^-(v)\}) \quad \cup \quad \{K^S_{v,\omega} | \omega \subset S^-(v)\}$
3. $\mu_v^S : X \to \mathbf{R_v^S(X)}$ (renames $K_{v,\omega}$ into $K^S_{v,\omega}$)
   $\mathbf{R_v^S}(\phi) \equiv \bigwedge_{\omega \subset S^-(V)} \mu_v^S(\Phi_v^\omega \Rightarrow \phi[v \leftarrow K_{v,\omega}])$
   $\mathbf{R_v^S(m)}$ where m is a multiplex : the formula is reduced *via* $\mathbf{R}(())$.
   multiplexes which have as unique target v, are suppressed.
4. $\mathbf{R_v^S(E)}$: the same except the edges towards v
5. $\mathbf{R_v^S(Ax)} = \mu_v^S(Ax)$

- A gene network $N = (S, \sigma)$ being given, the v-*reduction* of N is the gene network $\mathbf{R_v^S(S}, \sigma) = (\mathbf{R_v^S(S)} , \sigma \circ (\mu_v^S)^{-1})$.
- Transition Graph : $\mathbf{R_v^S}(\eta)$ is the restriction of η to $\mathbf{R_v^S(V)}$

Lemma 1 (Preservation of formulas' evaluation)

Let η, σ *s.t.* $\eta(v) = \sigma(K_{v,\rho(v,\eta)})$, *then*

$$(\eta \models \sigma(\varphi)) \quad \Leftrightarrow \quad \mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\eta) \models \sigma'(\mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\varphi)).$$

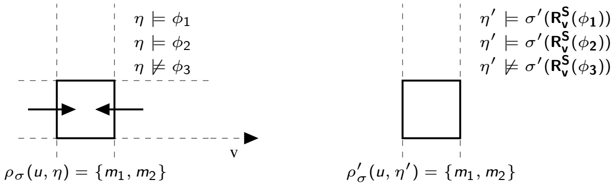
- if $v \notin var(\varphi)$, we have $\quad (\eta \models \sigma(\varphi)) \quad \Leftrightarrow \quad (\mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\eta) \models \sigma'(\mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\varphi)))$
- if $v \in var(\varphi)$,

$$\begin{aligned}
\mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\eta) \models \sigma'(\mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\varphi)) &\Leftrightarrow \eta \models \sigma'(\mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\varphi)) \quad \text{because } v \notin \mathbf{R}_{\mathbf{v}}^{\mathbf{S}}(\varphi) \\
&\Leftrightarrow \eta \models \sigma'(\bigwedge_{\omega \subset S^-(v)} \mu_v^S(\Phi_v^\omega \Rightarrow \varphi[v \leftarrow K_{v,\omega}])) \\
\text{using } \sigma' = \sigma \circ (\mu_v^S)^{-1} &\Leftrightarrow \eta \models \sigma(\bigwedge_{\omega \subset S^-(v)} \Phi_v^\omega \Rightarrow \varphi[v \leftarrow K_{v,\omega}]) \\
\text{using } \eta(v) = \sigma(K_{v,\rho(v,\eta)}) &\Leftrightarrow \eta \models \sigma(\bigwedge_{\omega \subset S^-(v)} \Phi_v^\omega \Rightarrow \varphi) \\
&\Leftrightarrow \eta \models \sigma(\varphi)
\end{aligned}$$

Lemma 2 (Resources Preservation)

Let η, σ, v *such that* $\eta(v) = \sigma(K_{v,\rho(v,\eta)})$ *and let* u *a variable s.t.* $u \neq v$.

$$\rho_\sigma(u, \eta) = \rho_{\sigma'}(u, \mathbf{R_v^S}(\eta))$$



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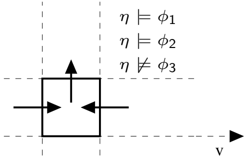
$$\rho_\sigma(u,\eta) = \rho_{\sigma'}(u, \mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\eta))$$

Lemma 3 (Transition Preservation)

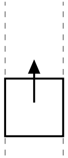
Let η, σ, v *such that* $\eta(v) = \sigma(K_{v,\rho(v,\eta)})$ *and let* $\eta \to \eta'$.

if $\mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\eta) \neq \mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\eta')$, *we have* $\mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\eta) \to \mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\eta')$.



$\eta \models \phi_1$
$\eta \models \phi_2$
$\eta \not\models \phi_3$

$\rho_\sigma(u,\eta) = \{m_1, m_2\}$
$K_{u,\{m_1,m_2\}} > \eta(u)$

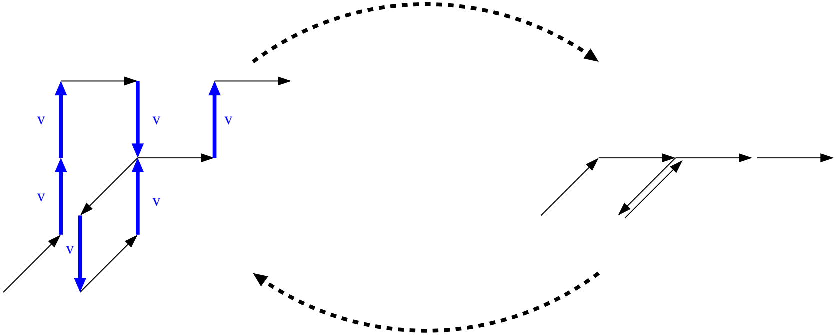


$\eta' \models \sigma'(\mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\phi_1))$
$\eta' \models \sigma'(\mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\phi_2))$
$\eta' \not\models \sigma'(\mathbf{R}^{\mathbf{S}}_{\mathbf{v}}(\phi_3))$

$\rho'_\sigma(u,\eta') = \{m_1, m_2\}$
$K_{u,\{m_1,m_2\}} > \eta(u)$

Lemma 4 (Path preservation)

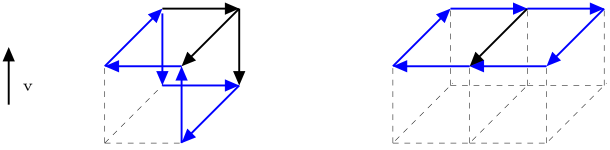
The set of paths "saturating first v" of $N = (S, \sigma)$ *is in canonical bijection with the set of paths of* $N' = (\mathbf{R_v^S}(\mathbf{S}), \sigma \circ (\mu_v^S)^{-1})$.



Preservation of dynamical properties

Lemma 5

Each attractor contains at least a cycle "saturating first v" (trivial)



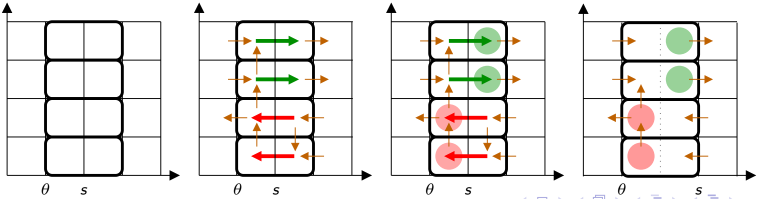
complex attractors with cycle saturating first v

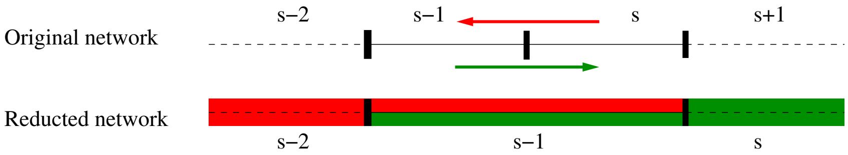
Theorem (preservation of dynamical properties)

- *preservation of stable states*
- *preservation of stable cycles*
- *the reduction of each complex attractor contains at least a cycle*

Extended reductions of network specifications (intuition)

- if v is a self-regulation free variable, v can be viewed as a relay for the transmission of information. v can be "replaced" by its focal value (which depends only on the other variables).
- if v is self-regulated at threshold θ, on either side of the threshold, v can be "replaced" by its focal value (which depends only on the other variables).
  One can merge state $s-1$ and s $(s \neq \theta)$, making the assumption that inside these two values, v elvolves immediately.





1. if $\eta(v) < s - 1$ in the reduced network,
   v behaves as v in the initial network
2. if $\eta(v) \geq s$ in the reduced network,
   v behaves as $v + 1$ in the initial network
3. if $\eta(v) = s - 1$, it depends on Φ_v^+ :
   - if Φ_v^+ is satisfied, v behaves as $v + 1$ in the initial network
   - if Φ_v^+ is not satisfied, v behaves as v in the initial network

Folding a formula

1. if $\eta(v) \geq s$ (folded) or ($\eta(v) = s - 1$ (folded) and Φ_v^+ (initial)) :

$$\text{init}, \eta \models \varphi \qquad \equiv \qquad \text{folded}, \eta' \models \varphi[v \leftarrow v+1]$$

2. if $\eta(v) < s - 1$ (folded) or ($\eta(v) = s - 1$ (folded) and $\neg\Phi_v^+$ (initial) :

$$\text{init}, \eta \models \varphi \qquad \equiv \qquad \text{folded}, \eta' \models \varphi$$

Definition of $\mathbf{fold}_{\mathbf{v},\mathbf{s}}^{\mathbf{S}}(\varphi) \quad \equiv \quad \psi_1 \wedge \psi_2$ where

$$\begin{array}{lcl} \psi_1 & = & ((v \geq s) \vee (v = s-1 \wedge \mu_v^S(\Phi_v^+))) \Rightarrow \mu_v^S(\varphi[v \leftarrow v+1]) \\ \psi_2 & = & ((v < s-1) \vee (v = s-1 \wedge \neg\mu_v^S(\Phi_v^+))) \Rightarrow \mu_v^S(\varphi) \end{array}$$

Suppressing a threshold in specif. $S = (V, X, M, E, Ax)$

The reduced network :

1. $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\mathbf{V}) = V$
2. $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\mathbf{X}) = X \quad \cup \quad \{K^S_{v,\omega} | \omega \subset S^-(v)\}$
3. $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\mathbf{M}) \; = \; \{\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\mathbf{m}) \mid m \in M\}$
4. $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\mathbf{E}) = E$ (the same edges)
5. $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\mathbf{Ax}) = \mu^S_v(Ax) \cup \{folded_s(K_{v,\omega}, \mu^S_v(K_{v,\omega})) \mid \omega \subset S^-(v)\}$
   where

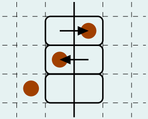
$$folded_s(t', t) \equiv (t < s \;\wedge\; t' = t) \;\vee\; (t \geqslant s \;\wedge\; t' = t - 1)$$

- Transition Graph :
  $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta)$ ...

Lemma 6 (Preservation of formulas' evaluation, $b_v > 1$)

Let η_0, σ *be a state and a realization, and let* η *be defined by*

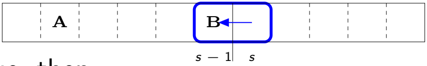
$$\eta = \eta_0 \left[v \leftarrow \begin{cases} \eta_0(v) + 1 & \text{if } \eta_0(v) = s - 1 \wedge \sigma(K_{v,\rho(v,\eta)}) \geq s \\ \eta_0(v) - 1 & \text{if } \eta_0(v) = s \wedge \sigma(K_{v,\rho(v,\eta)}) \leq s - 1 \\ \eta_0(v) & \text{otherwise} \end{cases} \right]$$



We have : $(\eta \models \sigma(\varphi)) \quad \Leftrightarrow \quad \mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \models \sigma'(\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\varphi))$.

- if $v \notin var(\varphi)$, we have $(\eta \models \sigma(\varphi)) \Leftrightarrow (\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \models \sigma'(\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\varphi)))$
- if $v \in var(\varphi)$, two cases...

- Case A and B :



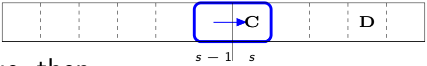
ψ_1 is trivially true, then

$$\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \models \sigma'(\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\varphi)) \quad \Leftrightarrow \quad \eta \models \sigma'(\mu^S_v(\varphi))$$

Using Axioms, we deduce $K^S_{v,\omega} = K_{v,\omega}$

$$\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \models \sigma(\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\varphi)) \quad \Leftrightarrow \quad \eta \models \sigma(\varphi)$$

- Case C and D :



ψ_2 is trivially true, then

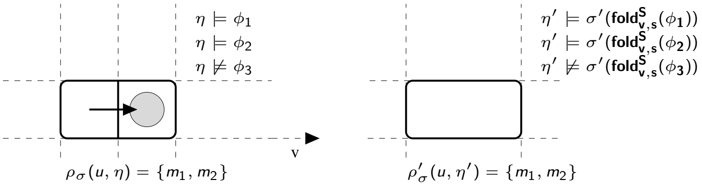
$$\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \models \sigma'(\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\varphi)) \quad \Leftrightarrow \quad \eta \models \sigma'(\mu^S_v(\varphi[v \leftarrow v+1]))$$

Using Axioms, we deduce $K^S_{v,\omega} = K_{v,\omega} + 1$

$$\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \models \sigma'(\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\varphi)) \quad \Leftrightarrow \quad \eta \models \sigma(\varphi)$$

Lemma 7 (Resources Preservation, $b_v > 1$)

Let η_0, σ, v and η defined as previously. Let u a variable.
$\rho_\sigma(u, \eta) = \rho_{\sigma'}(u, \mathbf{fold}^{\mathbf{S}}_{\mathbf{v},\mathbf{s}}(\eta))$



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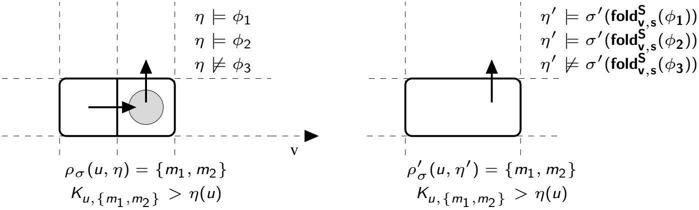
Let η_0, σ, v and η defined as previously. Let u a variable.
$\rho_\sigma(u, \eta) = \rho_{\sigma'}(u, \mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta))$

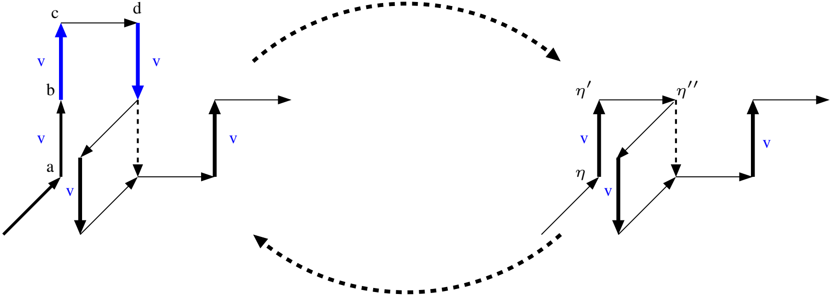
Lemma 8 (Transition Preservation, $b_v > 1$)

Let η_0, σ, v and η defined as previously. Let $\eta \to \eta'$.
If $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \neq \mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta')$, we have $\mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta) \to \mathbf{fold}^{\mathbf{S}}_{\mathbf{v,s}}(\eta')$.



Lemma 9 (Paths' preservation, $b_v > 1$)

The set of paths "saturating first v" of $N = (S, \sigma)$ is in canonical bijection with the set of paths of $N' = (\mathbf{fold}^{\mathbf{S}}_{\mathbf{v},\mathbf{s}}(\mathbf{S}), \sigma')$.



Proof of lemma 9 :

- With each path "saturating first v", one associates a path in N' (trivial)
- With each path in N', one associates the unique path "saturating first v" in N : Let be $\eta \to \eta' \to \eta''$
  - $\exists a, b, c, d \in \mathbf{R_v^S}^{-1}(\eta) \times \mathbf{R_v^S}^{-1}(\eta') \times \mathbf{R_v^S}^{-1}(\eta') \times \mathbf{R_v^S}^{-1}(\eta'')$ s.t. $\left\{ \begin{array}{l} a \to b \\ c \to d \end{array} \right.$ and $c(v) = b(v) + 1$ if $\sigma(K_{v,\dots}) > b(v)$...
  - in $\mathbf{R_v^S}^{-1}(\eta')$, because the resources do not change, there exists a unique path from b to c
  - there exists a unique path from $a \in \mathbf{R_v^S}^{-1}(\eta)$ towards d.

□

Preservation of dynamical properties

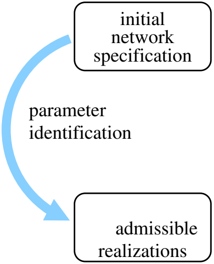
Lemma 10

Each attractor contains at least a cycle "saturating first v" (trivial)

Theorem (preservation of dynamical properties)

- *preservation of stable states*
- *preservation of stable cycles*
- *the folding of each complex attractor contains at least a cycle*

Global approach



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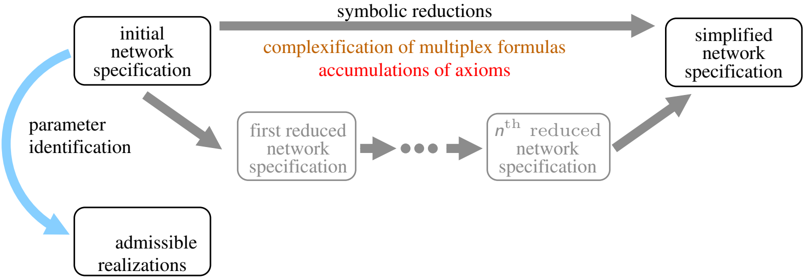

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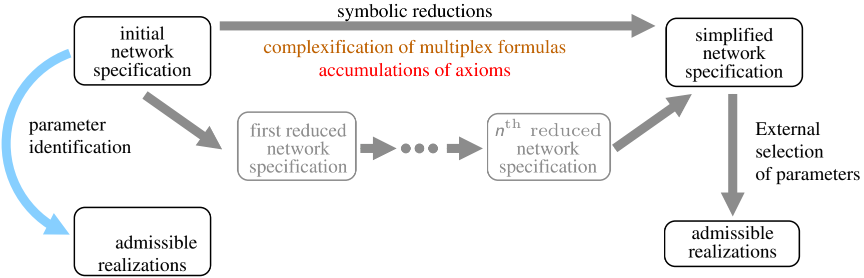

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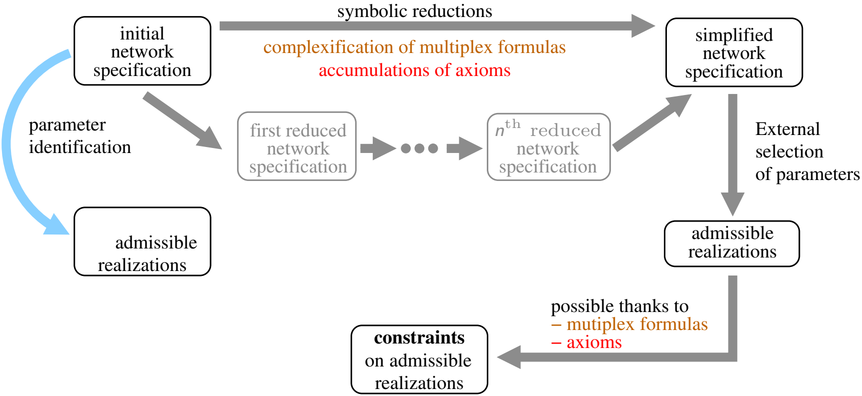

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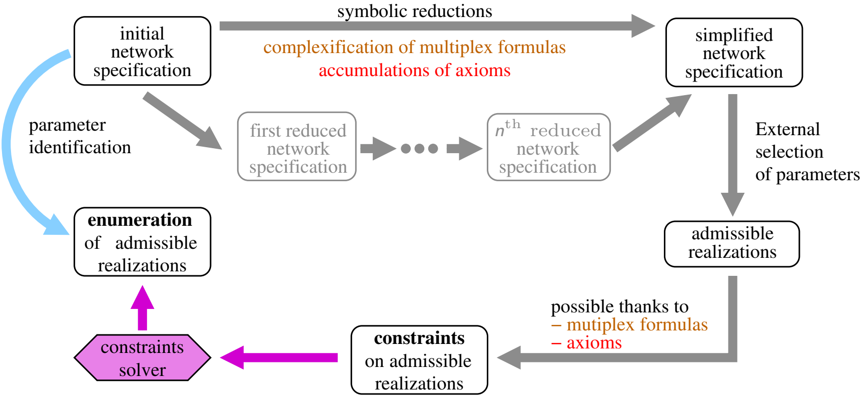

Conclusion

- Multiplex formulas code the situations where a regulation takes place
  even if the direct regulator has been abstracted
  $\Rightarrow$ Non proliferation of parameters
- Axioms allow the parameterization of the environment
  they memorize the different foldings of parameters
  during threshold suppression.
- Use of constraints solver