Master SVS – PARCOURS Bio-informatique et Biologie Computationnelle (BBC)

year 2024–2025

Formal methods for discrete modelling

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Université Côte d'Azur

24 September 2024

Teaching organization

- Lectures : 2 sessions of 2 hours each
- Tutorial : 2 sessions of 2 hours each
- Teacher :
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	Sessions	schedule	teacher	Lecture/tuto
1	24 September 2024	8h-12h	JPC	lecture+tuto
2	1 October 2022	8h-12h	JPC	lecture+tuto

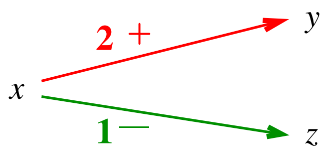
- Evaluation : A 2-hour exam on 8 October 2024 from 9 to 11 a.m.
- Course material + tutorials :
  https://www.i3s.unice.fr/~comet/SUPPORTS/

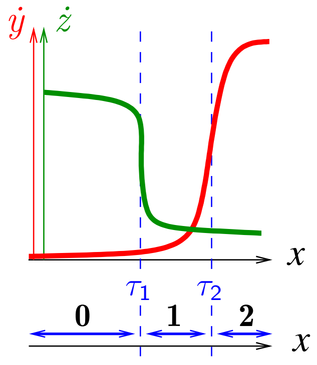
Plan

1. Discrete models for gene networks according to René Thomas
2. CTL
3. Techniques of software testing
4. General Schema for BRN
5. Genetically modified Hoare logic, and examples
   - Hoare Logic
   - Examples

Multivalued Regulatory Graphs

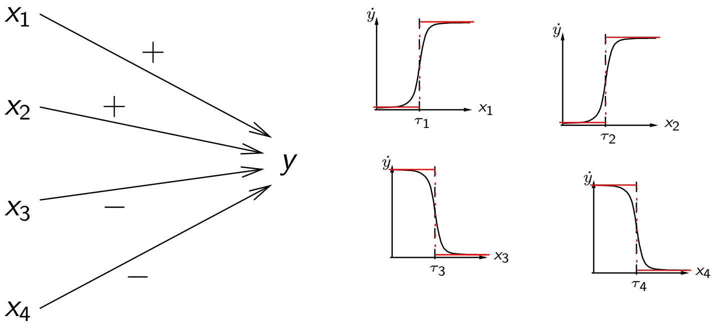
Derivatives are sigmoids w.r.t. the source gene





First simplification : piecewise linear

Approximate sigmoids as step functions :



Presence of an activator = Absence of an inhibitor

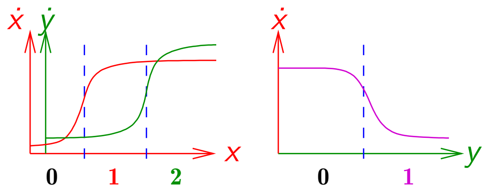
$\frac{dy}{dt} = k_0 + k_1.\mathbb{1}_{x_1 \geqslant \tau_1} + k_2.\mathbb{1}_{x_2 \geqslant \tau_2} + k_3.\mathbb{1}_{x_3 < \tau_3} + k_4.\mathbb{1}_{x_4 < \tau_4} - \gamma.y$

Solutions of the form $Ce^{-\gamma t} + \frac{\Sigma \mathbb{1} k_i}{\gamma}$ whose $\lim_{t\to\infty}$ is $\frac{\Sigma \mathbb{1} k_i}{\gamma}$

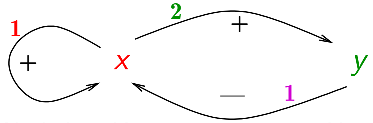
As many such equations as genes in the interaction graph

In each hypercube, all the trajectories have a unique *attractive point*, which can be outside de hypercube

Discrete Gene Networks (Thomas & Snoussi)



In each state, a variable v tries to go toward the interval numbered $K_{v,\omega}$: the one containing $\frac{\Sigma \mathbb{1} k_i}{\gamma}$



No help : K_x K_y
x helps : $K_{x,x}$ $K_{y,x}$
Absent y helps : $K_{x,\bar{y}}$
Both : $K_{x,x\bar{y}}$

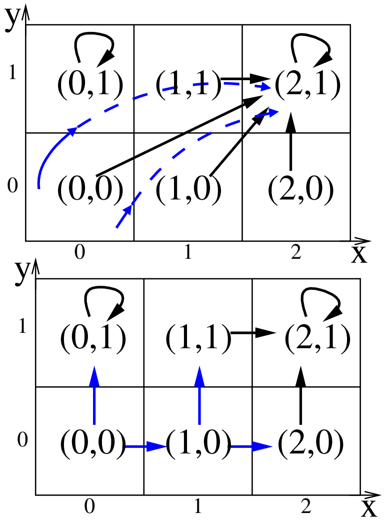
(x,y)	*Focal Point*
(0,0)	$(K_{x,\bar{y}}, K_y)$
(0,1)	(K_x, K_y)
(1,0)	$(K_{x,x\bar{y}}, K_y)$
(1,1)	$(K_{x,x}, K_y)$
(2,0)	$(K_{x,x\bar{y}}, K_{y,x})$
(2,1)	$(K_{x,x}, K_{y,x})$

Presence of an activator = Absence of an inhibitor = **A resource**

State Graphs

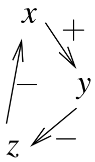
(x,y)	*Focal Point*
(0,0)	$(K_{x,\bar{y}}, K_y)$=(2,1)
(0,1)	(K_x, K_y)=(0,1)
(1,0)	$(K_{x,x\bar{y}}, K_y)$=(2,1)
(1,1)	$(K_{x,x}, K_y)$=(2,1)
(2,0)	$(K_{x,x\bar{y}}, K_{y,x})$=(2,1)
(2,1)	$(K_{x,x}, K_{y,x})$=(2,1)

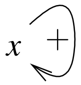
“desynchronization” ⟶
by **units** of Manhattan distance



Multistationarity vs. positive cycles

- A cycle in the interaction graph is *positive* if it contains an *even* number of inhibitions
- ***Theorem :*** *if the state graph exhibits several attraction basins then there is at least one positive cycle in the interaction graph*
- Was a conjecture from the 70's to 2004 ; proved by Adrien Richard (and by Christophe Soulé for the continuous case)

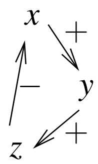


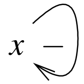


Oscillations vs. negative cycles

- A cycle in the interaction graph is *negative* if it contains a *odd* number of inhibitions
- ***Thomas conjecture :*** *if the state graph exhibits an homeostasy (stable oscillations) then there is at least one negative cycle in the interaction graph*
- Was a conjecture from the 70's to ≈2010. ***Counter-examples*** have been found (A. Richard, J.-P. Comet, P. Ruet)

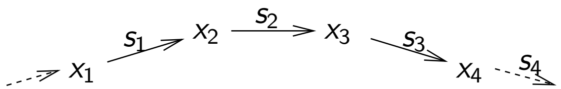
Nonetheless it remains a very useful tip in practice when modelling biological examples !





Characteristic state of a cycle

Helps characterizing the saddle point (resp. center of the oscillations) of the behaviour "driven" by a positive (resp. negative) cycle.



x_i = threshold $s_i - 1 \mid s_i$

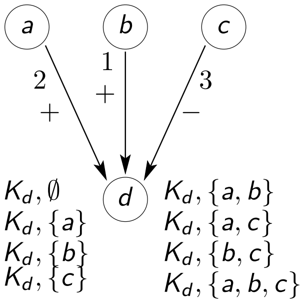
Whatever the sign of $x_i \to x_{i+1}$, for some set of resources ω one should have $K_{x_{i+1},\omega} < s_{i+1} \leqslant K_{x_{i+1},\omega x_i}$, all along the cycle

but it remains a heuristic, at least for negative cycles. . .

Thomas parameters : exponential number

2^i parameters
where i is the in-degree of the gene

$\prod_{genes} (o+1)^{2^i}$
possible parameter values
where o is the out degree of each gene



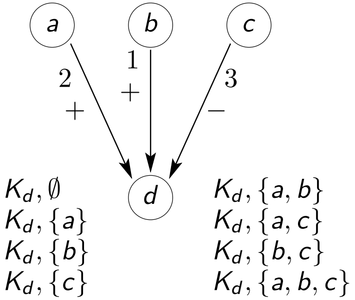
$K_d, \emptyset$
$K_d, \{a\}$
$K_d, \{b\}$
$K_d, \{c\}$

$K_d, \{a, b\}$
$K_d, \{a, c\}$
$K_d, \{b, c\}$
$K_d, \{a, b, c\}$

Yeast≈7000 genes Human≈25000 genes Rice≈40000 genes

Multiplexes : encode cooperation knowledge

"Proteins of *a* and *b* form a complex before acting on *d*. . ."



$K_d, \emptyset$
$K_d, \{a\}$
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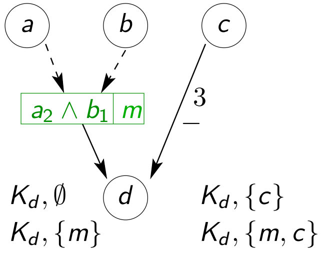


$K_d, \emptyset$
$K_d, \{m\}$

$K_d, \{c\}$
$K_d, \{m, c\}$

multiplex name = m

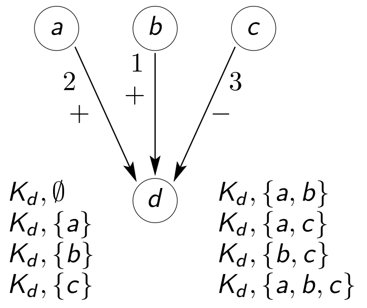
multiplex formula ≡ $a_2 \wedge b_1$

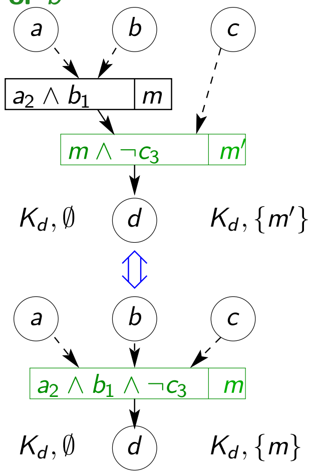
abbreviation :
$v_i \equiv (v \geq i)$

8 → 4 parameters

Any propositional formula + remove sign

"... and c inhibits d whatever a or b"





8 ⟶ 2 parameters,

$(o+1)^8 \rightarrow (o+1)^2$ **parameterizations**

The main problem

Exhaustively identify the sets of (integer) parameters that cope with known behaviours from biological experiments

Solution = perform reverse engineering *via* **formal logic**

- 2003 : enumeration + CTL + model checking (Bernot,Comet,Pérès,Richard)
- 2005 : path derivatives + model checking (Batt,De Jong)
- 2005 : PROLOG with constraints (Trilling,Corblin,Fanchon)
- 2007 : symbolic execution + LTL (Mateus,Le Gall,Comet)
- 2011 : traces + enumeration + CTL + model checking (Siebert,Bockmayr)
- 2015 : genetically modified Hoare logic + constraint solving (Bernot,Comet,Roux,Khalis,Richard)

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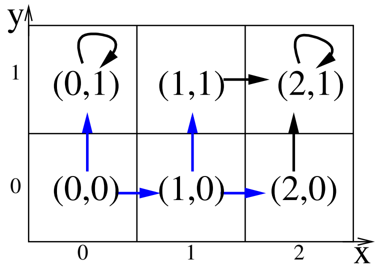
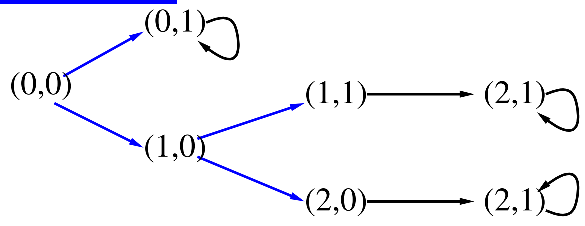
Time has a tree structure...



As many possible state graphs as possible parameter sets... (huge number)

... from each initial state :



CTL = Computational Tree Logic

- Atoms = comparaisons : $(x = 2), (y > 0) \dots$
  Logical Connectives = $(\varphi_1 \wedge \varphi_2), (\varphi_1 \Rightarrow \varphi_2) \dots$
  Temporal modalités = made de 2 characters :

first character	second caracter
A = for All path choices	X = neXt state
	F = for some future state
E = there Exists a choice	G = for all future state (Globally)
	U = Until

- Examples :
  AX (y=1) : the concentration level of y belongs to the interval 1 in all states directly following the considered initial state.
  EG(x=0) : there exists at least one path from the considered initial state where x always belongs to its lower interval.

Temporal Connectives of CTL

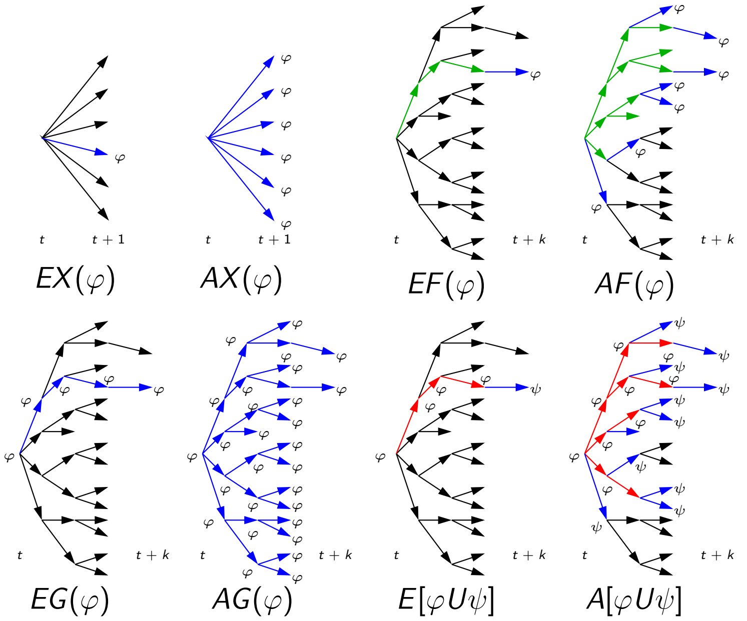
neXt state :
$EX\varphi$: φ can be satisfied in a next state
$AX\varphi$: φ is always satisfied in the next states

eventually in the Future :
$EF\varphi$: φ can be satisfied in the future
$AF\varphi$: φ will be satisfied at some state in the future

Globally :
$EG\varphi$: φ can be an invariant in the future
$AG\varphi$: φ is necessarilly an invariant in the future

Until :
$E[\psi U \varphi]$: there exist a path where ψ is satisfied until a state where φ is satisfied
$A[\psi U \varphi]$: ψ is always satisfied until some state where φ is satisfied

Semantics of Temporal Connectives (1)



$EX(\varphi)$ $AX(\varphi)$ $EF(\varphi)$ $AF(\varphi)$

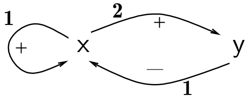
$EG(\varphi)$ $AG(\varphi)$ $E[\varphi U \psi]$ $A[\varphi U \psi]$

Semantics of Temporal Connectives (2)

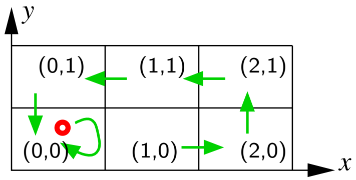
Let s_0 be a state. The CTL semantics is difined as follows

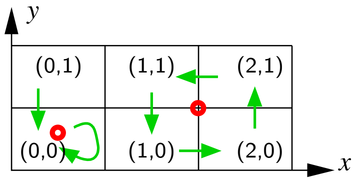
- $s_0 \models \top$ and $s_0 \not\models \bot$ $\forall p \in AP, s_0 \models p$ iff $p \in L(s_0)$,
- $s_0 \models \neg\varphi$ iff $s0 \not\models \varphi$,
- $s_0 \models \varphi_1 \wedge \varphi_2$ (resp. $\varphi_1 \vee \varphi_2$) iff $s_0 \models \varphi_1$ and (resp. or) $s_0 \models \varphi_2$,
- $s_0 \models \varphi_1 \Rightarrow \varphi_2$ iff $s_0 \not\models \varphi_1$ or $s_0 \models \varphi_2$,
- $s_0 \models \varphi_1 \Leftrightarrow \varphi_2$ iff $s_0 \models (\varphi_1 \Rightarrow \varphi_2) \wedge (\varphi_2 \Rightarrow \varphi_1)$,
- $s_0 \models AX\varphi$ iff for all successors s_1 of s_0, one has $s_1 \models \varphi$,
- $s_0 \models EX\varphi$ iff there exists a succussor s_1 of s_0 such that $s_1 \models \varphi$,
- $s_0 \models AG\varphi$ iff $\forall s_i$ from any path $s_0 s_1 \dots s_i \dots$, one has $s_i \models \varphi$,
- $s_0 \models EG\varphi$ iff $\exists$ a path $s_0 s_1 \dots s_i \dots$, s.t. $\forall s_i$, one has $s_i \models \varphi$,
- $s_0 \models AF\varphi$ iff $\forall$ path $s_0 s_1 \dots s_i \dots$, $\exists j$ s.t. $s_j \models \varphi$,
- $s_0 \models EF\varphi$ iff $\exists$ a path $s_0 s_1 \dots s_i \dots$, $\exists j$ s.t. $s_j \models \varphi$,
- $s_0 \models A[\varphi_1 U \varphi_2]$ iff $\forall$ path $s_0 s_1 \dots s_i \dots$, $\exists j$ s.t. $s_j \models \varphi_2$, and $\forall i < j, s_i \models \varphi_1$,
- $s_0 \models E[\varphi_1 U \varphi_2]$ iff $\exists$ path $s_0 s_1 \dots s_i \dots$, $\exists j$ s.t. $s_j \models \varphi_2$, and $\forall i < j, s_i \models \varphi_1$

CTL to encode Biological Properties



Common properties :
"functionality" of a sub-graph
Special role of "feedback loops"
– positive : *multistationnarity* (even number of —)
– negative : *homeostasy* (odd number of —)

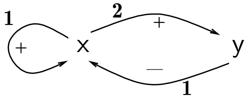




Characteristic properties : $\begin{cases} (x=2) \Longrightarrow AG(\neg(x=0)) \\ (x=0) \Longrightarrow AG(\neg(x=2)) \end{cases}$

They express *"the positive feedback loop is functional"*
(satisfaction of these formulas relies on the parameters $K_{...}$)

CTL to encode Biological Properties



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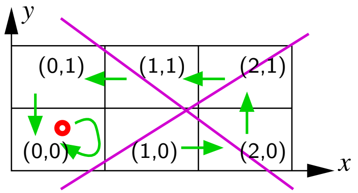

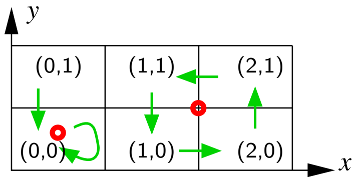

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They express *"the positive feedback loop is functional"*
(satisfaction of these formulas relies on the parameters $K_{...}$)

Model Checking

- Efficiently computes all the states of a state graph which satisfy a given formula : $\{\ \eta \ \mid\ M \ \models_\eta\ \varphi\ \}$.
- Efficiently select the models which globally satisfy a given formula.

Intensively used :

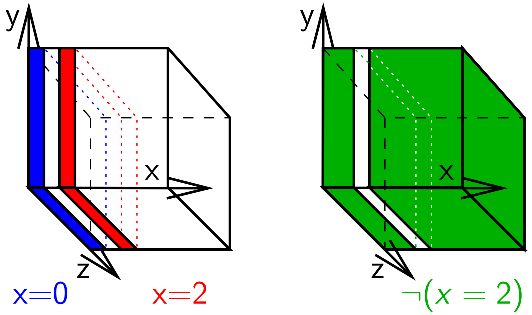
- to find the set of **all** possible discrete parameter values
- to check models under construction w.r.t. **known behaviours** (one often gets an empty set of parameter values !)
- and to prove the **consistency** of a biological **hypothesis**

Model Checking for CTL

Computes all the states of a discrete state graph that satisfy a given formula : $\{\ \eta \ \mid\ M \ \models_\eta\ \varphi\ \}$.
Idea 1 : work on the state graph instead of the path trees.
Idea 2 : check first the atoms of φ and then check the connectives of φ with a bottom-up computation strategy.
Idea 3 : (computational optimization) group some cases together using BDDs (Binary Decision Diagrams).
Example : $(x=0) \quad \Longrightarrow \quad AG(\neg(x=2))$

Obsession : *travel the state graph as less as possible*

$(x = 0) \implies AG(\neg(x = 2))$



and

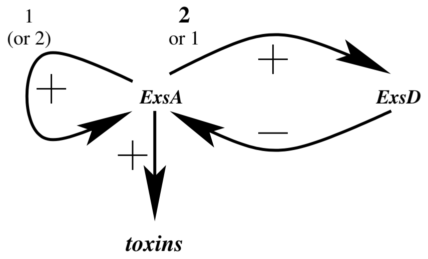
$AG(\neg(x = 2))$?

. . . one should **travel** **all** the paths from any green box and check if successive boxes are green : *too many boxes to visit.*

Trick : $AG(\neg(x = 2))$ is equivalent to $\neg EF(x = 2)$

start from the red boxes and follow the transitions backward.

Consistency of the epigenetic hypothesis



- 2 possible stable states :
  - $(\texttt{ExsA} = 2) \implies \texttt{AX AF}(\texttt{ExsA} = 2)$
  - $(\texttt{ExsA} = 0) \implies \texttt{AG}(\neg(\texttt{ExsA} = 2))$
- Question 1, consistency : proved by Model checking 8 models among 648, automatically extracted.
- Question 2, and *in vivo* ?

Formula = Model-Experiment Link

Formulas are valid or invalid in relation to a set of given traces starting from a given state.

They can be compared with

- all possible traces of the theoretical model
- all known experiments

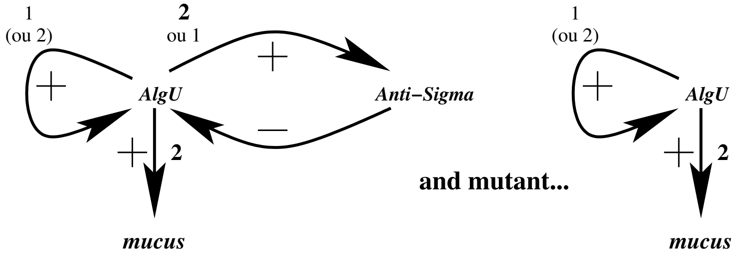
⇒ They are therefore the link between models and biological objects.

A simple example

- Phenotype modification, terminology :
  - genetic modification : heritable and irreversible (mutation)
  - epigenetic modification : heritable but reversible
  - Adaptation : non-heritable and reversible
- Biological questions :
  - Is cytotoxicity (and/or muco-toxicity) in the bacterium *Pseudomonas aeruginosa* epigenetic in nature ?
  - [⟶ Cystic Fibrosis]

Mucoid Pseudomonas aeruginosa

wild pseudomonas aeruginosa :



Epigenetic hypothesis (i.e. without mutation)

→ The positive cycle is functional in spite of the negative cycle, with one state non-mucoid and the other mucoid.

→ An external signal (produced by the diseased lung) could potentially switch AlgU from the low state to the high state.

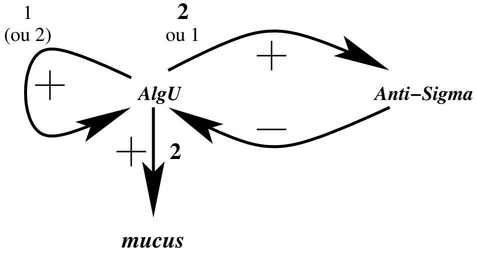
→ Selection pressure then favours mutants in the mucosal environment ⇒ New perspectives for therapy.

Validating the epigenetic hypothesis

- Question 2 = Validate the stability of the two states in vivo.
- Non-mucoid state : $(\texttt{AlgU} = 0) \Rightarrow \texttt{AG}(\texttt{AlgU} < 2)$
  A bacterium with its basal level of AlgU will not spontaneously become mucoid : validated daily
- Mucoid state : $(\texttt{AlgU} = 2) \Rightarrow \texttt{AX AF}(\texttt{AlgU} = 2)$
- Working hypothesis :
  AlgU can be brought to saturation, not measured
- Experimental design : *pulse AlgU and then, after a transition period, test whether mucus production continues pulse de AlgU puis après une phase transitoire, tester si la production de mucus persiste* (⟺ check for hysteresis)
- Experimental designs can be generated automatically

Test $(\texttt{AlgU} = 2) \Rightarrow \texttt{AG}\ (\texttt{AlgU} = 2)$

- $\texttt{AlgU} = 2$ cannot be checked directly, but $\texttt{mucus} = 1$ can



- Lemma : $\texttt{AG}(\texttt{AlgU} = 2) \Leftrightarrow \texttt{AF AG}(\texttt{mucus} = 1)$
- (... Computer-aided proofing ...)

→ **Experiment : $(\texttt{AlgU} = 2) \Rightarrow \texttt{AF AG}(\texttt{mucus} = 1)$**

$(\texttt{AlgU} = 2) \Rightarrow \texttt{AF AG}(\texttt{mucus} = 1)$

$A \Rightarrow B$	True	False
True	True	False
False	True	True

Karl Popper :
Validate = attempt to refute

So A false is useless
So start with a pulse...

Pulse allows to reach initial state $\texttt{AlgU} = 2$.
Otherwise we would have to establish a lemma :

$$(\texttt{AlgU} = 2) \Leftrightarrow (\text{something } \underline{\text{achievable}})$$

General form of a test :

$$(\text{something } \underline{\text{achievable}}) \Rightarrow (\text{something } \underline{\text{observable}})$$

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Techniques of software testing

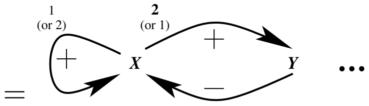
Similar problem = does the software meet its specification ?
Infinite number of possible test scenarios, select revealing ones
Solution= divide into scenario domains
Behaviour assumed to be "*uniform*" within a domain

- Formula unfolding is used to divide the domains
- Probabilistic approach : few unfolding, few (but large) domains, probabilistic drawing of many tests in each domain.
- Deterministic approach : many unfoldings, small domains, selection of a single test per domain.

99% of defects can be detected automatically

Selection of experimental plans

- $\Phi = \{\varphi_1, \varphi_2, \dots \varphi_n\}$ and $M =$



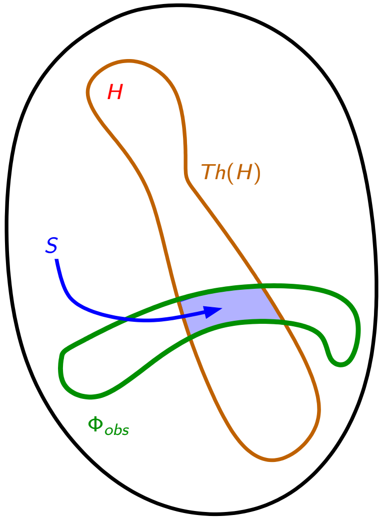
- Set of formulae resulting from the hypothesis :
  $Th(H) = \{\psi \mid \Phi, M \models \psi\}$
- Observable formulae : Φ_{obs}
  $\{\psi \mid \psi$ of the form "achievable" ⇒ "observable" $\}$
- Problem : $\Phi_{obs} \cap Th(H)$ is infinite
  → Selecting "Revealers" in $\Phi_{obs} \cap Th(H)$
- P. aeruginosa : By luck, there are 2 observable formulae $\psi_1, \psi_2 \in \Phi_{obs} \cap Th(H)$ such that $\{\psi_1, \psi_2\} \models \Phi$
- General computer science solution : unfolding techniques ($\simeq$ case-by-case reasoning) should make it possible to make explicit the assumptions made when limited to a fixed number of experiments.

Selection of experimental plans

- H : hypothesis
- Φ_{obs} : possible experiments
- $Th(H)$: logical consequences of H
- S : experiments in relationship with H

Refutability : $S \Rightarrow H$

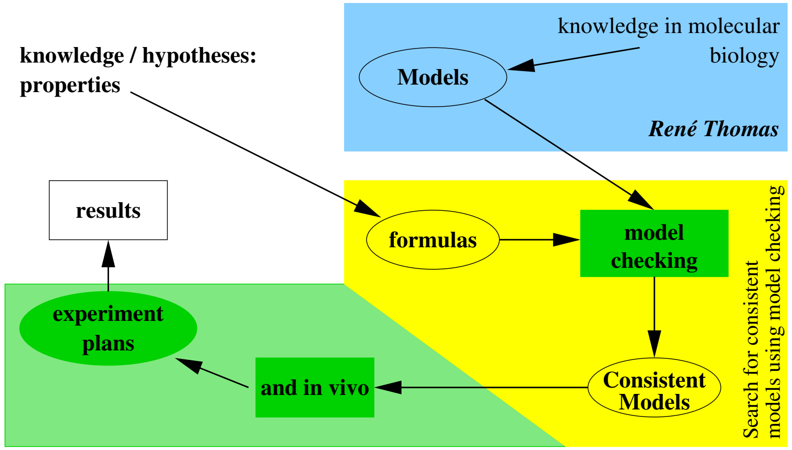
The set S is infinite...
Choice of experiments in S ?
... optimizations



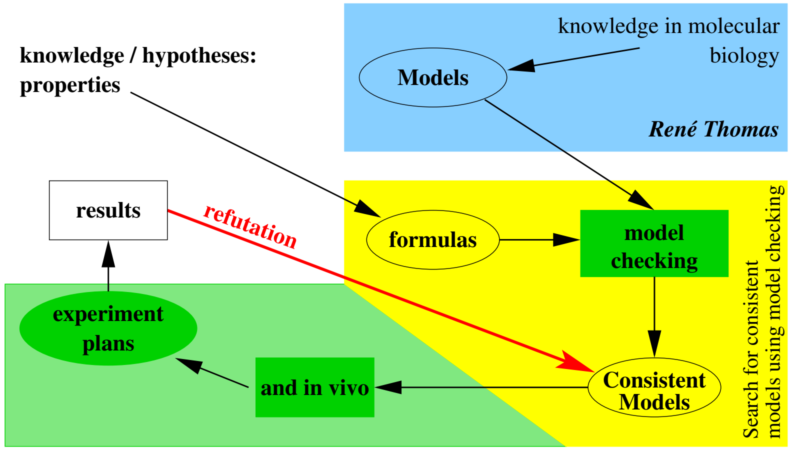
Plan

1. Discrete models for gene networks according to René Thomas
2. CTL
3. Techniques of software testing
4. General Schema for BRN
5. Genetically modified Hoare logic, and examples

General Schema for BRN


knowledge in molecular biology
Models
René Thomas
knowledge / hypotheses: properties
results
formulas
model checking
experiment plans
and in vivo
Consistent Models
Search for consistent models using model checking

General Schema for BRN


knowledge in molecular biology
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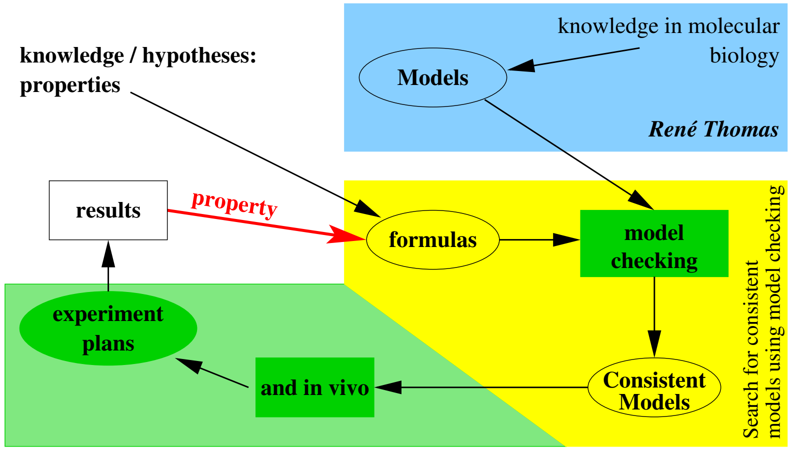
General Schema for BRN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property
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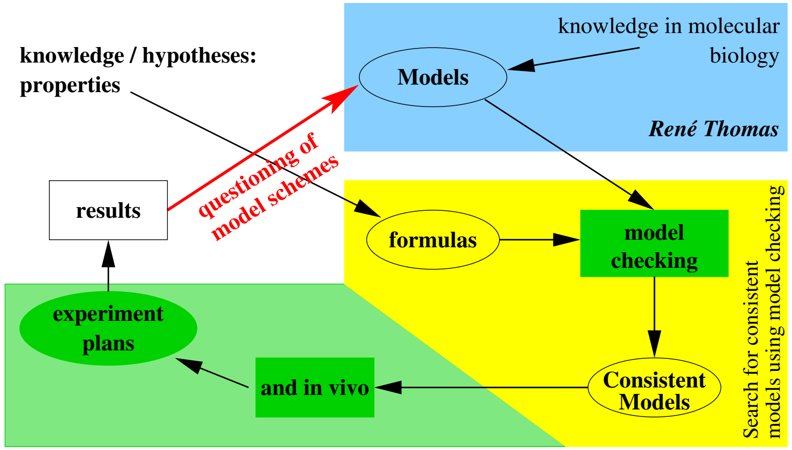
General Schema for BRN


knowledge / hypotheses: properties

Models

knowledge in molecular biology

René Thomas

results

questioning of model schemes

formulas

model checking

experiment plans

and in vivo

Consistent Models

Search for consistent models using model checking

Automatic extraction of experiment patterns

- Given a set of models
- Given a set of models Given a set of possible experiments (in the form of formulas)
- Questions :
  - What experiment must be performed to reduce the set of consistent models ? (equiprobable / non equiprobable models)
  - Ditto for *n* experiments (order, decision tree) ?
  - Ditto with cost ?

Choose an experiment

- $M = \{M_1, M_2, \ldots, M_m\}$ and $F = \{F_1, F_2, \ldots, F_f\}$

  using model checking :

	F_1	F_2	$\ldots$	F_f
M_1	1	1	$\ldots$	0
M_2	1	0	$\ldots$	0
$\ldots$	$\ldots$	$\ldots$	$\ldots$	$\ldots$
M_m	0	1	$\ldots$	0

- If the models are equi probable, we implement F_i which balances the 2 sets

$$E_i = \{M_j | M_j \models F_i\} \quad \text{and} \quad \overline{E_i} = \{M_j | M_j \not\models F_i\}$$

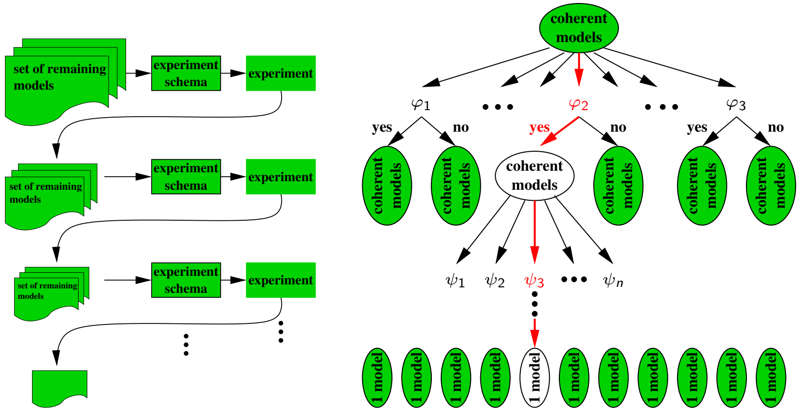
- otherwise F_i which balances the 2 probabilities

$$p(\{M_j | M_j \models F_i\}) \quad \text{and} \quad p(\{M_j | M_j \not\models F_i\})$$

In fact, we're looking to minimize E[Size of set after exp.]

- $min(|E_i| \times |E_i| + |\overline{E_i}| \times |\overline{E_i}|) = min(|E_i|^2 + (N - |E_i|)^2)$
- $min(N^2 - 2N|E_i| + 2|E_i|^2)$
- minimum in $N/2$

Choosing a complete strategy (1)


set of remaining models

experiment schema

experiment

coherent models

φ_1 $\ldots$ φ_2 $\ldots$ φ_3

yes no

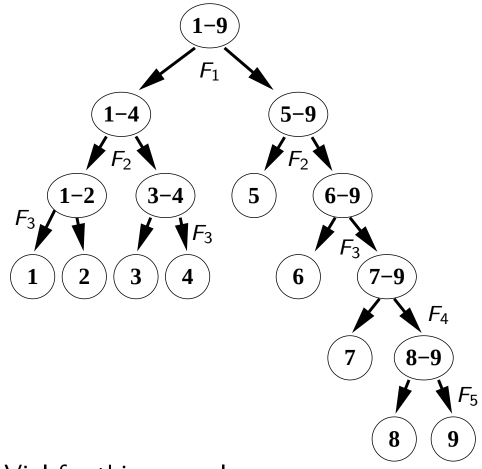
ψ_1 ψ_2 ψ_3 $\ldots$ ψ_n

1 model

Choosing a complete strategy (2)

- The previous strategy doesn't give the minimum depth tree.
- Ex : 9 models ; 5 formulas, min. height $= log_2(9) = 4$

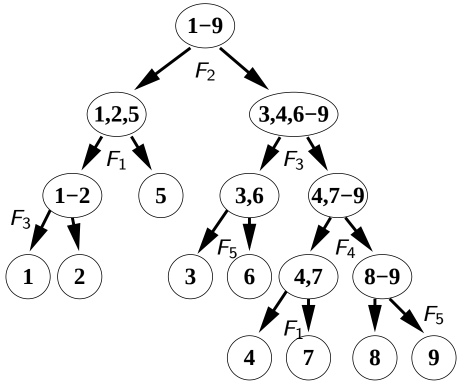
	F_1	F_2	F_3	F_4	F_5
M_1	1	1	1	0	0
M_2	1	1	0	1	1
M_3	1	0	1	0	1
M_4	1	0	0	1	0
M_5	0	1	0	0	0
M_6	0	0	1	0	0
M_7	0	0	0	1	0
M_8	0	0	0	0	1
M_9	0	0	0	0	0
	4/5	3/6	3/6	3/6	3/6



Thanks to S. Vial for this example

Choosing a complete strategy (3)

	F_1	F_2	F_3	F_4	F_5
M_1	1	1	1	0	0
M_2	1	1	0	1	1
M_3	1	0	1	0	1
M_4	1	0	0	1	0
M_5	0	1	0	0	0
M_6	0	0	1	0	0
M_7	0	0	0	1	0
M_8	0	0	0	0	1
M_9	0	0	0	0	0
	4/5	3/6	3/6	3/6	3/6



Choosing an optimal decision tree = NP-complete problem
(reduction to the 3-DM problem, L. Hyafil and R.L. Rivest [1975])

Choosing a complete strategy (4)

	Temporal formulas	Coherent models
1	$x = 0 \Rightarrow$ $AXAF(x = 0)$	1, 3, 6, 7, 8, 9, 10
2	$x = 2 \Rightarrow$ $AXAF(x = 2)$	1, 2, 3, 4, 5, 7, 10
3	$x = 1 \Rightarrow$ $AXAF(x = 0)$	1, 3
4	$x = 1 \Rightarrow$ $AXAF(x = 2)$	7, 10
5	$y = 0 \Rightarrow$ $AXAF(y = 0)$	1, 2, 3, 6 1, 2, 3, 6

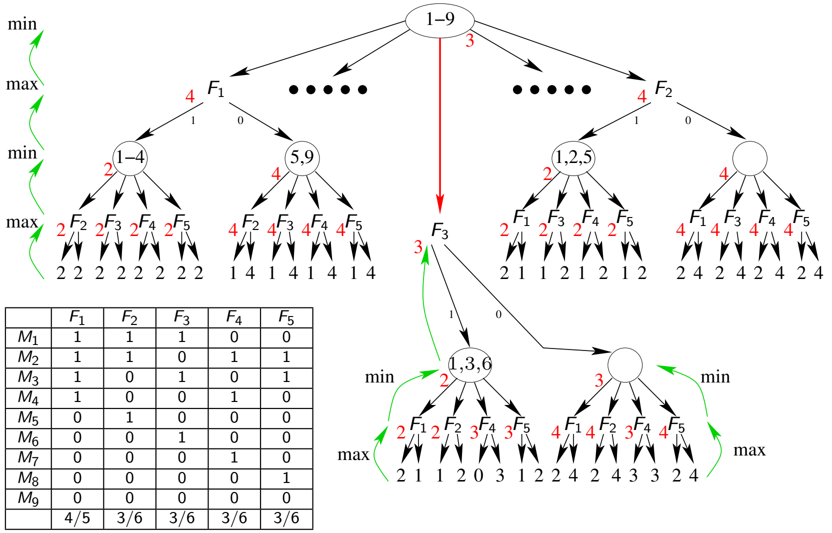
If you don't want to :

- choose a discriminating formula at random
- choose a formula that is easy to implement in vivo (cost)
- adjust this choice according to intuition
- choose the formula that best cuts M

Using the min-max algorithm to optimize selection :

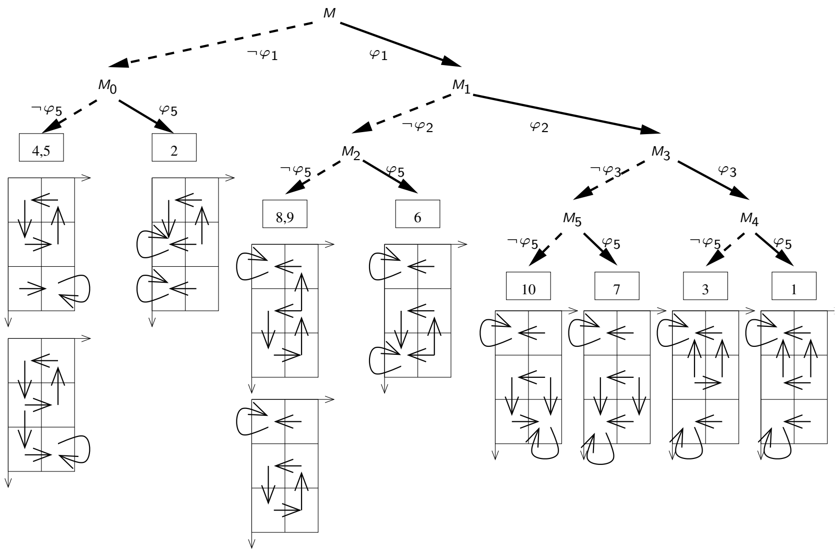
1. determine observable formulas
2. limit tree depth (here, prof = 3)
3. find the tree for which the cost is minimal

Choosing a complete strategy (4-b)


min
max
min
max
1–9
3
4
F_1
• • • • •
• • • • •
4
F_2
1
0
1
0
1–4
5,9
1,2,5
2
4
2
4
2 F_2 2 F_3 2 F_4 2 F_5
4 F_2 4 F_3 4 F_4 4 F_5
F_3
2 F_1 2 F_3 2 F_4 2 F_5
4 F_1 4 F_3 4 F_4 4 F_5
2 2 2 2 2 2 2 2
1 4 1 4 1 4 1 4
3
2 1 1 2 1 2 1 2
2 4 2 4 2 4 2 4
1
0
min
1,3,6
2
3
min
max
2 F_1 2 F_2 3 F_4 3 F_5
4 F_1 4 F_2 3 F_4 4 F_5
max
2 1 1 2 0 3 1 2 2 4 2 4 3 3 2 4

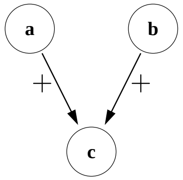
	F_1	F_2	F_3	F_4	F_5
M_1	1	1	1	0	0
M_2	1	1	0	1	1
M_3	1	0	1	0	1
M_4	1	0	0	1	0
M_5	0	1	0	0	0
M_6	0	0	1	0	0
M_7	0	0	0	1	0
M_8	0	0	0	0	1
M_9	0	0	0	0	0
	4/5	3/6	3/6	3/6	3/6

Choosing a complete strategy (5)



Semantics of signs

- Signs and parameters



$$K_c = 1 \quad K_{c,a} = 0 \quad K_{c,b} = 2 \quad K_{c,ab} = 1$$

Positive Actions of b

$$K_c = 1 \quad K_{c,a} = 0 \quad K_{c,b} = 2 \quad K_{c,ab} = 1$$

Negative Actions of a

Relationship between signs and parameters

Semantics for Thomas-Snoussi

- ODE system $\frac{dx_3}{dt} = (k + k_1.\mathbf{1}_{x_1 \to x_3} + k_2.\mathbf{1}_{x_2 \to x_3}) - \lambda \times x_3$
- Discretisation :

if neither x_1 nor x_2 acts on x_3 :	$d(k)$	K_{x_3}
if only x_1 acts on x_3 :	$d(k + k_1)$	K_{x_3,x_1}
if only x_2 acts on x_3 :	$d(k + k_2)$	K_{x_3,x_2}
if both x_1 and x_2 act on x_3 :	$d(k + k_1 + k_2)$	K_{x_3,x_1x_2}

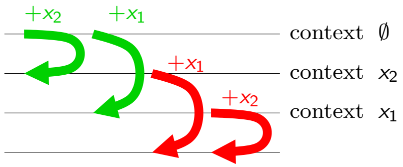
- Sum of positive numbers : Snoussi conditions :

$$\forall a \in \forall G^-(x), \forall \omega \subseteq G^-(x), K_{x,\omega} \leq K_{x,\omega\cup\{a\}}$$

Everywhere, the addition of a resource cannot reduce the the attractor

- Consequence : XOR is not possible

x_1	x_2	$X_3 = x_1$ XOR x_2
0	0	$K_{x_3} = 0$
0	1	$K_{x_3,x_2} = 1$
1	0	$K_{x_3,x_1} = 1$
1	1	$K_{x_3,x_1x_2} = 0$



Another possible semantic

- Everywhere, the addition of a resource cannot reduce the the attractor
- There is a configuration where the addition of a resource creates an increase in the attractor

$$\forall a \in \forall G^-(x), \exists \omega \subseteq G^-(x), K_{x,\omega} < K_{x,\omega\cup\{a\}}$$

- The sign thus becomes a constraint on the parameters.
- Notation : $+_{obs}$, $-_{obs}$ to be distinguished from $+_{snoussi}$, $-_{snoussi}$