Symbolic AI for complex biological networks: Differential Models vs Discrete Models

GB5 BIMB – year 2024–2025

Symbolic AI for
Complex Regulatory Networks (n.1)

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Why do we model ?

- What is a *model ?*
  - the reference to be imitated (photographer's model, model organism model)
  - result of this imitation = representation of an object
  - → symbol system (textual, graphical, math.., logical...)
  - a *good* model = composition rules for addressing the consequences of the proposed model (reasoning)
- Integrate a wide range of knowledge
- Abstract to understand
- Revise contradictory preconceptions
- Suggest "wet" experiments
- Minimize costs and numbers
- Perform "*in silico*" experiments that would be impossible "*in vivo*" or "*in vitro*".

Predictivity

Genetic regulation networks

- Advances in genomics
  the genome's essential role in the functioning of an organism
- Proteins
  - Participate in the body's various functions
  - Transcription : DNA ⟶ RNA
  - Translation : RNA ⟶ Proteins
- Regulation of macromolecule synthesis
- Regulation network = system **complex**

One have **local rules**, one looks for **global behavior**

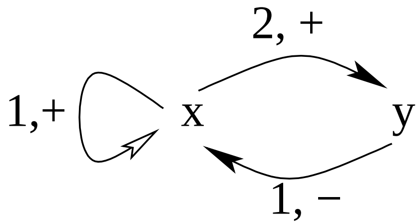
  - Interaction : positive/negative regulation
    + certain knowledge : activation thresholds
    Incompatibilities of simultaneous interactions ? (expertise)
  - From 2 different configurations :
    - Different behaviors
    - Epigenesis (epi : on, above)

Genetic regulation networks

- Interactions between entities of interest : genes, proteins
- Molecular model : set of known relationships
  - Genes / regulatory proteins
  - Positive / negative effects
  - Post-translational regulation is often omitted
  - A protein can have several targets
  - Self-regulation possible
- Graph modeling
  - Nodes : biological entities
  - Arcs : interactions

Static aspects

- Static aspects well taken into account (Mol. Bio.)



- Each node is assigned a numerical value (concentration)
- Temporal evolution of the system : dynamics
- Another way to study the organism

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Dyn.
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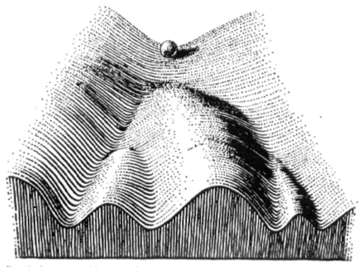
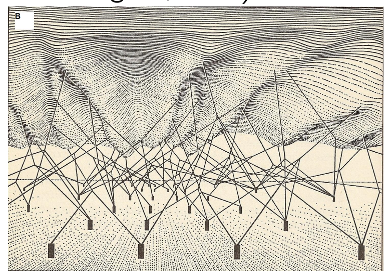
Extraction

Initial approaches

- Quantum model (M. Delbrück, 1935) :
  study of mutation frequencies (rays) high-energy barrier separating 2 gene states (mutation).
- Epigenetic landscape (C.H. Waddington, 1940)





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CTL
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From differential equations to discrete abstractions

- Systems of differential equations : since 1960
  - complex systems and biology (since 1950)
  - Biochemical kinetics (Michaelis-Menten)
  - oscillators, biological switches, delay equations ...
- Phage group (Delbrück) : qualitative reasoning
- 1970s : Boolean approach (R. Thomas)
  - each entity : on / off
  - qualitatively captures the dynamics of Diff. systems.
  - importance of feedback circuits (system behavior)
    - multistationarity : positive feedback circuit required
    - homeostasis : necessary negative feedback circuit (equilibrium state towards which the system converges or around which it oscillates)
- 1990s : discrete approach (with all stationary states)
  - advantage : biological data are rarely quantitative

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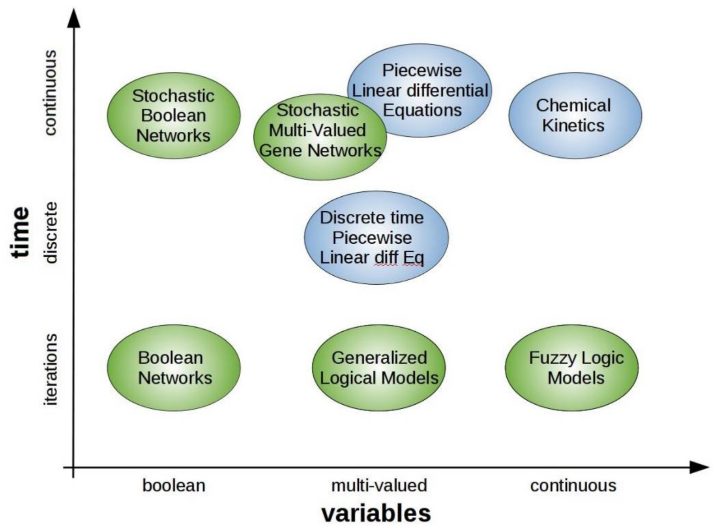
The different modeling frameworks



GRN : some definitions

- A regulatory network : directed graph $G = (V, E)$.
  - V : set of biological entities of interest
  - $E \subseteq V \times V$: set of interactions
  - Each arc is labelled with a s_{ij} sign,
- We denote $G^+(v)$ (resp. $G^-(v)$) the set of successors (resp. predecessors)

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GRN modeling : differential equations

- Each variable v is associated with a value $x_v \in \mathbb{R}^+$.
- Network state : $(x_v)_{v \in V}$
- System of differential equations :

$$\frac{dx_v}{dt} = F_v(x) - \lambda_v x_v \qquad \forall v \in \{1, 2, \dots n\}$$

With

$$\begin{cases} \lambda_v \geq 0 & : \text{degradation coefficient} \\ F_v(x) & : \text{variable synthesis rate } v \end{cases}$$

The synthesis rate is often additive :

$$F_v(x) = \sum_{u \in G^-(v)} I^{\alpha_{uv}}_{\Theta_{uv}}(x_u)$$

Θ_{uv} : threshold $\qquad \alpha_{uv}$: sign of interaction

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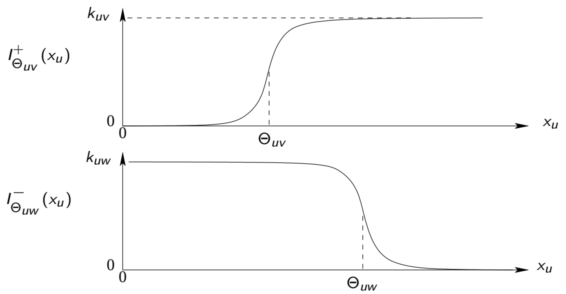
The synthesis rate

- Often, u has almost no effect below Θ_{uv} and a saturated effect above
- Sigmoidal function (e.g. Hill function) : $f(x) = \frac{x^n}{K + x^n}$)



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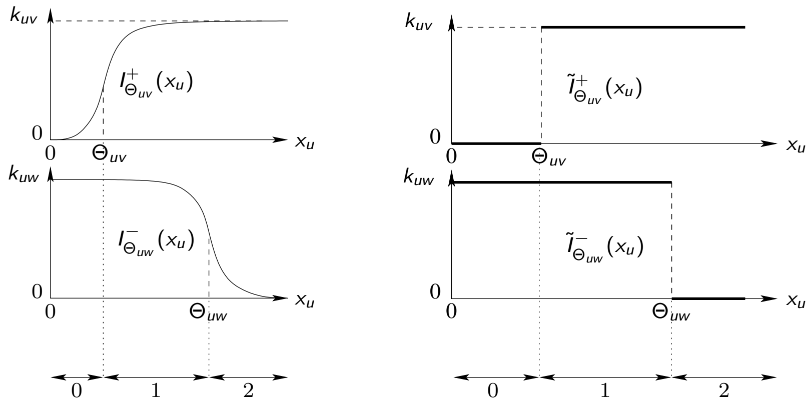
Phase space discretization (1)



$\tilde{I}^+_{\Theta_{uv}}(.)$ is not defined at Θ_{uv}
$\tilde{I}^-_{\Theta_{uw}}(.)$ is not defined at Θ_{uw}

Phase space discretization (2)

- $x_u < \Theta_{uv}$, u is present at too low a level to regulate v
- $x_u > \Theta_{uv}$, u is in sufficient quantity to regulate v
- $x_u = \Theta_{uv}$, the function I is not defined, we don't know whether u regulates or not v

u participes to the synthesis of v if

- if u is an activator of v and if $x_u > \Theta_{uv}$
- if u is an inhibitor of v and if $x_u < \Theta_{uv}$

Absence of an inhibitor = presence of an activator

- Notion of a gene's **Resource** : the set of regulators involved in its synthesis

Phase space discretization (3)

- Outgoing thresholds are ordered
- Abstract thresholds are the ranks of thresholds
- Discretization function :

$$d_u(x_u) = \begin{cases} q & si \quad \Theta_u^q < x_u < \Theta_u^{q+1} \\ s_u^q & si \quad x_u = \Theta_u^q \end{cases}$$

- The discretization function is increasing
- The synthesis rate is then equal to :

$$F_v(x) = k_v + \sum_{u \in \text{ressources}(v)} k_{uv}$$

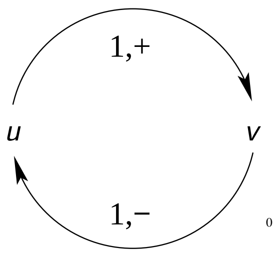
Qualitative Regulatory Network

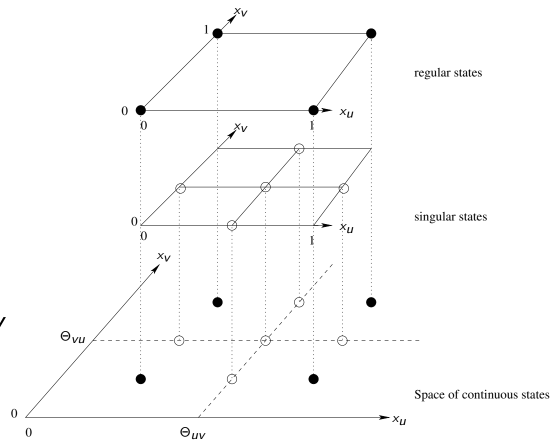
- **Definition :** A qualitatif regulatory Network is a directed graph $G = (V, E)$
  - V : set of biological entities of interest
  - $E \subseteq V \times V$: set of interactions
  - each arrow (u, v) is labelled with a couple $(\alpha_{uv}, q_{uv}) \in \{+, -\} \times \{0, 1, \dots, b_u\}$
  - b_u is the number of outgoing thresholds ($|\{\Theta_{uw}, w \in G^+(u)\}|$)
  - $\forall m \in \{1, \dots, b_u\}, \ \exists v \in G^+(u)$ such that $q_{uv} = m$
- For $G = (V, E)$ a QRN, there exists a finite number of qualitative RN
- Enumeration when $i \to j_1, i \to j_2, \dots, i \to j_n$,
  - choose $b_i \leq n$
  - associate with each interaction, a outgoing threshold

Different types of states

- Quantitative state : $(x_v)_{v \in V}$ with $x_v \in \mathbb{R}^+$
- Qualitative state : $(x_v)_{v \in V}$ with $x_v \in \{0, 1, 2, \dots, b_v\}$
- A qualitative variable is said **singular** when it corresponds to the discretisation of a threshold
- It is said **regular** in the other case
- A state is said **singular** when it has a singular coordinate

The different types of states (example)





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CTL
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Reminders on diff. eq. : 1st order Linear Diff. Eq.

- $x \to a(x)$, $x \to b(x)$, $x \to c(x)$: 3 continuous functions on $I \subset \mathbb{R}$.
  1st Order Linear Differential Equation :
  $$a(x).y' + b(x).y = c(x), \qquad x \in I$$
- If one knows a particular equation y_0 :
  - One defines $Y = y - y_0$
  - One gets : $a(x).Y' + b(x).Y = 0$ eq. *without* 2^d *member*
  - one *separates* the variables :
    $$\frac{Y'}{Y} = -\frac{b(x)}{a(x)} \qquad Y(x) \text{ and } a(x) \text{ not null}$$
  - The general solution is then $Y = k.e^{-A(x)}$
    where $A(x)$: primitive of $b(x)/a(x)$ and k : constant
- The solution with a second member is obtained by adding y_0 :
  $$y = y_0 + k.e^{-A(x)}$$
  The value k depends on the initial condition

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Inside a regular domain

- System of independant equations – For variable x_v :
  $$x'_v + \lambda_v x_v = \mu$$
- particular solution :
  $$x_v(t) = \frac{\mu}{\lambda_v}$$
- Solution of the equation without second member $x' + \lambda_v x = 0$:
  $$X(t) = k.e^{-\lambda_v.t}$$
- Solution of the equation with second member : $x(t) = \frac{\mu}{\lambda_v} + k.e^{-\lambda_v.t}$
- Computation of k – let us suppose $x(0) = x_0$
  $$x_0 = \frac{\mu}{\lambda_v} + k$$
  $$k = -(\frac{\mu}{\lambda_v} - x_0)$$
- Solution : $x_v(t) = \frac{\mu}{\lambda_v} - (\frac{\mu}{\lambda_v} - x_0).e^{-\lambda_v t}$

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Search for a particular solution : variation of constants

- The solution to the diff. equation lies in
  - finding a primitive $A(x)$ de $b(x)/a(x)$
  - searching for a particular solution
- Method of the variation of constants (Laplace)
  - Let Y be a solution of the equation $a(x).Y' + b(x).Y = 0$ that does not cancel on I.
    Let's look for a particular solution of eq. with 2d member of the form :
    $$y = k(x).Y(x)$$
    where $k(.)$ is a function to be determined
  - However, k is derivable and we have : $y' = k'Y + kY'$.
  - Carrying over into $a(x).y' + b(x).y = c(x)$ one gets
    $$[a(x).Y' + b(x).Y].k + a(x).k'Y = c(x)$$
  - $[a(x).Y' + b(x).Y]$ is identically zero
  - then $k'(x) = \frac{c(x)}{a(x).Y}$

General solutions of a linear diff. eq. of 1^{er} order

- Constant variation method

$$k'(x) = \frac{c(x)}{a(x).Y} = \frac{c(x)}{a(x)}.e^{A(x)}$$

where $A(x)$: primitive of $b(x)/a(x)$

- Denoting $B(x)$ a primitive of the function $\frac{c(x)e^{A(x)}}{a(x)}$, the set of solutions is

$$k(x) = B(x) + C^{ste}$$

- The general solution can then be written as

$$f(x) = (B(x) + C)e^{-A(x)}$$

- That is, finally

$$f = \exp\left(-\int \frac{b(x)}{a(x)}\mathrm{d}x\right)\left\{C + \int \frac{c(x)}{a(x)} \exp\left(\int \frac{b(x)}{a(x)}\mathrm{d}x\right)\mathrm{d}x\right\}$$

Inside a regular domain

- System of independent equations – For the variable x_v :

$$x'_v + \lambda_v x_v = \mu$$

- Solution of equation without second member $x' + \lambda_v x = 0$:

$$X(t) = k.e^{-\lambda_v.t}$$

- Solution of equation with second member

$$\begin{aligned} x(t) &= (C_1 + \mu \int e^{\lambda_v t} dt).e^{-\lambda_v.t} \\ &= (C_1 + \tfrac{\mu}{\lambda_v}(e^{\lambda_v t} + C_2)).e^{-\lambda_v.t} \\ &= \tfrac{\mu}{\lambda_v} + C.e^{-\lambda_v.t} \end{aligned}$$

- Computation of C – Let us suppose $x(0) = x_0$

$$\begin{aligned} x_0 &= \tfrac{\mu}{\lambda_v} + C \\ C &= -(\tfrac{\mu}{\lambda_v} - x_0) \end{aligned}$$

- Solution :

$$x_v(t) = \frac{\mu}{\lambda_v} - (\frac{\mu}{\lambda_v} - x_0).e^{-\lambda_v t}$$

Consequences

- Solution : $x_v(t) = \frac{\mu_v}{\lambda} - (\frac{\mu_v}{\lambda} - x_0^v).e^{-\lambda t}$
- Derivative $x'_v(t) = (\mu_v - \lambda.x_0^v).e^{-\lambda t}$
- The sign of derivatives does not change over time $\Longrightarrow$ monotonic trajectories on each axis.
- Particular cases : $\lambda_v = \lambda, \forall v \in V$

$$\begin{aligned} \overrightarrow{v(t_1)} &= ((\mu_1 - \lambda.x_0^1), (\mu_2 - \lambda.x_0^2), \dots, (\mu_n - \lambda.x_0^n))^t \times e^{-\lambda t_1} \\ \overrightarrow{v(t_2)} &= ((\mu_1 - \lambda.x_0^1), (\mu_2 - \lambda.x_0^2), \dots, (\mu_n - \lambda.x_0^n))^t \times e^{-\lambda t_2} \\ &= \overrightarrow{v(t_1)}.e^{-\lambda(t_2 - t_1)} \end{aligned}$$

$\Longrightarrow$ The trajectories are straight

Definition of local interaction graph

- $i \xrightarrow{+} j$ if the increase in i has a $+$ influence on the evolution of j, in other words, the increase of i leads to an increase in $\frac{dx_j(t)}{dt}$.

$$i \xrightarrow{+} j \quad \text{if} \quad \frac{\partial^2 x_j(t)}{\partial t \partial x_i} > 0$$

- $i \xrightarrow{-} j$ if the increase in i has a - influence on the the evolution of j, in other words, the increase of i leads to an decrease in $\frac{dx_j(t)}{dt}$

$$i \xrightarrow{-} j \quad \text{if} \quad \frac{\partial^2 x_j(t)}{\partial t \partial x_i} < 0$$

- No interaction if $\frac{\partial^2 x_j(t)}{\partial t \partial x_i} = 0$
- The local interaction graph of the system in state x :

$$J(x) = \begin{pmatrix} \frac{\partial^2 x_1}{\partial t \partial x_1} & \dots & \frac{\partial^2 x_1}{\partial t \partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial^2 x_n}{\partial t \partial x_1} & \dots & \frac{\partial^2 x_n}{\partial t \partial x_n} \end{pmatrix}$$

Local Interaction Graph – PLDE

- Inside the regular domains :

$$\frac{\partial^2 x_i(t)}{\partial t \partial x_i} = -\lambda_i \qquad \frac{\partial^2 x_i(t)}{\partial t \partial x_j} = 0$$

- on the edge of regular states

$$\frac{\partial^2 x_i(t)}{\partial t \partial x_j} = +\infty \quad \text{si} \quad \mu_2 > \mu_1 \qquad \frac{\partial^2 x_i(t)}{\partial t \partial x_j} = -\infty \quad \text{si} \quad \mu_2 < \mu_1$$

- Degradation $\neq$ an interaction (we don't consider it)
- Interactions are only visible at points of discontinuity.
- Global Interaction Graph $\equiv \cup_{x \in \Omega} G(x)$

Solutions for regular states (1)

- Consider a regular state and one of its variables x_u.
- For any continuous value in the same domain, the synthesis rate is identical
- The diff. eq. system has a solution :
  - If initial state is x^0, solution of the system is

$$x_v(t) = \varphi_v(x^0) - (\varphi_v(x^0) - x_v^0)e^{-\lambda_v t}$$

  - with :

$$\varphi_v(x) = \frac{F_v(x)}{\lambda_v} = \frac{\sum_{u \in G^-(v)} \tilde{I}^{\alpha_{uv}}_{\Theta_{uv}}(x_u)}{\lambda_v}$$

  - $\varphi_v(x^0)$ plays the role of attractor
  - Rq 1 : $F_v(x)$ is constant ($F_v(x) = F_v(x^0)$)
  - Rq 2 : $\varphi_v(x)$ is constant inside a given domain.

Solutions for regular states (2)

- One has $lim_{t \to \infty} x(t) = \varphi_v(x^0), \forall v \in V$
- All domain states evolve towards the same constant state :

$$\Phi(x^0) = (\varphi_v(x^0))_{v \in V}$$

  called focal point, attractor, image, target...
- 2 possible cases :
  - $\Phi(x^0)$ belongs to the same domain, $\Phi(x^0)$ corresponds to a continuous stationary state,
    - All trajectories tend towards $\Phi(x^0)$
  - $\Phi(x^0)$ does not belong to the same domain
    - The trajectories are in the direction of $\Phi(x^0)$
    - Once outside the domain, the focal point changes.
    - $\Phi(x^0)$ may never be reached
    - Waiting time computation in regular state

Solutions for regular states (2)

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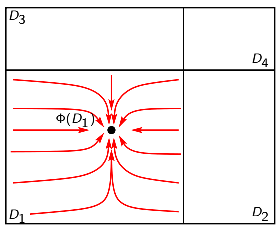

The focal point is in the current domain. The trajectories don't leave the domain :
$\Rightarrow$ no output

Solutions for regular states (2)

- One has $lim_{t \to \infty} x(t) = \varphi_v(x^0), \forall v \in V$
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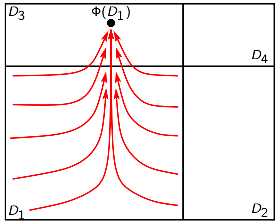

The focal point is in the domain D_3.
The trajectories do leave the domain :
⇒ to the North

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Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Solutions for regular states (2)

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- All domain states evolve towards the same constant state :

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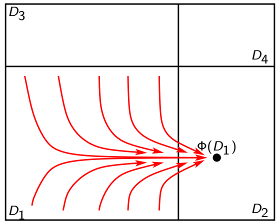
called focal point, attractor, image, target...

- 2 possible cases :



The focal point is in the domain D_2 .
The trajectories do leave the domain :
⇒ to the Est

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Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

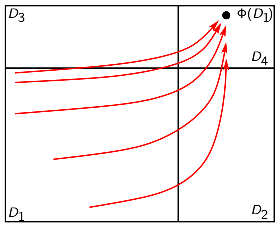
Solutions for regular states (2)

- One has $lim_{t \to \infty} x(t) = \varphi_v(x^0), \forall v \in V$
- All domain states evolve towards the same constant state :

$$\Phi(x^0) = (\varphi_v(x^0))_{v \in V}$$

called focal point, attractor, image, target...

- 2 possible cases :



The focal point is in the domain D_4 .
The trajectories do leave the domain :
⇒ to the Est
⇒ to the North

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Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
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CTL
Extraction

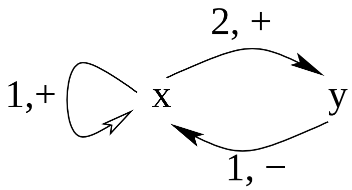
State graph construction

- Synchronous state graph :
  - From a state, we go directly to its focal point
  - Each focal point $\varphi_v(x^0)$ depends only on the predecessors of v = the set of predecessors that helps it express itself
  - $R(v, x^0)$ = the set of predecessors who help it express itself
  - Parameterization : $\varphi_v(x^0) = K_{v,R(v,x^0)}$
  - Transition table :

x				X			
x_1	x_2	...	x_n	X_1	X_2	...	X_n
0	0	...	0	$X_1(x)$	$X_2(x)$	...	$X_n(x)$
0	0	...	1	$X_1(x)$	$X_2(x)$	...	$X_n(x)$
0	1	...	0	$X_1(x)$	$X_2(x)$	...	$X_n(x)$

where $X_1((0,1,0,\dots,0)) = \varphi_{x_1}((0,1,0,\dots,0)) = K_{x_1,R(x_1,(0,1,\dots,0))}$

Example



Basal level	:	K_x	K_y
x helps	:	$K_{x,x}$	$K_{y,x}$
y absent helps	:	$K_{x,y}$	
both	:	$K_{x,xy}$	

(x, y)	focal points
$(0, 0)$	$(K_{x,y} , K_y)$
$(0, 1)$	(K_x , K_y)
$(1, 0)$	$(K_{x,xy} , K_y)$
$(1, 1)$	$(K_{x,x} , K_y)$
$(2, 0)$	$(K_{x,xy} , K_{y,x})$
$(2, 1)$	$(K_{x,x} , K_{y,x})$

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Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
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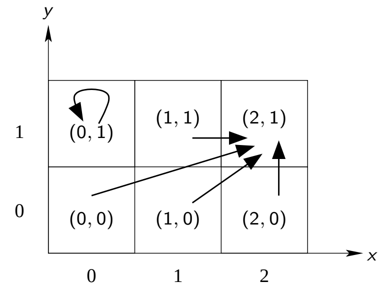
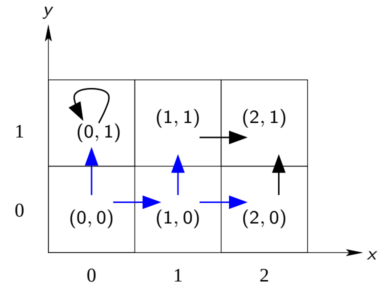
Extraction

Regulatory network $\longrightarrow$ State graph

(x, y)	focal point		
$(0, 0)$	$(K_{x,y}, K_y)$	$=$	$(2, 1)$
$(0, 1)$	(K_x, K_y)	$=$	$(0, 1)$
$(1, 0)$	$(K_{x,xy}, K_y)$	$=$	$(2, 1)$
$(1, 1)$	$(K_{x,x}, K_y)$	$=$	$(2, 1)$
$(2, 0)$	$(K_{x,xy}, K_{y,x})$	$=$	$(2, 1)$
$(2, 1)$	$(K_{x,x}, K_{y,x})$	$=$	$(2, 1)$



"Desynchronization" per unit Manhattan distance $\longrightarrow$



CÔTE D'AZUR
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Continuous and discrete models : consistency (1)

- Let M be a discrete model. There are continuous models **consistent** with M **iff** Snoussi's constraints are respected

$$K_{u,\omega} \leq K_{u,\omega'}, \text{ for each } u \text{ anf for each } \omega,\omega' \text{ s.t. } \omega \subseteq \omega'$$

- Proof :

$$d\left(\left(k_v + \sum_{u \in \text{ressources}(v)} k_{uv}\right)/\lambda\right) = K_{u,\text{ressources}(v)}$$

Each k_i is positive
The discretization function is increasing.
So the K must satisfy the Snoussi constraints.

CÔTE D'AZUR
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Continuous and discrete models : consistency (2)

- **Prop. 1 : regular steady states are the same**
  - If there exists a continuous model s.t. $x \in D(q)$ is a stable stationary state, then the associated regular state is stationary stable in the discrete model.
  - If q is a stable steady state, then for any continuous model, there exists a stable stationary state in the regular domain associated with the qualitative state q.
- **Proof :**
  - a state $x \in D(q)$ is stable **iff** $x_v = \varphi_v(q)$ for all $v \in V$. This implies $d_v(x_v) = d_v(\varphi_v(q)) \Rightarrow q_v = K_{v,\omega_v(q)}$. Thus q is stable.
  - If $q \in Q$ is stable, then $q_v = K_{v,\omega_v(q)} = d_v(\varphi_v(q))$ for all $v \in V$. Thus, $\varphi_v(q) \in D_v(q_v)$ for all $v \in V$ and consequently, $\varphi(q) \in D(q)$ is a stable stationary state.

Continuous and discrete models : consistency (3)

Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Proposition 2 : consistency of transitions

- Let's consider a continuous model s.t. a trajectory starting from $D(q)$ reaches the hyperplane separating $D(q)$ from an adjacent domain $D(q')$, then $q \to q'$ is a transition of the asynchronous discrete model.
- Let's consider a discrete model. There are continuous models s.t. for any successor q' of q of the discrete model, there is a trajectory that reaches from $D(q)$ the hyperplane separating $D(q)$ from another domain $D(q')$.

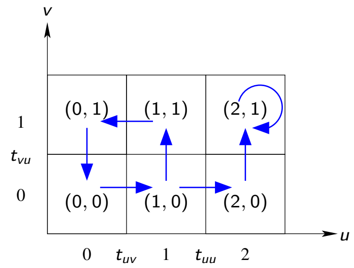
Proof :

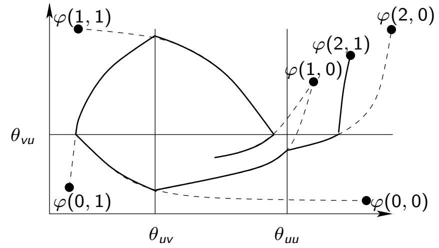
- *1st part :* there is only one variable that changes between q and q'. The asynchronous graph construction takes into account that the focal point is on the other side of the hyperplane.
- *2nd part :* let's consider a continuous model s.t. $\forall u \in V, \lambda_u = \lambda$ and an initial state $x^0 \in D(q)$. The trajectory from x^0 is linear.
  Let q' be a successor of q. We have $\varphi(q) \notin D(q)$. Let's choose a point x^1 on the edge of $D(q)$ belonging to the hyperplane between $D(q)$ and $D(q')$, with a single variable on a threshold. Let's draw a straight line through x^1 and $\varphi(q)$. The trajectory starting from a point on this line that belongs to $D(q)$, reaches x^1.

Continuous and discrete models : consistency (4)

Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

- Thus :
  - All regular stationary states are represented
  - All traces of continuous systems are present
  - False reciprocal (a discrete trajectory does not necessarily correspond to a continuous trajectory)
  - Infinity of continuous models $\Rightarrow$ finite number of discrete discrete models





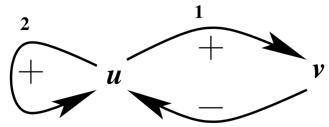
Stability of a singular state (1)

Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

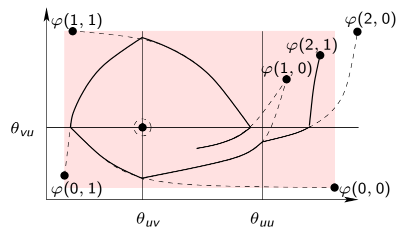
- At a singular state, the Diff. Eq. Syst. is not defined.
- Its focal point is included in the zone defined by the focal points of the adjacent regular states.
- **Definition :** A singular state is said **stationary** if it is included in that zone.
  $\Rightarrow$ Regular variables must be stable
- Computation in $O(2^{\#\text{singular variables}}) = O(2^{\#\text{variables}})$
- If all outgoing thresholds are different, and if Snoussi
  - each singular variable is a singular resource of at most one other variable.
  - We therefore look at the « max image » and « min image » corresponding to the regular states with (and without) these uncertain resources
  - Computation in $O(\#\text{singular variables}) = O(\#\text{variables})$

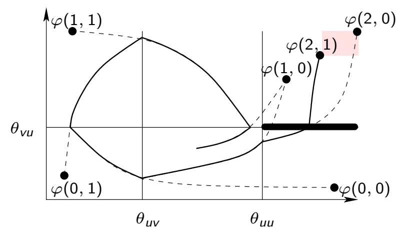
Stability of a singular state (2)

Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction



(x,y)	focal points
$(0,0)$	$(\ K_{u,v} = 2\ ,\ K_v = 0\ )$
$\mathbf{(0,1)}$	$(\ K_u = 0\ ,\ K_v = 0\ )$
$\mathbf{(1,0)}$	$(\ K_{u,v} = 2\ ,\ K_{v,u} = 1\ )$
$(1,1)$	$(\ K_u = 0\ ,\ K_{v,u} = 1\ )$
$(2,0)$	$(\ K_{u,uv} = 2\ ,\ K_{v,u} = 1\ )$
$(2,1)$	$(\ K_{u,u} = 2\ ,\ K_{v,u} = 1\ )$





Stability of a singular state (3)

- **Proposition 3 :** Let x be a singular state and v a variable. If for each $u \in G^-(v), x_u \neq \theta_{uv}$, then $\varphi_v(q)$ is constant for any neighboring regular state q.

  « *Given a qualitative state q, if all the predecessors of the variable v are not on their activation thresholds on v, the component v of the focal point is constant for all qualitative states neighboring q* »

- **Proof :**
  For each $u \in G^-(v)$, one has

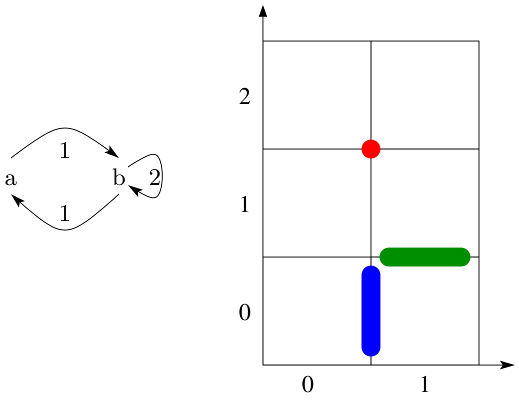
  $$\begin{cases} x_u \text{ régular} & \text{or} \\ x_u = \theta_{uv'} \neq \theta_{uv} & \text{with } v' \in G^+(u) \end{cases}$$

  - *1st case :* $\forall q$ regular state, neighbour of de x, one has $q_u = x_u$ (Cf previous page – right). The regulation of $u \to v$ does not change.
  - *2d case :* for all q, q' regular states, neighbours of x, q_u and q'_u belong to $\{\theta_{uv'} - 1, \theta_{uv'}\}$ and $\theta_{uv'} \neq \theta_{uv}$. q_u and q'_u are on the same side of θ_{uv}.

  Consequently, for each (q, q') of $N(x)$, one has $\omega_v(q) = \omega_v(q')$, that implies $\varphi_v(q) = \varphi_v(q')$.

Stability of a singular state (4)

- Property n.3 usage example



$v = a$
$x_b = s_{bb} \neq s_{ba}$
$\varphi_a(q) =$ Cte on the 4 regular neighbours

$v = b$
$x_a = 1$ regular
$\varphi_b(1,0) = \varphi_b(1,1)$

$v = a$
$x_b = 0$ regular
$\varphi_a(0,0) = \varphi_a(1,0)$

Positifs / negative circuits – Circuit Fonctionnality

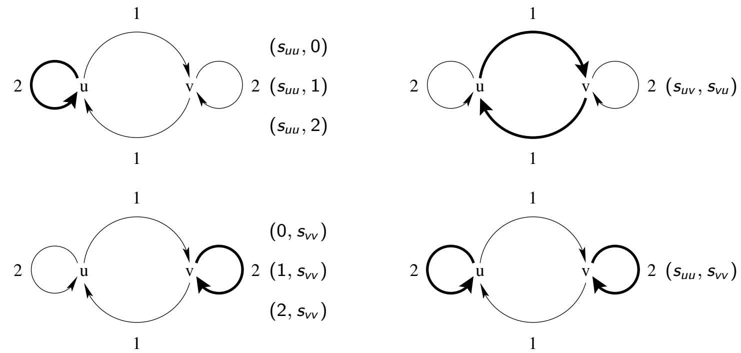
- Positive / negative circuits :
  - A circuit is said positive if each circuit's element has a positive influence (direct on indirect) on itself
  - A circuit is said negative if each circuit's element has a negative influence (direct on indirect) on itself
  - **Lemma :**
    - a circuit is positive if it contains an *even number* of negative interactions,
    - it is negative in other cases
- A circuit is said **fonctionnal** if it leads to a multistationnarity (positive circuits) or to a homeostasis (negative circuits).
  - Influence of negative circuits :
    - Oscillation (damped or not) of each variable

    $\Longrightarrow$ **Homeostasis**
  - Influence of positive circuits :
    - when we are above, we stay there
    - when we are down, we stay down

    $\Longrightarrow$ **Multistationarity**

Charasteristic States (1)

- A singular state is said characteristic of a circuit if
  - The regular components are the variables outside of the circuit
  - The singular variables
    - are the variable of the circuit
    - each singular variable is on the threshold of the interaction on its successor in the circuit



Charasteristic States (2)

- **Proposition 4 :**
  A stationnary singular state is characteristic of a circuit
- **Proof :**
  Let x be a singular state and consider $S = \{v \text{ singulière}\}$. If x is stationnary, one has for each $v \in S$:

$$\min_{q\in N(x)} \varphi_v(q) < x_v < \max_{q\in N(x)} \varphi_v(q)$$

By proposition 3, if for all $u \in G^-(v)$ one has $x_u \neq \theta_{uv}$ then

$$\min_{q\in N(x)} \varphi_v(q) = \max_{q\in N(x)} \varphi_v(q)$$

and x is not stationary.
Thus v has at least one predecessor u st $x_u = \theta_{uv}$, and thus $u \in S$. Moreover, as $\theta_{uv'} \neq \theta_{uv}$ for all $v' \in G^+(u)$, the successor v of u is the unique one st $x_u = \theta_{uv}$. Each variable v of S has thus a unique predecessor u in S st $x_u = \theta_{uv}$.

CÔTE D'AZUR
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Charasteristic States (3)

- **Proposition 5 :**
  Let G be a regulation graph containing a circuit $C = v_1, ..., v_n$. Consider a model and a characteristic state x of C.
  Let $q \in N(x)$. If x is stationary, then we have :

$$\begin{cases} K_{v,\omega_v(q)} = q_v & \text{for all } v \notin C \\ K_{v_i,\omega_{v_i}(q)\setminus\{v_{i-1}\}} < \theta_{v_i v_{i+1}} \leq K_{v_i,\omega_{v_i}(q)\cup\{v_{i-1}\}} & \text{for all } i \in \{1,\dots,n\} \end{cases}$$

- **Proposition 6 :**
  Let G be a regulation graph, a circuit $C = v_1, ..., v_n$ and a characteristic state q of C. If a discrete model $M(G)$ satisfies the Snoussi constraints and if

$$\begin{cases} K_{v,\omega_v(q)} = q_v & \text{for all } v \notin C \\ K_{v_i,\omega_{v_i}(q)\setminus\{v_{i-1}\}} < \theta_{v_i v_{i+1}} \leq K_{v_i,\omega_{v_i}(q)\cup\{v_{i-1}\}} & \text{for all } i \in \{1,\dots,n\} \end{cases}$$

then, for any continuous model of $M(G)$, there exists a unique stationary characteristic state x of C st

$$d_u(x_u) = q_u \text{for all } u \notin C.$$

CÔTE D'AZUR
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Use of Charasteristic States

- We know that the system is multi-stationary / homeostatic
  - Using **Theorem :** A circuit is functional if one of these characteristic states is stationary
  - Using **Property 4 :** among singular states, only characteristic states can be stationary.
  - Consider only the parameters which lead to a dynamic having a characteristic state (of a circuit of the right sign) stationary
- If we know a characteristic stationary state :
  Using **Property 5 :** constraints on parameters
- Acceleration of the search for focal points : **Property 3.**
- **Property :**
  - Necessary condition to have multistationarity : a positive circuit is functional
  - m functional positive circuits generate $3m$ stationary states of which $2m$ are not characteristic states

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Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Stationnary characteristic States

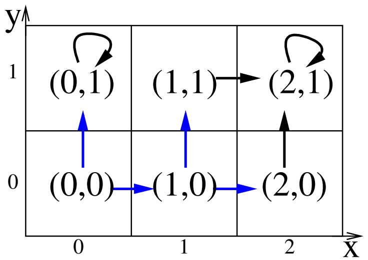
- Adjacent states of a characteristic state :
  - Minimal adjacent state : each variable in the circuit is not a resource of its successor in the circuit
  - Maximum adjacent state : each variable in the circuit is a resource of its successor in the circuit
- The circuit C is functional if there exists a characteristic state included in the domain defined by the focal points of the adjacent states min and max

All these theorems are only valid under constraints of distinct outgoing thresholds

What should we do if we want to relax this constraint ?

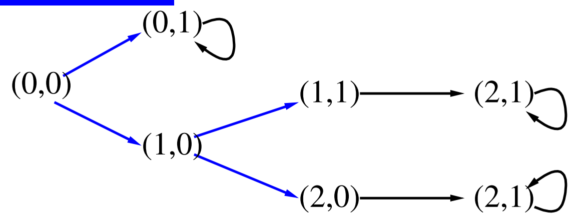
Use other information to constrain possible dynamics.

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 = comparisons : $(x = 2), (y > 0) \dots$
  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

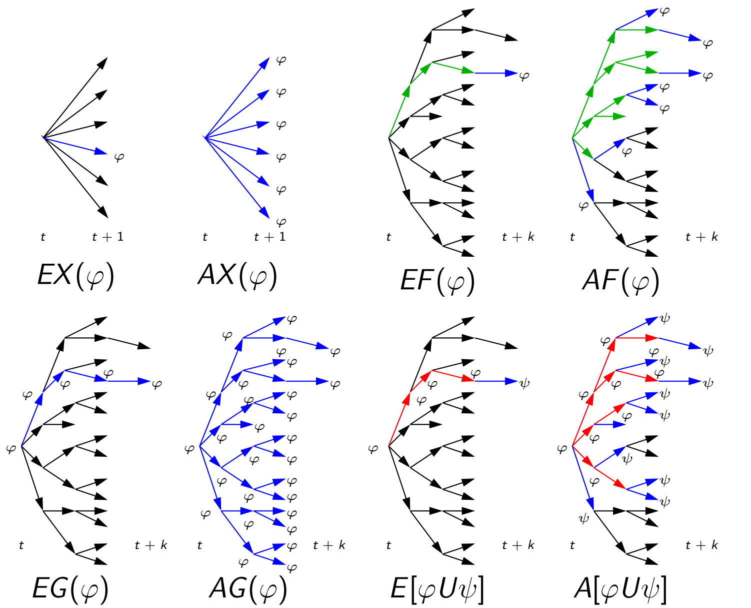
neXt state :
- $EX\varphi$: φ can be satisfied in a next state
- $AX\varphi$: φ is always satisfied in the next states

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)



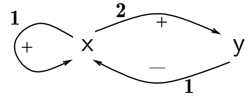
Semantics of Temporal Connectives (2)

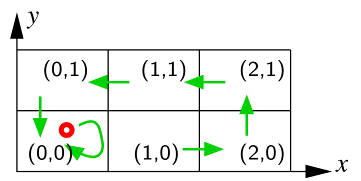
Let s_0 be a state. CTL semantics is defined inductively :

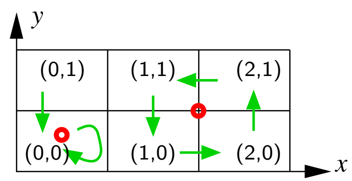
- $s_0 \models \top$ and $s_0 \not\models \bot$ $\quad \forall p \in AP, s_0 \models p$ iff $p \in L(s_0)$,
- $s_0 \models \neg\varphi$ iff $s0 \not\models \varphi$,
- $s_0 \models \varphi_1 \wedge \varphi_2$ (resp. $\varphi_1 \vee \varphi_2$) iff $s_0 \models \varphi_1$ and (resp. or) $s_0 \models \varphi_2$,
- $s_0 \models \varphi_1 \Rightarrow \varphi_2$ 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 of s_1 of s_0, one have $s_1 \models \varphi$,
- $s_0 \models EX\varphi$ iff there exists a successor s_1 of s_0 s.t. $s_1 \models \varphi$,
- $s_0 \models AG\varphi$ iff $\forall s_i$ of each path $s_0 s_1 \dots s_i \dots$, one have $s_i \models \varphi$,
- $s_0 \models EG\varphi$ iff $\exists$ a path $s_0 s_1 \dots s_i \dots$, s.t. $\forall s_i$, one have $s_i \models \varphi$,
- $s_0 \models AF\varphi$ iff $\forall$ path $s_0 s_1 \dots s_i \dots$, $\exists j$ tq $s_j \models \varphi$,
- $s_0 \models EF\varphi$ iff $\exists$ a path $s_0 s_1 \dots s_i \dots$, $\exists j$ tq $s_j \models \varphi$,
- $s_0 \models A[\varphi_1 U \varphi_2]$ 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 $K_{\dots}$)

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CTL to encode Biological Properties

Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

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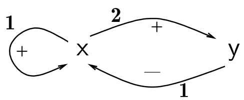
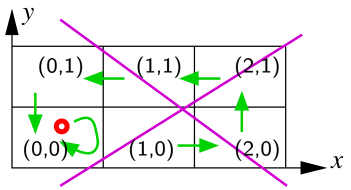
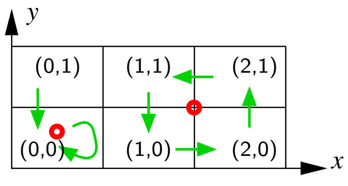






Characteristic properties : $\begin{cases} (x = 2) \Longrightarrow AG(\neg(x = 0)) \\ (x = 0) \Longrightarrow AG(\neg(x = 2)) \end{cases}$

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

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**

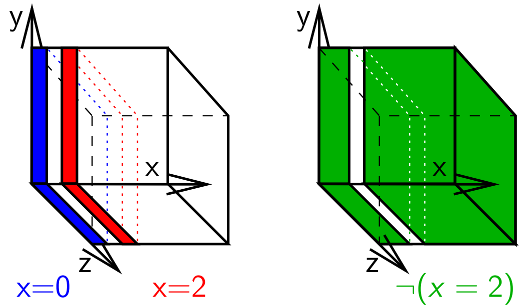
Model Checking for CTL

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

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

CÔTE D'AZUR
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

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



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.

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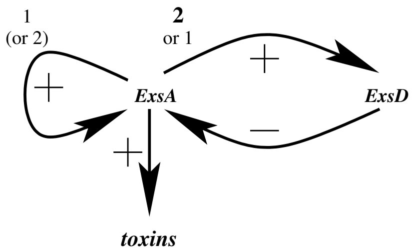
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

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* ?

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Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Formula = models-experiments 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 the possible traces of the theoretical model
- with all known experiments

⇒ They therefore provide the link between models and biological objects

A simple example

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Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

- Modification de phenotype, terminology :
  - genetic modification : heritable and non-reversible (mutation)
  - epigenetic modification : heritable but reversible
  - Adaptation : non-heritable and reversible
- Biological questions :
  - Is cytotoxicity (and/or mucoidism) in the bacterium *Pseudomonas aeruginosa* epigenetic in nature ?
  - [$\longrightarrow$ cystic fibrosis]

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Mucoidy in pseudomonas aeruginosa

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Intro
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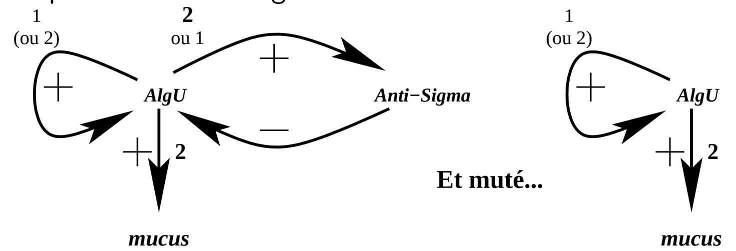
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Wild pseudomonas aeruginosa :



Epigenetic Hypothesis (i.e. without mutation)

$\rightarrow$ The positive cycle is fonctionnal despite the negative cycle, with a non mucoid state and another mucoid state

$\rightarrow$ An external signal (produced by the diseased lung) could possibly cause AlgU to move from the low state to the high state.

$\rightarrow$ Selection pressure *subsequently* favours mutants in a mucosal environment $\Rightarrow$ New prospects for therapy

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Validation of the epigenetic hypothesis

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Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

- 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 become mucoid spontaneously : validated on a daily basis
- Mucoid state : $(\texttt{AlgU} = 2) \Rightarrow \texttt{AX AF}(\texttt{AlgU} = 2)$
- Working hypothesis
  You can take AlgU to saturation, but you can't measure it
- Experiment design : *pulse of AlgU then after a transitional phase, test whether mucus production persists ($\Longleftrightarrow$ check for hysteresis) ($\Longleftrightarrow$ vérifier une hystérésis)*
- Experimental designs can be generated automatically

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

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Intro
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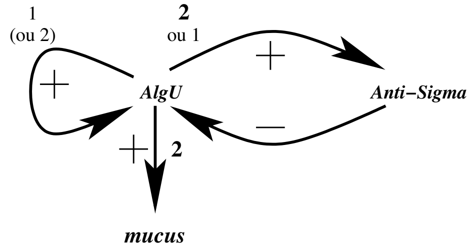
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

- $\texttt{AlgU} = 2$ is not directly verifiable but $\texttt{mucus} = 1$ is



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

$\rightarrow$ **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 for refutation

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

The pulse enables the initial state to be reached $\texttt{AlgU} = 2$.
Otherwise, we would have had to establish a lemma :

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

General Form of a test :

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

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Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Software testing techniques

Similar Problem = Does a software meet its specification ?
Infinite possible test scenarios, by selecting revelators
Solution = divide into scenario areas
Assumed "*uniform*" behaviors within a domain

- The unfolding of the formula is used to divide the domains
- Probabilisticapproach : we unfold a few, few domains (but large), probabilistic drawing of numerous tests in each domain.
- Deterministic approach : we unfold a lot, small domains, choice of only one test per domain.

99% of bugs are detectable automatically

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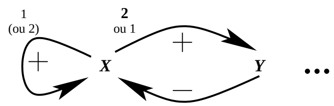
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Selection of experimental designs

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

- Set of formulae, consequences of hypothesis :
  $Th(H) = \{\psi \mid \Phi, M \models \psi\}$
- Observable Formulae : Φ_{obs}
  $\{\psi \mid \psi$ of the form "operable"$\Rightarrow$ "observable"$\}$
- Problem : $\Phi_{obs} \cap Th(H)$ is infinite
  $\rightarrow$ Choose "revelators" in $\Phi_{obs} \cap Th(H)$
- P. aeruginosa : by chance, there are 2 observable formulas $\psi_1, \psi_2 \in \Phi_{obs} \cap Th(H)$ such that $\{\psi_1, \psi_2\} \models \Phi$
- Computer Science general solution : unfolding techniques ($\simeq$ case-based reasoning) should make it possible to make it possible to explain the hypotheses made when we limit ourselves to a a fixed number of experiments.

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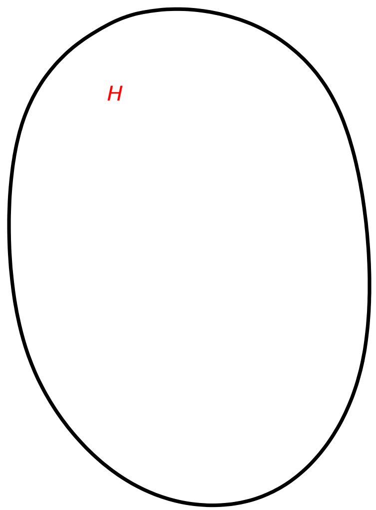
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

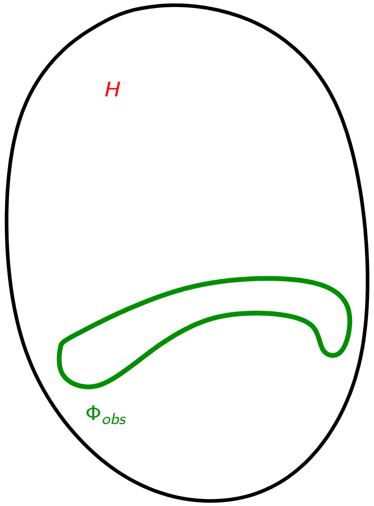
Selection of experimental plans

- *H* : hypothesis



Selection of experimental plans

- H : hypothesis
- Φ_{obs} : possible experiments



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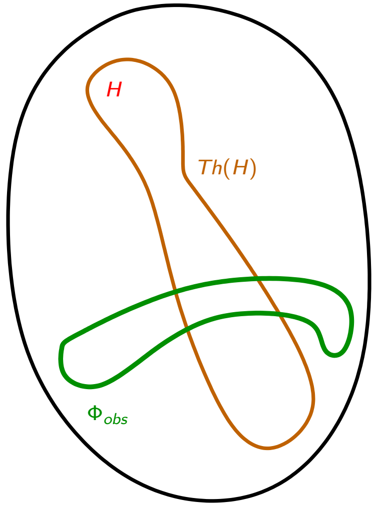
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Selection of experimental plans

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



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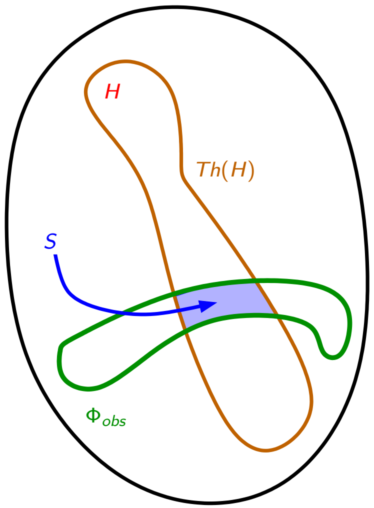
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Selection of experimental plans

- H : hypothesis
- Φ_{obs} : possible experiments
- $Th(H)$: logical consequences of H
- S : experiments linked to H



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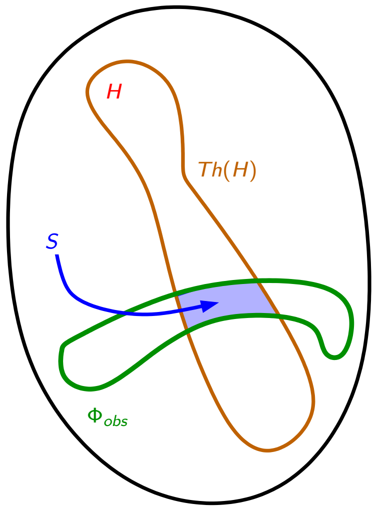
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Selection of experimental plans

- H : hypothesis
- Φ_{obs} : possible experiments
- $Th(H)$: logical consequences of H
- S : experiments linked to H

Refutability : $S \Rightarrow H$

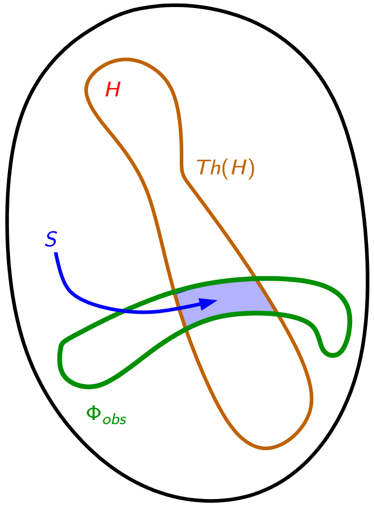


Selection of experimental plans

- H : hypothesis
- Φ_{obs} : possible experiments
- $Th(H)$: logical consequences of H
- S : experiments linked to H

Refutability : $S \Rightarrow H$

Set S infinite...
Choice of experiments in S ?
... optimisations



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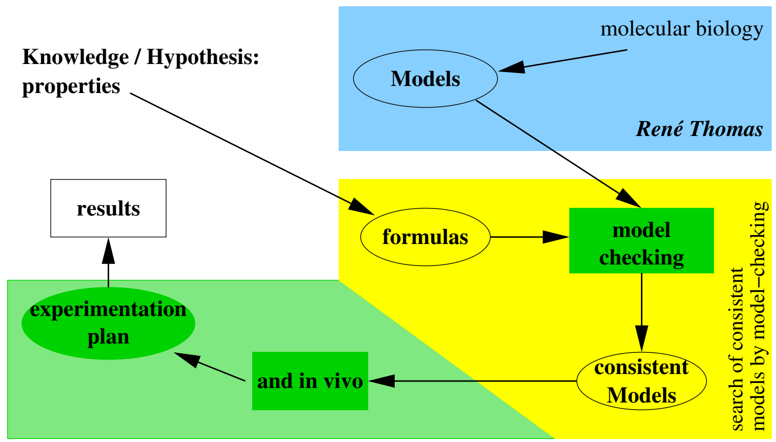
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Overview of RRB modeling



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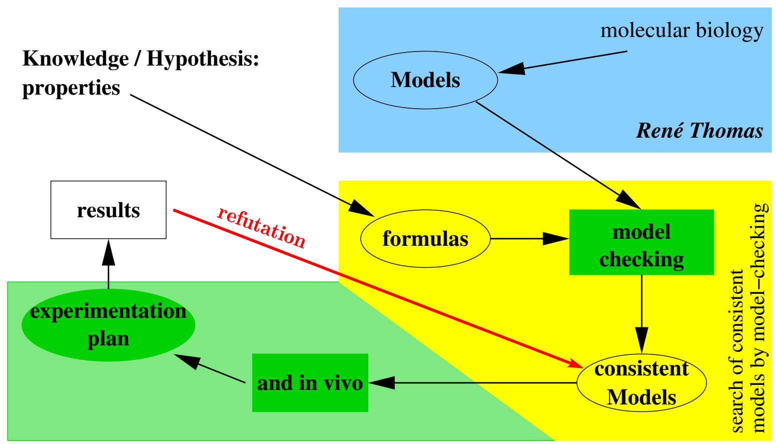
Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Overview of RRB modeling



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Symbolic AI & biol. networks
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

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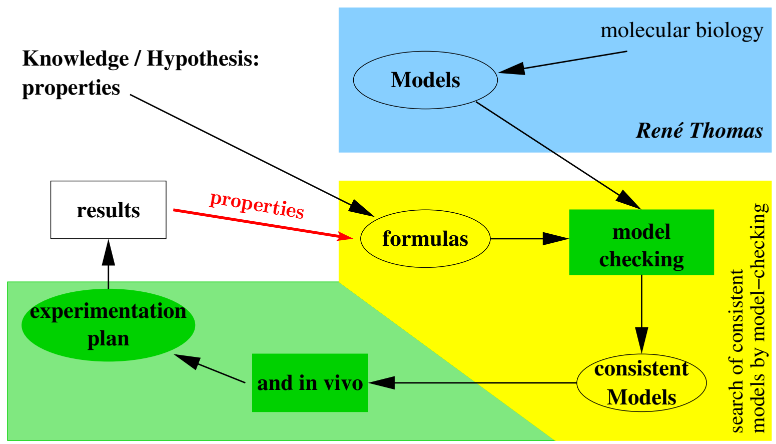
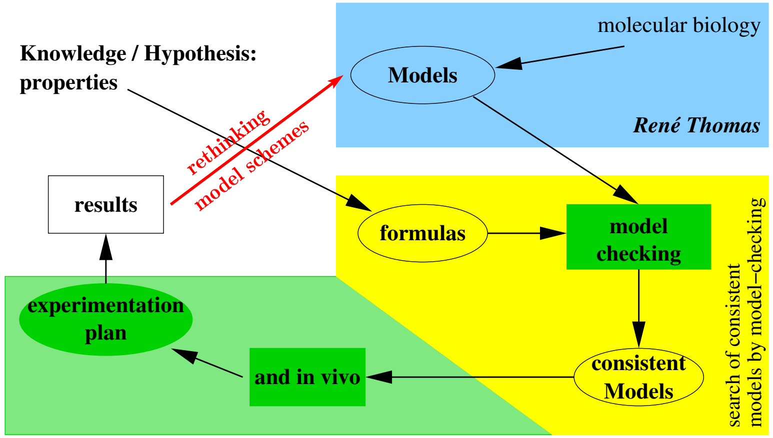


Overview of RRB modeling



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Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Automatic extraction of experiment patterns

- a set of models is given
- a set of possible experiments (in the form of formulas) is also given
- 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 ?

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Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

Select an experience

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

by model checking :

	F_1	F_2	...	F_f
M_1	1	1	...	0
M_2	1	0	...	0
...	...	...	...	...
M_m	0	1	...	0

- If the models are equi probable, one selects F_i wich balances

  both sets : $E_i = \{M_j | M_j \models F_i\}$ and $\overline{E_i} = \{M_j | M_j \not\models F_i\}$

- In the other case F_i which balances

  both probabilities : $p(\{M_j | M_j \models F_i\})$ and $p(\{M_j | M_j \not\models F_i\})$

In fact, the aim is to minimize E[Sizeof the 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 at $N/2$

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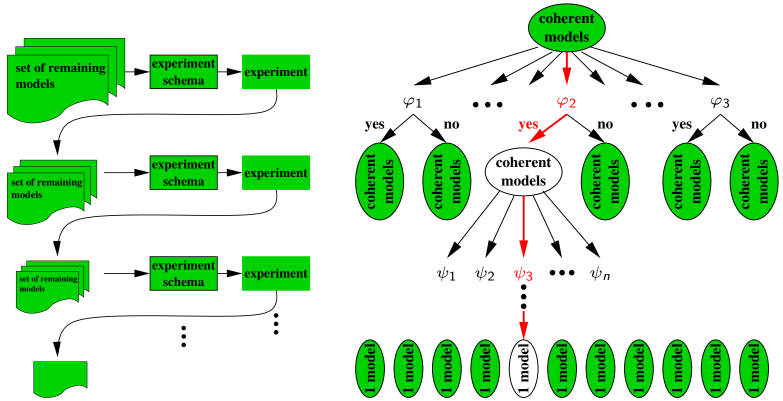
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

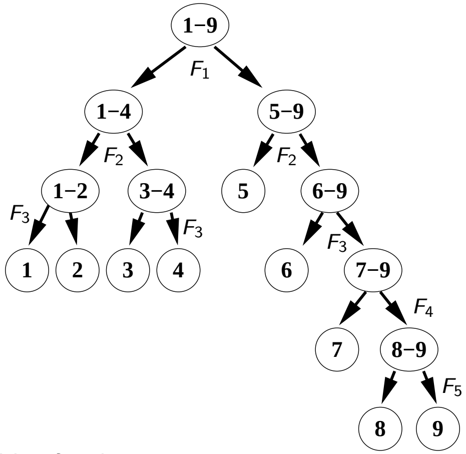
Choose a comprehensive strategy (1)



Choose a comprehensive strategy (2)

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

	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

Choose a comprehensive strategy (3)

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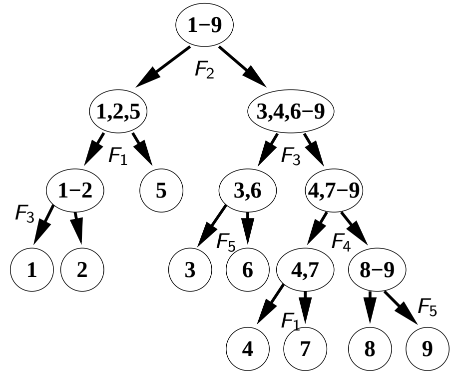
Jean-Paul Comet
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

	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 3-DM problem, L. Hyafil & R.L. Rivest [1975])

Choose a comprehensive strategy (4)

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Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

	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 we don't want to

- to choose a discriminating formula at random,
- nor choose a formula that's easy to implement *in vivo* (costs)
- nor adjust this choice according to intuition,
- nor choose the formula that best cuts M

Using the min-max algorithm to optimize selection :

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

Choose a comprehensive strategy (4-b)

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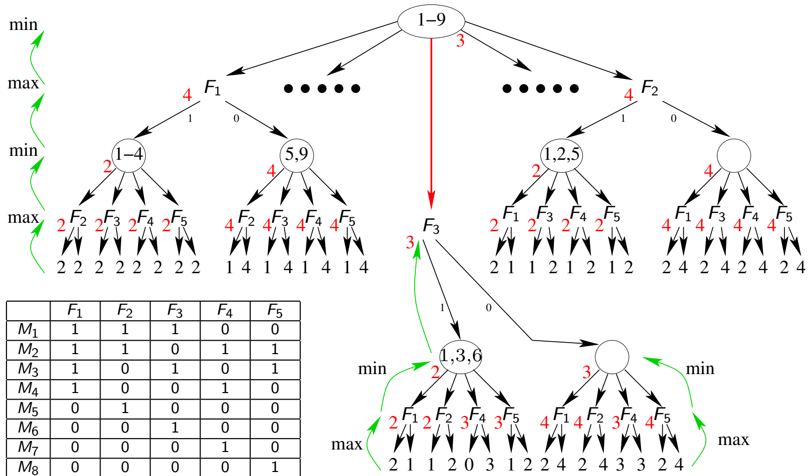
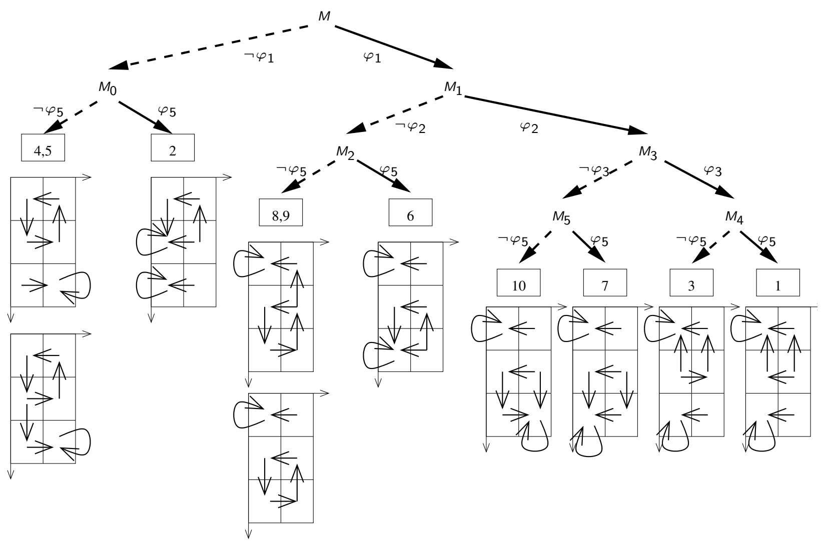
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction



	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

Choose a comprehensive strategy (5)



Sign semantics

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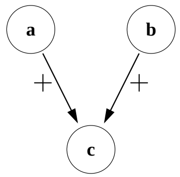
Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

- Signs and parameters



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

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

Link between signs and parameters

Sign Semantics for Thomas-Snoussi

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Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

- diff. eq. 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 x_1 and x_2 act on x_3 :	$d(k+k_1+k_2)$	K_{x_3,x_1x_2}

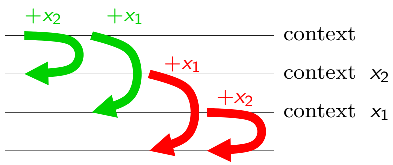
- Sum of positive numbers, Snoussi conditions :

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

Everywhere, the addition of a resource cannot reduce the 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	$K_{x_3,x_1x_2} = 0$



Other possible semantics

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Intro
cont. mod.
Discretisation
Diff.Eq.
Sol.
Dyn.
Consistency
Fonct.
CTL
Extraction

- Everywhere, adding a resource cannot reduce 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 $+_{snoussi}$, $-_{snoussi}$