Cell cycle modelling: a new hybrid approach based on Hoare Logic for parameters identification.

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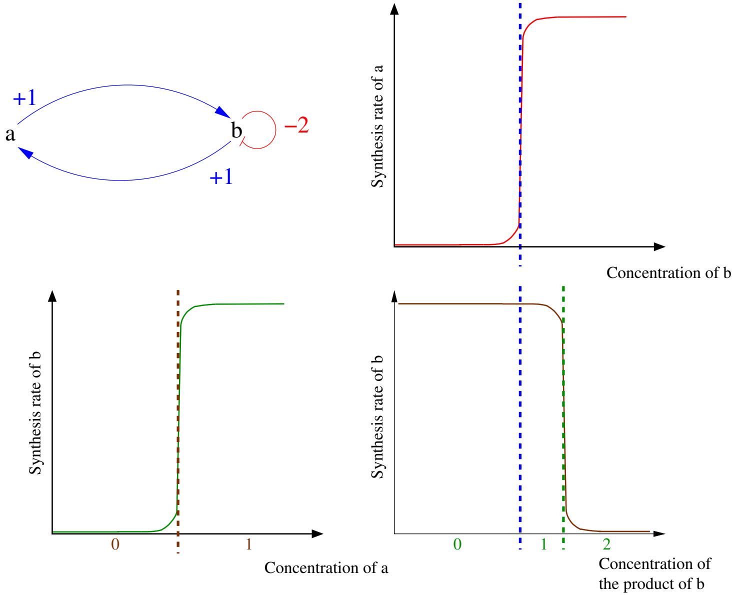
René Thomas' discrete modelling framework - Interaction graph



René Thomas' discrete modelling framework - State graph

Variables		Parameters	
A	**B**	**A**	**B**
0	0	$K_{A,\{\}}$	$K_{B,\{B\}}$
0	1	$K_{A,\{B\}}$	$K_{B,\{B\}}$
0	2	$K_{A,\{B\}}$	$K_{B,\{\}}$
1	0	$K_{A,\{\}}$	$K_{B,\{A,B\}}$
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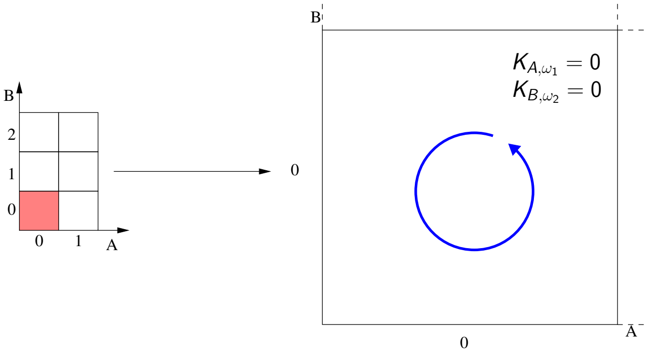

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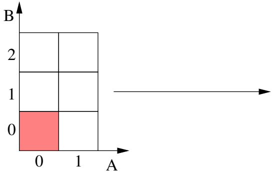

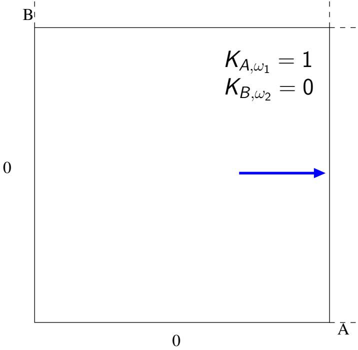

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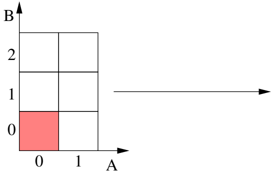

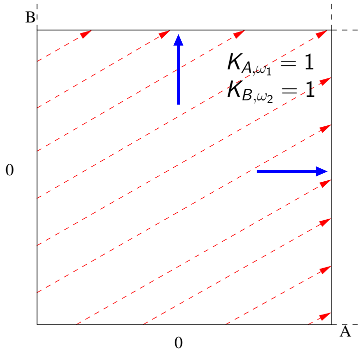

A gene regulatory network (GRN) is a tuple $R = (V, M, E)$ where :

- V is a set whose elements are called *variables* of the network. Each variable $v \in V$ is associated with a boundary $b_v \in \mathbb{N}$.

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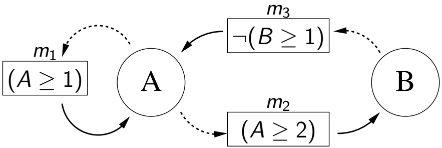
- E is a set of edges of the form $(m \to v) \in M \times V$.



Let $R = (V, M, E)$ be a GRN. The state graph of N is the directed graph S defined as follows : the set of vertices is the set of states of N, and there exists an edge (or transition) $\eta \rightarrow \eta'$ if one of the following conditions is satisfied :

- there is no $v \in V$ such that $\eta(v) \neq K_{v,\rho(\eta,v)}$ and $\eta' = \eta$.
- there exists $v \in V$ such that $\eta(v) \neq K_{v,\rho(\eta,v)}$ and
$$\eta'(v) = \begin{cases} \eta(v) + 1 \ \textit{if} \ \eta(v) < K_{v,\rho(\eta,v)} \\ \eta(v) - 1 \ \textit{if} \ \eta(v) > K_{v,\rho(\eta,v)} \end{cases} \textit{and} \ \forall u \neq v, \eta'(u) = \eta(u)$$

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- Formal method allowing the proof of imperative program,
- Give constraints on parameters in discrete modelling,

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Hoare Triple :

$$\{P\}Q\{R\}$$

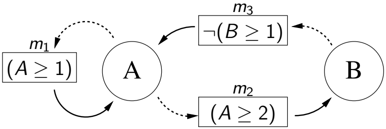
- P and R : predicates called respectively precondition and postcondition,
- Q : imperative program.

Hoare Triple :

$$\{P\}Q\{R\}$$

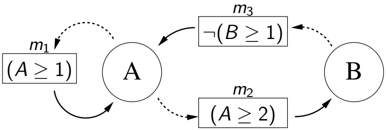
If the precondition P is satisfied before the execution of the program Q, the postcondition R will be satisfied after Q.

Example : $\{x = 0\}x := x + 1\{x = 1\}$



$$\left\{ \begin{array}{c} A = ? \\ B = ? \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{c} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**



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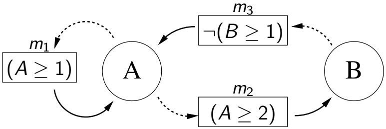
(1,0)	A	$\omega 4$		



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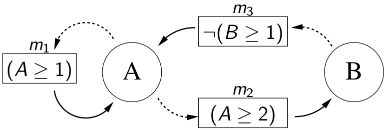
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		



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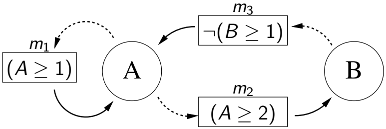
(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,1)	A	$\omega 2$		
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		



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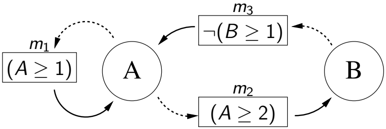
(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,0)	B	$\omega 1$		
(2,1)	A	$\omega 2$		
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		



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(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,0)	B	$\omega 1$	m_2	$K_{B,\{m_2\}} > 0$
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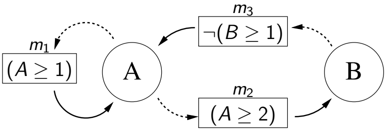

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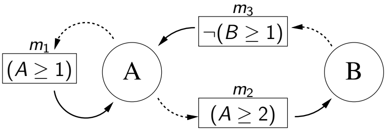

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(1,1)	B	$\omega 3$	$\emptyset$	$K_{A,\emptyset} < 1$
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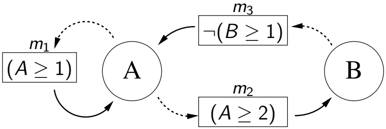

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(1,1)	B	$\omega 3$	$\emptyset$	$K_{A,\emptyset} < 1$
(1,0)	A	$\omega 4$	m_1, m_3	$K_{A,\{m_1,m_3\}} > 1$

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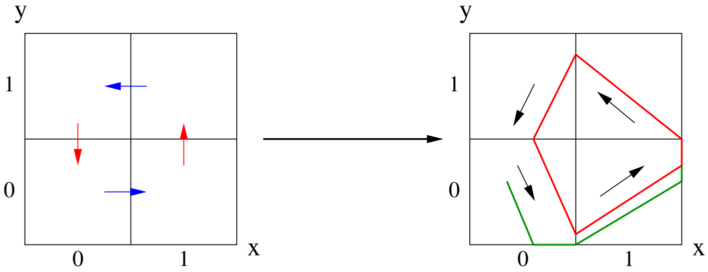
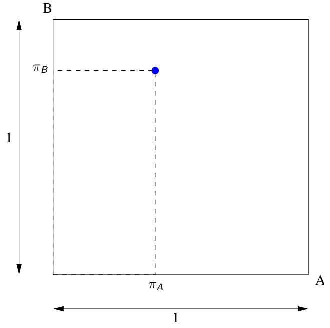


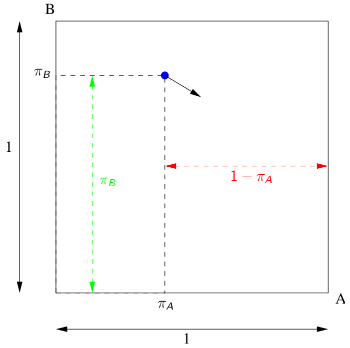
- $\mathcal{C} = \{C_{v,\omega,n}\}$ is a family of real numbers indexed by the tuple (v, ω, n) where v, ω and n verify the tree following conditions :
  1. $v \in V$,
  2. ω is a subset of $R^-(v)$ where $R^-(v) = \{m \mid (m \to v) \in E\}$, that is, ω is a set of predecessors of v,
  3. n is an integer such that $0 \leqslant n \leqslant b_v$.

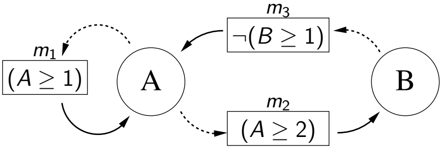
$C_{v,\omega,n}$ is called the *celerity* of v for ω at the level n.

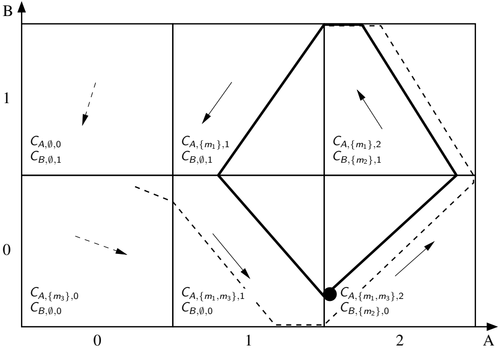
- A hybrid state is a couple $h = (\eta, \pi)$ where :
  - η is a function of V in $\mathbb{N}$ such as $\forall v \in V$, $0 \leqslant \eta(v) \leqslant b_v$; η is called the discrete state of h.
  - π is a function of V in the real interval $[0, 1]$, π is called the fractional part of h



- The *touch delay* of v noted $\delta_h(v)$ is the time allowing v to reach the border of the current discrete state. For each $v \in V$, δ_h is the function of V in $\mathbb{R}^+$ defined by :
  - If $C_{v,\rho(\eta,v),\eta(v)} = 0$, then $\delta_h(v) = +\infty$
  - If $C_{v,\rho(\eta,v),\eta(v)} > 0$, then $\delta_h(v) = \frac{1-\pi(v)}{C_{v,\rho(\eta,v),\eta(v)}}$
  - If $C_{v,\rho(\eta,v),\eta(v)} < 0$, then $\delta_h(v) = \frac{\pi(v)}{|C_{v,\rho(\eta,v),\eta(v)}|}$

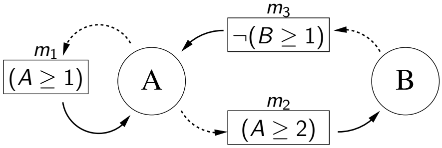


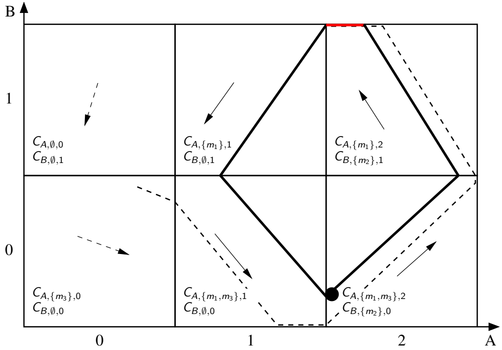




- Limit cycle of a 2-variable interaction graph,

Hybrid modelling framework - Example





- Limit cycle of a 2-variable interaction graph,
- Slide of the variable B,

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We note **terms** the following variables :

- the variables of $\mathbb{R}$ and $\mathbb{N}$,
- the variables η_u, π_u, π'_u, $C_{u,\omega,n}$,
- the constants of $\mathbb{R}$ and $\mathbb{N}$.

We note $Terms_d$ (resp. $Terms_h$) the set of **discrete terms** (resp. **hybrid terms**) built on variables η_u and on variables and constants of $\mathbb{N}$ (resp. on variables η_u, π_u, π'_u, $C_{u,\omega,n}$ and on variables and constants of $\mathbb{R}$ and of $\mathbb{N}$).

The **atoms** of the *property language* are of two types :

- **Discrete atoms** are of the form : $n \,\square\, n'$ where $n, n' \in Terms_d$;
- **Hybrid atoms** are of the form : $f \,\square\, f'$ where $f, f' \in Terms_h$;

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- **Discrete atoms** are of the form : $n \square n'$ where $n, n' \in Terms_d$;
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The **discrete conditions** are defined by :
$D \quad ::= \quad a_d \mid \neg D \mid D \wedge D \mid D \vee D$ where a_d is a discrete atom.
The **hybrid conditions** are defined by :
$H \quad ::= \quad a_d \mid a_h \mid \neg H \mid H \wedge H \mid H \vee H$ where a_d and a_h are respectively a discrete atom and a hybrid one.

- **Property language** $\mathcal{L}_C$:

A **property** is a couple (D, H) formed by a discrete and a hybrid condition. All properties form the **property language** $\mathcal{L}_C$.

$$Pre \equiv \{D, H\}$$

$$Post \equiv \{D', H'\}$$

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- **Path language** $\mathcal{L}_P$:

The **discrete path atoms** (dpa) are defined by : $dpa \quad :== \quad v+ \mid v-$ where $v \in V$ is a variable name.
The **discrete paths** are defined by : $\quad p :== \varepsilon \mid (\Delta t, assert, dpa) \mid p \; ; \; p$ where Δt is either a real constant or a variable, *assert* is an assertion, and *dpa* is a discrete path atom.

A **Hoare triple** for a given GRN is an expression of the form $\{Pre\}\ p\ \{Post\}$ where *Pre* and *Post*, called *precondition* and *postcondition* respectively, are properties of $\mathcal{L}_C$, and p is a path from $\mathcal{L}_P$.

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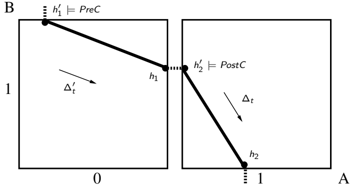

- If $p \equiv (\Delta t, assert, v+)$ then for all $h'_1 = (\eta_1, \pi'_1) \models Pre$, there exists $h_1 = (\eta_1, \pi_1)$ and $h'_2 = (\eta_1 + 1, \pi'_2)$ such that :
  - $(h'_1, h_1) \models (\Delta t, assert)$ (**continuous transition**),
  - **discrete transition** from h_1 towards h'_2,
  - $h'_2 \models Post$;

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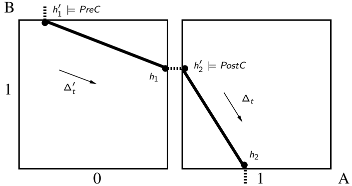

- If $p = p_1; p_2$, then there exist $Post_1$ and Pre_2 such that $\{Pre\}\ p_1\ \{Post_1\}$ and $\{Pre_2\}\ p_2\ \{Post\}$ are satisfied and $Post_1 \Rightarrow Pre_2$.

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The **weakest precondition** attributed to p and $Post$ is a property
$\mathrm{WP}^i_f(p, Post) \equiv (D', H'_{i,f})$
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$\mathrm{WP}^i_f(p, Post) \equiv (D', H'_{i,f})$
defined by :

- If $p = \varepsilon$, then $D' \equiv D$ and $H'_{i,f} \equiv H_f$;
- If $p = (\Delta t, assert, v+)$:
  - $D' \equiv D[\eta_v \backslash \eta_v + 1]$,
  - $H'_{i,f} \equiv H_f \wedge \Phi^+_v(\Delta t) \wedge \neg \mathcal{W}^+_v \wedge \mathcal{F}_v(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_v$;
- If $p = (\Delta t, assert, v-)$:
  - $D' \equiv D[\eta_v \backslash \eta_v - 1]$,
  - $H'_{i,f} \equiv H_f \wedge \Phi^-_v(\Delta t) \wedge \neg \mathcal{W}^-_v \wedge \mathcal{F}_v(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_v$;

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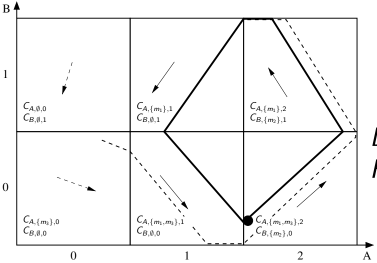
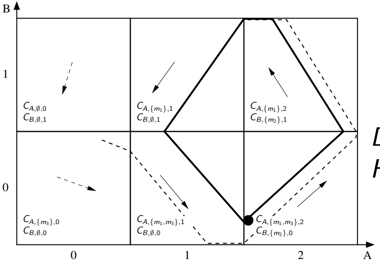
- If $p = (\Delta t, assert, v-)$:
  - $D' \equiv D[\eta_v \backslash \eta_v - 1]$,
  - $H'_{i,f} \equiv H_f \wedge \Phi^-_v(\Delta t) \wedge \neg \mathcal{W}^-_v \wedge \mathcal{F}_v(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_v$;
- If $p = p_1; p_2$:
  - $\mathrm{WP}^i_f(p_1; p_2, Post) \equiv \mathrm{WP}^i_m(p_1, \mathrm{WP}^m_f(p_2, Post))$

  parameterized by a fresh intermediate state index m ;



$$\begin{Bmatrix} D_1 \\ H_1 \end{Bmatrix} (T_1, \top, A+) \begin{Bmatrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{Bmatrix}$$

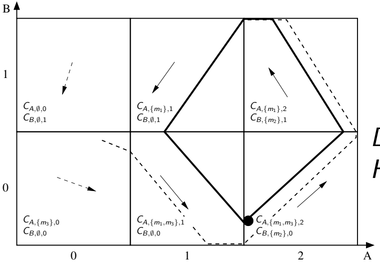
$$D_1 \equiv D_0[\eta_A \backslash \eta_A + 1]$$
$$H_1 \equiv H_0 \wedge \Phi_A^+(T_1) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A$$



$$\left\{\begin{matrix} D_1 \\ H_1 \end{matrix}\right\} (T_1, \top, A+) \left\{\begin{matrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{matrix}\right\}$$

$$\begin{aligned} D_1 &\equiv D_0[\eta_A \backslash \eta_A + 1] \\ H_1 &\equiv H_0 \wedge \Phi_A^+(T_1) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A \end{aligned}$$

$$D_1 \equiv (\eta_A + 1 = 2) \wedge (\eta_B = 0) \equiv (\eta_A = 1) \wedge (\eta_B = 0)$$



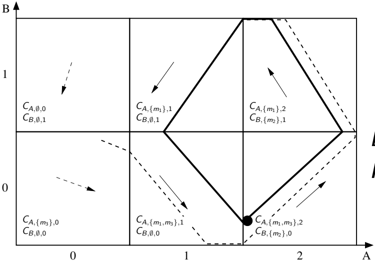
$$\begin{Bmatrix} D_1 \\ H_1 \end{Bmatrix} (T_1, \top, A+) \begin{Bmatrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{Bmatrix}$$

$$D_1 \equiv D_0[\eta_A \backslash \eta_A + 1]$$
$$H_1 \equiv H_0 \wedge \Phi_A^+(T_1) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A$$

$\Phi_A^+(T_1)$ describes the conditions in which A increases its discrete expression level.

$$\Phi_A^+(T_1) \equiv (\pi_{A_1} = 1) \wedge (C_{A,\{m_1,m_3\},1} > 0) \wedge (\pi'_{A_1} = \pi_{A_1} - C_{A,\{m_1,m_3\},1} \cdot T_1)$$

Weakest precondition calculus - Example



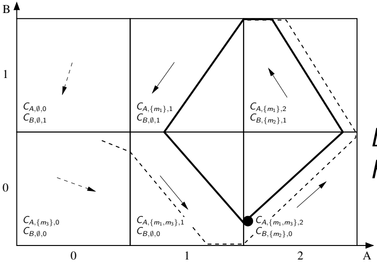
$$\begin{Bmatrix} D_1 \\ H_1 \end{Bmatrix} (T_1, \top, A+) \begin{Bmatrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{Bmatrix}$$

$$D_1 \equiv D_0[\eta_A \backslash \eta_A + 1]$$
$$H_1 \equiv H_0 \wedge \Phi_A^+(T_1) \wedge \neg\mathcal{W}_A^+ \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A$$

$\neg\mathcal{W}_A^+$ states that there is not an internal or external wall preventing A to increase its qualitative state.

$$\neg\mathcal{W}_A^+ \equiv \top$$

Weakest precondition calculus - Example

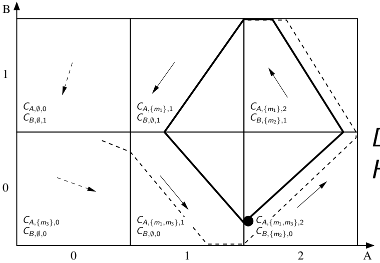


$$\left\{\begin{matrix} D_1 \\ H_1 \end{matrix}\right\} (T_1, \top, A+) \left\{\begin{matrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{matrix}\right\}$$

$$D_1 \equiv D_0[\eta_A \backslash \eta_A + 1]$$
$$H_1 \equiv H_0 \wedge \Phi_A^+(T_1) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A$$

$\mathcal{F}_A(T_1)$ states that A is the variable which can first change its qualitative state.

$$\mathcal{F}_A(T_1) \equiv \neg(C_{B,\emptyset,0} > 0) \vee \neg(\pi'_{B_1} > \pi_{B_1} - C_{B,\emptyset,0} \cdot T_1)$$

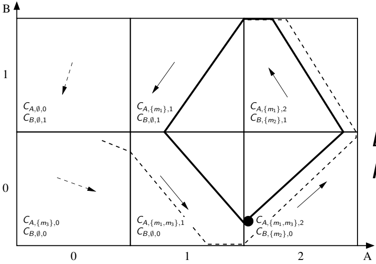


$$\begin{Bmatrix} D_1 \\ H_1 \end{Bmatrix} (T_1, \top, A+) \begin{Bmatrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{Bmatrix}$$

$$D_1 \equiv D_0[\eta_A \backslash \eta_A + 1]$$
$$H_1 \equiv H_0 \wedge \Phi_A^+(T_1) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A$$

$\mathcal{A}(T_1)$ translates all assertion symbols given in *assert* expressing constraints on celerities and slides into property language

$$\mathcal{A}(T_1) \equiv \top$$

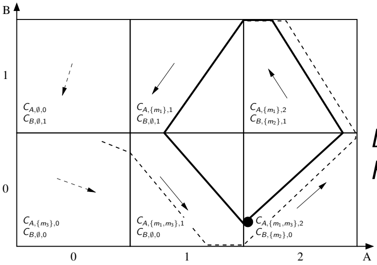


$$\begin{Bmatrix} D_1 \\ H_1 \end{Bmatrix} (T_1, \top, A+) \begin{Bmatrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{Bmatrix}$$

$$D_1 \equiv D_0[\eta_A \backslash \eta_A + 1]$$
$$H_1 \equiv H_0 \wedge \Phi_A^+(T_1) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A$$

$\mathcal{J}_A$ establishes a junction between the fractional parts of two successive states linked by a discrete transition

$$\mathcal{J}_A \equiv (\pi_{B_1} = \pi'_{B_0}) \wedge (\pi_{A_1} = 1 - \pi'_{A_0})$$



$$\begin{Bmatrix} D_1 \\ H_1 \end{Bmatrix} (T_1, \top, A+) \begin{Bmatrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{Bmatrix}$$

$$D_1 \equiv D_0[\eta_A \backslash \eta_A + 1]$$
$$H_1 \equiv H_0 \wedge \Phi^+_A(T_1) \wedge \neg \mathcal{W}^+_A \wedge \mathcal{F}_A(T_1) \wedge \mathcal{A}(T_1) \wedge \mathcal{J}_A$$

$$D_1 \equiv (\eta_A = 1) \wedge (\eta_B = 0)$$

$$H_1 \equiv \Big(\neg(C_{B,\emptyset,0} > 0) \vee \neg(\pi'_{B_1} > \pi'_{B_0} - C_{B,\emptyset,0} \cdot T_1)\Big) \wedge (C_{A,\{m_1,m_3\},1} > 0)$$
$$\wedge(\pi'_{A_1} = 1 - C_{A,\{m_1,m_3\},1} \cdot T_1) \wedge (\pi'_{A_0} = 0)$$

$$
\begin{aligned}
H_F \equiv\ & \big(\neg(C_{B,\emptyset,0} > 0) \vee \neg(1 > \pi'_{B_0} - C_{B,\emptyset,0} \cdot T_1)\big) \\
& \wedge (C_{A,\{m_1,m_3\},1} > 0) \wedge (\pi'_{A_1} = 1 - C_{A,\{m_1,m_3\},1} \cdot T_1) \\
& \wedge \big(\neg(C_{A,\{m_1\},1} > 0) \vee \neg(1 > \pi'_{A_1} - C_{A,\{m_1\},1} \cdot T_2)\big) \\
& \wedge \big((C_{A,\emptyset,0} > 0) \vee \neg(C_{A,\{m_1\},1} < 0) \vee \neg(1 < \pi'_{A_1} - C_{A,\{m_1\},1} \cdot T_2)\big) \\
& \wedge (C_{B,\emptyset,1} < 0) \wedge (1 = 0 - C_{B,\emptyset,1} \cdot T_2) \\
& \wedge \big(\neg(C_{B,\{m_2\},1} < 0) \vee \neg(0 < 1 - C_{B,\{m_2\},1} \cdot T_3)\big) \\
& \wedge \big(C_{A,\{m_1\},2} < 0 \wedge (\pi'_{A_3} = 0 - C_{A,\{m_1\},2} \cdot T_3)\big) \\
& \wedge \big(\neg(C_{B,\{m_2\},1} > 0) \vee (0 > 1 - C_{B,\{m_2\},1} \cdot T_3)\big) \\
& \wedge \big(\neg(C_{A,\{m_1,m_3\},2} < 0) \vee \neg(0 < \pi'_{A_3} - C_{A,\{m_1,m_3\},2} \cdot T_4)\big) \\
& \wedge (C_{B,\{m_2\},0} > 0) \wedge (\pi'_{B_0} = 1 - C_{B,\{m_2\},0} \cdot T_4)
\end{aligned}
$$

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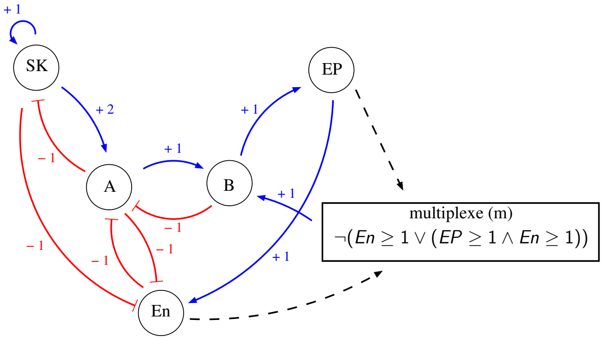
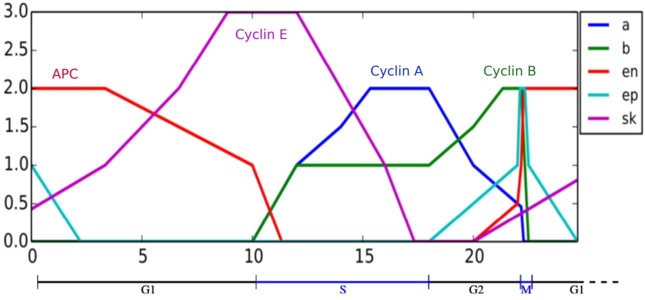
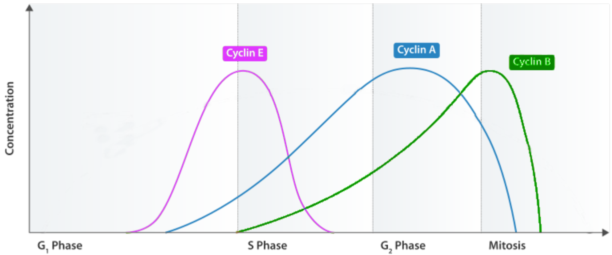


Entity	Proteins or complexes
SK	Cyclin E/Cdk2, CAK
A	Cyclin A/Cdk1
B	Cyclin B/Cdk1
En	APC^{G_1}, CKI (p21, p27), Wee1
EP	APC^{M}, Phosphatases



3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
Cyclin E
APC
Cyclin A
Cyclin B
a
b
en
ep
sk
G1
S
G2
M
G1



Concentration
Cyclin E
Cyclin A
Cyclin B
G1 Phase
S Phase
G2 Phase
Mitosis

Conclusion :

- Suitable approach to identify new constraints,
- Take into account more biological data,
- One constraint for each parameter.

Conclusion :

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- Take into account more biological data,
- One constraint for each parameter.

Perspectives :

- Simplify on the fly all intermediate formulas,
- Use constraint solver,
- Automate the identification of the constraints.