Mammalian cell cycle: formalizing phases

Déborah Boyenval
Journée annuelle du GT Bioss 2021

November 23, 2021

Context: pluridisciplinary research project

DIGITAL SYSTEMS FOR HUMANS
GRADUATE SCHOOL AND RESEARCH

UNIVERSITÉ CÔTE D'AZUR

Understanding the interactions between oscillating biological systems

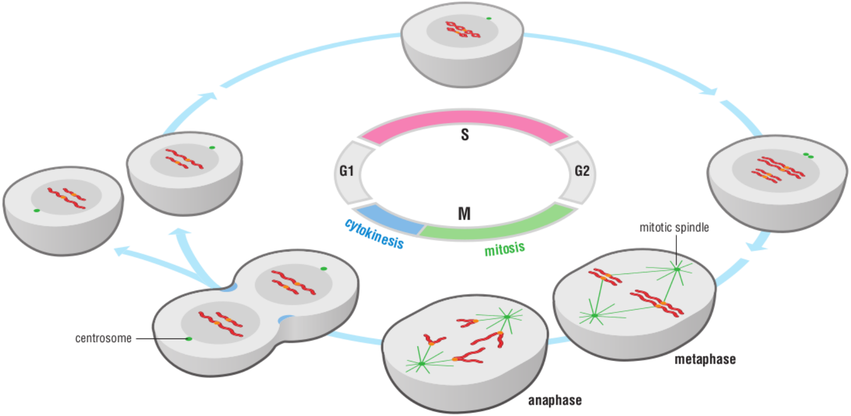
i3S sophia antipolis

SPARKS Team
Gilles Bernot and Jean-Paul Comet

institut Valrose Biologie

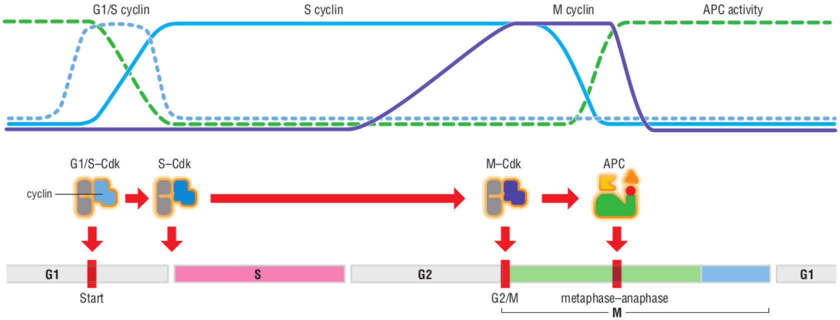
Franck Delaunay Team

Mammalian cell cycle



The Cell Cycle
Principles of Control - D. Morgan - Primers in Biology. 2006.

Molecular regulators of the cell cycle



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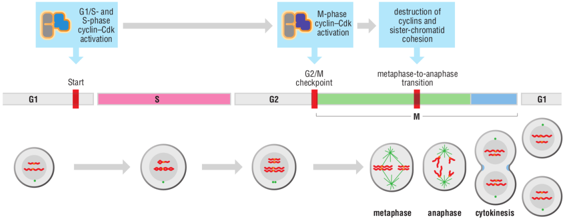
- **G1/S cyclin/Cdk**: cycD/Cdk4-6, cycE/Cdk2
- **S cyclin/Cdk**: cycA/Cdk2-1
- **M cyclin/Cdk**: cycB/Cdk2-1
- **APC**: APC-cdh1, APC-cdc20

Cell cycle modelling: three observations



The Cell Cycle - Principles of Control - D. Morgan - Primers in Biology. 2006.

1. Numerous models of the cell cycle: a wide variety of formalisms

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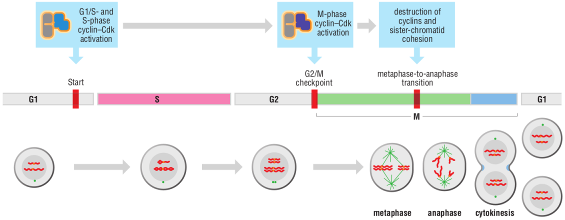

The Cell Cycle - Principles of Control - D. Morgan - Primers in Biology. 2006.

1. Numerous models of the cell cycle: a wide variety of formalisms
2. Inter-**phase** checkpoints (G1/S, S/G2 and G2/M) and intra-**M** checkpoint (SAC) are integral of the cell cycle
3. But the *prior* question of the formalization of the phases is not widely questioned

Inspiring cell cycle models

Model	**Semantics**	**About phases**
Fauré *et al.* 2006	Boolean	Cell cycle SCC (Strongly Connected Component)
Tyson and Novàk 2008	Differential	A few deterministic trajectories
Gérard *et al.* 2009	Differential	A few deterministic trajectories
Traynard *et al.* 2016	Multivaluated	Cell cycle SCC
Behaegel *et al.* 2016	Hybrid	Hoare triple (a few paths) UNIVERSITÉ CÔTE D'AZUR
Diop *et al.* 2019	Boolean	State partition of SCC

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- Some experimental traces reflected: not exhaustive ordering of events
- Checkpoints are characterised by the irreversibility of phase transitions.

Formalization of cell cycle phases: should be properly questionned

A cell cycle phase is a series of events → discrete description.

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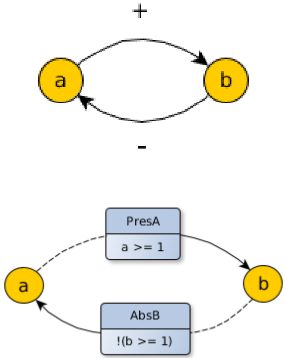
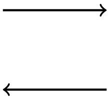
Formalization of a phase where the order of events is comprehensively questioned.

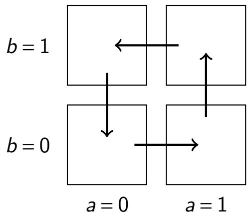
The René Thomas' formalism

Static description (BRGM):



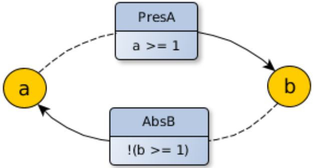


Dynamic description (ATG): asynchronous semantics



The René Thomas' formalism

(1)



$$\left\{ \begin{array}{l} K_{a,\{\}} = 0 \\ K_{a,\{AbsB\}} = 1 \\ K_{b,\{\}} = 0 \\ K_{b,\{PresA\}} = 1 \end{array} \right\}$$

(2)

	$a = 0$ (inactive)	$a = 1$ (active)
$b = 1$ (active)	$K_{a,\{\}}$ $K_{b,\{\}}$	$K_{a,\{\}}$ $K_{b,\{PresA\}}$
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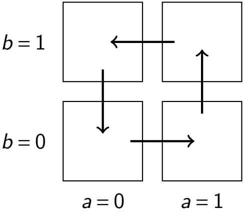

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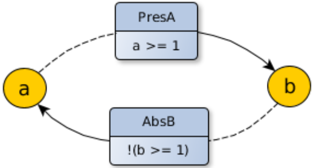

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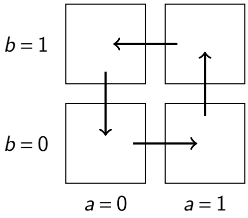
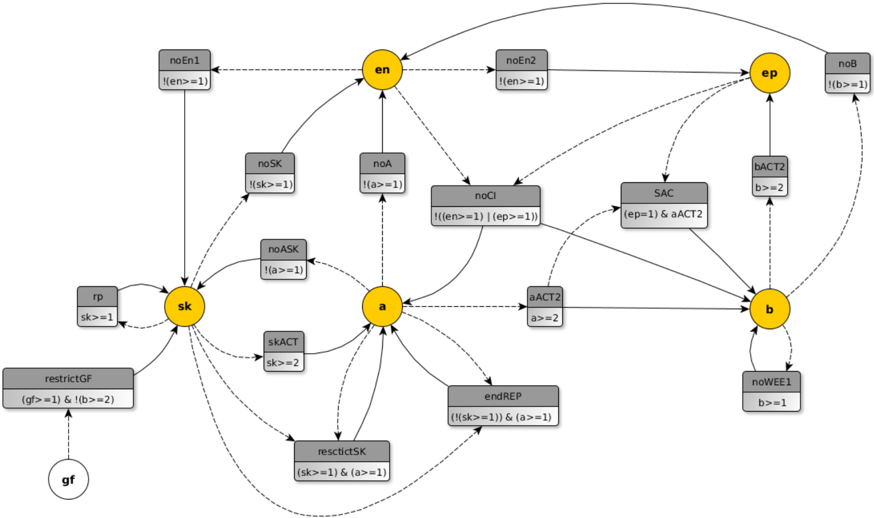


Model $=$ all $K_{v,\omega}$ are instanciated

Our updated model: does it reflect checkpoints?



Three steps to define a phase

An exemple of a phase π_i :

$$\{P_{\pi_i}\} \quad p_{\pi_i} \quad \{Q_{\pi_i}\}$$

$$\{v_1 = 3 \wedge v_2 = 0\} \qquad v_1+; v_2-; v_2-; v_1+; v_2-; v_1+ \qquad \{v_1 = 3 \wedge v_2 = 0\}$$

1. **Canonical phase** : Elementary Hoare Triple (one canonical path)

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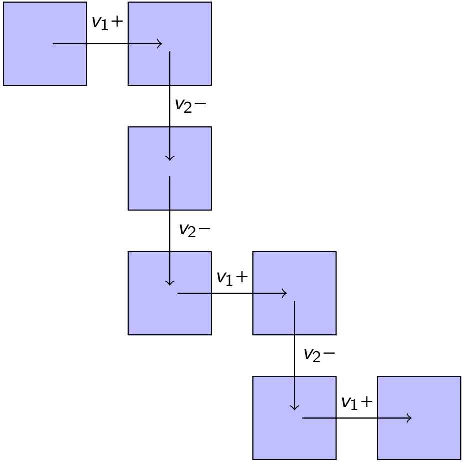
2. **Its hyper-rectangle** : All permutations of the canonical path
3. **Admissible hyper-rectangle** : Paths within the hyper-rectangle that are compatible with biological knowledge given a set of cell cycle models (automated formal verification)

Canonical phase encoded by $\{P_{\pi_i}\}$ p_{π_i} $\{Q_{\pi_i}\}$

$P_{\pi_i} \equiv (v_1 = 0 \wedge v_2 = 3)$



Canonical phase

$Q_{\pi_i} \equiv (v_1 = 3 \wedge v_2 = 0) \equiv P_{\pi_{i+1}}$

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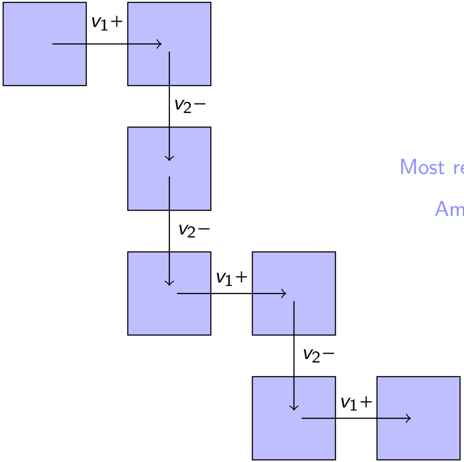

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Canonical phase

Most represented sequence of states

Among several possible ones

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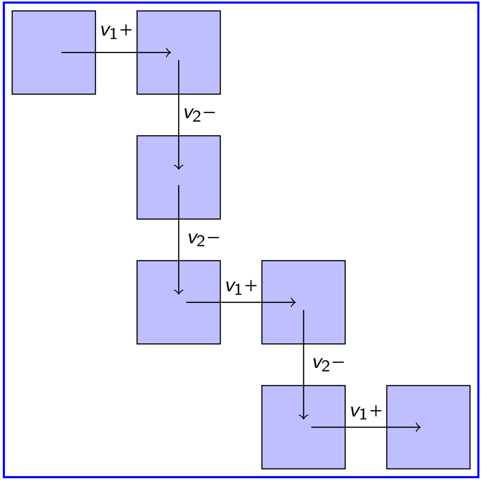

Canonical phase

Hyper-rectangle

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Hyper-rectangle extracted from the canonical phase

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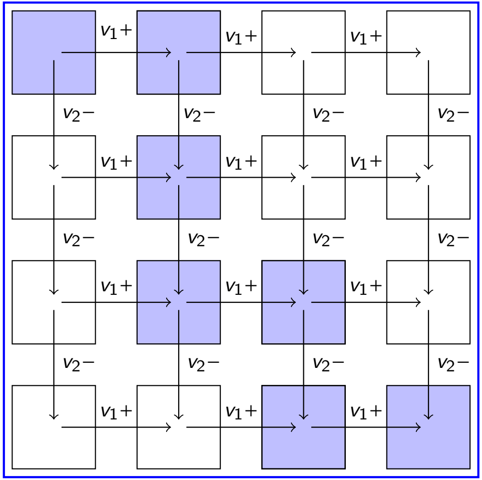

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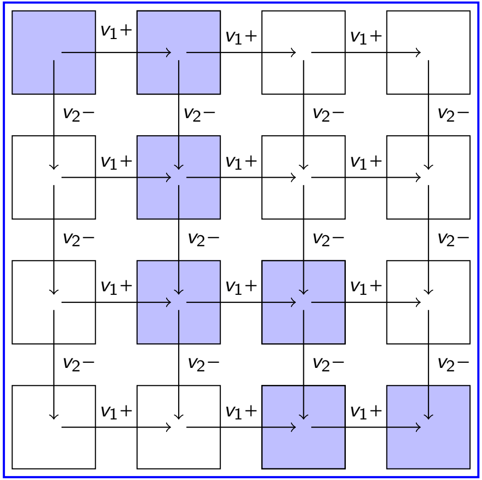

Canonical phase

Hyper-rectangle

$$\psi_{H_\pi} \equiv \bigwedge_{v \in V} (v \geqslant min_v^{H_\pi} \wedge v \leqslant max_v^{H_\pi})$$

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Some permutations inside the hyper-rectangle are not admissible

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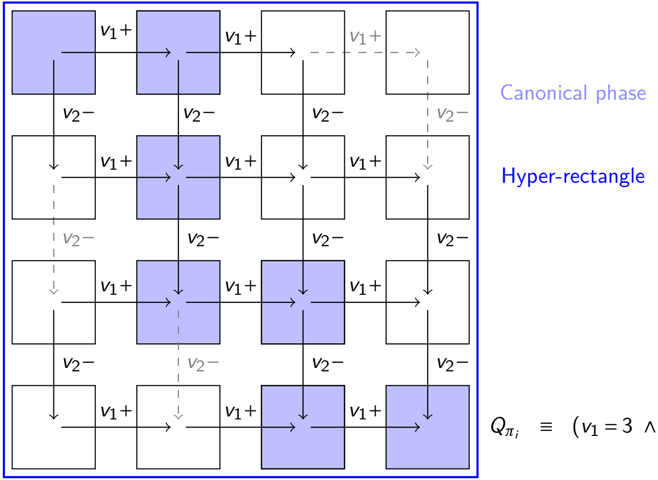

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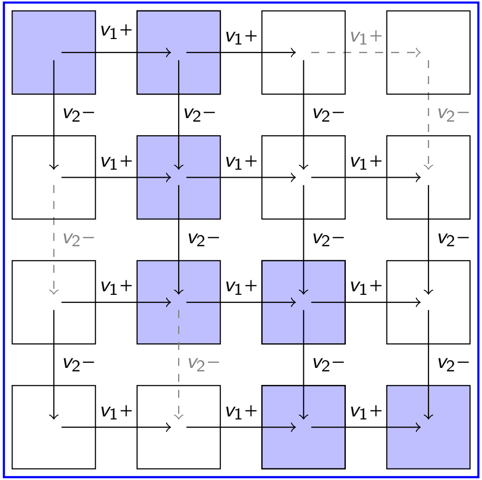

Canonical phase

Hyper-rectangle

Transitions not mathematically feasible

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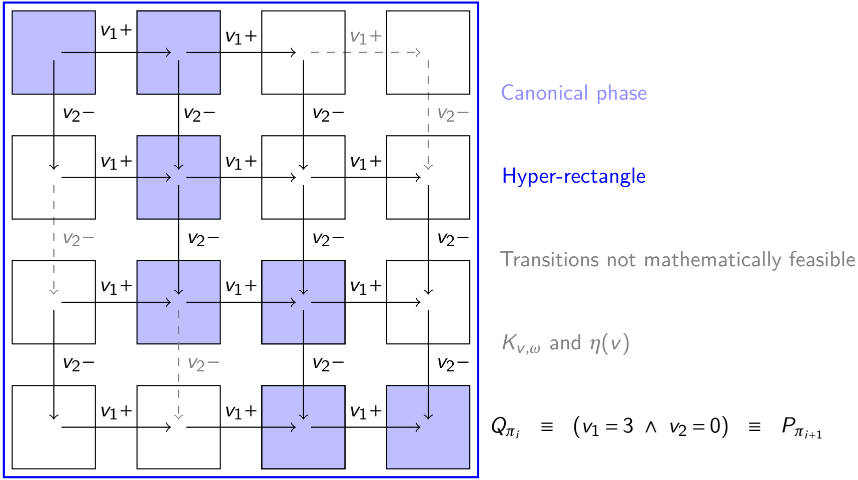

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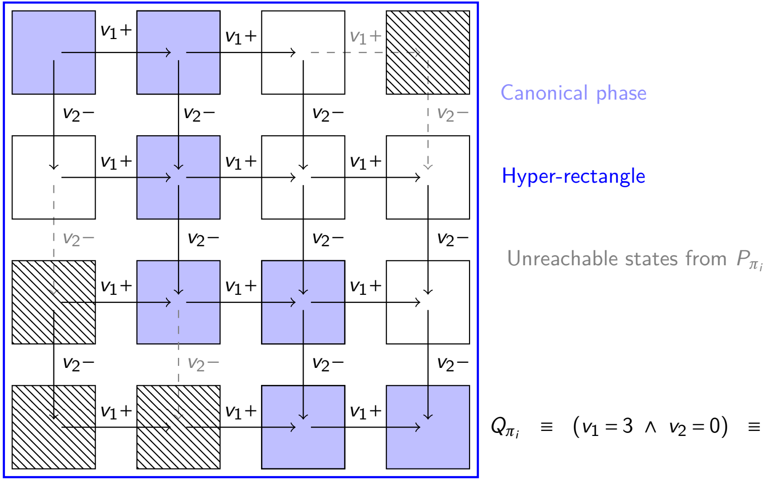

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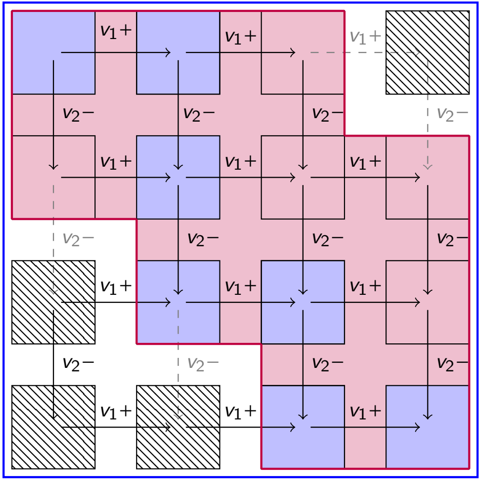

Canonical phase

Hyper-rectangle

Feasible paths and reachable states

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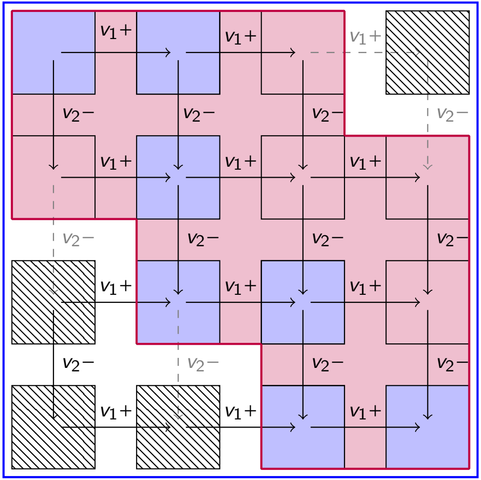
Weakest precondition ($K_{v,\omega}$)



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Feasible hyper-rectangle computation

1. Canonical cell cycle phase $\{P_{\pi_i}\}$ p_{π_i} $\{Q_{\pi_i}\}$:
2. Hyper-rectangle
3. Feasible paths in the hyper-rectangle

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```
isFeasible(EtatI,P,Perm):- permutation(P,Perm), wp(EtatI,Perm).
```

SWI Prolog

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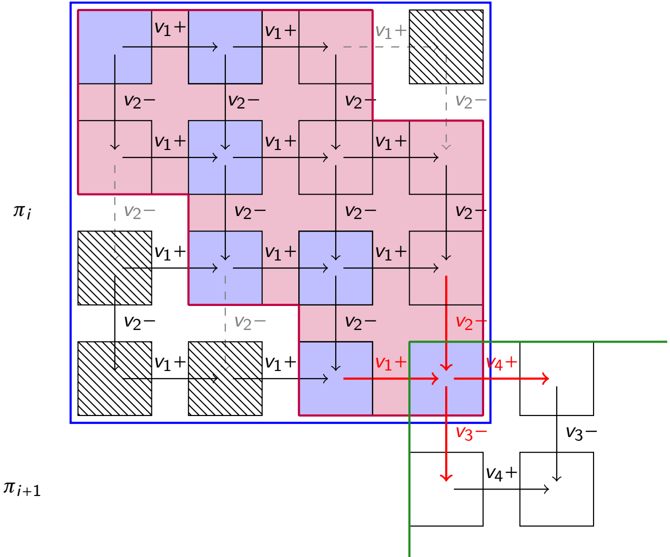
Boyenval et al. 2020, CMSB

Tool paper about TotemBioNet

gitlab.com/totembionet/

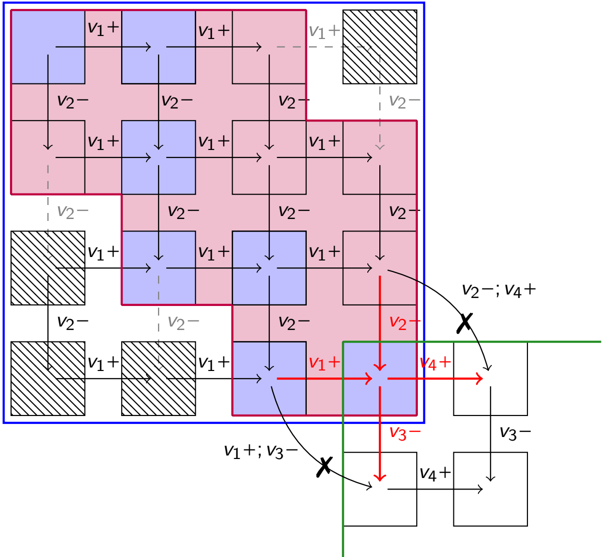
Checkpoint between two adjacent phases



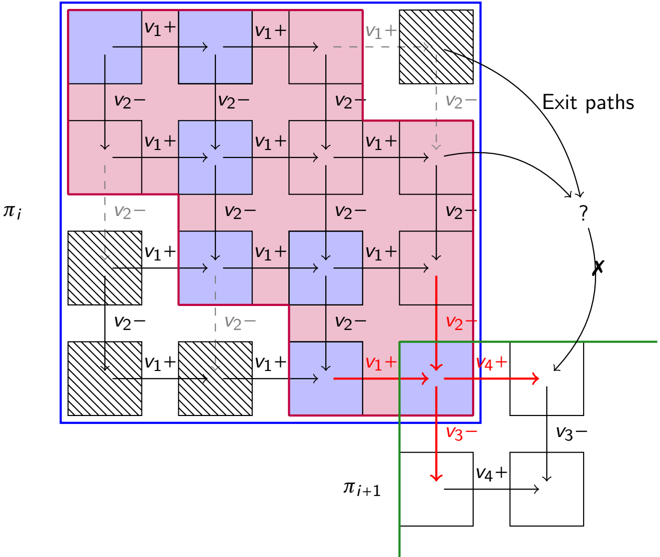
Checkpoint between two adjacent phases

π_i

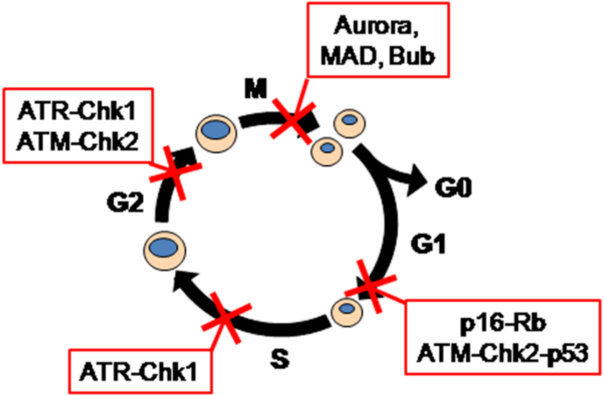
π_{i+1}



Checkpoints in the case of phase exits (outside G1, S, G2, M and G0)



Integration of DNA damage response pathways

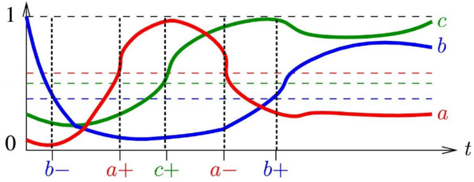


Gabrielli et al. 2012

The genetically modified Hoare logic

A Hoare triple H

- H : {PRE} PATH {POST}
- PRE : a=0, b=1, c=0
- PATH : b-; a+; c+; a-; b+
- POST : a=0, b=1, c=1



Normalized expression or activity profiles of biological species

$$H_{ex}: \quad \{a=0, b=1, c=0\} \quad b- \; ; \; a+ \; ; \; c+ \; ; \; a- \; ; \; b+ \quad \{a=0, b=1, c=1\}$$

↓

Postcondition Q

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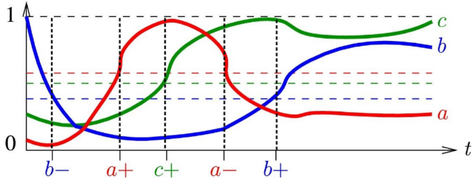

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↓

New postcondition Q_1 :

$$\underline{\mathbf{K_{b,\omega_1}} \geq \mathbf{1}} \wedge a=0 \wedge b=0 \wedge c=1$$

A genetically modified Hoare logic
Bernot et al., 2019

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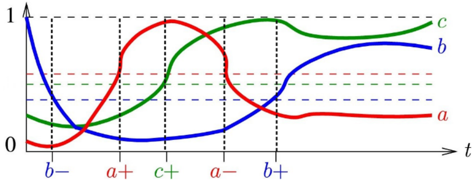

Normalized expression or activity profiles of biological species

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↓

New postcondition Q_2 :

$$\underline{(\mathbf{K_{b,\omega_1}} \geq \mathbf{1}) \wedge (\mathbf{K_{a,\omega_2}} < \mathbf{1})} \wedge a=1 \wedge b=0 \wedge c=1$$

The genetically modified Hoare logic

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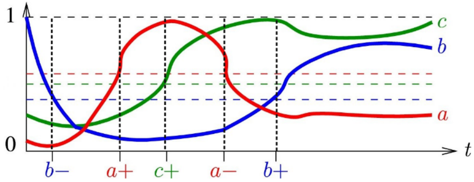

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New postcondition Q_2 :

$$\ldots \qquad \underline{(\mathbf{K}_{\mathbf{b},\omega_1} \geq \mathbf{1}) \wedge (\mathbf{K}_{\mathbf{a},\omega_2} < \mathbf{1})} \wedge a = 1 \wedge b = 0 \wedge c = 1$$

The genetically modified Hoare logic

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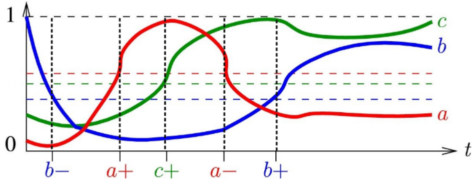

Normalized expression or activity profiles of biological species

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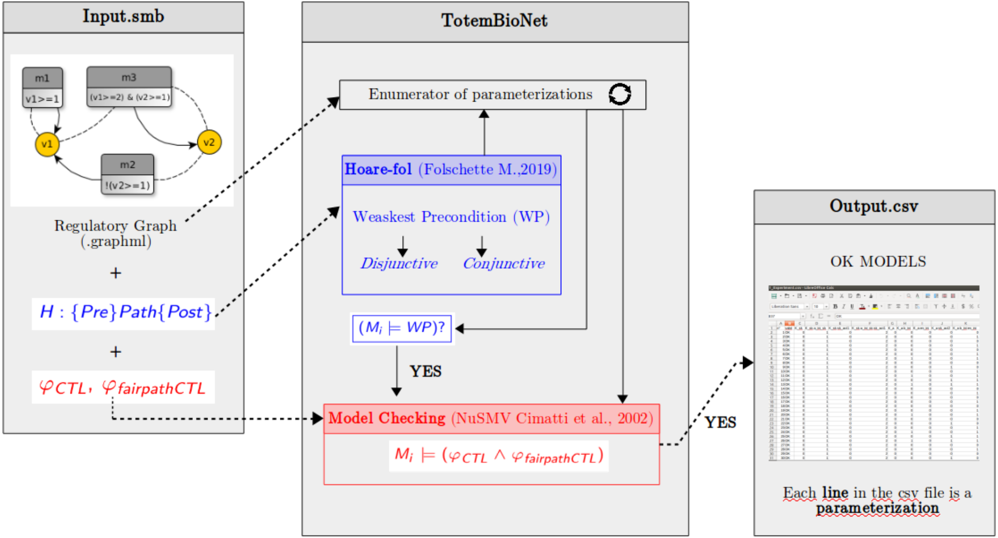
↓

Q_5

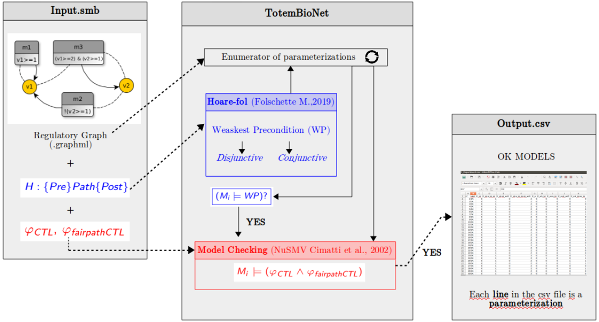
Weakest Precondition (WP)

$$\underline{(\mathbf{K}_{\mathbf{b},\omega_1} \geq \mathbf{1}) \wedge (\mathbf{K}_{\mathbf{a},\omega_2} < \mathbf{1}) \wedge (\mathbf{K}_{\mathbf{c},\omega_3} \geq \mathbf{1}) \wedge (\mathbf{K}_{\mathbf{a},\omega_4} \geq \mathbf{1}) \wedge (\mathbf{K}_{\mathbf{b},\omega_5} < \mathbf{1})} \wedge a=0 \wedge b=1 \wedge c=0$$

TotemBioNet a tool for exhaustive identification of K



TotemBioNet : a tool for exhaustive identification of K



- `https://gitlab.com/totembionet/totembionet`
- Boyenval *et al.*, What is a cell cycle checkpoint ? The TotemBioNet answer, CMSB20.
- `www.i3s.unice.fr/~boyenval/video/CMSB20_DeborahBOYENVAL.flv`