



Exhaustive checking of dynamical properties in multi-valued Biological Regulatory Networks using Answer Set Programming

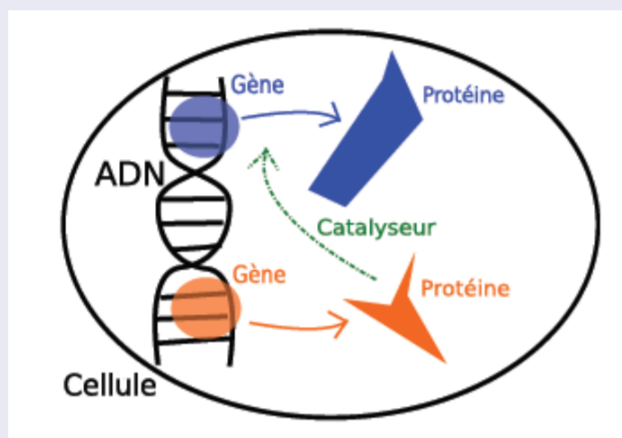
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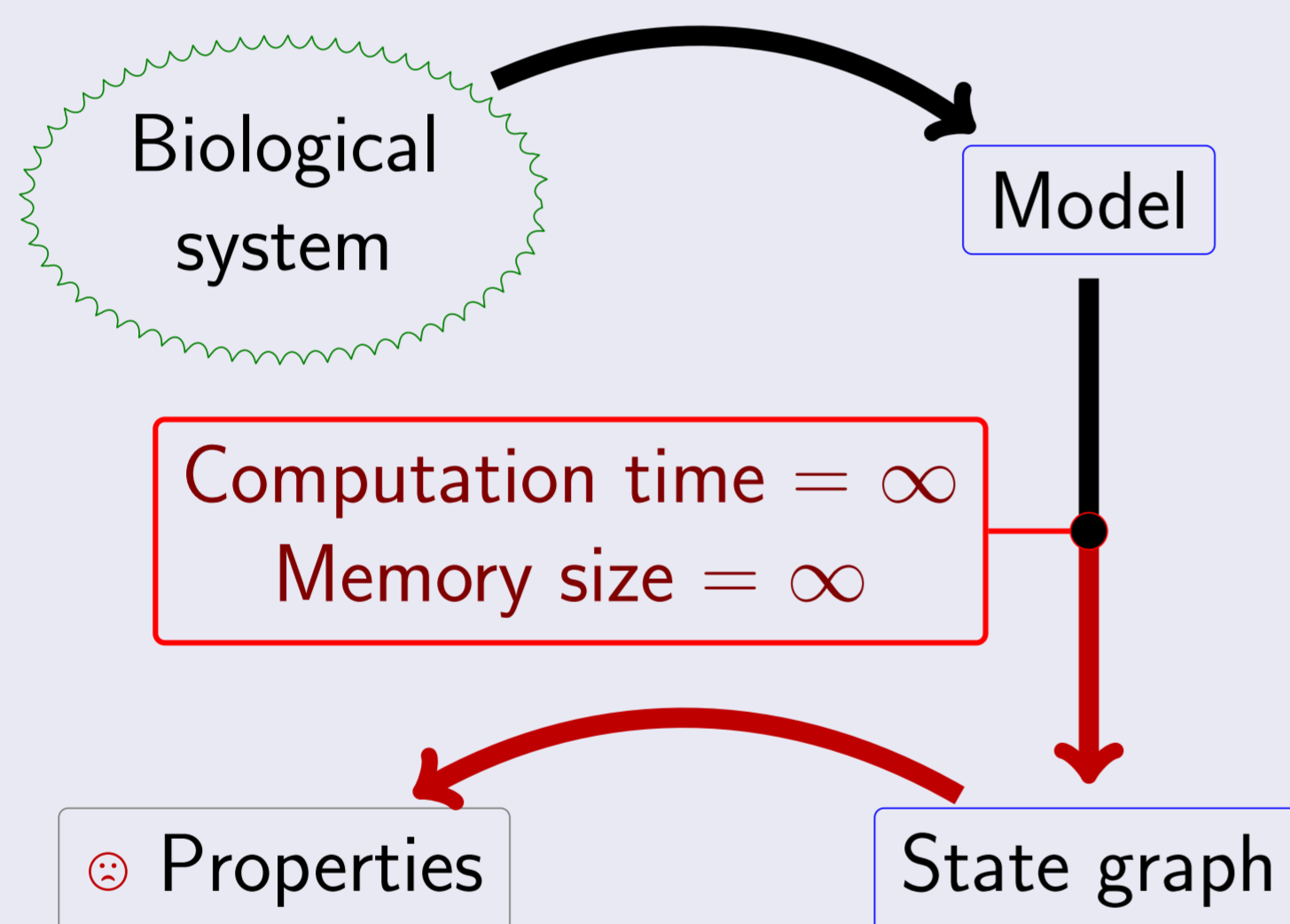
Introduction

- **Systems biology** = studying and understanding of interactions inside biological systems
 - A gene produces a protein
 - Many proteins activate/inhibit other genes
- Biological systems are **very complex**, and studying them is time/CPU consuming



Studying models

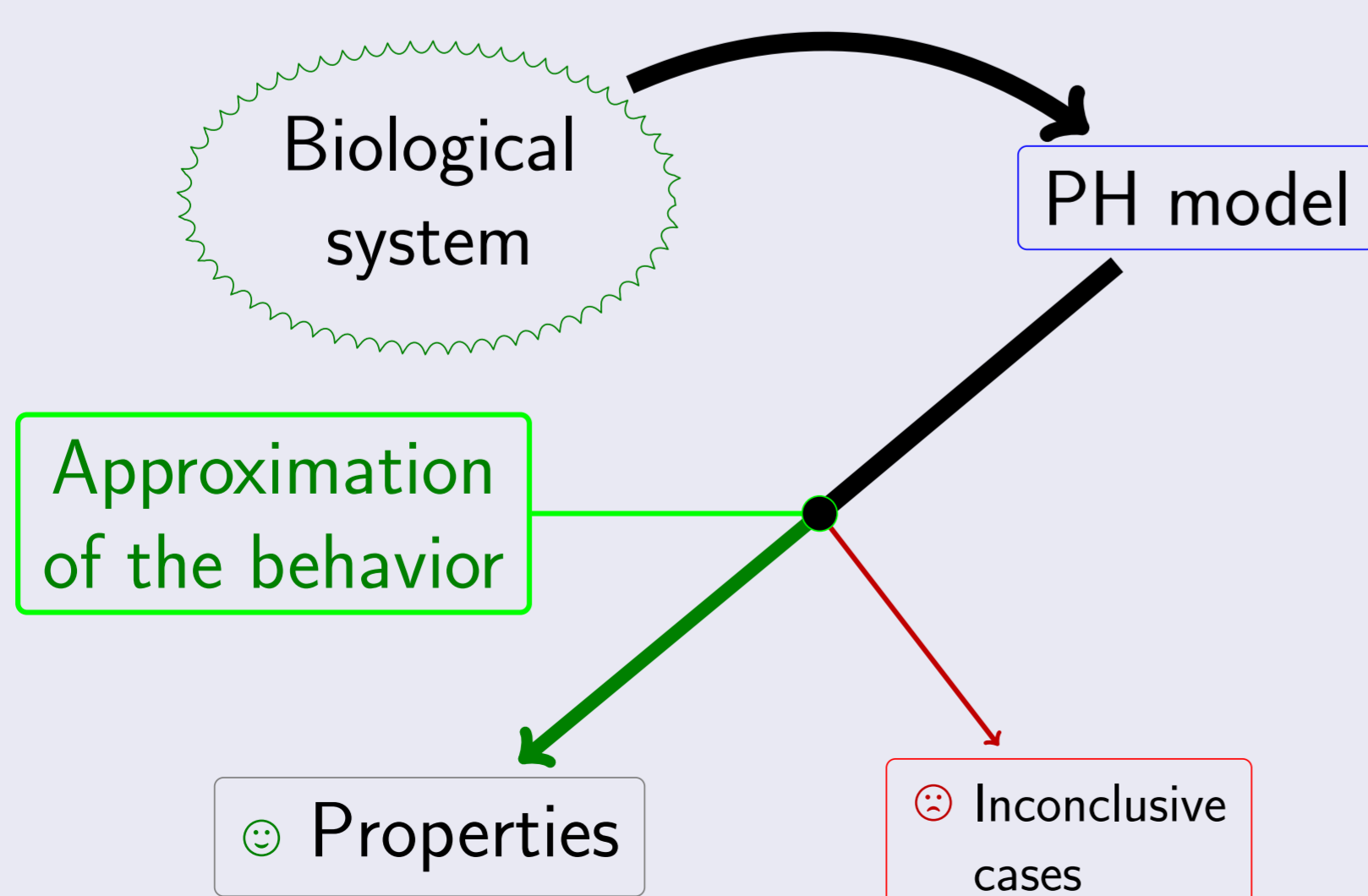
- Models are often **too large to be studied** exhaustively
- Usual model-checkers have to compute all states



The Process Hitting framework

Process Hitting (PH)

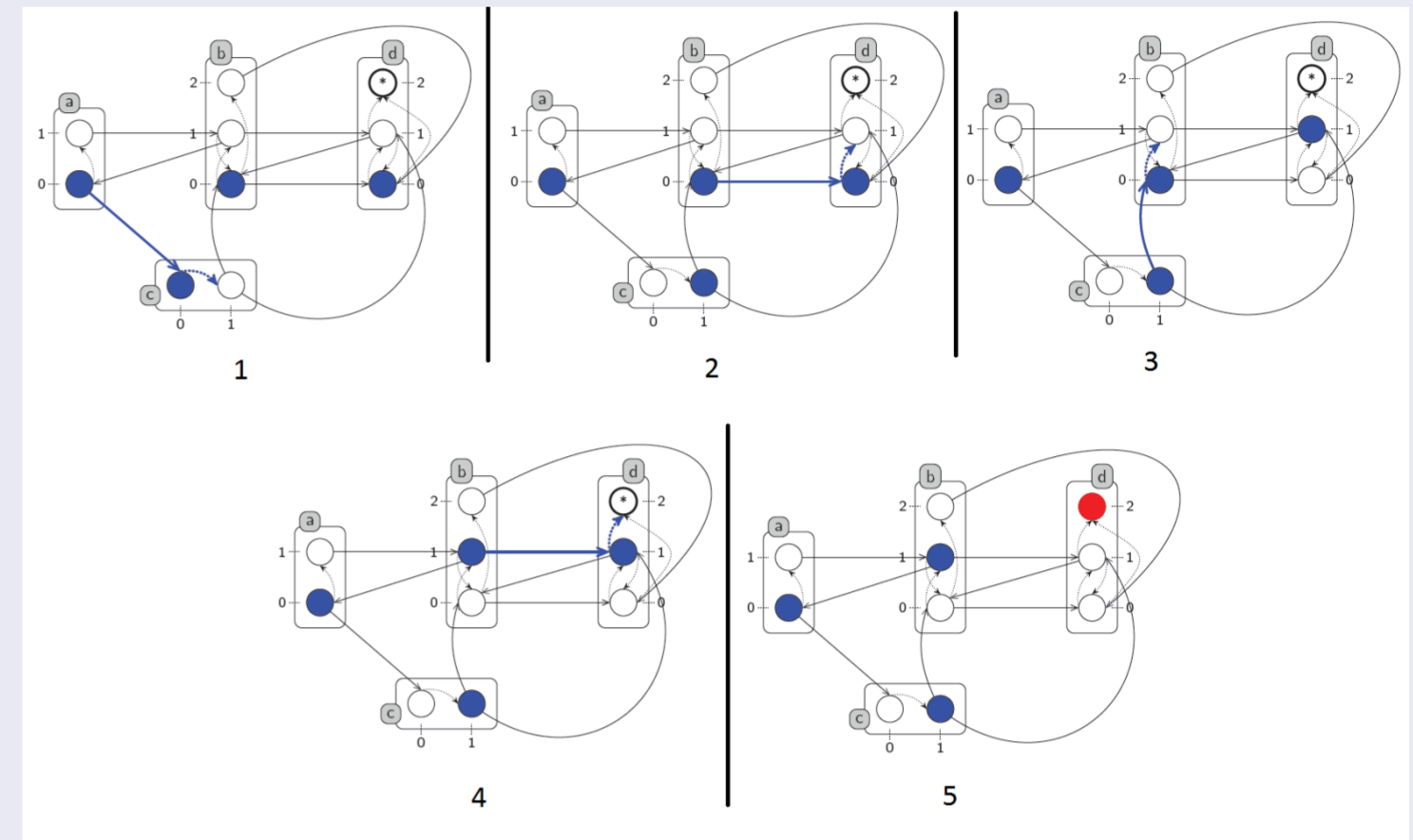
- Recent framework well adapted to large-scale models
- Atomistic representation of actions
- Very efficient **reachability approximations** [1,2]



Analysing key properties w.r.t. Biology

Reachability:

Initial context: $\langle a_0, b_0, c_0, z_0 \rangle$ Objectives: $[\uparrow d_2]$



Fixed Points:

states where no action can be played
 $\langle a_0, b_1, c_1, d_2 \rangle, \langle a_0, b_1, c_1, d_0 \rangle, \langle a_1, b_0, c_0, d_2 \rangle \dots$

Studying PH using Answer Set Programming [3]

Translate PH to ASP:

```
sort(A) . process(A,I) . action(A,I,B,J,K) .
```

Dynamic behaviour:

```
2{activeFromTo(B,J,K,T)} ← playableAction(A,I,B,J,K,T),
    instate(activeProcess(A,I),T), instate(activeProcess(B,J),T),
    J!=K, time(T) .
```

Reachability verification:

```
reached(F,T) ← goal(F), instate(F,T) .
getNbreGoals(X) ← X={ goal(.) } .
reachedAllGoals(T) ← X={reached(F,T):goal(F)},
    getNbreGoals(Y),X=Y,time(T) .
← reachedAllGoals(T) .
```

Fixed point identification:

```
1 selectedProcess(A,I) : shownProcess(A,I) 1 ← sort(A) .
← hit(A,I,B,J), selectedProcess(A, I), selectedProcess(B, J), A != B .
```

Results and Benchmarks

- Compare performances with existing methods:
- Efficient results on large models (up to 50 genes)

System	Model specifications		Fixed points		Reachability $\Delta t(s)$		
	Genes	States	$\Delta t(s)$	# results	Pint[1]	GinSim[4]	ASP-PH
ttr	20	2^{19}	0.004	0	0.97	2.05	1.90
erbb	42	2^{70}	0.017	3	Inconc	151.64	5.02
tcr	54	2^{73}	0.021	1	Inconc	-	95.08

Work in progress

- Identification of attractors
- Add delays for actions : towards timed PH
- Infer PH models from time series data