

Modelling Biological Systems with Boolean Networks

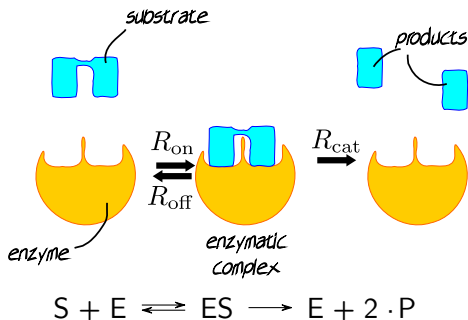


Athénaïs Vaginay, Taha Boukhobza, Malika Smail-Tabbone

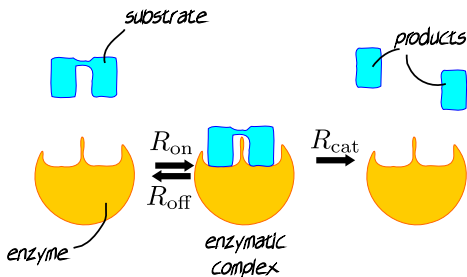
November 18, 2021



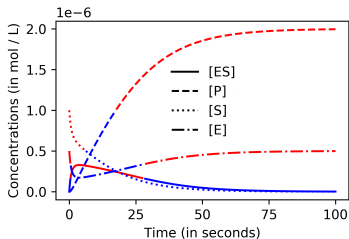
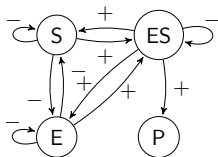
Modelling of biological systems — Example: enzymatic reaction



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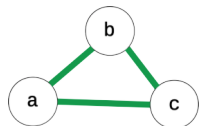


constraints: known structure (= domain) and dynamics (= to reproduce)



Many formalisms exist \leadsto Ulysse Herbarch's presentation

Statistical
based on
correlations,
undirectional

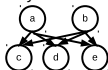


Mechanistic
based on the processes, directional

Boolean network



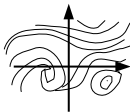
Bayesian network



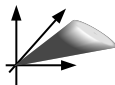
Process algebras

$((b(x, de)[E]) \parallel (B(y, dI)[I]))$
 $bh(x, dE) bh(y, dI) (E \parallel I)$

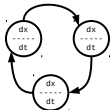
Differential equation



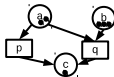
Constraint based model



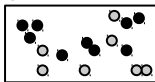
Hybrid systems



Petri Nets



Agent-based model



Cellular automata



Interacting state machine

Compartment based

Rule based

...

Boolean (automata) Networks (BNs)

a set of n components (= automata)

Boolean status $\mathbb{B} = \{0; 1\}$

n local update functions $f_X : \mathbb{B}^n \rightarrow \mathbb{B}$

\neg : “not”; \vee : “or”; \wedge : “and”



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Boolean network

$$\mathcal{B} = \begin{cases} f_E := \neg E \\ f_{ES} := E \wedge S \\ f_P := ES \wedge (\neg E \vee P) \\ f_S := \neg E \end{cases}$$

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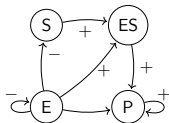
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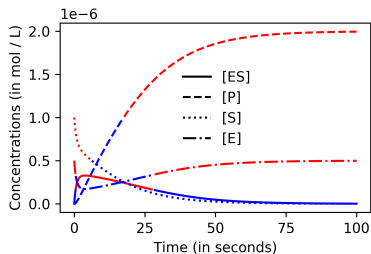
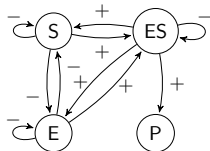
Boolean network, its interaction graph
= structure

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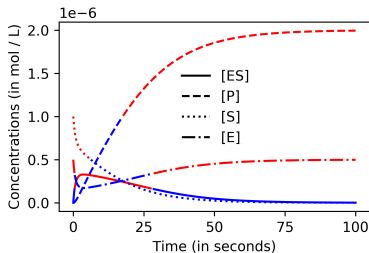
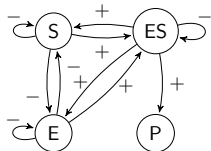
Boolean Networks Synthesis

constraints: known structure (= domain) and dynamics (= to reproduce)



Boolean Networks Synthesis

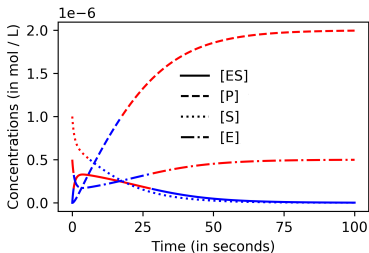
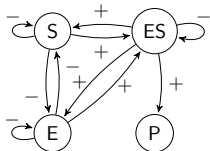
constraints: known structure (= domain) and dynamics (= to reproduce)



output: (exhaustive set of) BNs compatible with the constraints

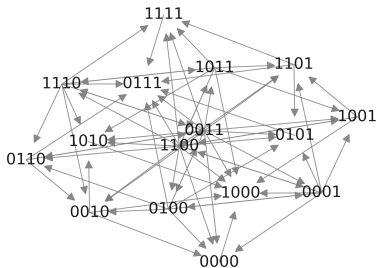
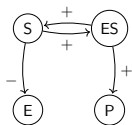
Boolean Networks Synthesis

constraints: known structure (= domain) and dynamics (= to reproduce)



output: (exhaustive set of) BNs compatible with the constraints

$$\mathcal{B}_1 = \begin{cases} f_{ES} := S \\ f_P := ES \\ f_S := ES \\ f_E := \neg S \end{cases}$$



And then what?

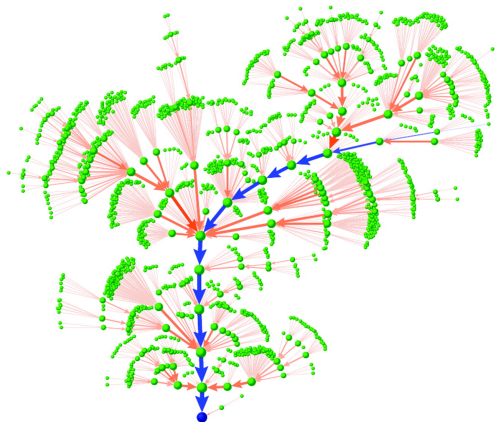
Analysis on Boolean networks (even large ones !)

- ▶ reachability, attractors
- ▶ control
- ▶ ...

Despite their simplicity, BNs can fit complex biological phenomena: cell cycle, cancer (breast, bladder, ...), ...

Trajectory and attractors — example of biology mapping

Attractors often map to relevant biological properties (physiological state, cellular types, ...).



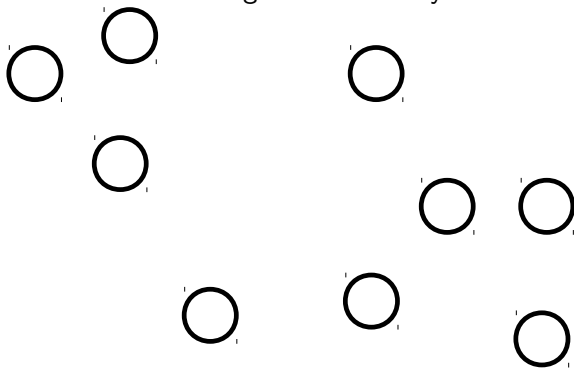
Dynamical trajectories of the 1,764 protein states (green nodes) flowing to the G1 fixed point (blue node). Arrows between states indicate the direction of dynamic flow from one state to another. The cell-cycle sequence is coloured in blue. The size of a node and the thickness of an arrow are proportional to the logarithm of the traffic flow passing through them.

→ the model fits biology

From “The yeast cell-cycle network is robustly designed.” Li et al. 2004

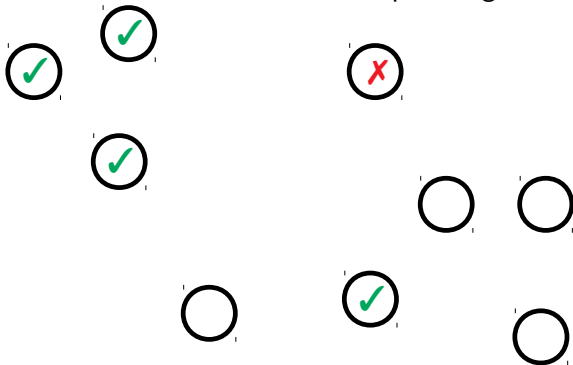
BN control

Possible configurations of a system



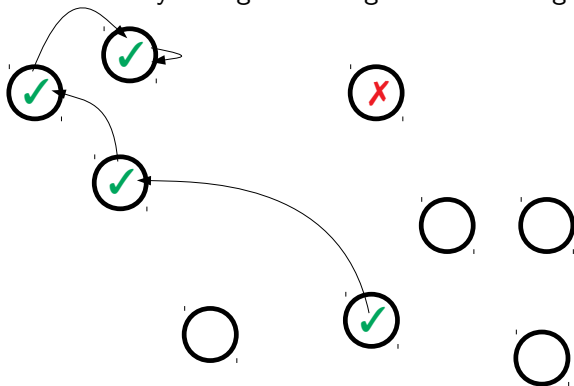
BN control

some are “normal”, some are “pathological”



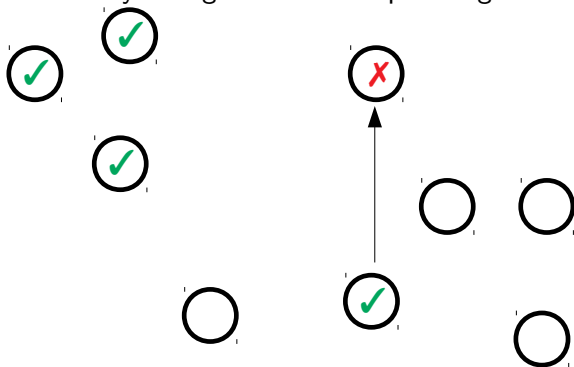
BN control

behaviour of a **sane** system goes through normal configurations...



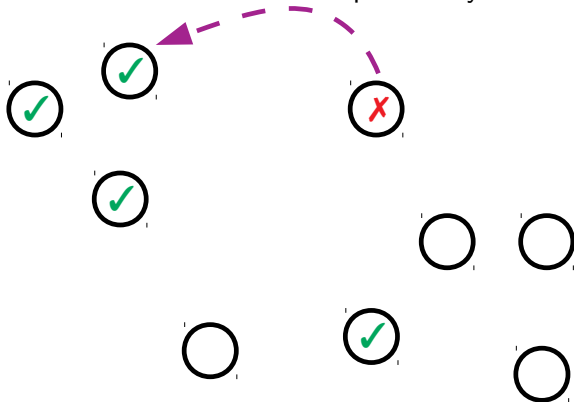
BN control

... while a **broken** system gets stuck in a pathological configuration



BN control

Which interventions can repair the system?



Ongoing project — Context (unpublished results)

collaborators from CRAN:

Hélène Dubois-Pot-Schneider, Hélène Dumond, Alex Hirtz and Nolwenn Lebourdais

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- ▶ Glioblastoma (GBM) affects men twice as much as woman

Ongoing project — Context (unpublished results)

collaborators from CRAN:

Hélène Dubois-Pot-Schneider, Hélène Dumond, Alex Hirtz and Nolwenn Lebourdais

- ▶ Glioblastoma (GBM) affects men twice as much as woman
- ▶ G-Protein-Coupled Estrogen Receptor (GPER) correlated to survival of GBM patients

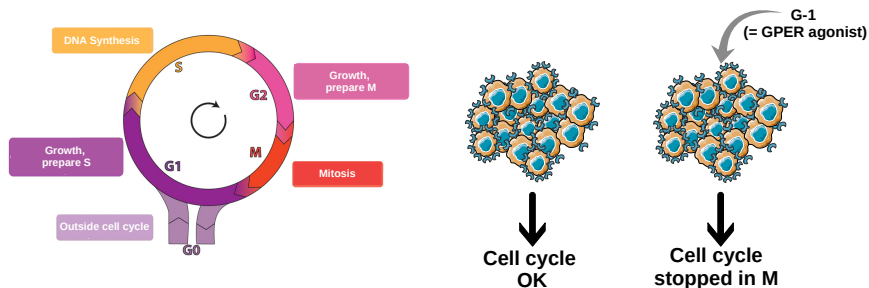


low GPER
→ less survival



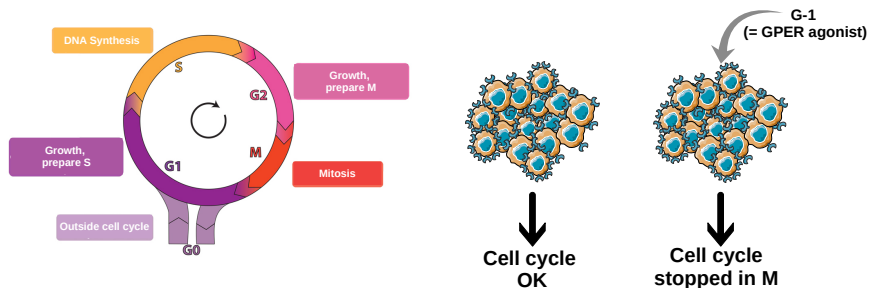
high GPER
→ better survival

Ongoing project — Context (unpublished results)



G-1 (= GPER agonist) blocks GBM cell proliferation in M phase

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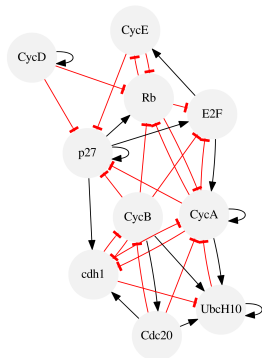


G-1 (= GPER agonist) blocks GBM cell proliferation in M phase

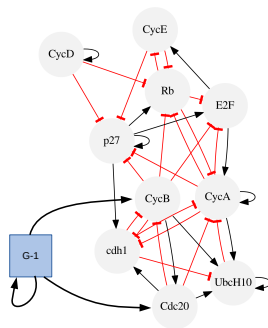
Can we model this with Boolean networks?

Ongoing project — Boolean network

Extension of an existing BN modelling mammals cell cycle¹
original model:



our current model:



¹[Fauré et al. 2006]

Ongoing project — BN dynamics and predictions

Does our BN reproduce biologists observations?

Analysis of the synchronous STG = $2^{11} = 2048$ nodes and edges

- ▶ dynamics without G-1, with CycD: no perturbation of the cell cycle compared to the original model ✓
- ▶ dynamics with G-1, with CycD: cell cycle blocked ✓
- ▶ other checks need to be done. . .

Once all the checks will be passed:

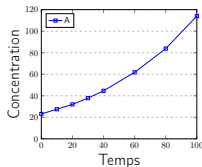
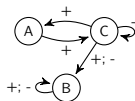
Can our BN make useful predictions?

Conclusion

Boolean networks:

- ▶ simple, yet powerful formalism to study biological processes
- ▶ simple to set up: their construction requires very few data compared to other formalisms
- ▶ once built, one can run prediction analysis, control, etc. . .

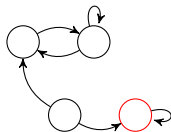
Structural & dynamical constraints



Boolean Networks(BN)

$$\begin{cases} f_A := C \\ f_B := B \oplus C \\ f_C := A \wedge \neg C \end{cases}$$

Control



Thanks for your attention.

Any questions?

athenais.vaginay@loria.fr

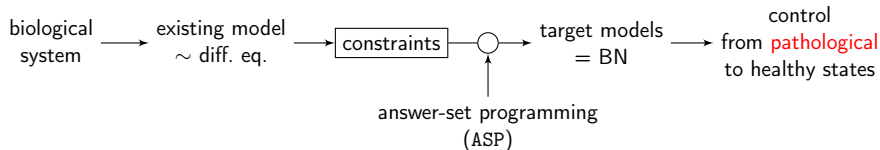
Enjoy the FCH day!

Our collaborators:

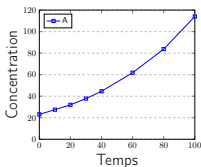
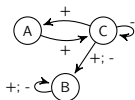
Hélène Dubois-Pot-Schneider, Hélène Dumond, Alex Hirtz and
Nolwenn Lebourdais

I used some Servier Medical Art in this presentation

“Selection and analysis of models for biology using knowledge on the domain; application to pathological systems.”



Structural & dynamical constraints



Boolean Networks (BN)

$$\begin{cases} f_A := C \\ f_B := B \oplus C \\ f_C := A \wedge \neg C \end{cases}$$

Control

