

Introduction to Boolean modelling for biological systems

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Basic concepts and theory

- Computational systems biology methods have widely employed dynamic models to describe the biological functions from the dynamic system point of view.
- **Keywords:** system / dynamic



What is the advantage of adding a dynamic layer?

provide quantitative/qualitative descriptions of the network

predict the behavior of the network under different conditions, i.e., gene knockout, treatment with an external agent, etc.

Biological functions: Dynamic!

A biological function must be considered as a dynamic process

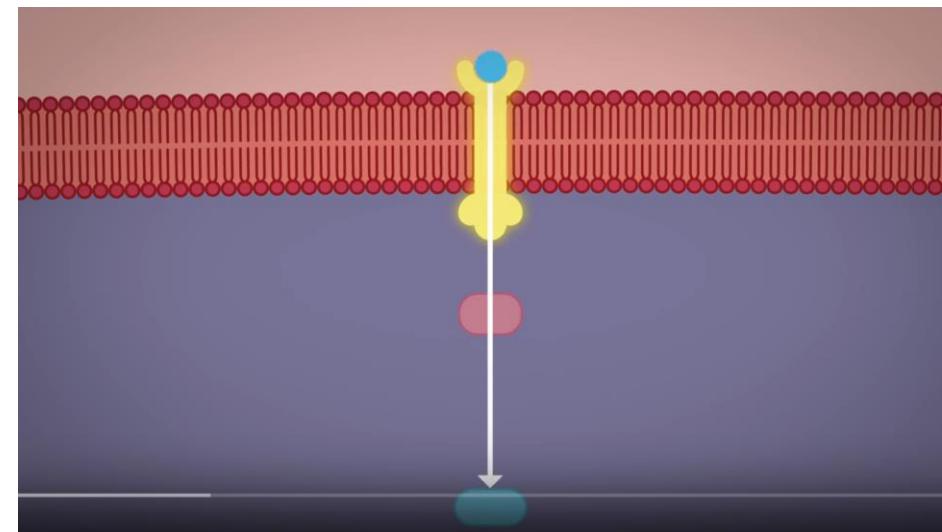
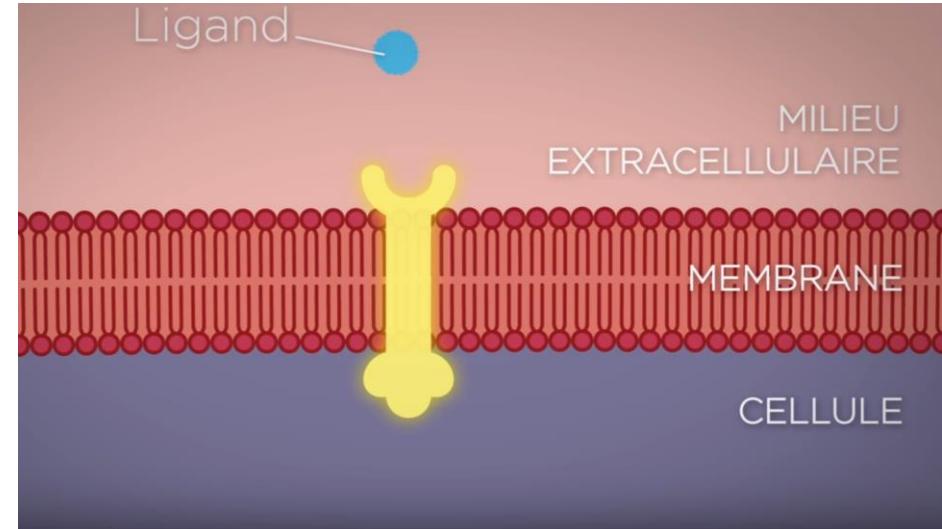
Within a cell, all the elements vary over time (energy production, respiration, formation of complexes, etc.)

For our explorations: A cell frozen in time t

After or before: Definitely different function!

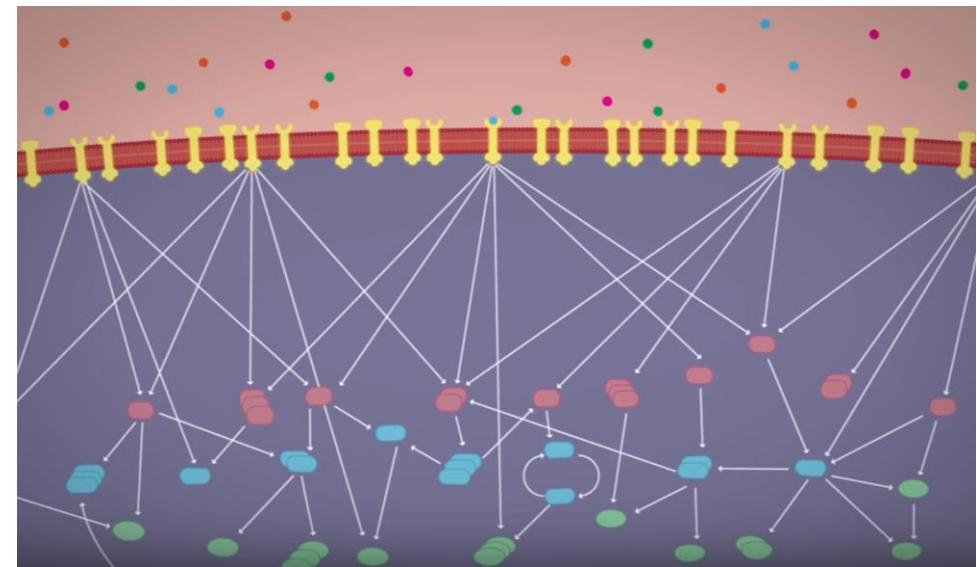
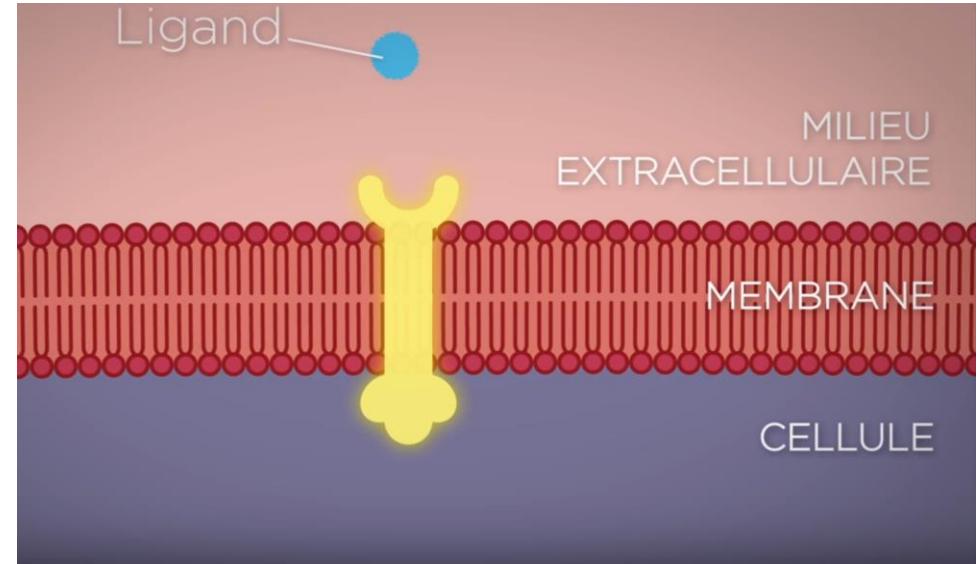
Many different layers

- Cellular functions involve multiple layers/ levels in the cell
- Functions cannot be defined independently of the context in which they operate



Several causes and consequences (effects)

- Several causes and several consequences coexist at the same time within the cell
- In the context of cellular interactions, it is impossible to associate a single cause with each consequence and a single consequence with each cause



MILIEU EXTRACELLULAIRE

MEMBRANE

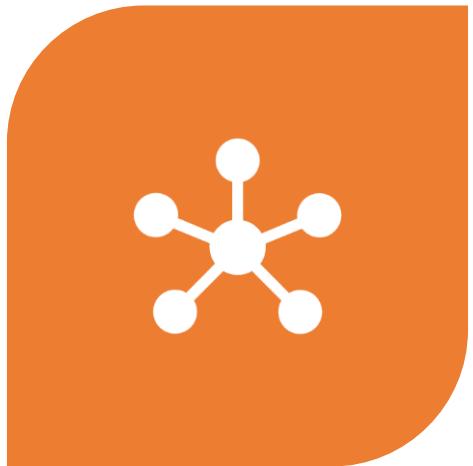
CYTOPLASME

NOYAU

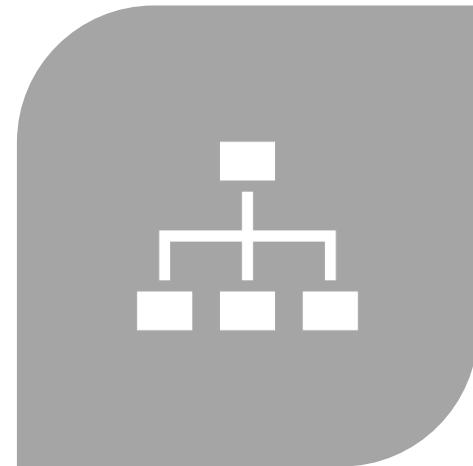
Interactions!

- Information flows in a multidirectional manner
- Cellular actors only exist in interaction

Cellular context: complex!



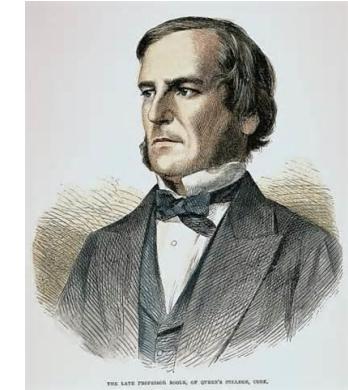
COMPLEXITY OF CELLULAR
CONTEXT:



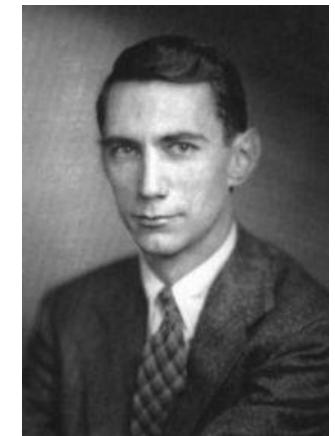
ADOPT A DYNAMIC, SYSTEMS
POINT OF VIEW TO ADDRESS IT

Boolean Algebra

- Boolean Algebra is a mathematical system for formulating logical statements with appropriate symbols, so that logical problems can be solved algebraically (in a manner similar to ordinary algebra).
- Boolean Algebra is introduced by an English mathematician, George Boole (1815-1864).
- The widespread use of Boolean Algebra is initiated by an American mathematician, Claude Shannon (1916-2001).
- He is credited with founding both digital computer and digital circuit design theory.



• George Boole



• Claude Shannon

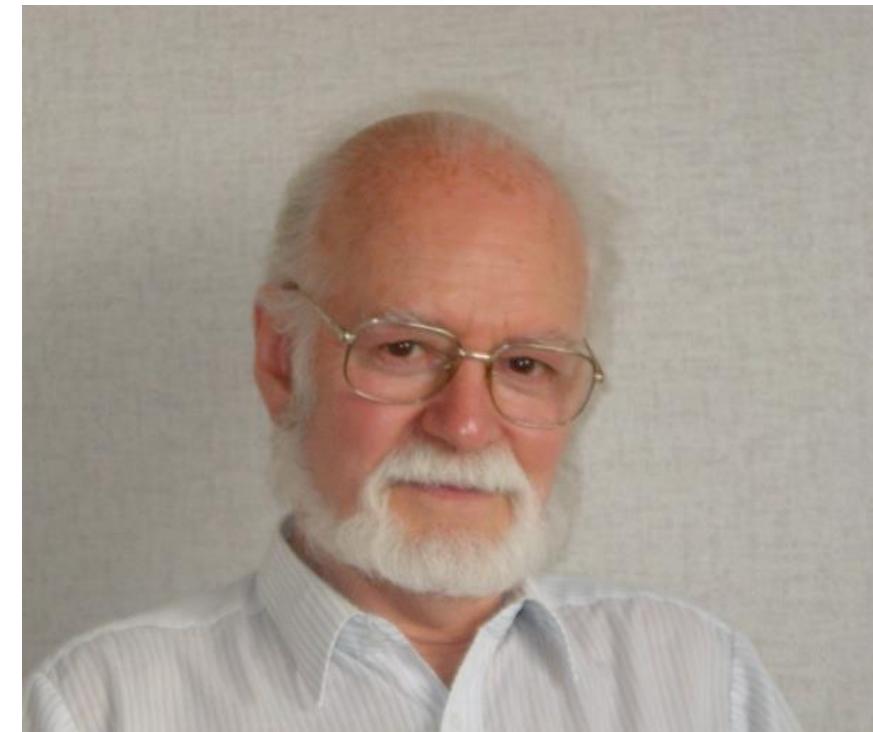
Boolean Algebra

- The variables in Boolean Algebra are the truth values of True (1) and False (0).
- The main operations of Boolean Algebra are :
 - The conjunction (**and**)
 - The disjunction (**or**)
 - The negation (**not**)



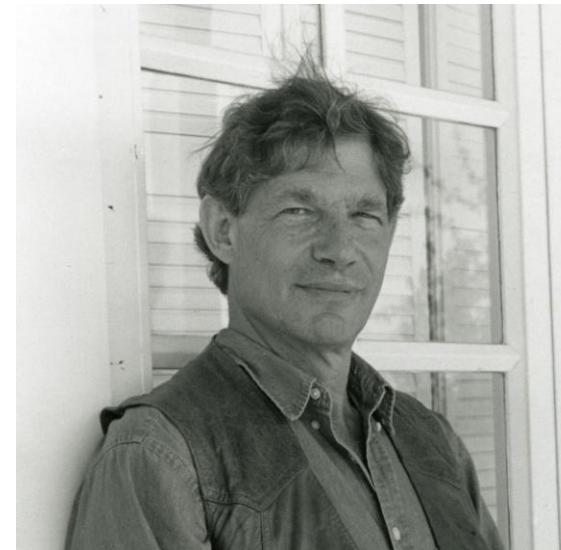
Boolean algebra for modelling regulatory networks

The experimental advances in the large-scale mapping of regulatory networks are fairly recent, but modeling efforts date back to the end of 1960s. Pioneering work of Stuart Kauffman and Rene Thomas.



In the absence of experimental results, Stuart Kauffman considered an idealized representation of a typical gene network

He assumed that genes are equivalent, and their interactions form a directed graph in which each gene receives inputs from a fixed number K of randomly selected neighbors.



Focus on asymptotic behaviour

Two types of attractors: stable states or simple cycles

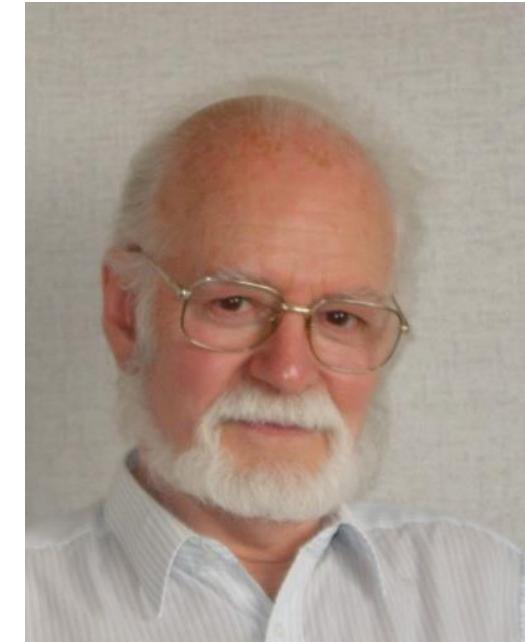
Deterministic behaviour (only one possible following state)
=> Synchronous strategy

How does this work?

- The state of genes is described by binary (ON/OFF : 1/0) variables at a time point (t), and the dynamic behavior of each variable, that is, whether it will be ON (=1) or OFF (=0) at next moment ($t+1$), is governed by a Boolean function.
- A Boolean or logical function is written using the logical operators “and”, “or” and “not” to describe regulation.

Logical description of transcriptional regulation

René Thomas developed a detailed logical description of the mechanisms governing transcriptional regulation, including the effects of DNA domains such as promoters, initiators, terminators, and the concepts of genetic dominance and recessivity



Regulatory circuits: positive and negative

Non-deterministic behaviour
(more than one possibility following state)
=> Asynchronous strategy

Feedback loops and multivariate variables

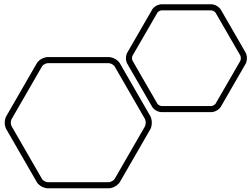
This formalism was later refined to include multilevel variables and used to study feedback loops, i.e. circular chains of interaction.



These loops can be classified into two categories based on the number of negative (inhibitory) interactions in the loop:

if this number is even,
the loop is positive,
and if the number of

negative interactions is
odd, the loop is a
negative feedback loop.



Associating feedback loops with dynamic behaviour and biological functions

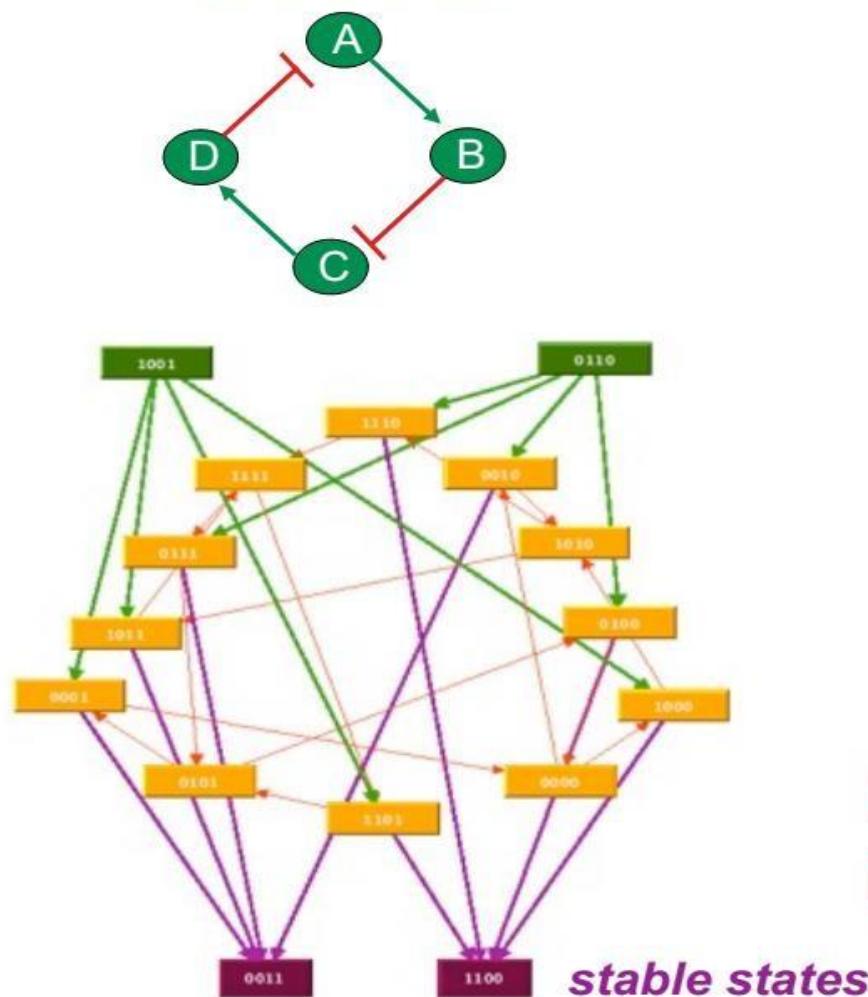
Thomas found that a positive feedback loop is a necessary condition for the existence of multiple steady states, while a negative feedback loop with two or more elements is a necessary condition for stable limit cycles .



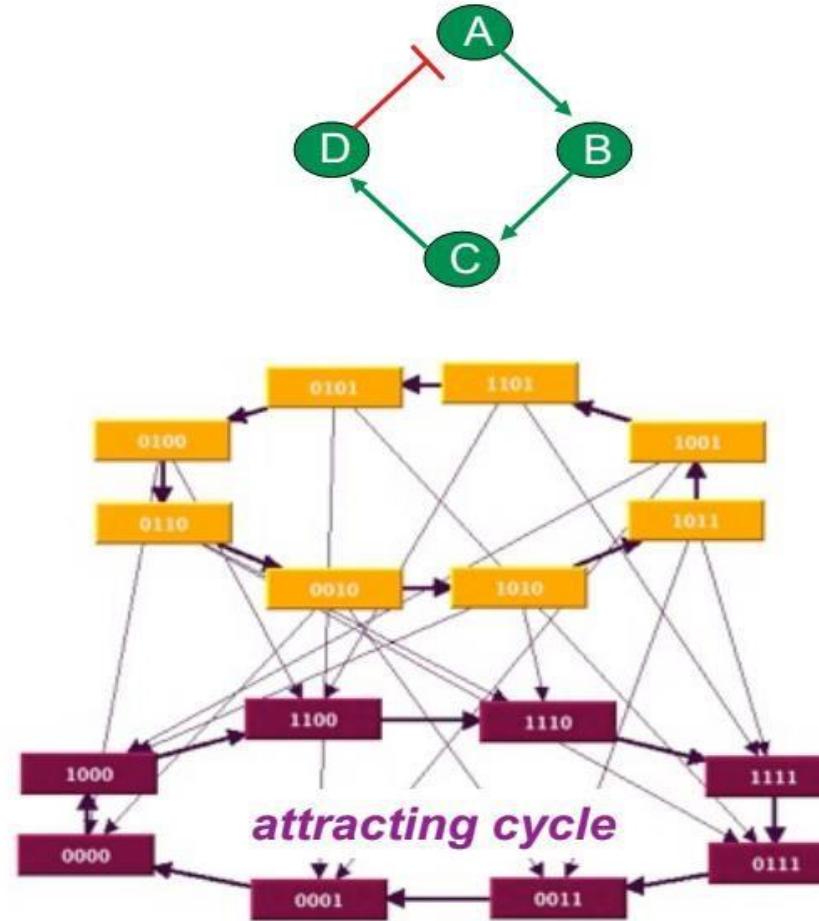
Biologically this means that cell differentiation is based on positive feedback loops, and homeostasis (stability to small perturbations) is based on negative feedback loops.

Regulatory circuits: dynamics in isolation

Positive circuit



Negative circuit





Important relevant readings

Regulatory circuits & Thomas' rules

- A positive regulatory circuit is necessary to generate multiple stable states or attractors
- A negative regulatory circuit is necessary to generate sustained oscillatory behaviour
- Thomas R (1988). *Springer Series in Synergics* **9**: 180-93.

Mathematical theorems and demonstrations:

- In the differential framework:
 - Thomas (+, 1994), Plathe *et al.* (\pm , 1995), Snoussi (\pm , 1998), Gouzé (\pm , 1998), Cinquin & Demongeot (+, 2002), Soulé (+, 2003).
- In the discrete framework:
 - Aracena *et al.* (+, 2001), Remy *et al.* (\pm , 2005), Richard & Comet (+, 2005).

When to use logical modelling?

- There is no quantitative information about the processes (rates of reaction, association/dissociation constants, quantities, etc.)
- The details of some interactions are unknown
- The biological question is qualitative (e.g. how does a cell chooses from a survival or an apoptotic phenotype?)



Discrete models: Boolean networks

Boolean networks have been widely used in modeling gene regulation

Switch-like behaviour of gene regulation resembles logic circuit behaviour

Conceptually easy framework: models easy to interpret

Boolean networks extend naturally to dynamic modeling

Boolean network modeling

- Boolean: either true or false (1 or 0)
- Binarization
 - reduces the noise in biological data
 - captures the dynamic behavior in complex systems
 - need a threshold value
 - leads to loss of information
- Biological entities are modeled as switch like dynamic elements
 - either on or off

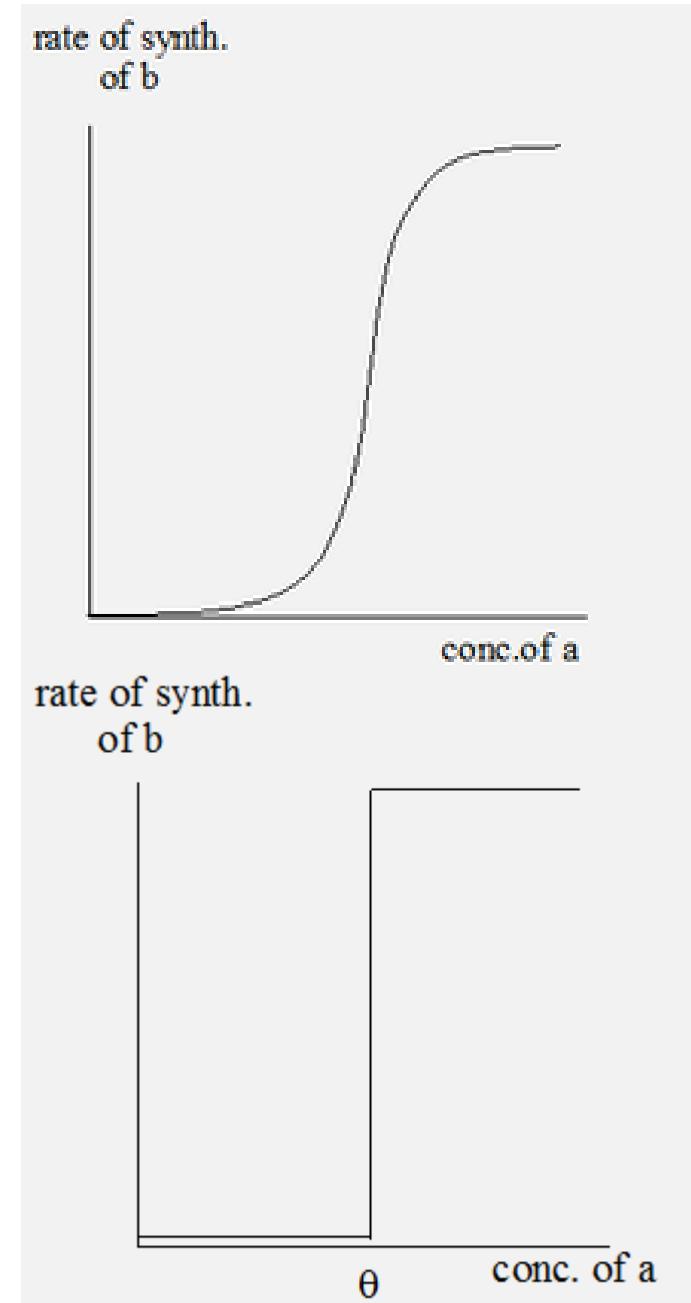
Boolean networks

A Boolean network $G(V, F)$
contains

- Nodes $V = \{x_1, \dots, x_n\}$, $x_i = 0$ or $x_i = 1$
- Boolean functions
 $F = \{f_1, \dots, f_n\}$
- Boolean function f_i is assigned to node x_i
- Dynamic behaviour can be simulated
- State of a variable x_i at time $t+1$ is calculated by function f_i with input variables at time t

Logical Variable and Functions

- Logical variables are associated with the elements of the system to describe the state of the system.
- They consist of the logical values. For example, a system whose state is appropriately described by the levels of substances a, b, and c, each of which can be absent, present at low level, or present at high level are represented by logical values 0, 1, and 2 respectively.
- If a product a acts to stimulate the production of b, it is a positive regulator. In this case, the rate of synthesis of b increases with increasing concentration of a, and makes a curve similar to that shown in figure A.
- There is little effect of a, until it reaches a threshold concentration θ , and at higher concentrations a plateau is reached which shows the maximal rate of synthesis of b.
- Such a nonlinear, bounded curve is called a sigmoid.
- It can be suggested that a is "absent" for $a < \theta$ and "present" for $a > \theta$. The sigmoid curve can be approximated by the step function, as in figure B.



Example of Boolean network dynamics

- Consider a Boolean network with 3 variables x_1 , x_2 and x_3 and functions given by
 - $x_1 := x_2 \text{ and } x_3$
 - $x_2 := \text{not } x_3$
 - $x_3 := x_1 \text{ or } x_2$

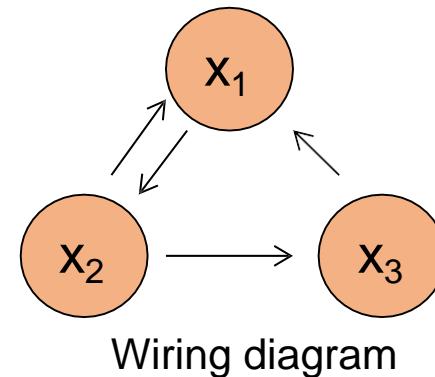
t	x1	x2	x3
0	0	0	0
1	0	1	0
2	0	1	1
3	1	0	1
4	0	0	0
		...	

Example Graph (G) with 3 genes

$G(V, F)$,

$$V = \{x_1, x_2, x_3\}$$

$$F = \{f_1 = x_2 \& x_3, f_2 = x_1, f_3 = x_2\}$$



Input (t-1)			Output(t)		
0	0	0			
0	0	1			
0	1	0			
0	1	1			
1	0	0			
1	0	1			
1	1	0			
1	1	1			

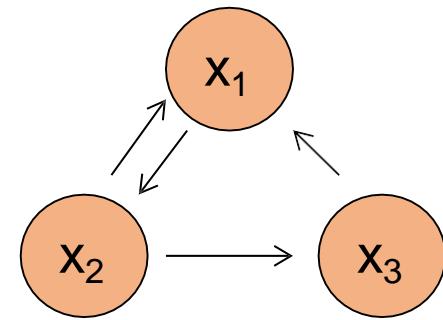
Truth table

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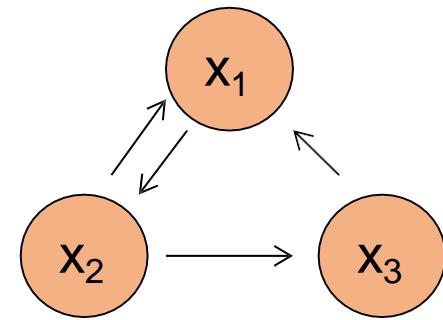
Input (t-1)			Output(t)		
0	0	0	0		
0	0	1			
0	1	0			
0	1	1			
1	0	0			
1	0	1			
1	1	0			
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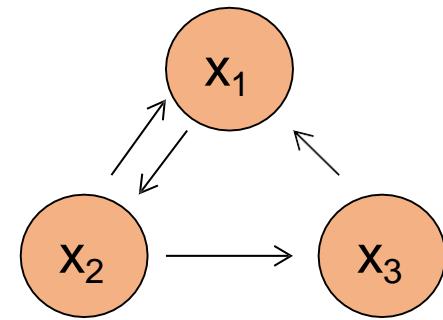
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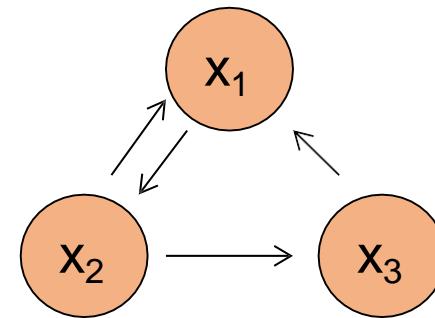
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0	0	1			
0	1	0			
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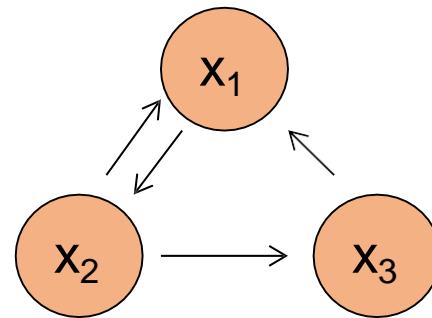
Input (t-1)			Output(t)		
0	0	0	0	0	0
0	0	1	0	0	0
0	1	0	0	0	1
0	1	1	1	0	1
1	0	0	0	1	0
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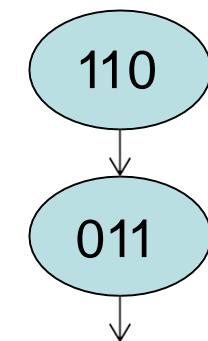
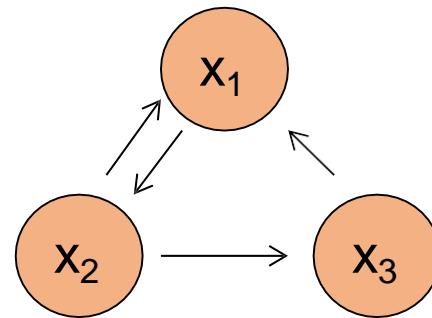
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0	0	1	0	0	0
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0	1	1	1	0	1
1	0	0	0	1	0
1	0	1	0	1	0
1	1	0	0	1	1
1	1	1	1	1	1

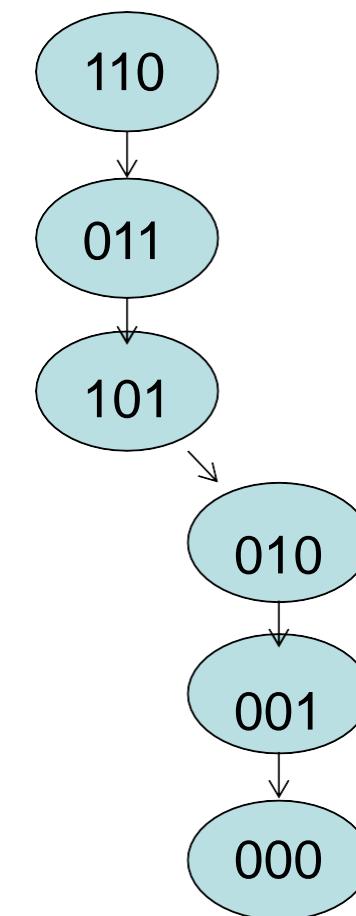
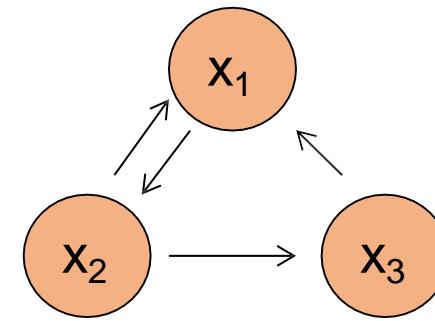
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0	1	0	0	0	1
0	1	1	1	0	1
1	0	0	0	1	0
1	0	1	0	1	0
1	1	0	0	1	1
1	1	1	1	1	1



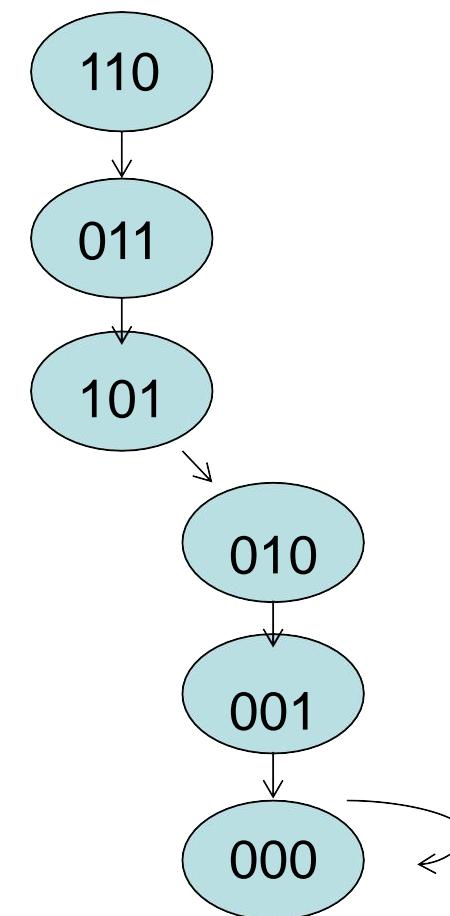
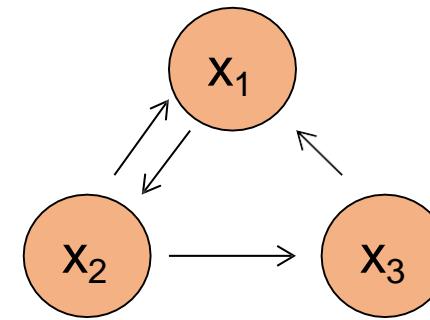
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Input (t-1)			Output(t)		
0	0	0	0	0	0
0	0	1	0	0	0
0	1	0	0	0	1
0	1	1	1	0	1
1	0	0	0	1	0
1	0	1	0	1	0
1	1	0	0	1	1
1	1	1	1	1	1



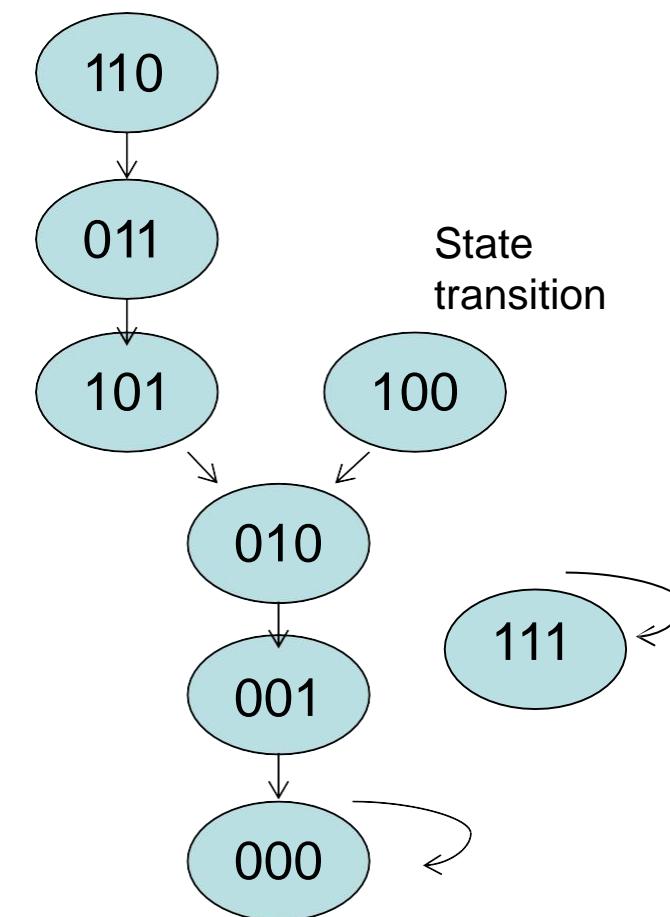
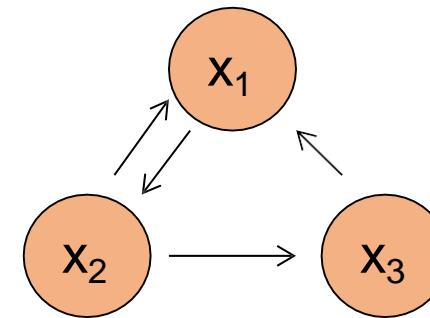
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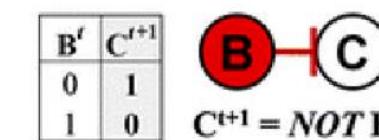
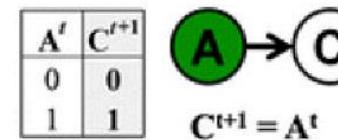
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0	1	1	1	0	1
1	0	0	0	1	0
1	0	1	0	1	0
1	1	0	0	1	1
1	1	1	1	1	1



Logic -based models

- Form of mathematical model governed by logic operators (AND, OR, NOT).
- Parameter free.
- Suitable for modeling gene regulatory networks.
- *In silico* simulations, qualitative predictions.
- Each node in a logic model has a corresponding logic function that controls its regulation each time the model is updated.
- Two updating schemes: synchronous and asynchronous.

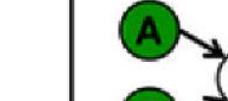
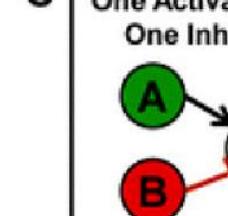
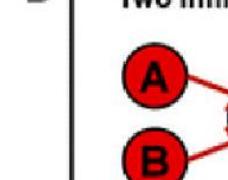
A Logic functions with one molecular regulator



Truth table

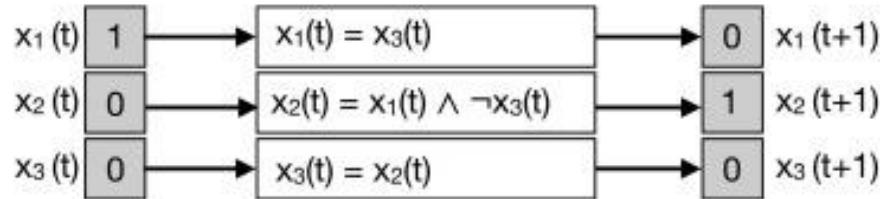
Truth table

Logic functions with two molecular regulators

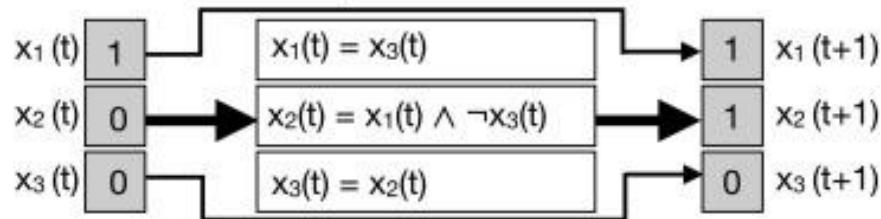
Non-specific Interaction Network	AND C is only <i>ON</i> in one condition	OR C is only <i>OFF</i> in one condition																														
B Two Activators 	<p>$C^{t+1} = A^t \text{ AND } B^t$</p> <table border="1"> <tr><th>A^t</th><th>B^t</th><th>C^{t+1}</th></tr> <tr><td>0</td><td>0</td><td>0</td></tr> <tr><td>1</td><td>0</td><td>0</td></tr> <tr><td>0</td><td>1</td><td>0</td></tr> <tr><td>1</td><td>1</td><td>1</td></tr> </table> <p>The presence of A <u>and</u> the presence of B activates C.</p>	A^t	B^t	C^{t+1}	0	0	0	1	0	0	0	1	0	1	1	1	<p>$C^{t+1} = A^t \text{ OR } B^t$</p> <table border="1"> <tr><th>A^t</th><th>B^t</th><th>C^{t+1}</th></tr> <tr><td>0</td><td>0</td><td>0</td></tr> <tr><td>1</td><td>0</td><td>1</td></tr> <tr><td>0</td><td>1</td><td>1</td></tr> <tr><td>1</td><td>1</td><td>1</td></tr> </table> <p>Either the presence A <u>or</u> the presence of B activates C.</p>	A^t	B^t	C^{t+1}	0	0	0	1	0	1	0	1	1	1	1	1
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1	1	1																														
D Two Inhibitors 	<p>$C^{t+1} = \text{NOT } A^t \text{ AND NOT } B^t$</p> <table border="1"> <tr><th>A^t</th><th>B^t</th><th>C^{t+1}</th></tr> <tr><td>0</td><td>0</td><td>1</td></tr> <tr><td>1</td><td>0</td><td>0</td></tr> <tr><td>0</td><td>1</td><td>0</td></tr> <tr><td>1</td><td>1</td><td>0</td></tr> </table> <p>The absence of A <u>and</u> the absence of B activates C.</p>	A^t	B^t	C^{t+1}	0	0	1	1	0	0	0	1	0	1	1	0	<p>$C^{t+1} = \text{NOT } A^t \text{ OR NOT } B^t$</p> <table border="1"> <tr><th>A^t</th><th>B^t</th><th>C^{t+1}</th></tr> <tr><td>0</td><td>0</td><td>1</td></tr> <tr><td>1</td><td>0</td><td>1</td></tr> <tr><td>0</td><td>1</td><td>1</td></tr> <tr><td>1</td><td>1</td><td>0</td></tr> </table> <p>Either the absence of A <u>or</u> the absence of B activates C.</p>	A^t	B^t	C^{t+1}	0	0	1	1	0	1	0	1	1	1	1	0
A^t	B^t	C^{t+1}																														
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A^t	B^t	C^{t+1}																														
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Updating schemes

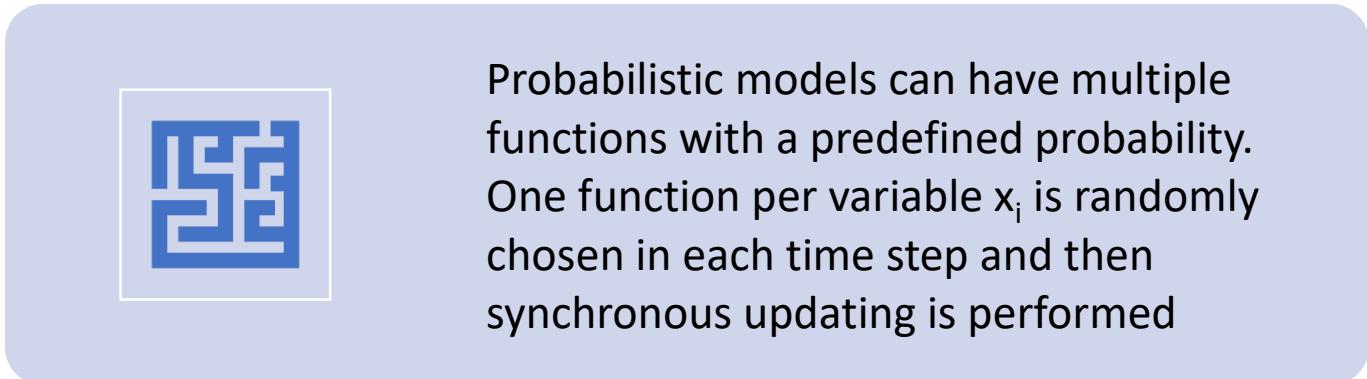
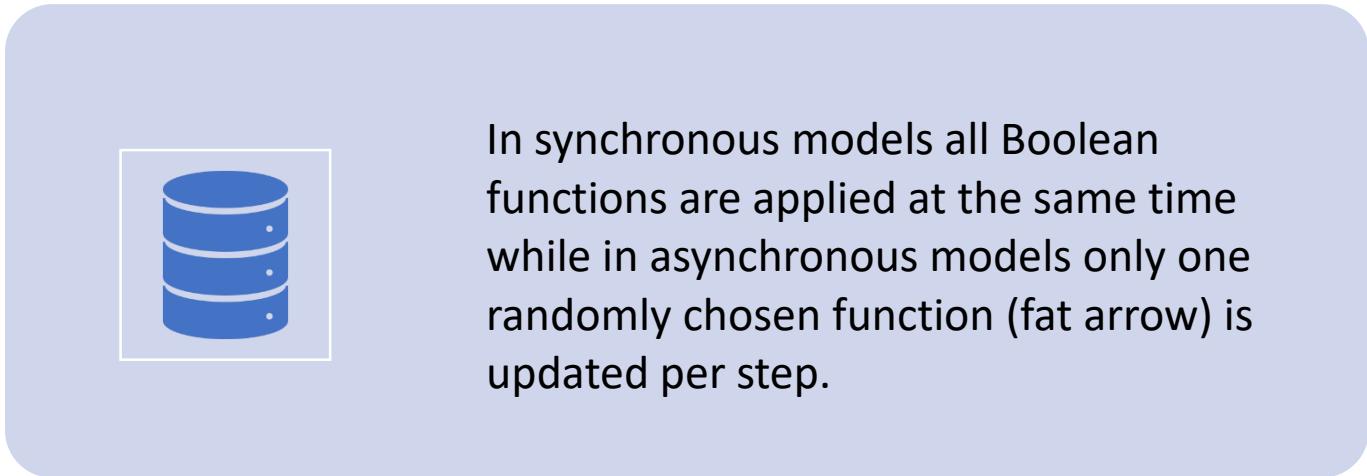
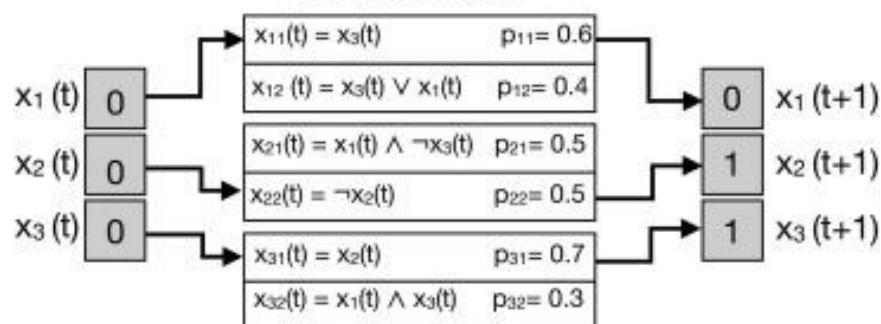
synchronous



asynchronous



probabilistic

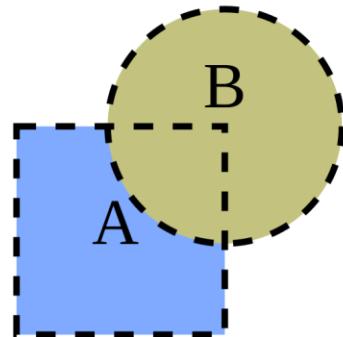


stable state (terminal nodes in the state transition graphs)
cyclic attractor (terminal strongly connected components)

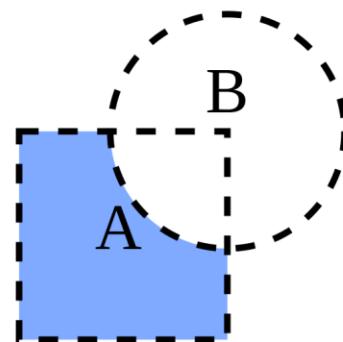
transient cycle(s) (non-terminal strongly connected components)

basins of attraction (subsets of transient states)

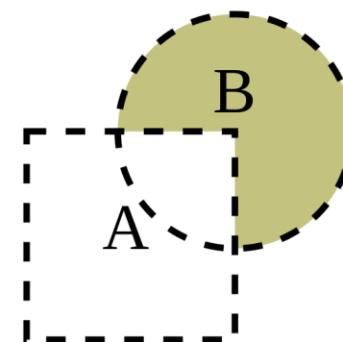
Two shapes
A and B



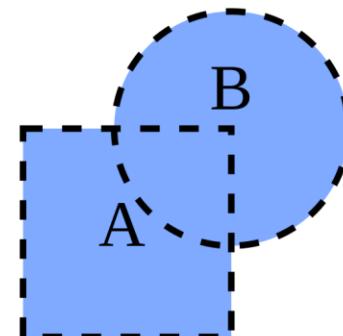
A not B



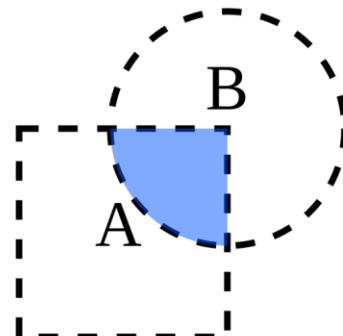
B not A



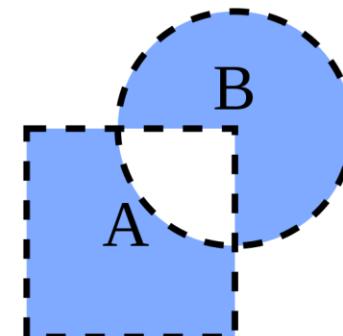
A union B (OR)



A intersection B (AND)



A XOR B



1. Biological
Regulatory
Network

2. Logical
Variables &
Functions

3. Graph of
Interactions and
Logical
Equations

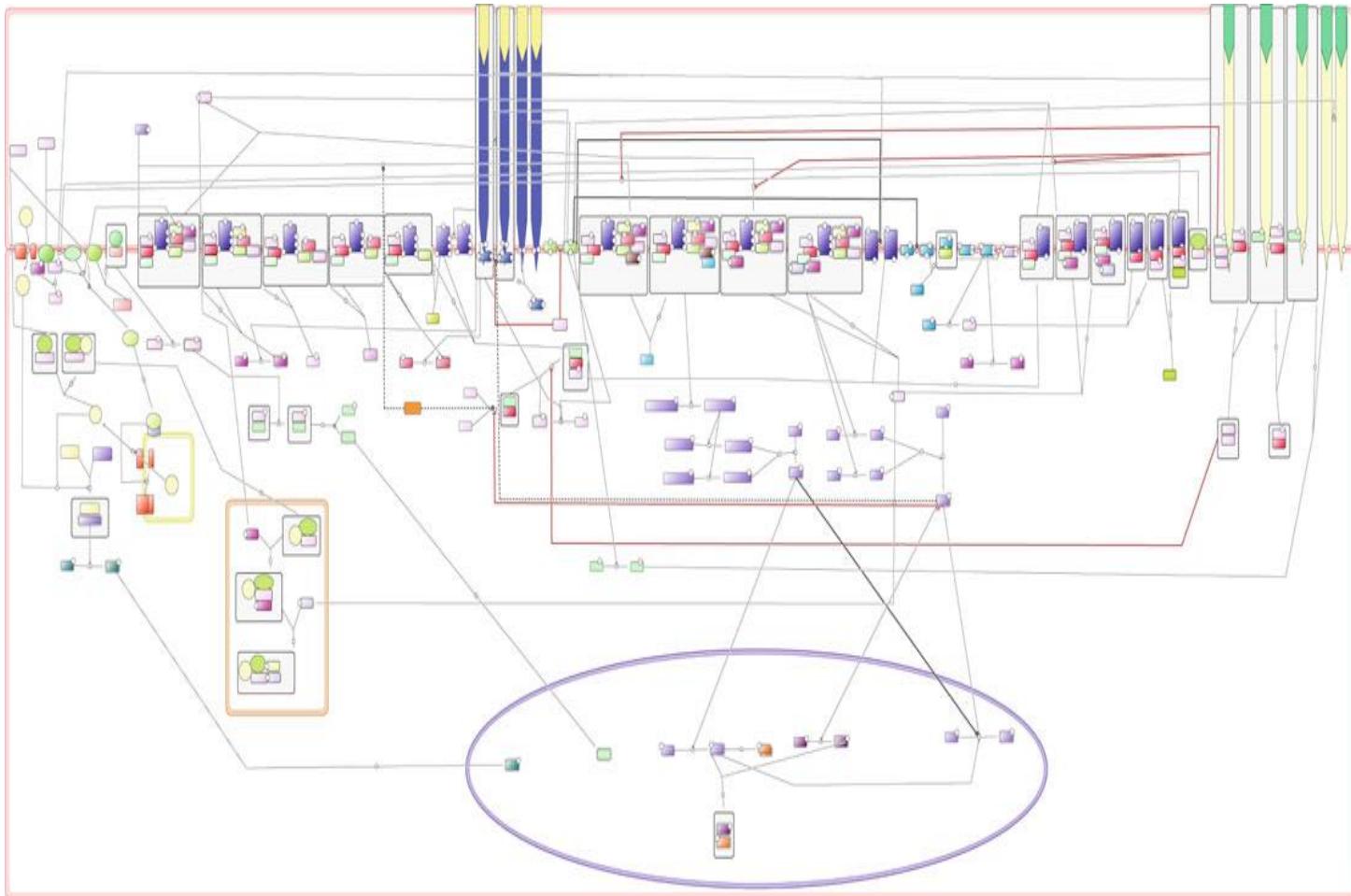
6. Analysis

5. Cycles and
Stable Steady
States

4. State Table
and State Graph



Mast cell activation signaling pathway map created with CellDesigner



Anna Niarakis

ORCID

<https://orcid.org/0000-0002-9687-7426>

Are you Anna Niarakis? Register or Connect your ORCID

Affiliation

Université d'Évry-Val-d'Essonne, Département de Biologie

Expand All

Authored Pathways (5/5)

Date	Identifier	Pathway	Reference
2012-12-21	R-HSA-2454202	Fc epsilon receptor (FcεRI) signaling	BibTex
2012-12-21	R-HSA-2730905	Role of LAT2/NTAL/LAB on calcium mobilization	BibTex
2012-12-21	R-HSA-2871809	FCER1 mediated Ca ²⁺ mobilization	BibTex
2012-12-21	R-HSA-2871796	FCER1 mediated MAPK activation	BibTex
2012-12-21	R-HSA-2871837	FCER1 mediated NF-κB activation	BibTex

Show all authored pathways...

Authored Reactions (15/52)

Date	Identifier	Reaction	Reference
2012-12-21	R-HSA-2730888	Phosphorylation of PLC-gamma	BibTex
2012-12-21	R-HSA-2730867	Translocation of CaN:CaM:NFAT to nucleus	BibTex
2012-12-21	R-HSA-2730849	Calcineurin binds and dephosphorylates NFAT	BibTex
2012-12-21	R-HSA-2730858	Autophosphorylation of BTK/ITK	BibTex
2012-12-21	R-MMU-2730850	Recruitment of Tec kinases to p-SLP-76	BibTex
2012-12-21	R-HSA-2730885	Recruitment of TEC kinases to p-SLP-76	BibTex
2012-12-21	R-RNO-2730881	Phosphorylation of PLC-gamma	BibTex
2012-12-21	R-HSA-2730844	Interaction of GRB2:SOS complex with p-SHC1	BibTex
2012-12-21	R-HSA-2730886	Phosphorylation of SHC by SYK kinase	BibTex
2012-12-21	R-HSA-2730868	Phosphorylation of MEK7 by MEKK1	BibTex
2012-12-21	R-HSA-2730887	Autophosphorylation and activation of MEKK1	BibTex
2012-12-21	R-HSA-2730856	Autophosphorylation of PAK	BibTex
2012-12-21	R-HSA-2730889	Recruitment of PAK to the membrane by binding active RAC1	BibTex
2012-12-21	R-HSA-2730840	Activation of RAC1 by VAV	BibTex
2012-12-21	R-HSA-2730841	Phosphorylation and activation of VAV	BibTex

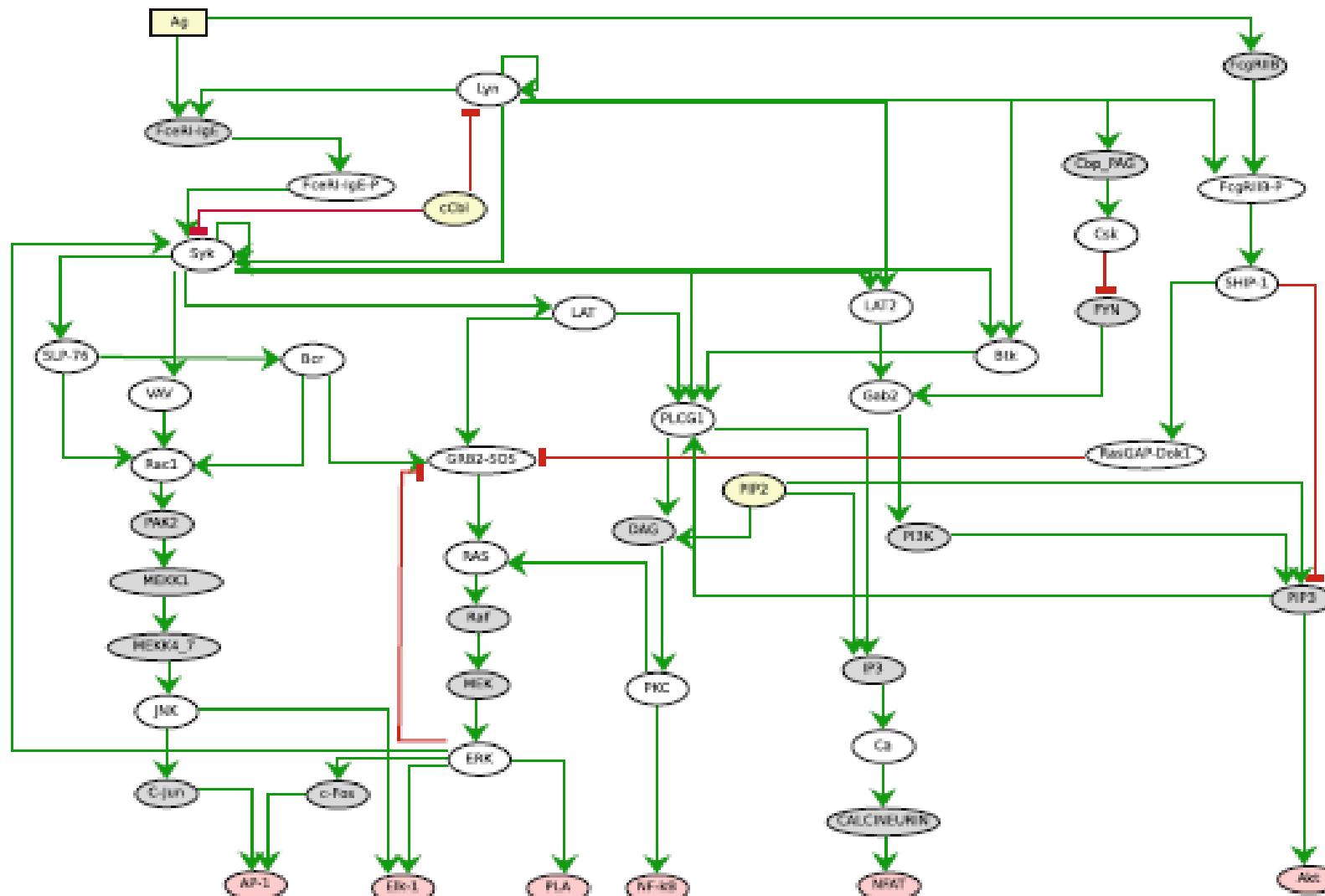
Show all authored reactions...

Reviewed Reactions (2/2)

Date	Identifier	Reaction	Reference
2021-03-31	R-HSA-9724685	IgE binds omalizumab	BibTex
2021-03-31	R-HSA-9725206	IgE binds FCER1	BibTex

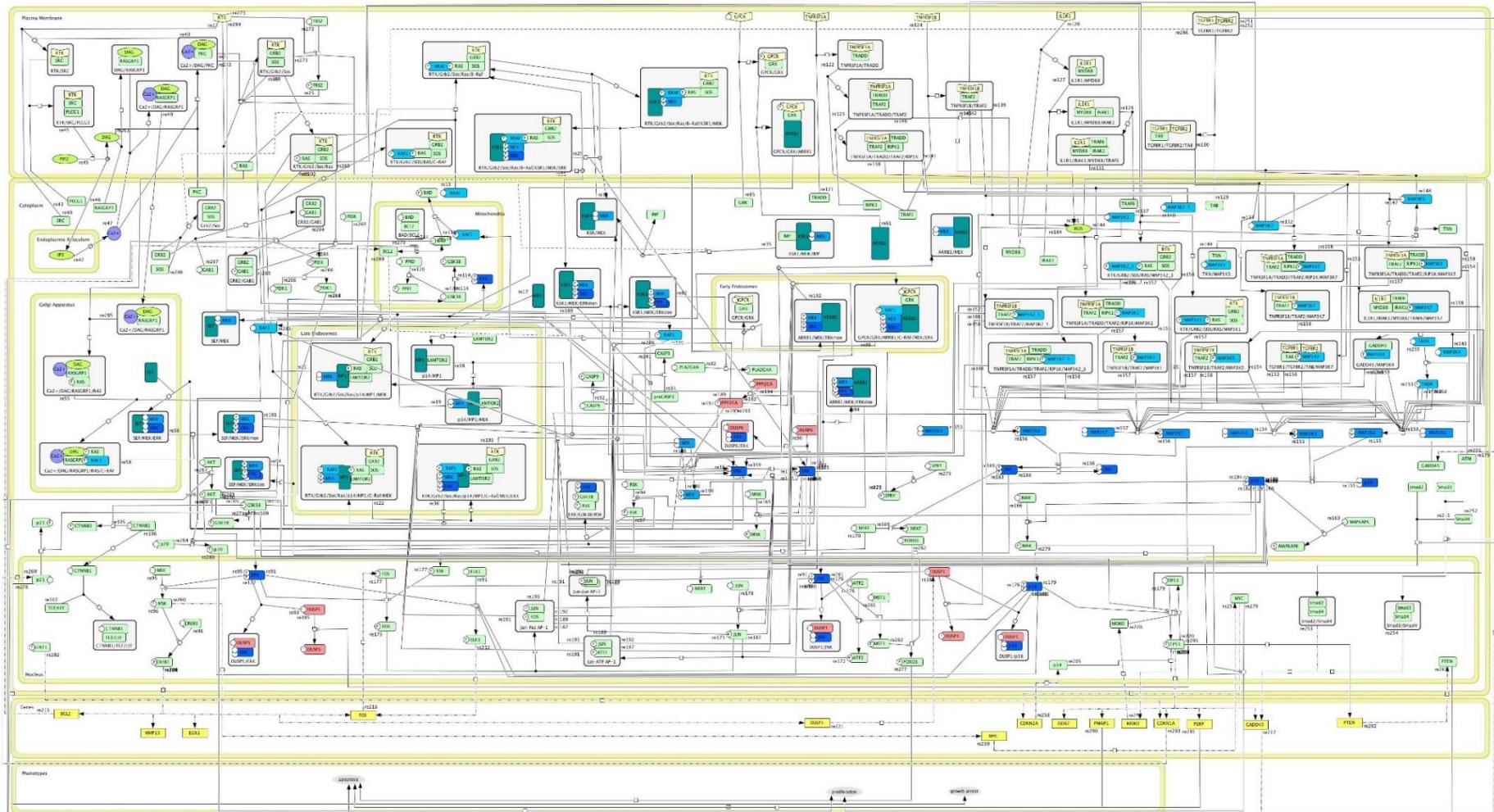
Show all reviewed reactions...

Regulatory graph of the mast cell signaling logical model



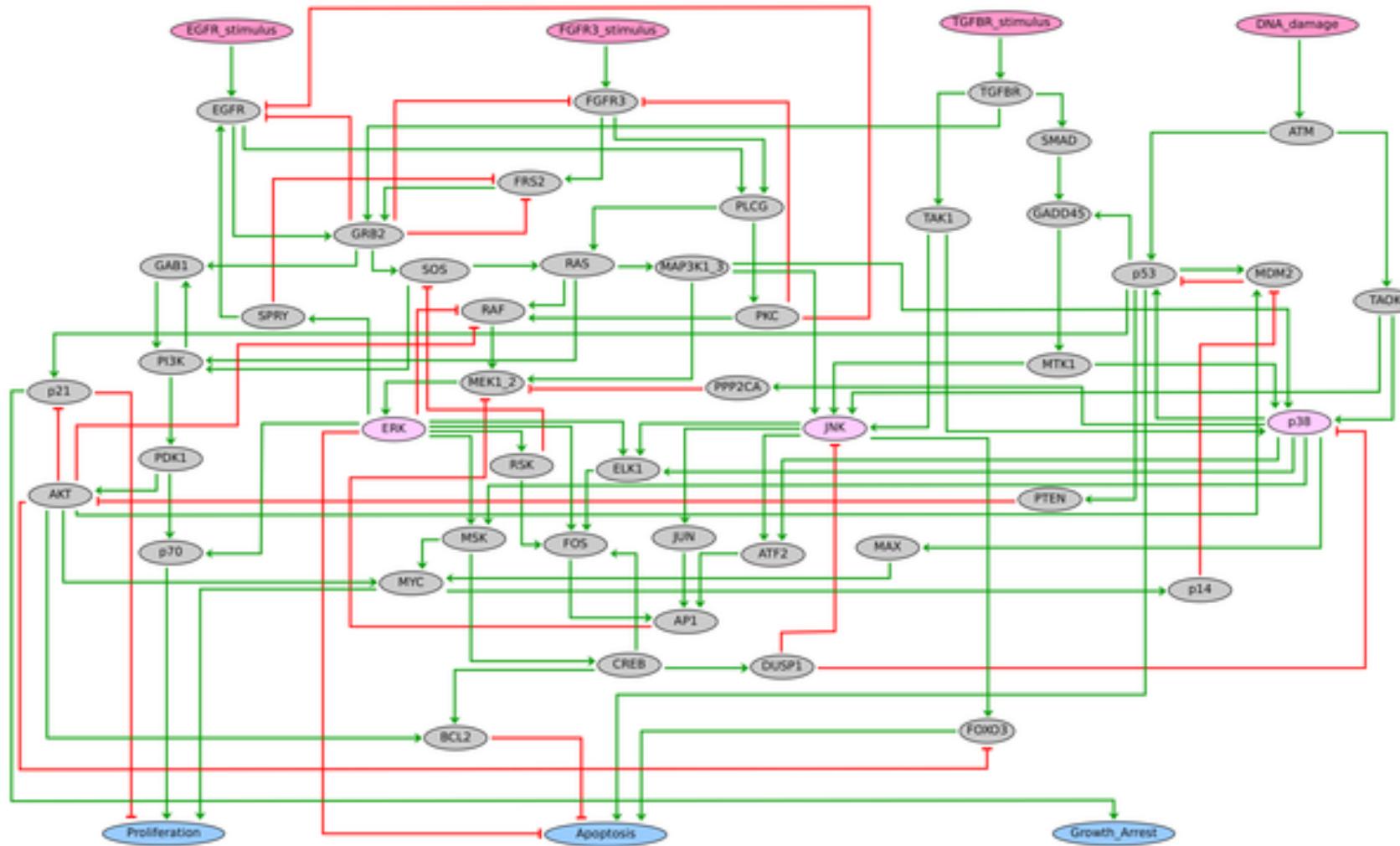
Niarakis, Anna, et al. "Computational modeling of the main signaling pathways involved in mast cell activation." *Fc Receptors*. Springer International Publishing, 2014. 69-93.

Molecular map for MAPK pathway

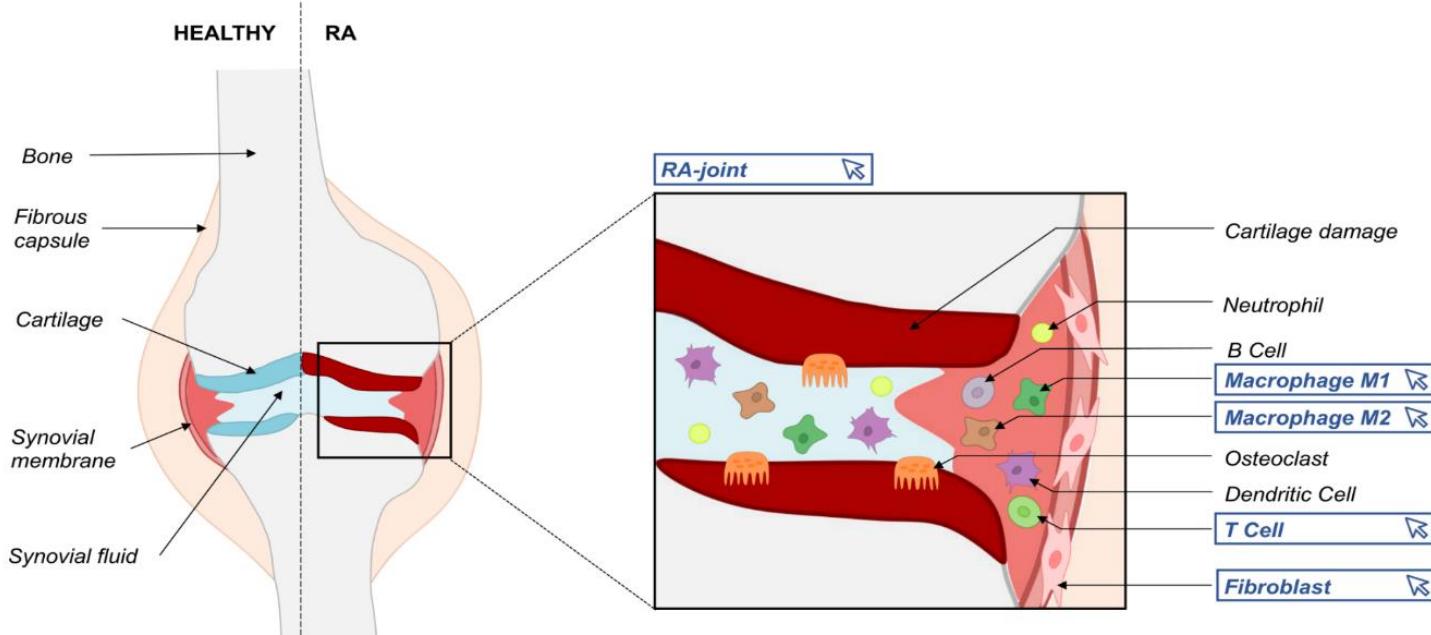
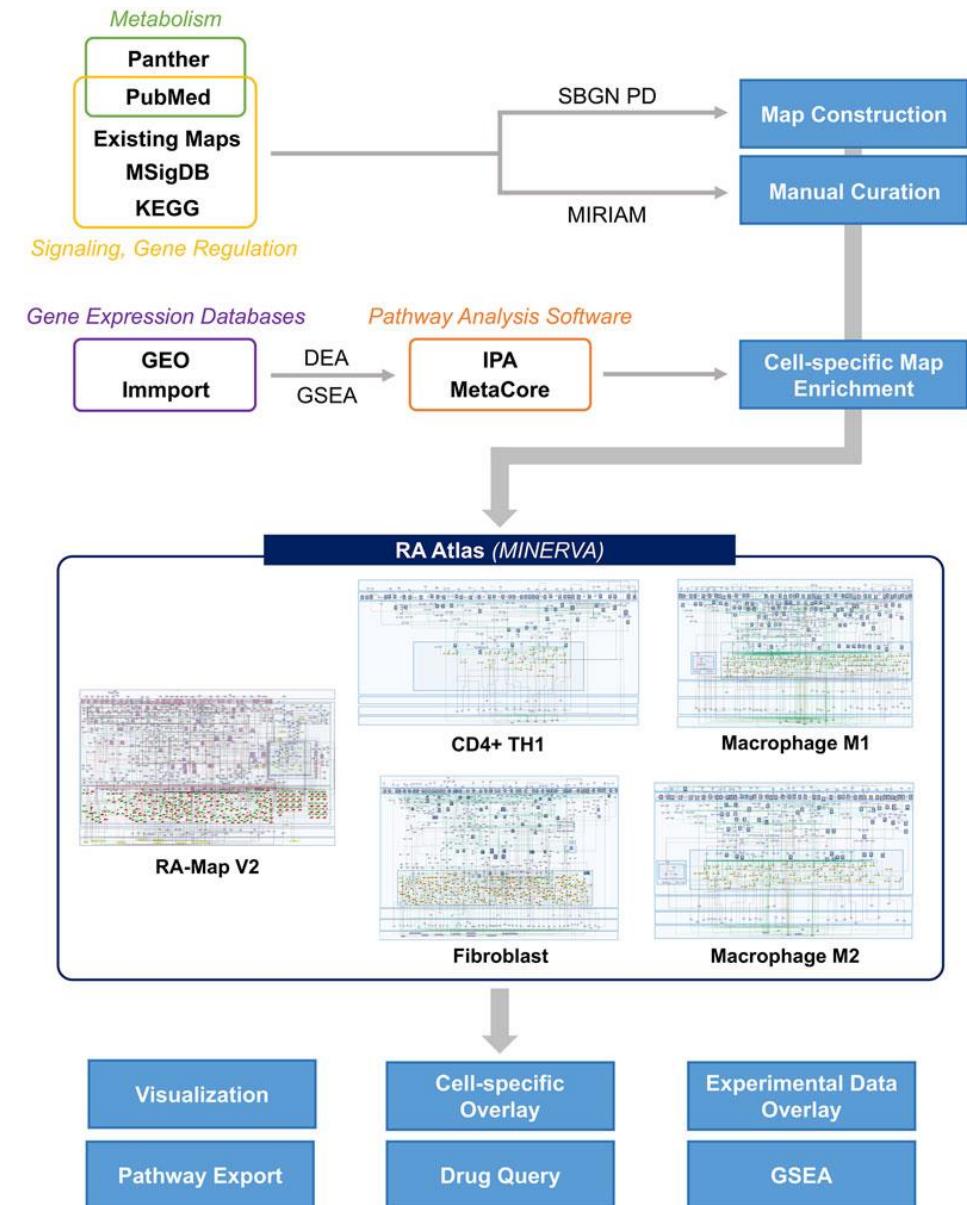


Grieco L, Calzone L, Bernard-Pierrot I, Radvanyi F, Kahn-Perlès B, et al. (2013) Integrative Modelling of the Influence of MAPK Network on Cancer Cell Fate Decision. *PLoS Comput Biol* 9(10): e1003286. doi:10.1371/journal.pcbi.1003286
<http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1003286>

Regulatory graph of the MAPK logical model.



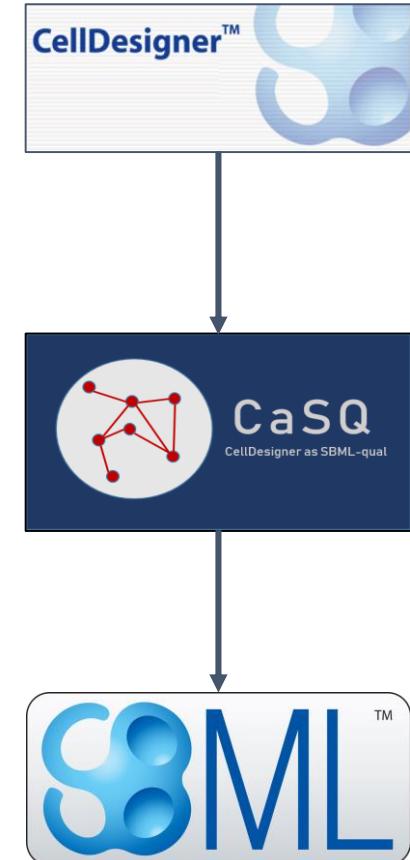
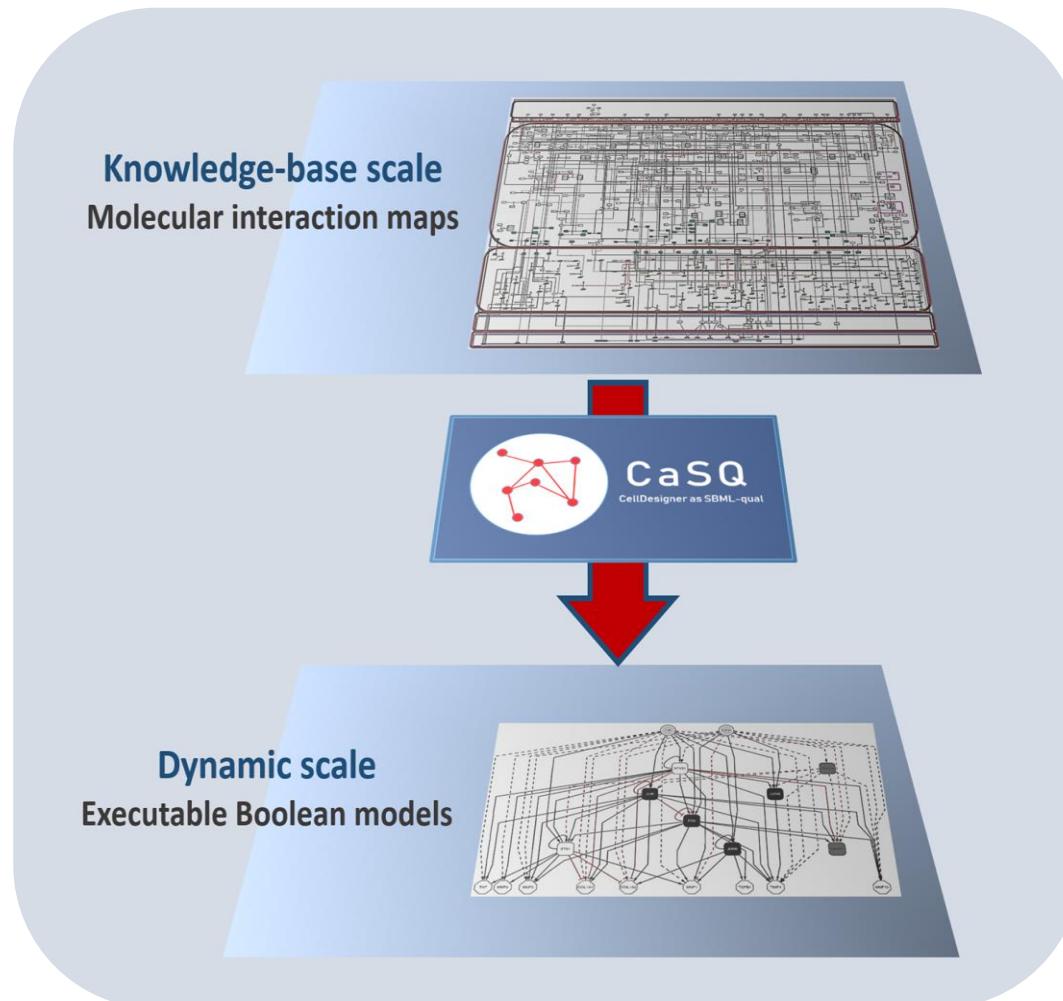
Grieco L, Calzone L, Bernard-Pierrot I, Radvanyi F, Kahn-Perlès B, et al. (2013) Integrative Modelling of the Influence of MAPK Network on Cancer Cell Fate Decision. PLoS Comput Biol 9(10): e1003286. doi:10.1371/journal.pcbi.1003286
<http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1003286>



Maps	Species	Reactions	Phenotypes
Fibroblast	853	509	9
M1 macrophage	640	448	8
M2 macrophage	520	342	7
CD4+ Th1	321	179	7

(Zerrouk et al., 2022)

From Static Representations To Dynamic Models



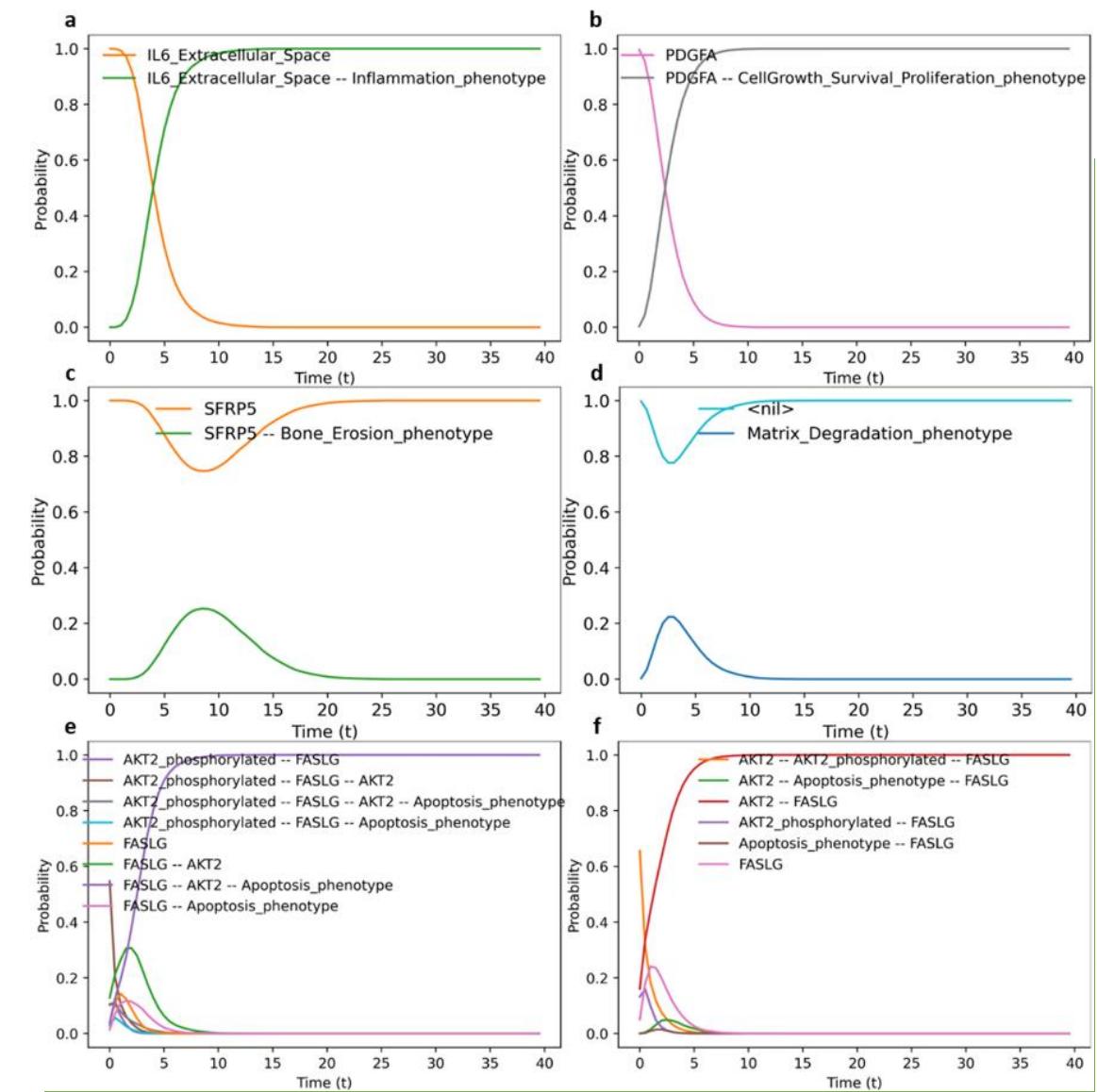
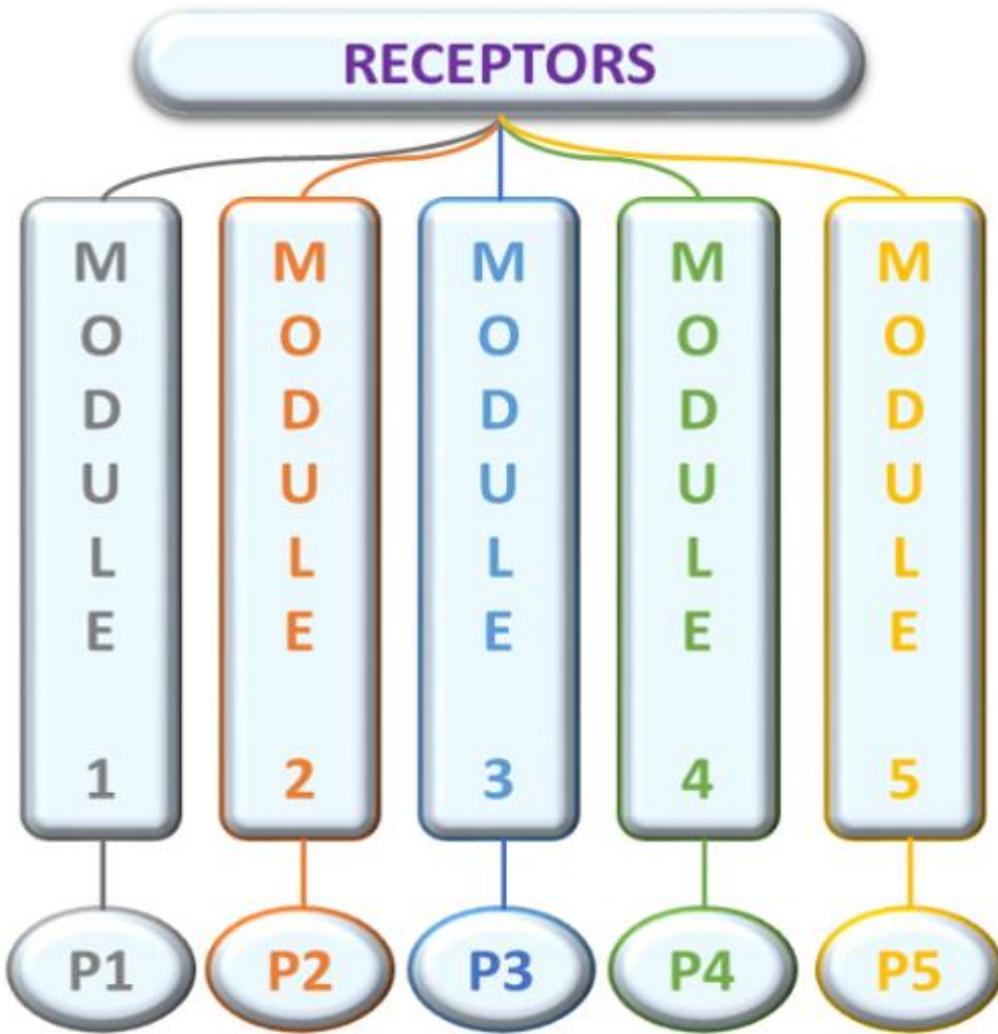
Input: CellDesigner XML file

Python package

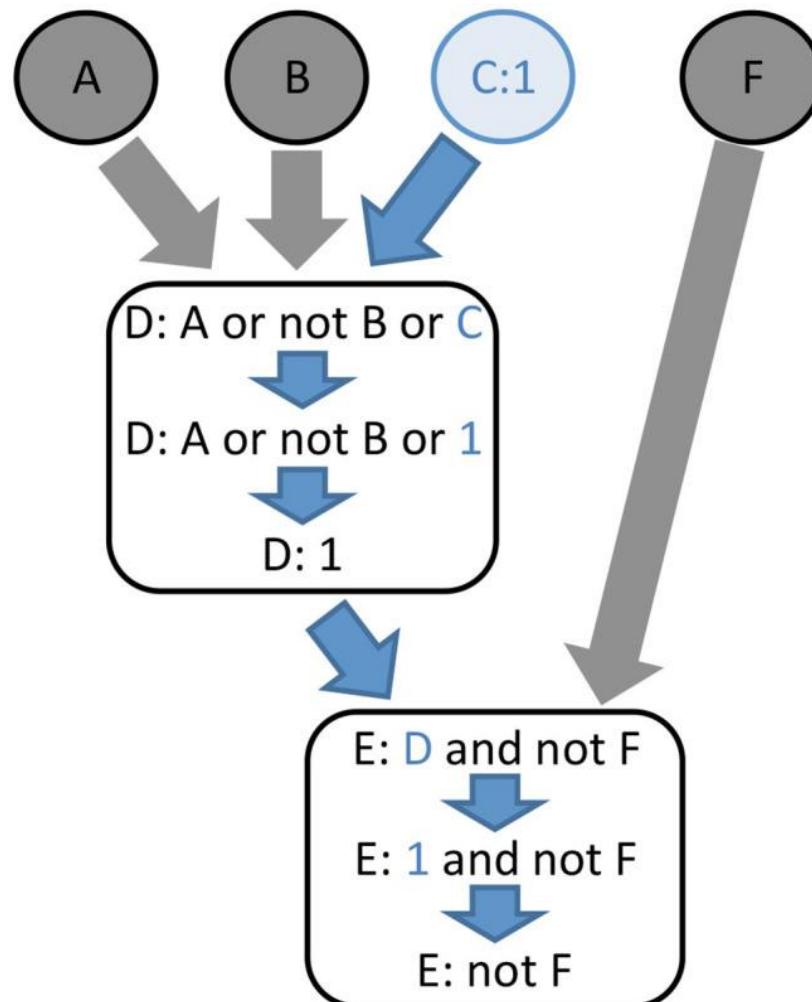
Output: SBML-Qual file

¹ Aghamiri S. S., Singh V., et al. Automated inference of Boolean models from molecular interaction maps using CaSQ. *Bioinformatics* (2020).

A large-scale Boolean model for RA-FLS



Input propagation



- When given a set of logical rules and a cellular context, this iterative algorithm allows the computation of specific components' dynamical consequences on the model's behavior.
- It reveals the influence specific compounds may exert on the network's dynamics.
- Note that this method does not impact the asymptotic behavior of the model: all dynamical consequences calculated in this manner would occur regardless
- Interestingly, Saadatpour and collaborators showed that this method conserves the stable states and complex attractors under the fully asynchronous updating assumption

Modelling the effect of mono/ combined treatment

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A large-scale Boolean model of the rheumatoid arthritis fibroblast-like synoviocytes predicts drug synergies in the arthritic joint

Vidisha Singh, Aurelien Naldi, Sylvain Soliman & Anna Niarakis 

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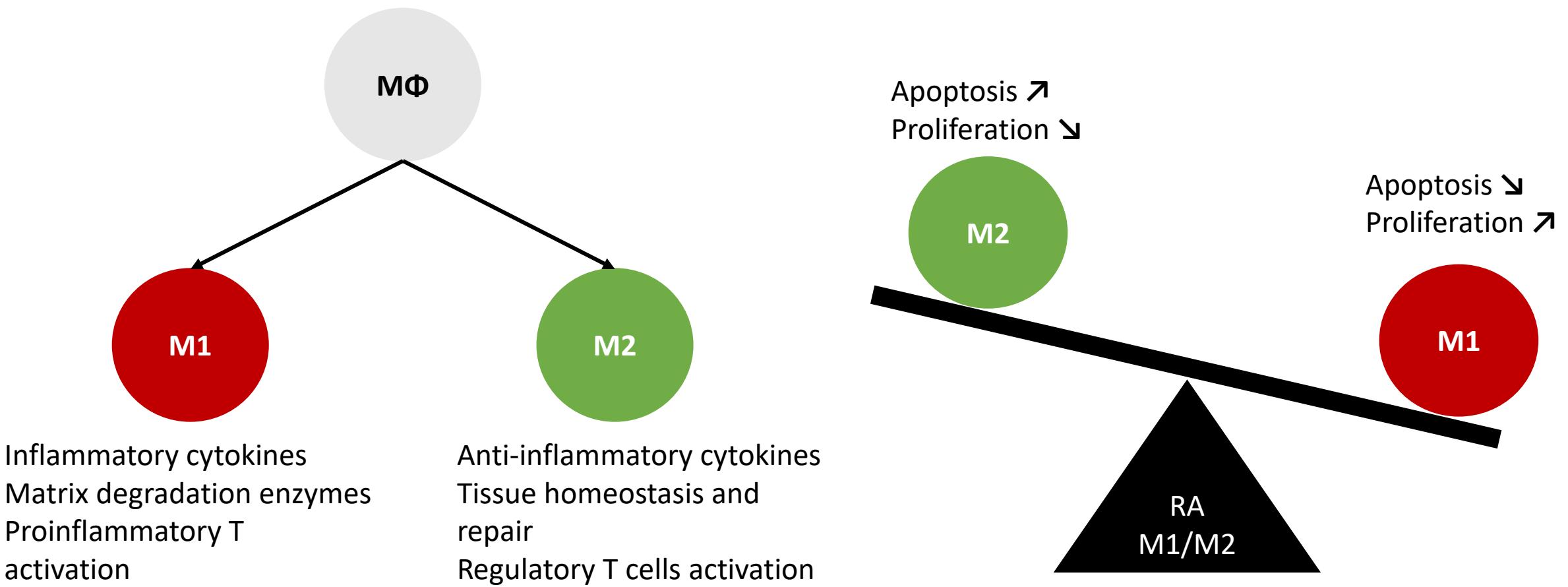
Abstract

Rheumatoid arthritis (RA) is a complex autoimmune disease with an unknown aetiology.

However, rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) play a significant role in initiating and perpetuating destructive joint inflammation by expressing immuno-modulating cytokines, adhesion molecules, and matrix remodelling enzymes. In addition, RA-FLS are primary drivers of inflammation, displaying high proliferative rates and an apoptosis-resistant phenotype. Thus, RA-FLS-directed therapies could become a complementary approach to

Identified drugs	Target components	Target phenotypes and expected effect
Pamidronate, Incadronate, and Zoledronic Acid	CAV1↑	Apoptosis ↑
Sarilumab, Tocilizumab	IL-6	Inflammation ↓
GSK2618960, and T-5224, Acitretin	IL7 AP-1	Bone erosion ↓
Batimastat	MMP3	Matrix degradation ↓
666-15 and AS1842856	CREB1 YWHAQ (FOXO1)	Cell proliferation ↓

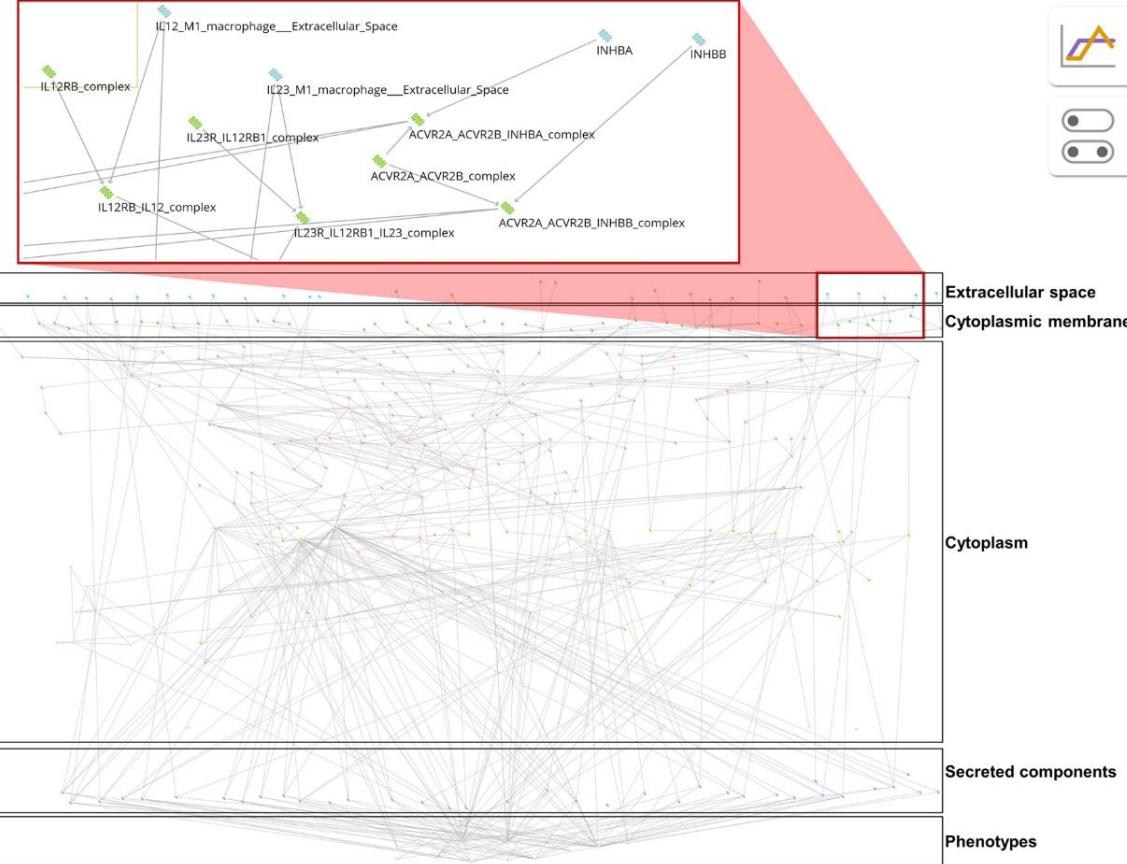
Targeting macrophages in RA



Building an efficient computational framework, reproducible and interoperable



RA M1 macrophage >



- New version of BioModelAnalyzer (BMA)
- Linux
- Suitable for HPC
- Interoperable with CaSQ (JSON format)
- Suitable for keeping the architecture of the original networks
- Stability proof
- Attractor identification
- Synchronous updating

Rheumatoid Arthritis

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A large-scale Boolean model of the rheumatoid arthritis fibroblast-like synoviocytes predicts drug synergies in the arthritic joint

Vidisha Singh, Aurelien Naldi, Sylvain Soliman & Anna Niarakis ✉

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Abstract

Rheumatoid arthritis (RA) is a complex autoimmune disease with an unknown aetiology. However, rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) play a significant role in initiating and perpetuating destructive joint inflammation by expressing immuno-modulating cytokines, adhesion molecules, and matrix remodelling enzymes. In addition, RA-FLS are primary drivers of inflammation, displaying high proliferative rates and an apoptosis-resistant

Open Access Published online by De Gruyter February 6, 2024

MetaLo: metabolic analysis of logical models extracted from molecular interaction maps

Sahar Aghakhani, Anna Niarakis and Sylvain Soliman ✉

From the journal Journal of Integrative Bioinformatics
https://doi.org/10.1515/jib-2023-0048

Cite this Share this

Abstract

Molecular interaction maps (MIMs) are static graphical representations depicting complex biochemical networks that can be formalized using one of the Systems Biology Graphical Notation languages. Regardless of their extensive coverage of various biological processes, they are limited in terms of dynamic insights. However, MIMs can serve as templates for developing dynamic computational models. We present MetaLo, an open-source Python package that enables the coupling of Boolean models inferred from process description MIMs with generic core metabolic networks. MetaLo provides a framework to study the impact of signaling cascades, gene regulation processes, and metabolic flux distribution of central energy production pathways. MetaLo computes the Boolean model's asynchronous asymptotic behavior, through the identification of trap-spaces, and extracts metabolic constraints to contextualize the generic metabolic network. MetaLo is able to handle large-scale Boolean models and genome-scale metabolic models without requiring kinetic information or manual tuning. The framework behind MetaLo enables in depth analysis of the regulatory model, and may allow tackling a lack of omics data in poorly addressed biological fields to contextualize generic metabolic networks along with improper automatic reconstructions of cell- and/or disease-specific metabolic networks. MetaLo is available at <https://pypi.org/project/metaLo/> under the terms of the GNU General Public License v3.

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Article | Open access | Published: 26 January 2024

Large-scale computational modelling of the M1 and M2 synovial macrophages in rheumatoid arthritis

Naouel Zerrouk, Rachel Alcraft, Benjamin A. Hall, Franck Augé & Anna Niarakis ✉

npj Systems Biology and Applications 10, Article number: 10 (2024) | Cite this article

343 Accesses | 4 Altmetric | Metrics

Abstract

Macrophages play an essential role in rheumatoid arthritis. Depending on their phenotype (M1 or M2), they can play a role in the initiation or resolution of inflammation. The M1/M2 ratio in rheumatoid arthritis is higher than in healthy controls. Despite this, no treatment targeting specifically macrophages is currently used in clinics. Thus, devising strategies to selectively deplete proinflammatory macrophages and promote anti-inflammatory macrophages

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ORIGINAL RESEARCH article

Front. Syst. Biol. 11 July 2022
See: Data and Model Integration
Volume 2 - 2022 | https://doi.org/10.3389/fysb.2022.925791

This article is part of the Research Topic
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A Mechanistic Cellular Atlas of the Rheumatic Joint

Naouel Zerrouk^{1,2*}, Sahar Aghakhani^{1,3†}, Vidisha Singh¹, Franck Augé², Anna Niarakis^{1,3*}

¹ GenHotel—Laboratoire Européen de Recherche Pour La Polyarthrite Rhumatoïde, University Paris-Saclay, University Evry, Evry, France
² Sanofi R&D, AI and Deep Analytics—Omics Data Science, Chilly-Mazarin, France
³ Lifeware Group, Inria Saclay, Palaiseau, France

Rheumatoid Arthritis (RA) is an autoimmune disease of unknown aetiology involving complex interactions between environmental and genetic factors. Its pathogenesis is suspected to arise from intricate interplays between signalling, gene regulation and metabolism, leading to synovial inflammation, bone erosion and cartilage destruction in the patients' joints. In addition, the resident synoviocytes of macrophage and fibroblast types can interact with innate and adaptive immune cells and contribute to the disease's debilitating symptoms. Therefore, a detailed, mechanistic mapping of the molecular pathways and cellular crosstalks is essential to understand the complex biological processes and different disease manifestations. In this regard, we present the RA-Atlas, an SBGN-standardized, interactive, manually curated representation of existing knowledge related to the onset and progression of RA. This state-of-the-art RA-Atlas includes an updated version of the global

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RESEARCH ARTICLE

Metabolic reprogramming in Rheumatoid Arthritis Synovial Fibroblasts: A hybrid modeling approach

Sahar Aghakhani, Sylvain Soliman, Anna Niarakis ✉

Version 2 Published: December 12, 2022 • https://doi.org/10.1371/journal.pcbi.1010408

Article	Authors	Metrics	Comments	Media Coverage	Peer Review
▼					

Abstract

Author summary

1. Introduction
2. Methods
3. Results
4. Discussion
5. Perspectives
6. Conclusion

Supporting information
References

Reader Comments
Figures

Abstract

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by a highly invasive pannus formation consisting mainly of Synovial Fibroblasts (RASFs). This pannus leads to cartilage, bone, and soft tissue destruction in the affected joint. RASFs' activation is associated with metabolic alterations resulting from dysregulation of extracellular signals' transduction and gene regulation. Deciphering the intricate mechanisms at the origin of this metabolic reprogramming may provide significant insight into RASFs' involvement in RA's pathogenesis and offer new therapeutic strategies. Qualitative and quantitative dynamic modeling can address some of these features, but hybrid models represent a real asset in their ability to span multiple layers of biological machinery. This work presents the first hybrid RASF model: the combination of a cell-specific qualitative regulatory network with a global metabolic network. The automated framework for hybrid modeling exploits the regulatory network's trap-spaces as additional constraints on the metabolic network. Subsequent flux balance analysis allows assessment of RASFs' regulatory outcomes' impact on their metabolic flux distribution. The hybrid RASF model reproduces the experimentally observed metabolic reprogramming induced by signaling and gene regulation in RASFs. Simulations also enable further hypotheses on the potential reverse Warburg effect in RA. RASFs may undergo metabolic reprogramming to turn into "metabolic factories", producing high levels of energy-rich fuels and nutrients for neighboring demanding cells through the crucial role of HIF1.

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Article | Open access | Published: 01 October 2020

Identification of putative master regulators in rheumatoid arthritis synovial fibroblasts using gene expression data and network inference

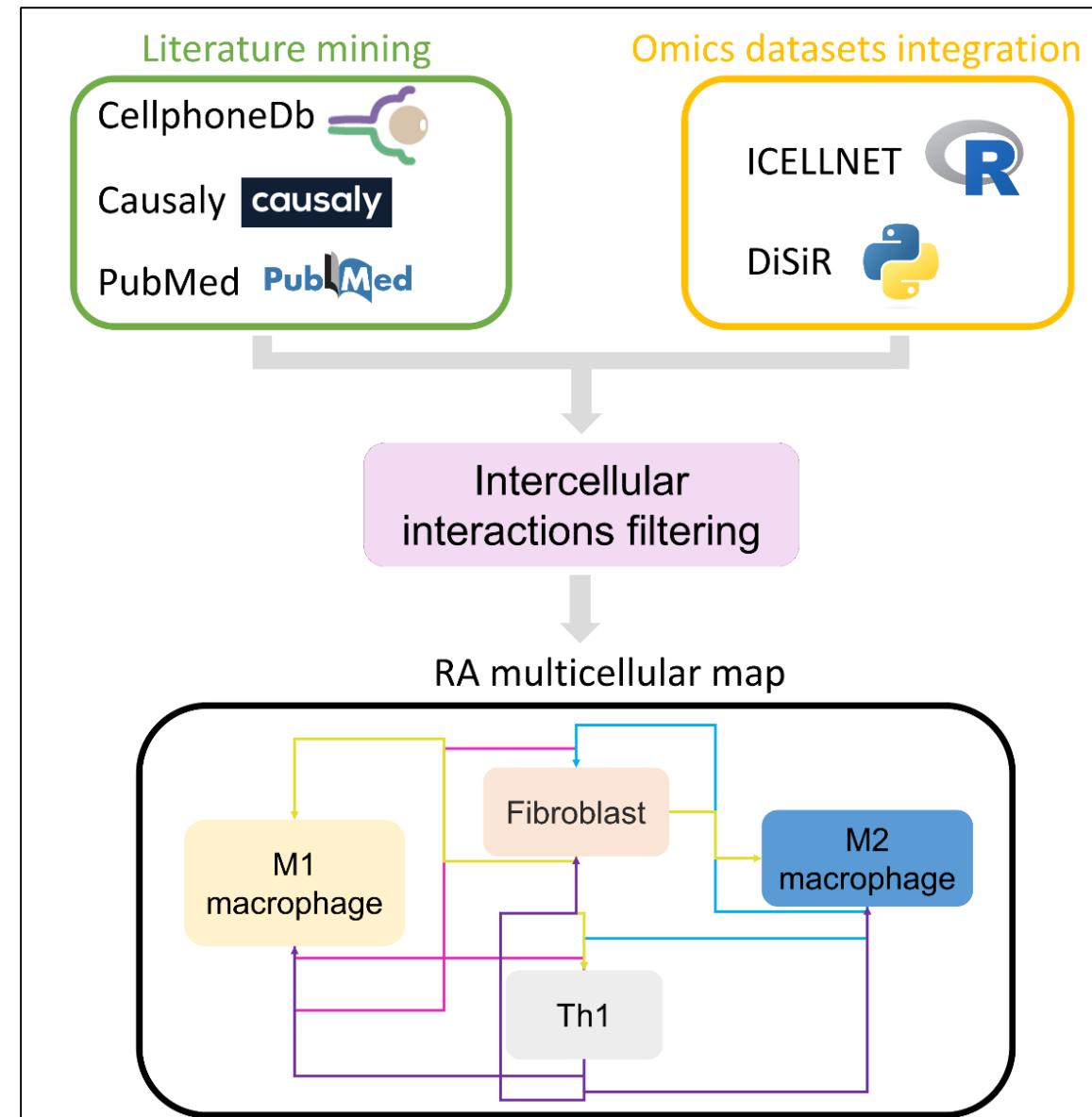
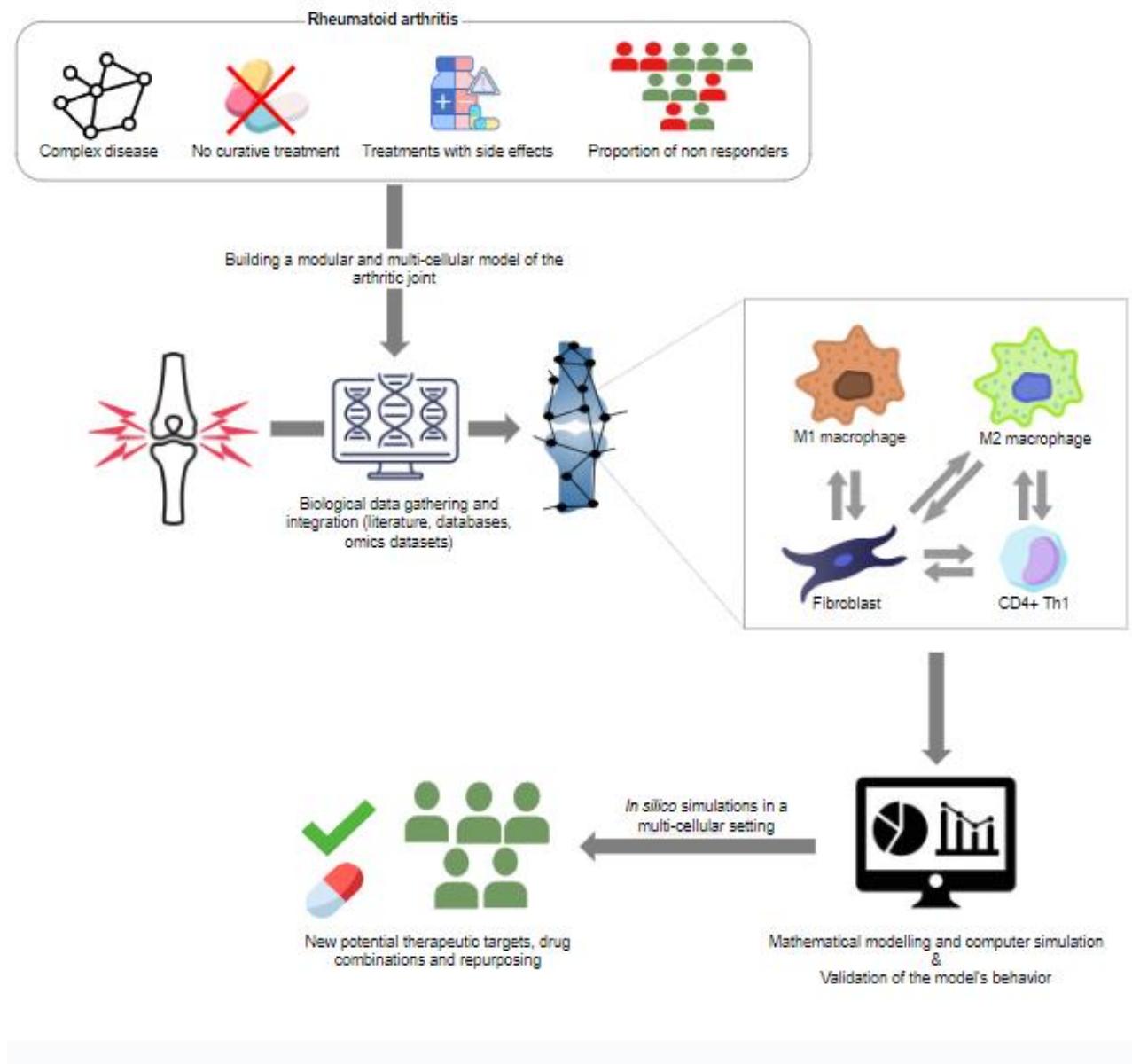
Naouel Zerrouk, Quentin Miagoux, Aurelien Dispot, Mohamed Elati & Anna Niarakis

Scientific Reports 10, Article number: 16236 (2020) | Cite this article

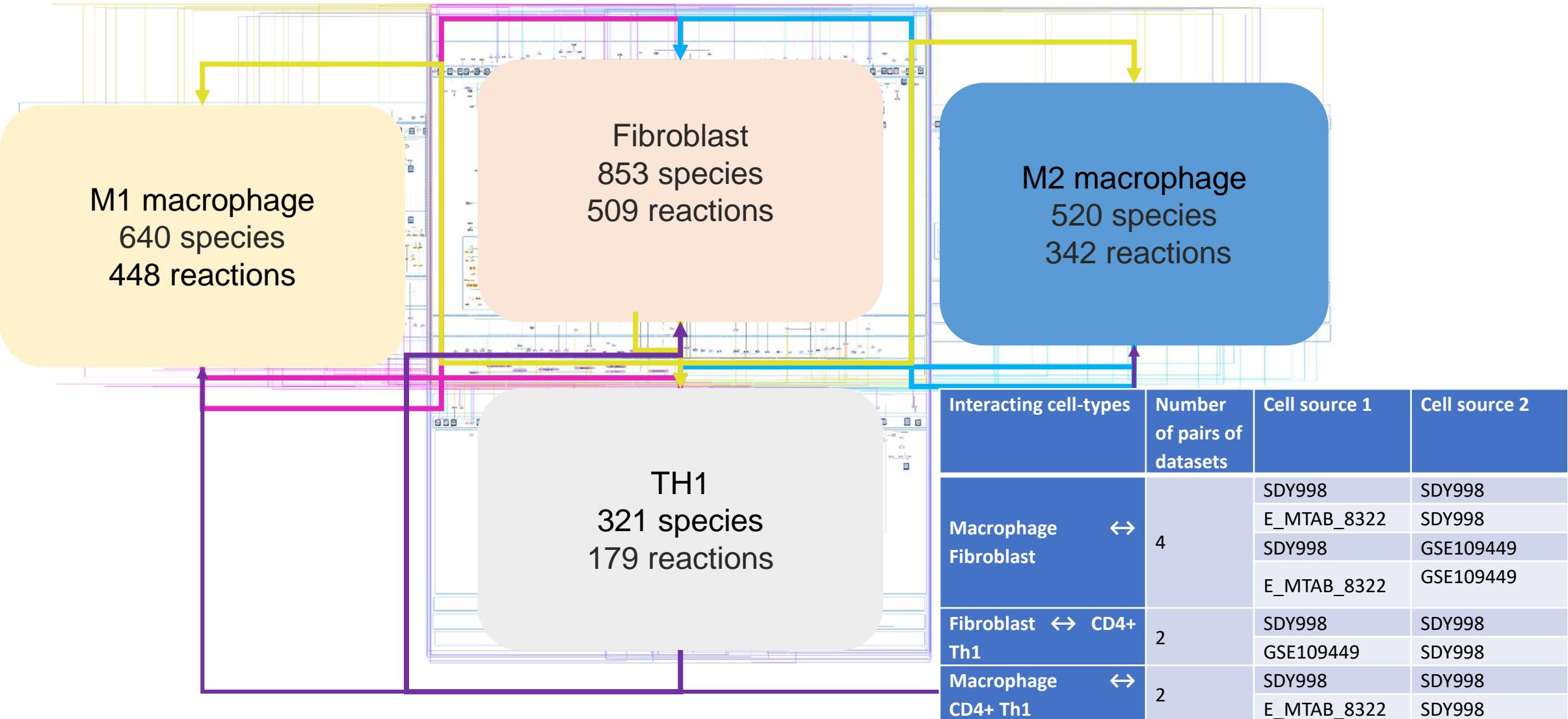
4034 Accesses | 11 Citations | 5 Altmetric | Metrics

Abstract

Building a multicellular model for RA – SANOFI R&D



Integrating detailed cellular crosstalk between cell specific maps (source of multiple challenges)



How does it work?

- Attractors are filtered to keep only the steady states.
- Next, the filtered steady states are validated. Differentially expressed biomolecules present in the models are identified .
- The expressions are discretized and converted to a binary vector of experimentally observed Boolean values.
- After that, similarity scores are computed to describe the similarity between the steady states and the experimentally observed values.
- The steady states with the highest score are selected, their mean vector represents the calibrated model's state.

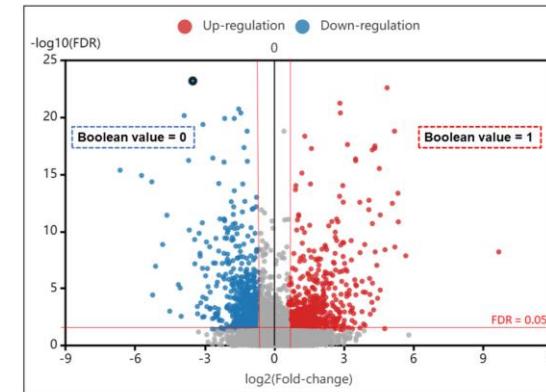
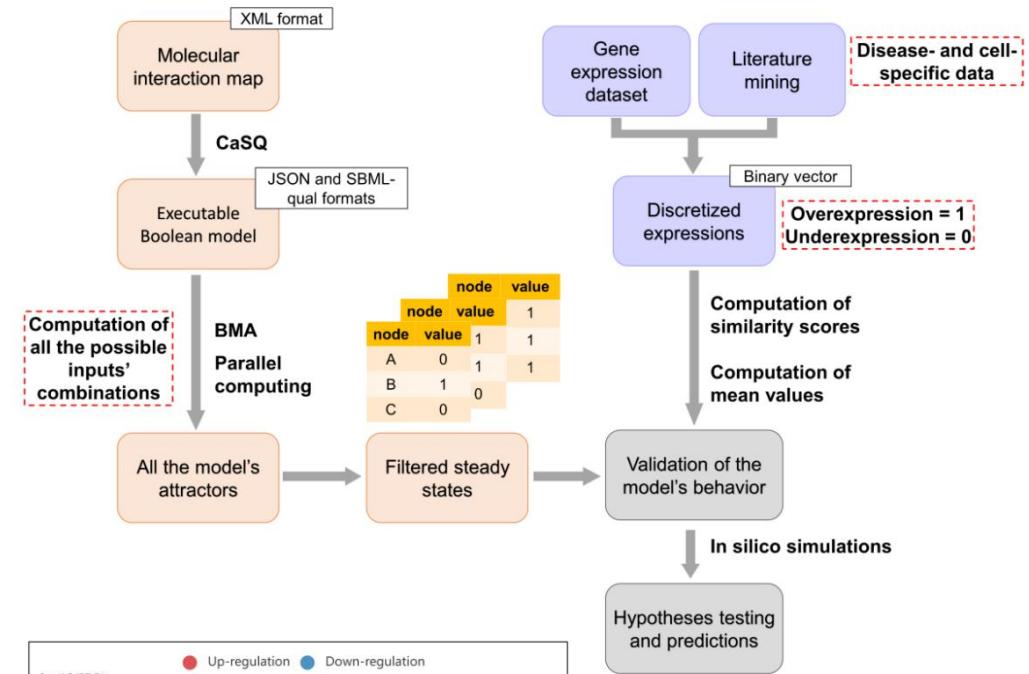
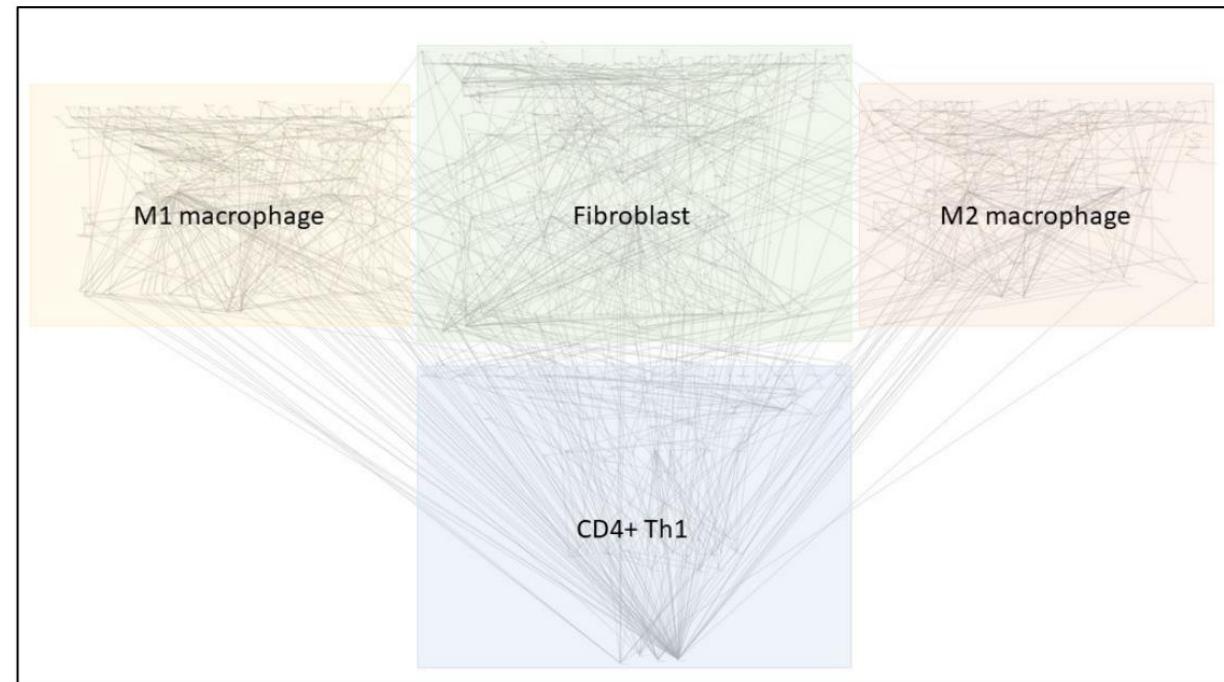


Figure 39. Example of gene expression discretization on a volcano plot showing the DEGs between RA and osteoarthritis synovial fibroblasts from GSE109449 dataset. DEGs were filtered using an FDR equal to 0.05 and a $\log_2(\text{FC})$ equal to 0.584. Overexpressed DEGs are associated with the value one while under expressed molecules are associated with the value zero.

Multi-cellular model: 1103 nodes comprising 240 inputs

Model	M1 macrophage	M2 macrophage	Th1	Fibroblast
Similarity score	99%	96,5%	100%	98%
Fixed nodes	227/233	162/169	120/120	256/275

- **219/240** inputs fixed from the cell-specific models calibration **AND** literature and data mining
- The nodes that are still not fixed are regulated by **inputs** with unknown activity in the literature



Multi-cellular model

- Biggest machine available in Magellan : 160 virtual CPUs (80 physical CPUs) and 3844 GB of RAM
- Biggest cluster available in Magellan : 29 worker nodes
 - 2^{32} combinations in 4 weeks
 - 2^{31} combinations in two weeks
- 2^{21} possible combinations → a few hours

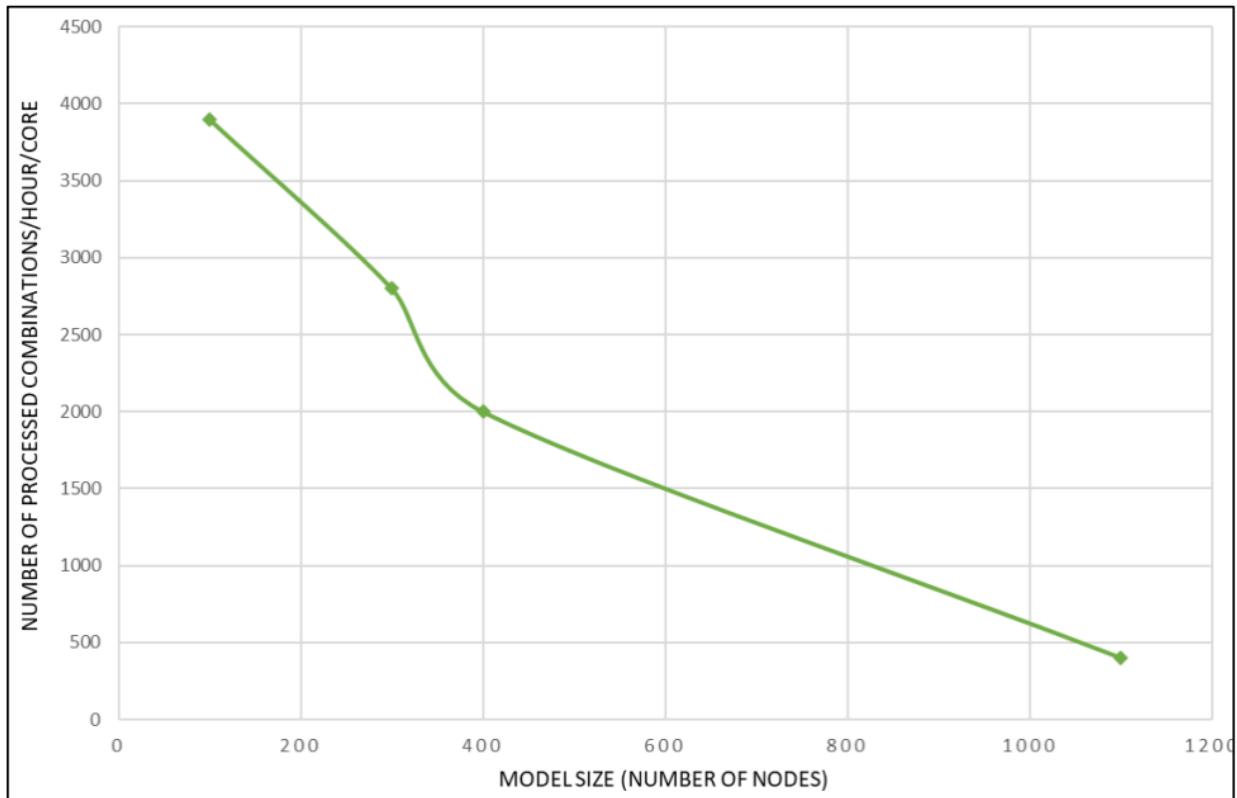


Figure 38. Plot showing the number of processed inputs' combinations by BMA per hour using a single core machine with a base frequency of 2.3 GHz.

Figure 38 illustrates the number of input combinations the BMA console tool can process per hour using one core and various model sizes. As the attractor search is slower on larger models, the number of processed combinations decreases proportionally with the model size. Therefore, Figure 38 can be used to estimate the computational resources required to execute the analysis depending on the model's size. We utilized the Joblib python package as well (297) to parallelize the process and considerably reduce the running time of the framework.