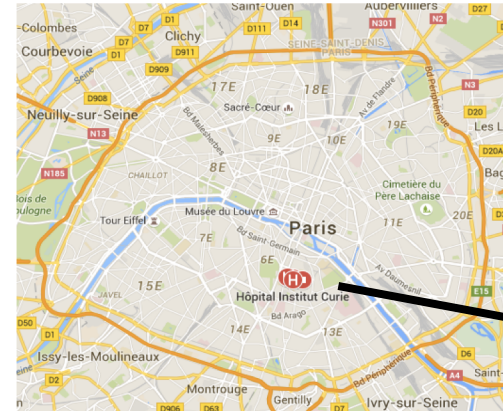


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# Computational methods for logical modelling applied to a model of the early steps of metastasis

Laurence Calzone  
22 March 2018

# Institut Curie



Research center

Hospital

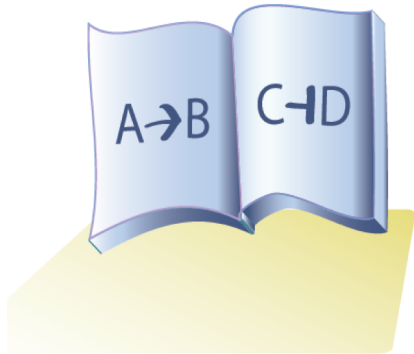


2100 members in the Hospital  
1100 members in the research center

# Computational Systems Biology group

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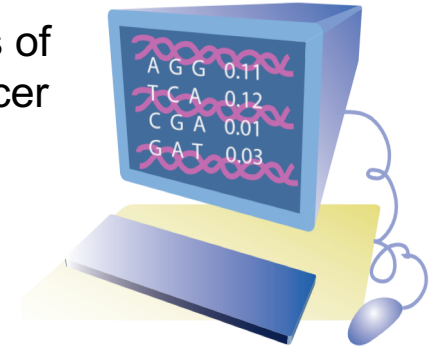
**Objective of our group:** based on existing knowledge and data, we would like to be able to explain **why** certain mutations of normal genome can lead to tumorigenesis, and **how** to reverse their effect



e.g. <https://acsn.curie.fr/>

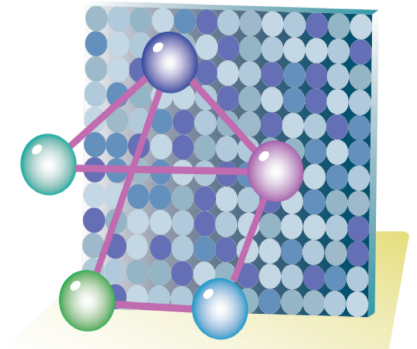
Formalizing  
biological  
knowledge

Integrative analysis of  
omics data for cancer  
research



Mathematical  
modeling of cell  
fate decisions to  
understand  
cancer biology

Computational  
methods for  
systems biology

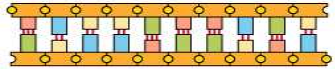


<http://sysbio.curie.fr/>

## Data Exploration

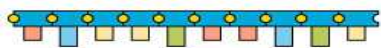
*A priori knowledge of biological mechanisms & experimental obs.*

### DNA



*Mutations, CNV, methylation, ChIPSeq, etc.*

### RNA

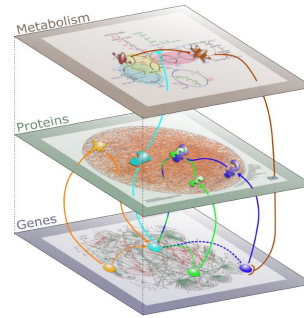
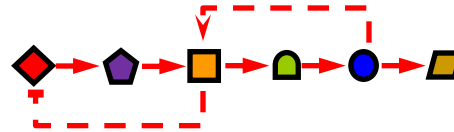


*Transcriptomics, small RNAs, etc.*

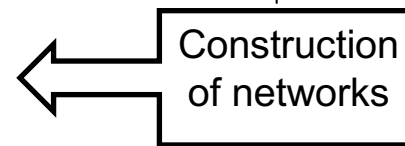
### Protein



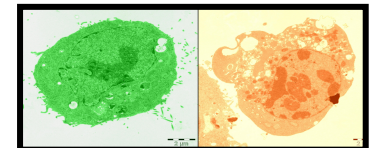
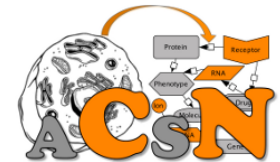
*Proteomics, phosphoproteomics*



<http://www-dsv.cea.fr>

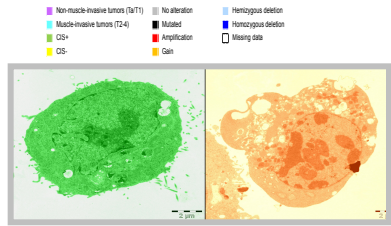
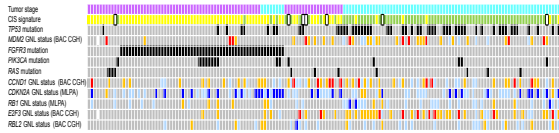


- Use a priori knowledge and data analyses to create these networks
- Perform network analysis to identify biomarkers, key driver genes
- Use network as a first step towards mathematical modelling





# The modelling cycle



Observations / data  
Physical situation

CASP8=(DISC\_FAS | DISC\_TNF) & !cFLIP  
BAX=CASP8 & !BCL2  
RIP1=(TNFR | DISC\_FAS) & !CASP8  
...

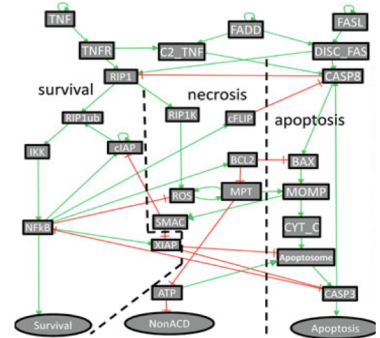
(1) Formulate question

(2) Gather knowledge into a network

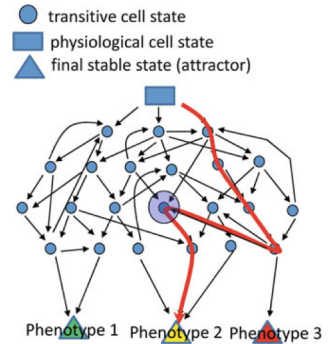
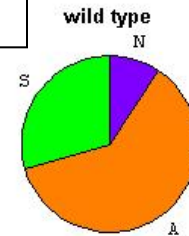
Introduce physical laws  
Translate into mathematical terms (3)

Mathematical modelling

Mathematical solutions



Simulate  
Solve (4)



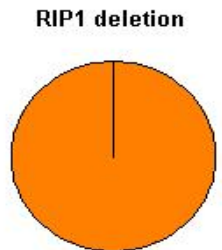
Compare with observations (5)

Conclusions

Predictions

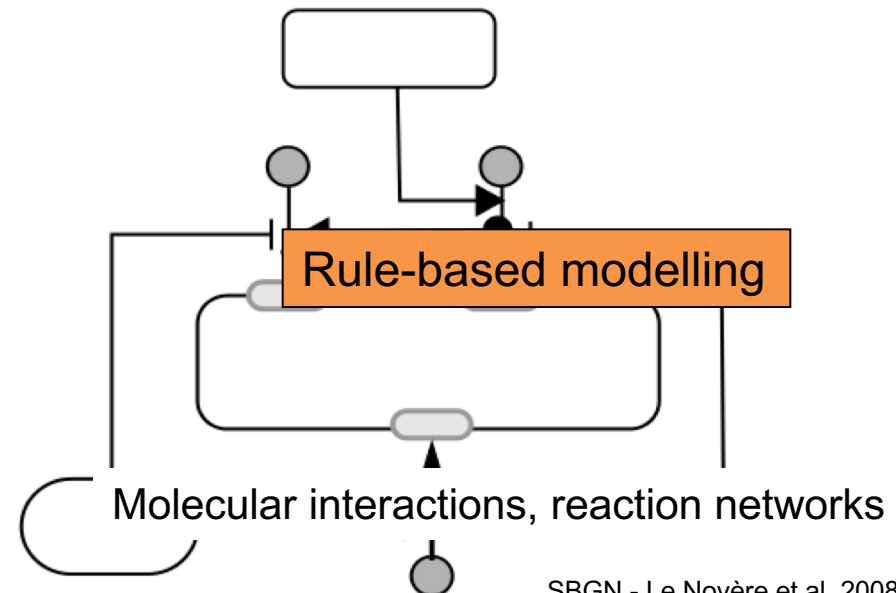
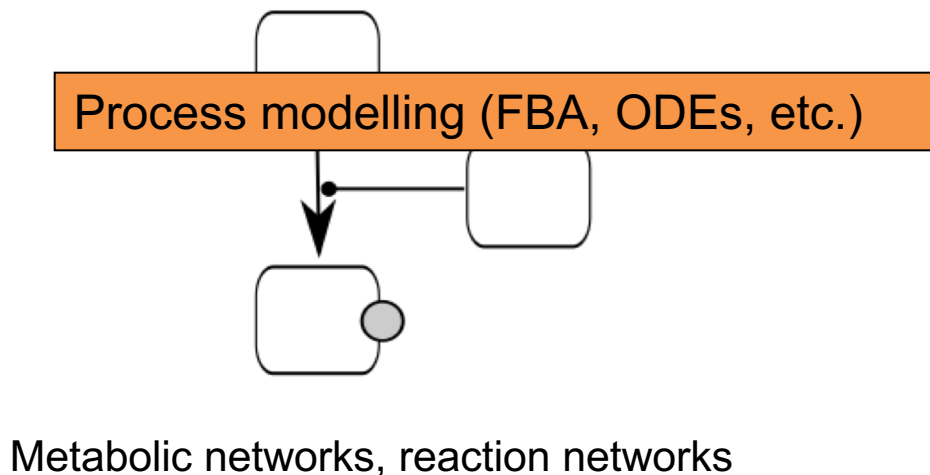
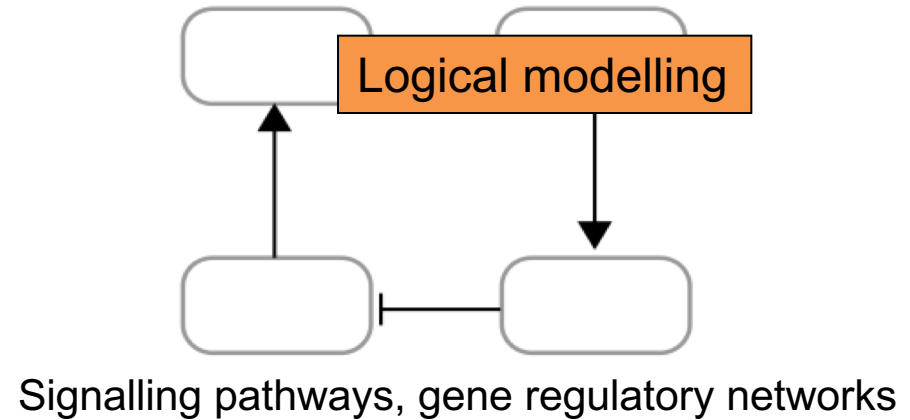
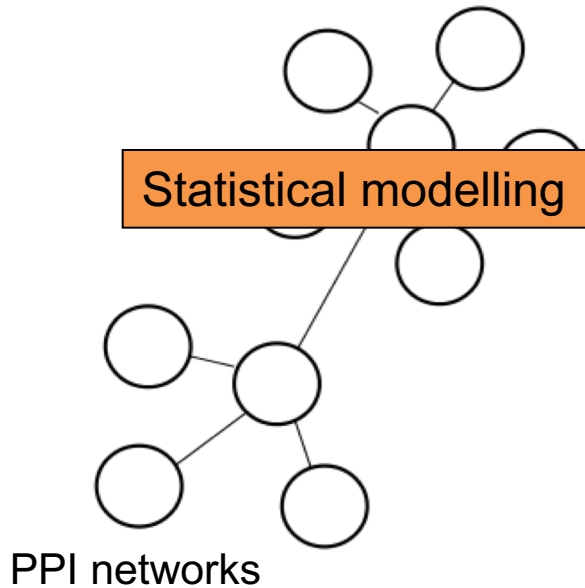
not in agreement

in agreement



Transient activity of RIP1 in necrotic cells

# From a network to a model: different types of standard networks and their preferred formalism



# Choosing the appropriate format for a mathematical model

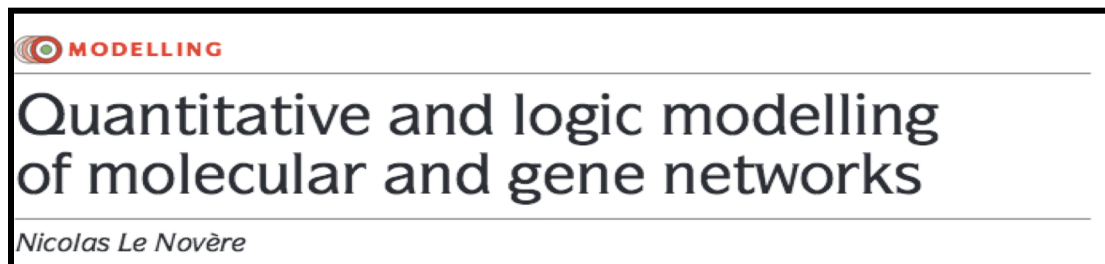
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Different formalisms:

- Logical
- ODEs (ordinary differential equations)
- PDEs (partial differential equations)
- Algebraic equations
- Cell automata
- ...

Different types of simulations:

- Discrete approach
- Deterministic approach
- Stochastic approach
- ...

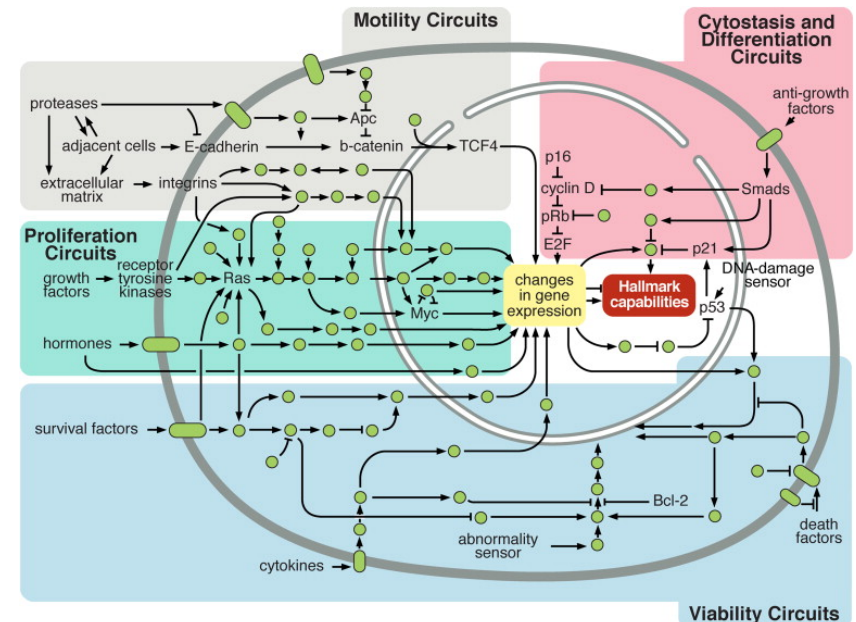


# Building a model in the context of cancer

- Summarize into a model (network)  
what is known about altered processes  
(including feedbacks)
- Understand the importance of alterations:  
mutations, copy number variations,...
- Identify the main players of a process
- Identify the possible intervention points:  
suggest single or combinations of drugs
- Anticipate effects of some drugs
- Explore effects of clonality
- Predict / explain mechanisms of resistance

## « Cancer is a network disease »

Goh et al. PNAS, 2007



Hanahan and Weinberg, 2011

# Two questions are addressed today

---

**Application:** How do the two signalling pathways, p53 and Notch, interact to trigger metastasis in colon cancer?

→ A logical model of early steps of metastasis

**Methodology:** How to automatize these analyses and extract knowledge and predictions from any logical model?



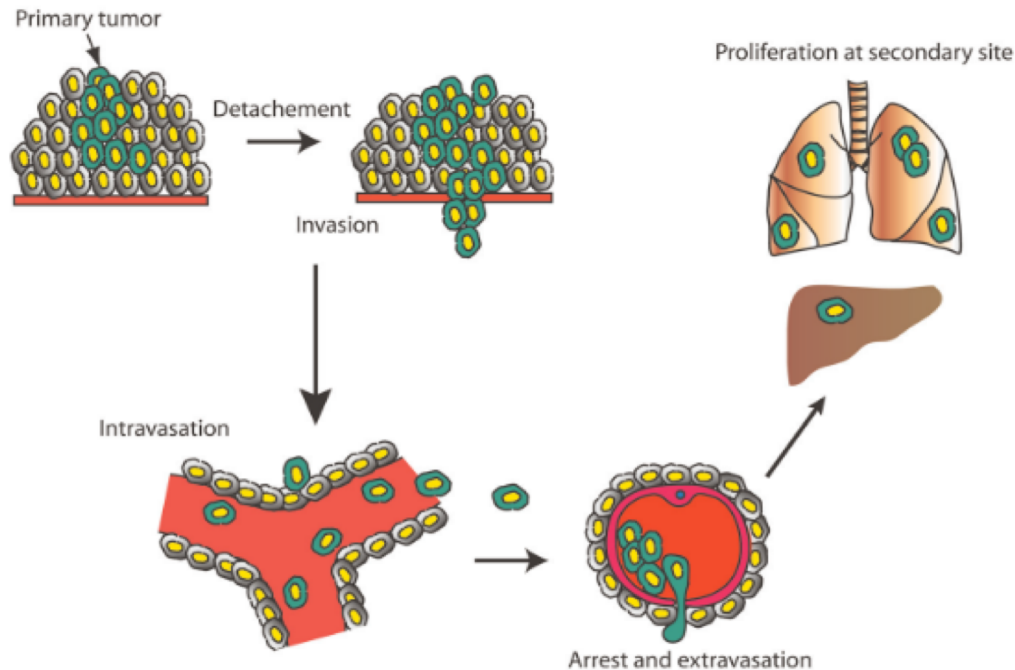
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Application to cancer:

A logical model of the early steps of  
metastasis



# Metastasis

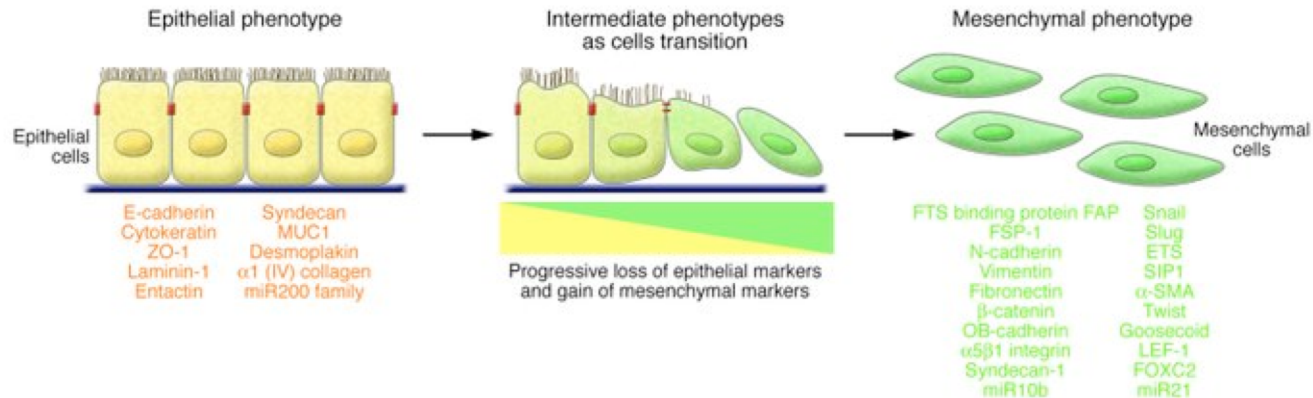


Cancer cell spreads from its primary site to a distant site

It occurs through a series of steps:

- local invasion (of neighboring tissues),
- intravasation,
- transport (through the blood or the lymph system),
- extravasation (re-enter a distant tissue), and
- colonization.

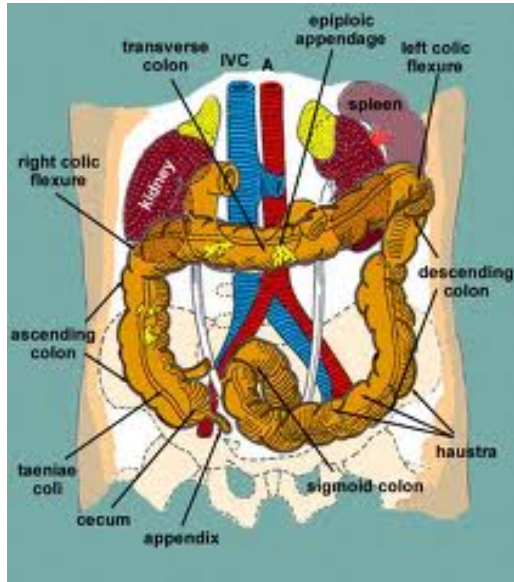
# EMT – the players



Kalluri and Weinberg (2009) J Clin Invest. 2009

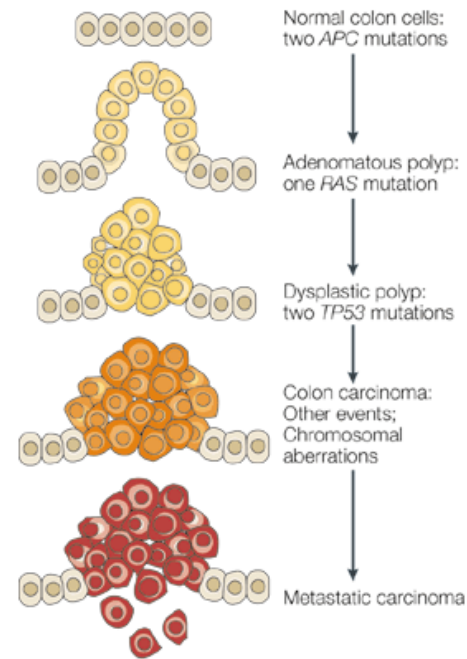
EMT (Epithelial to mesenchymal transition) is a biological process by which cells lose epithelial characteristics (e.g., cell-cell adhesion), gain invasive properties and acquire mesenchymal phenotype.

# Colon cancer



Affected area: Large intestine (colon),  
Rectum (end of the colon)

Historically well studied: progressive  
accumulation of mutations, APC, RAS, p53



Nature Reviews | Cancer



## Experimental system:

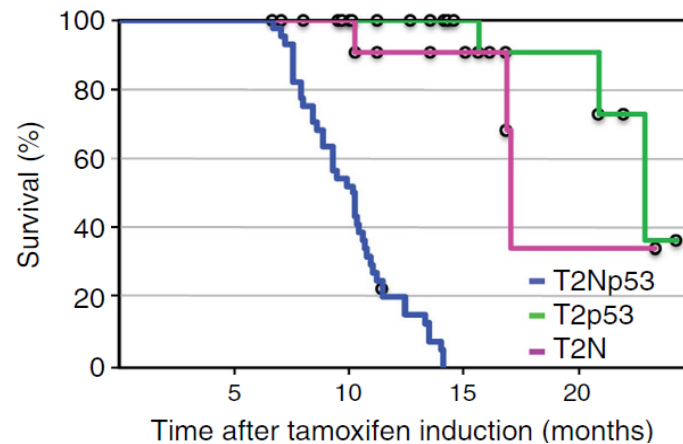
mice with a possibility of conditional mutations in gut  
(villin-CreERT2 tamoxifen-dependent intestine-specific recombination)

# Mice model of colorectal cancer

## Experimental results:

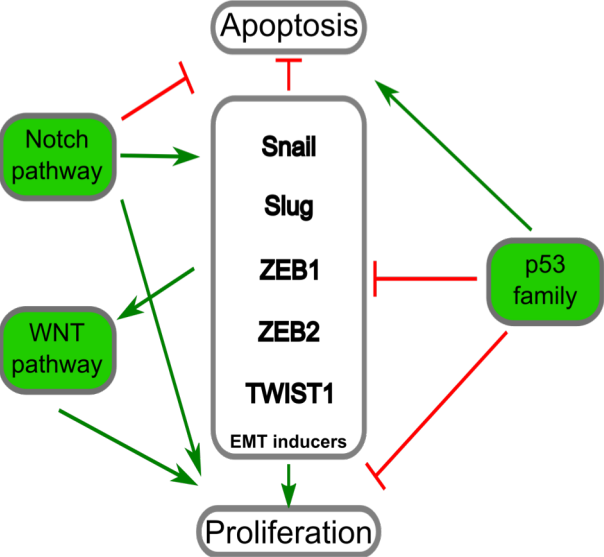
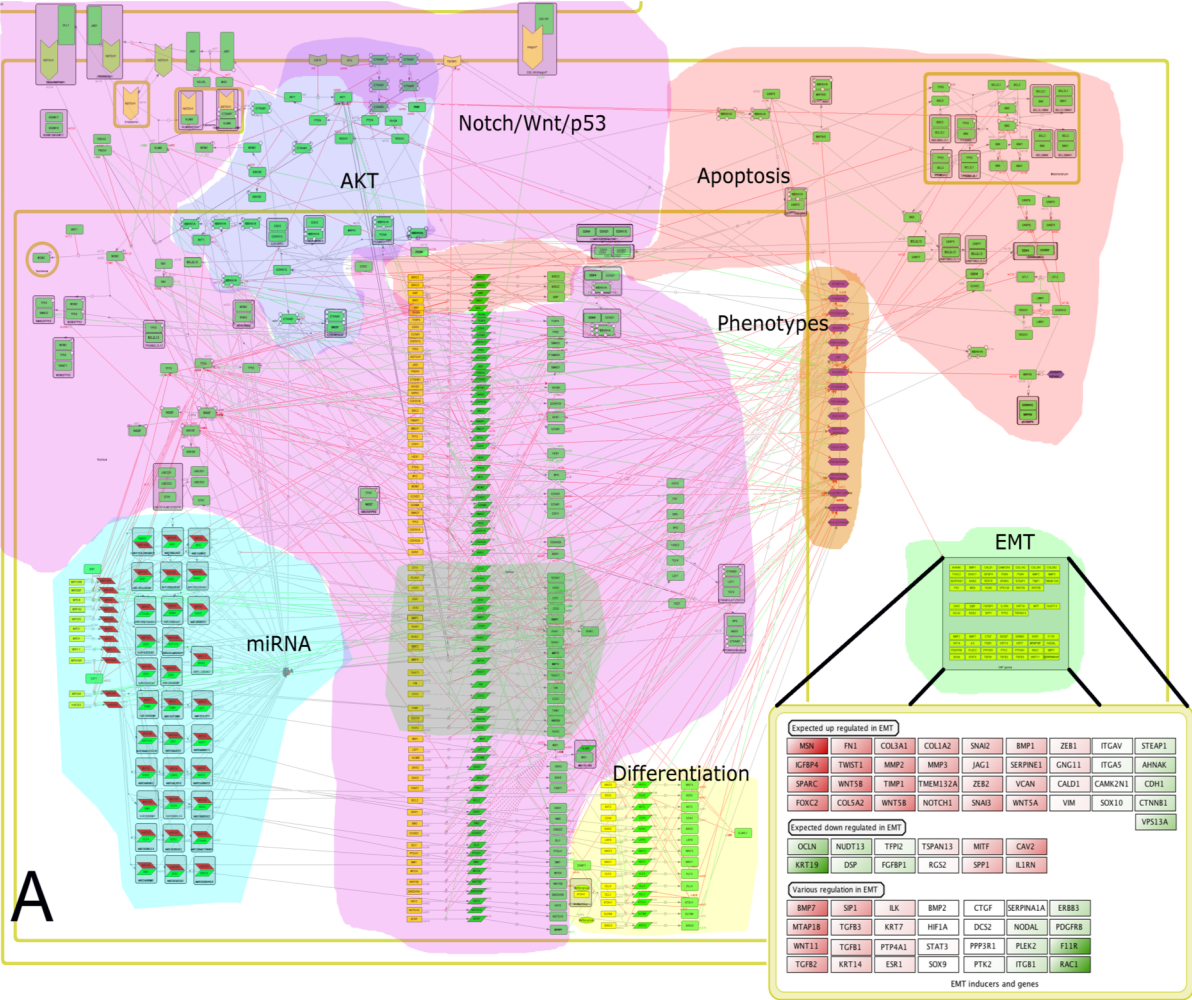
Two signaling pathways, Notch and p53, are involved in triggering metastasis in mice

- Single mutations (NICD<sup>++</sup> or p53<sup>--</sup>) do not induce metastases
- NICD<sup>++</sup>/p53<sup>--</sup> mice developed adenocarcinoma 15 months post induction
- Compared to single mutant mice, double mutant mice show drastic decrease in survival





# Network description and hypothesis



➔ Metastasis (EMT) occurs

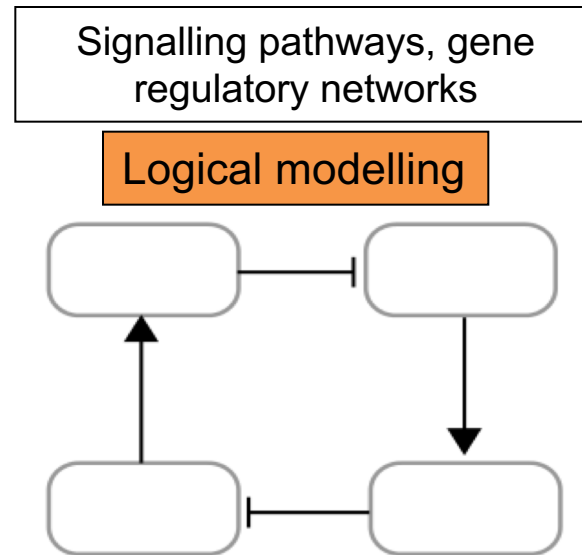
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Can we formally confirm, with a mathematical model, the appearance of metastasis in mice carrying the double mutation: NICD +/+ p53 -/-?



# Why to model with logical formalism?

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In general:

- The question is qualitative
- The data are discrete (mutations, copy number, etc.)
- Expression data are not absolute values
- No information over time
- No details about the precise biochemical reactions

Here:

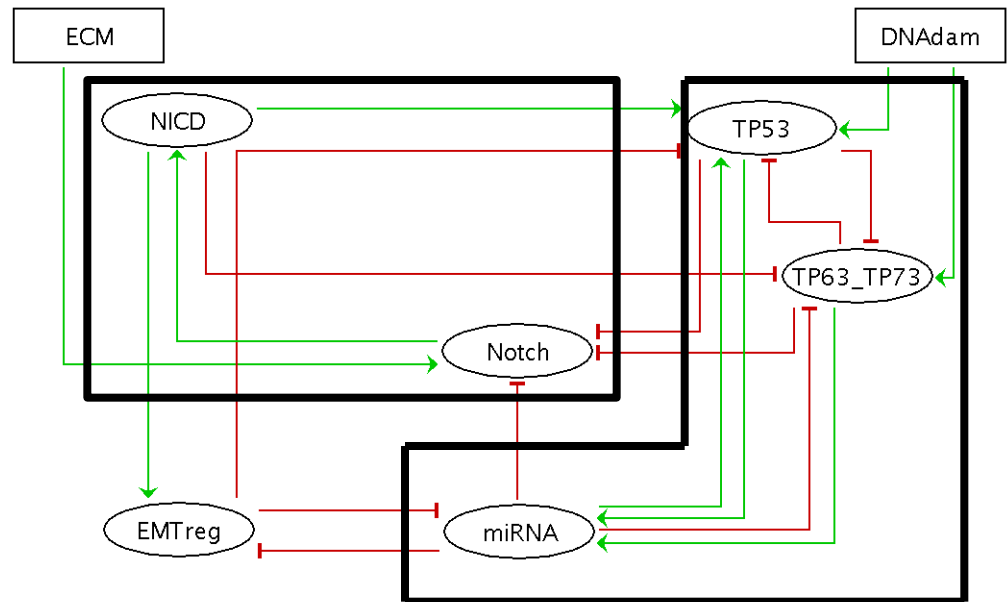
- The question is qualitative
- The data are phenotypes (or survival info)
- No information about time
- Only hand-waving hypotheses

# A small network of the p53 and Notch pathway interactions

- The hypothesis: the two pathways regulate the activity of the EMT regulators
- Notch pathway activates the EMT regulators
  - p53 pathway inhibits the EMT regulators through miRNA

*Notch pathway players:*  
Notch, NICD

*p53 pathway players:*  
TP53  
TP63 / TP73  
miRNA



➔ Translation into a logical model

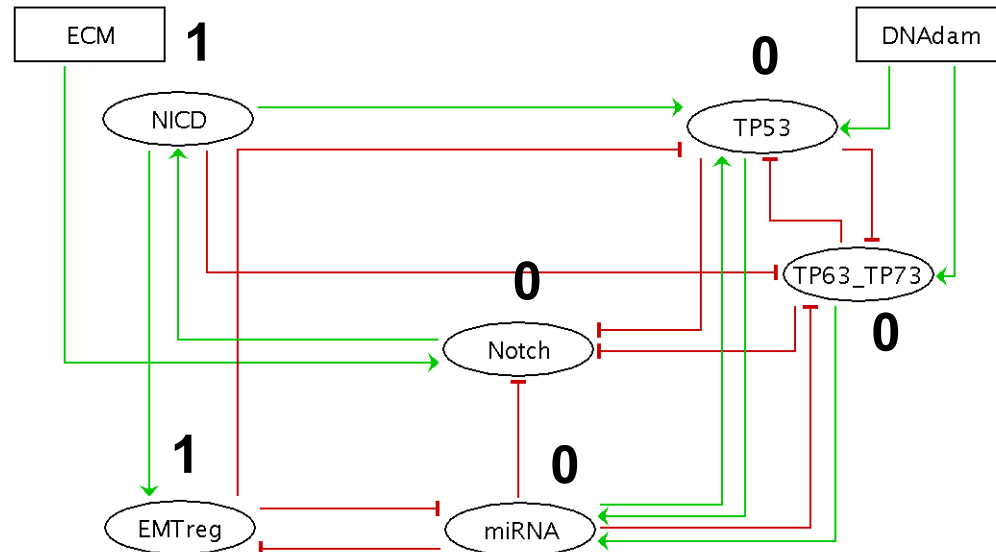
# The logical model

## Boolean logic:

Connectors: AND (&), OR (|), NOT (!), XOR (/)

Logic depends on incoming arrows

ID	Val	Logical function
NICD	1	• Notch
Notch	1	• $ECM \& !miRNA \& !TP63\_TP73 \& !TP53$
TP53	1	• $(DNAdam   NICD   miRNA) \& !EMTreg \& !TP63\_TP73$
TP63_TP73	1	• $DNAdam \& !miRNA \& !NICD \& !TP53$
miRNA	1	• $(TP53   TP63\_TP73) \& !EMTreg$
EMTreg	1	• $NICD \& !miRNA$
DNAdam		no function
ECM		no function



Construction and first analyses of the model using



- Identifications of attractors\* (solutions of system)
- Functionality of circuits

\* **Attractors** are subgraphs of the **state transition graph** with no outgoing arrows.  
Ex: stable steady states & cyclic attractors



# MaBoSS

*Idea of MaBoSS (Markovian Boolean Stochastic Simulator):*

Fill the gap between ODE and discrete time Boolean formalisms with **continuous time Boolean modeling**



Markovian Boolean Stochastic Simulator



- Home
- Installation
- How To
- Models
  - Toy Model
  - Cell Cycle
  - Cell Fate
  - p53 / MDM2
  - Drosophila
  - Patterning
- Publication
- Documentation
- The Team

## MaBoSS Project

MaBoSS is a C++ software for simulating continuous/discrete time Markov processes, applied on a Boolean network.

MaBoSS uses a specific language for associating transition rates to each node. Given some initial conditions, MaBoSS applies Monte-Carlo kinetic algorithm (or Gillespie algorithm) to the network to produce time trajectories. Time evolution of probabilities are estimated. In addition, global and semi-global characterizations of the whole system are computed.

<https://maboss.curie.fr>

Stoll et al. *BMC Systems Biology* 2012, **6**:116  
<http://www.biomedcentral.com/1752-0509/6/116>

BMC  
Systems Biology

METHODOLOGY ARTICLE Open Access

### Continuous time boolean modeling for biological signaling: application of Gillespie algorithm

Gautier Stoll<sup>1,2,3\*</sup>, Eric Viara<sup>4</sup>, Emmanuel Barillot<sup>1,2,3</sup> and Laurence Calzone<sup>1,2,3</sup>

Application Note Bioinformatics, in press

### MaBoSS 2.0: an environment for stochastic Boolean modeling

Gautier Stoll<sup>1,2,3,4\*</sup>, Barthélémy Caron<sup>5</sup>, Eric Viara<sup>6</sup>, Aurélien Dugourd<sup>5</sup>, Andrei Zinovyev<sup>5</sup>, Aurélien Naldi<sup>7</sup>, Guido Kroemer<sup>1,2,3,4,8,9,10</sup>, Emmanuel Barillot<sup>5</sup> and Laurence Calzone<sup>5,\*</sup>

➔ Use MaBoSS to quantify the solutions and explore the transient events

# Motivation for continuous time algorithm

---

Synchronized / asynchronous algorithms are defined on discrete time steps.

→ Problems:

- Comparison between model and experimental results mainly on final states (when does a biological experimental system reach its final state?)
- Difficulty of modeling transient effects (e.g. in cell cycle)
- Difficulty of implementing different time scales of events (e.g., a phosphorylation is faster than a transcription)

→ General idea: fill the gap between ODE and discrete time Boolean modeling with **continuous time Boolean modeling**

The model is defined by:

- Initial condition: probability distribution over network states at time 0
- a rate of change associated to each transition (separate rate up and rate down)

Method: continuous time Markov process / Gillespie algorithm

→ To each Boolean state, a probability is associated over time

```
CurrentOp.bnd
Node NICD {
  logic = (Notch);
  rate_up = @logic ? $u_NICD : 0;
  rate_down = @logic ? 0 : $d_NICD;
}

Node Notch {
  logic = (!miRNA & ECM & !TP53 & !TP63_TP73);
  rate_up = @logic ? $u_Notch : 0;
  rate_down = @logic ? 0 : $d_Notch;
}

Node TP53 {
  logic = (!NICD & !TP63_TP73 & !miRNA & !EMTreg & DNAdam) | (!
NICD & !TP63_TP73 & miRNA & !EMTreg) | (NICD & !TP63_TP73 & !
EMTreg);
  rate_up = @logic ? $u_TP53 : 0;
  rate_down = @logic ? 0 : $d_TP53;
}

Node TP63_TP73 {
  logic = (!NICD & !TP53 & !miRNA & DNAdam);
  rate_up = @logic ? $u_TP63_TP73 : 0;
  rate_down = @logic ? 0 : $d_TP63_TP73;
}

Node miRNA {
  logic = (!TP53 & TP63_TP73 & !EMTreg) | (TP53 & !EMTreg);
  rate_up = @logic ? $u_miRNA : 0;
  rate_down = @logic ? 0 : $d_miRNA;
}

Node EMTreg {
  logic = (NICD & !miRNA);
  rate_up = @logic ? $u_EMTreg : 0;
  rate_down = @logic ? 0 : $d_EMTreg;
}

Node DNAdam {
  logic = (DNAdam);
  rate_up = @logic ? $u_DNAdam : 0;
  rate_down = @logic ? 0 : $d_DNAdam;
}

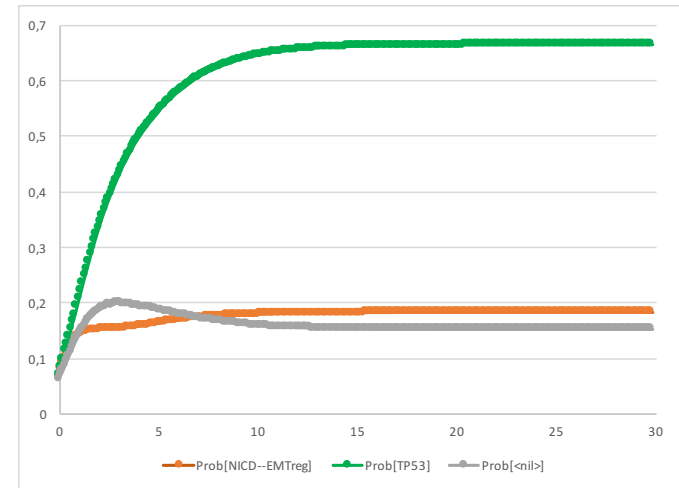
Node ECM {
  logic = (ECM);
  rate_up = @logic ? $u_ECM : 0;
  rate_down = @logic ? 0 : $d_ECM;
}

CurrentOp.bnd.cfg
$u_NICD = 1;
$d_NICD = 1;
$u_Notch = 1;
$d_Notch = 1;
$u_TP53 = 1;
$d_TP53 = 1;
$u_TP63_TP73 = 1;
$d_TP63_TP73 = 1;
$u_miRNA = 1;
$d_miRNA = 1;
$u_EMTreg = 1;
$d_EMTreg = 1;
$u_DNAdam = 1;
$d_DNAdam = 1;
$u_ECM = 1;
$d_ECM = 1;

//[NICD].istate = 1 [0] , 0 [1];
//[Notch].istate = 1 [0] , 0 [1];
//[TP53].istate = 1 [0] , 0 [1];
//[TP63_TP73].istate = 1 [0] , 0 [1];
//[miRNA].istate = 1 [0] , 0 [1];
//[EMTreg].istate = 1 [0] , 0 [1];
//[DNAdam].istate = 1 [0] , 0 [1];
//[ECM].istate = 1 [0] , 0 [1];

NICD.is_internal = 0;
Notch.is_internal = 1;
TP53.is_internal = 0;
TP63_TP73.is_internal = 0;
miRNA.is_internal = 1;
EMTreg.is_internal = 0;
DNAdam.is_internal = 1;
ECM.is_internal = 1;

time_tick = 0.1;
max_time = 30;
sample_count = 50000;
discrete_time = 0;
use_physrandgen = 1;
seed_pseudorandom = 0;
display_traj = 0;
statdist_traj_count = 0;
statdist_cluster_threshold = 1;
thread_count = 1;
statdist_similarity_cache_max_size = 20000;
```

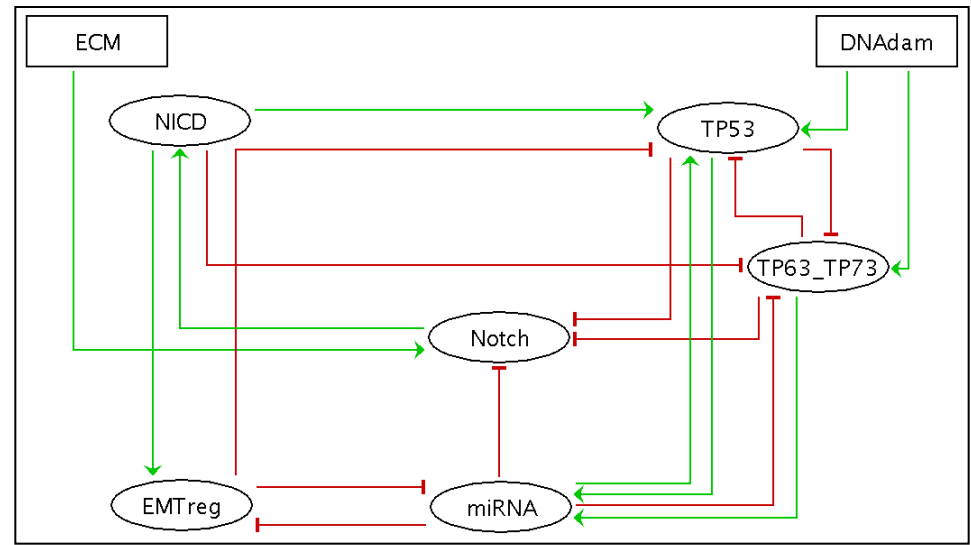


Time trajectories

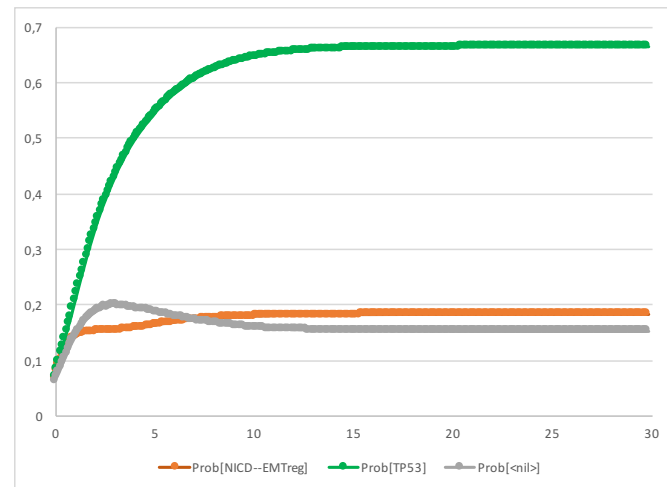
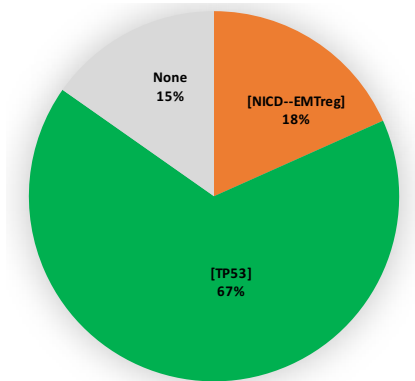
Tools:



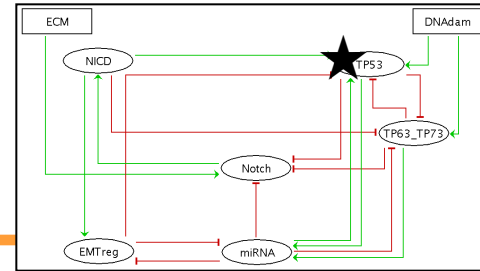
# Simulation of the simple network



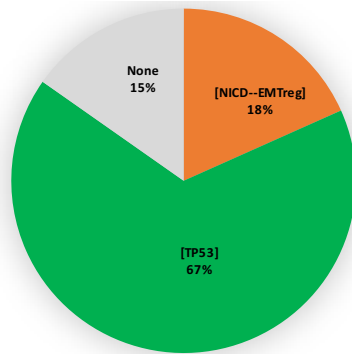
Probability	DNAdam	ECM	Notch	NICD	miRNA	TP53	TP63_TP73	EMTreg	Phenotypes
0.12396	0	1	1	1	1	0	0	1	EMT ON Apoptosis OFF
0.05912	1	1	1	1	1	0	0	1	EMT ON Apoptosis OFF
0.12538	0	1	0	0	0	1	1	0	EMT OFF Apoptosis ON
0.19072	1	1	0	0	0	1	1	0	EMT OFF Apoptosis ON
0.09788	0	0	0	0	0	1	1	0	EMT OFF Apoptosis ON
0.25044	1	0	0	0	0	1	1	0	EMT OFF Apoptosis ON
0.1525	0	0	0	0	0	0	0	0	None None



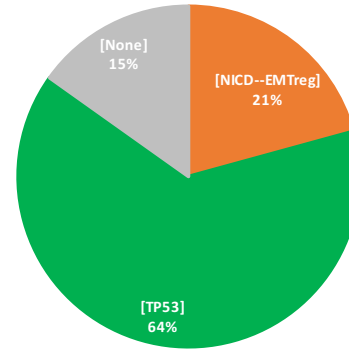
# Mutant simulations



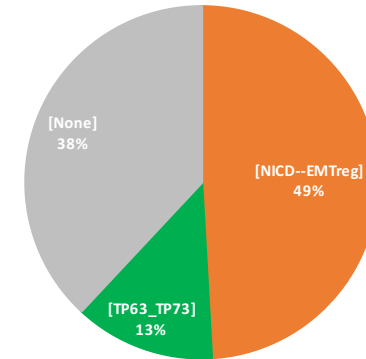
Wild type



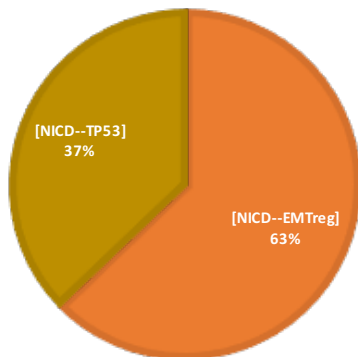
TP63 ↓



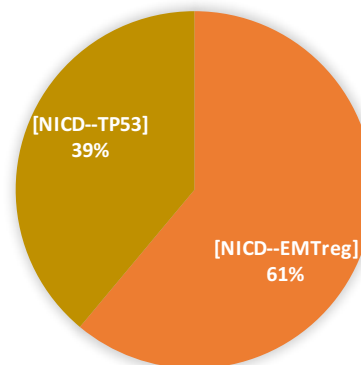
TP53 ↓



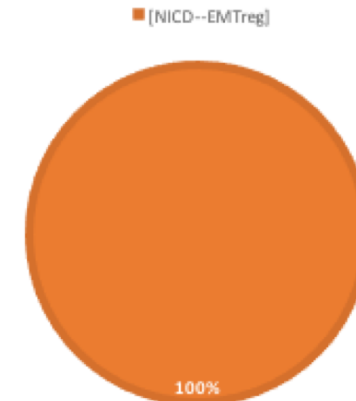
NICD ↑



NICD ↑ TP63 ↓



NICD ↑ TP53 ↓



→ coherent with experimental evidence



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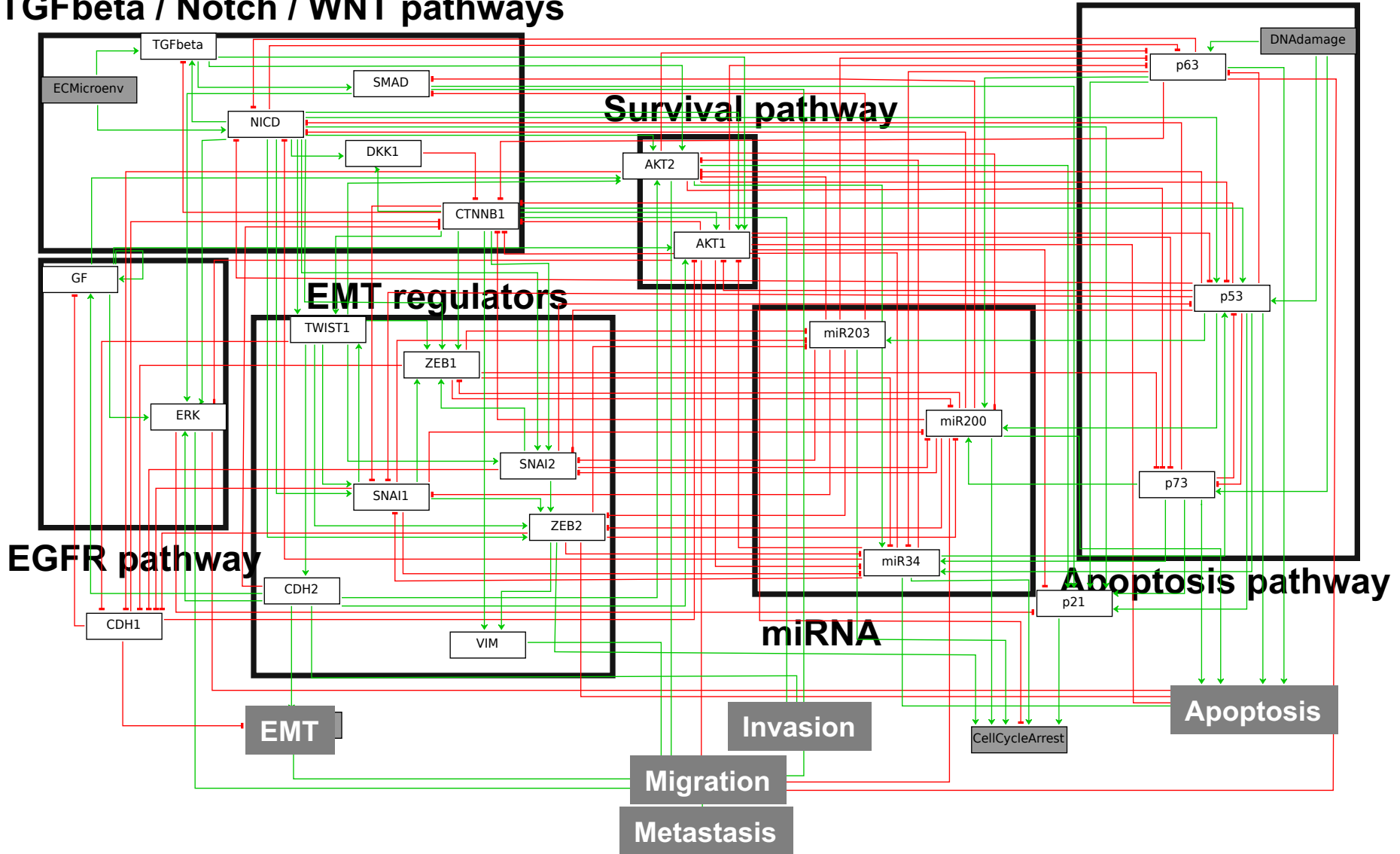
A more complex view of the process

# A regulatory network of p53 and Notch pathways

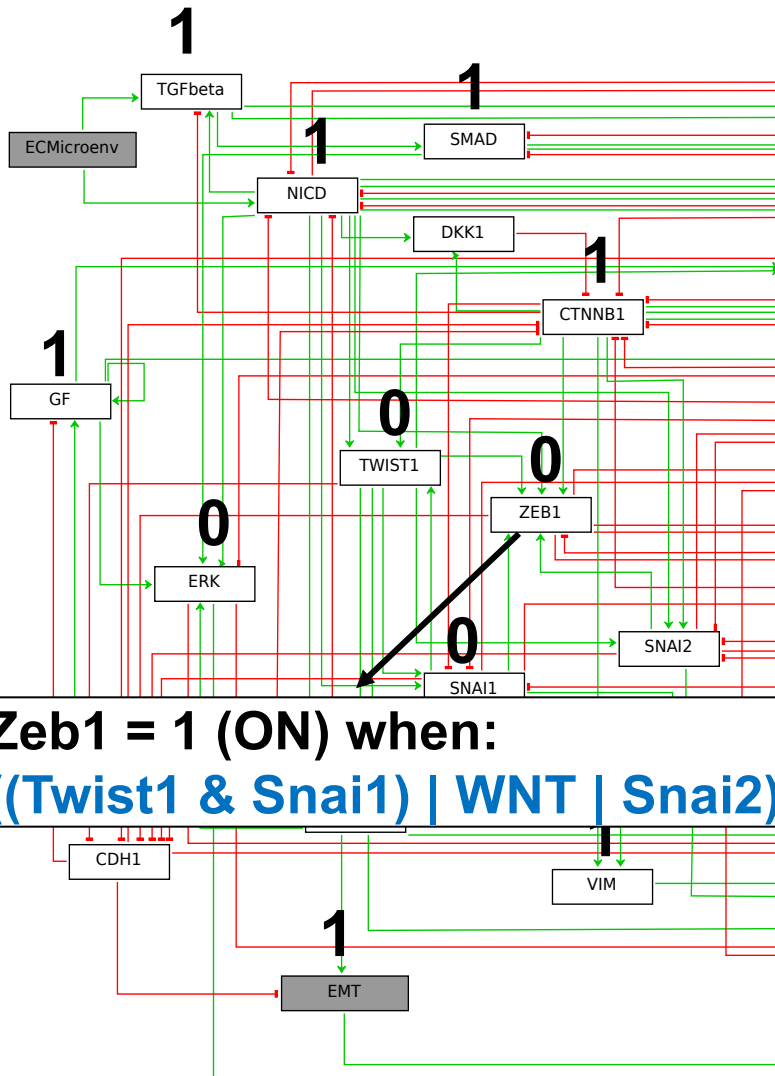
David Cohen



## TGFbeta / Notch / WNT pathways

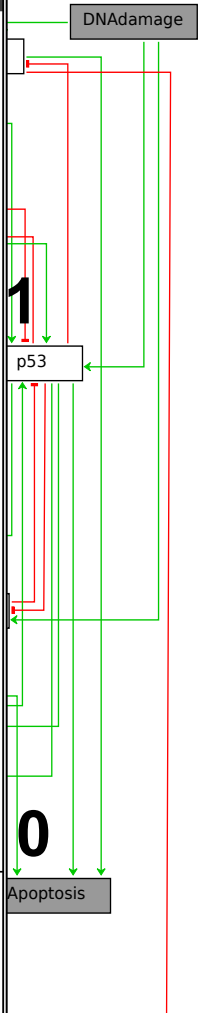


# Discrete mathematical model of metastases

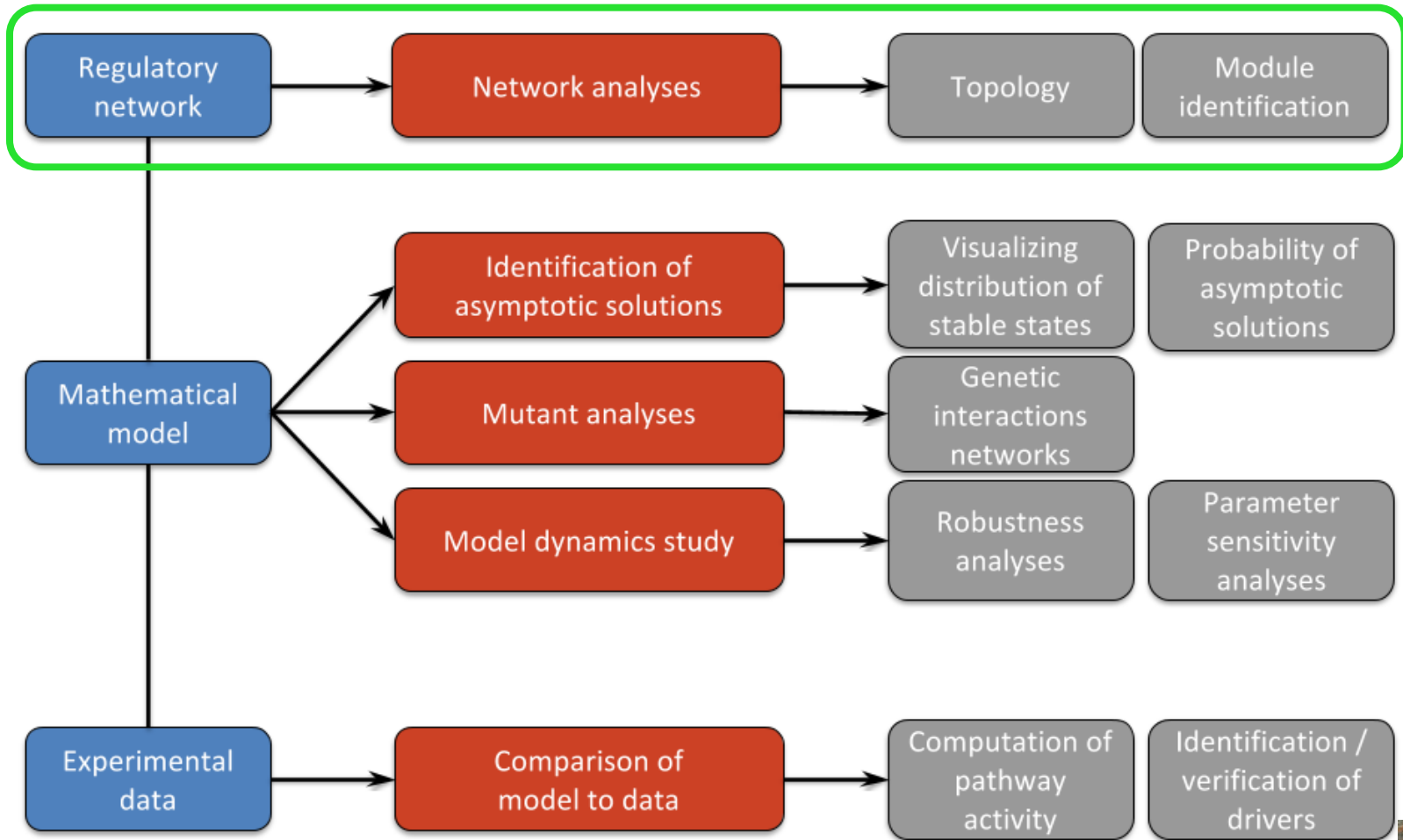


**Zeb1 = 1 (ON) when:**  
 **$((Twist1 \& Snai1) | WNT | Snai2)$**

Node	Rule
AKT1	CTNNB1 & (NICD   TGFbeta   GF   CDH2) & !p53 & !miR34 & !CDH1
AKT2	TWIST1 & (TGFbeta   GF   CDH2) & !(miR203   miR34   p53)
CDH1	!TWIST1 & !SNAI2 & !ZEB1 & !ZEB2 & !SNAI1 & !AKT2
CDH2	TWIST1
CTNNB1	!DKK1 & !p53 & !AKT1 & !miR34 & !miR200 & !CDH1 & !CDH2 & !p63
DKK1	CTNNB1   NICD
ERK	(SMAD   CDH2   GF   NICD) & !AKT1
GF	!CDH1 & (GF   CDH2)
miR200	(p63   p53   p73) & !(AKT2   SNAI1   SNAI2   ZEB1   ZEB2)
miR203	p53 & !(SNAI1   ZEB1   ZEB2)
miR34	!(SNAI1   ZEB1   ZEB2) & (p53   p73) & AKT2 & !p63 & !AKT1
NICD	!p53 & !p63 & !p73 & !miR200 & !miR34 & ECM
p21	((SMAD & NICD)   p63   p53   p73   AKT2) & !(AKT1   ERK)
p53	(DNADamage   CTNNB1   NICD   miR34) & !SNAI2 & !p73 & !AKT1 & !AKT2
p63	DNADamage & !NICD & !AKT1 & !AKT2 & !p53 & !miR203
p73	DNADamage & !p53 & !ZEB1 & !AKT1 & !AKT2
SMAD	TGFbeta & !miR200 & !miR203
SNAI1	(NICD   TWIST1) & !miR203 & !miR34 & !p53 & !CTNNB1
SNAI2	(TWIST1   CTNNB1   NICD) & !miR200 & !p53 & !miR203
TGFbeta	(ECM   NICD) & !CTNNB1
TWIST1	CTNNB1   NICD   SNAI1
VIM	CTNNB1   ZEB2
ZEB1	((TWIST1 & SNAI1)   CTNNB1   SNAI2   NICD) & !miR200
ZEB2	(SNAI1   (SNAI2 & TWIST1)   NICD) & !miR200 & !miR203
CellCycleArrest	(miR203   miR200   miR34   ZEB2   p21) & !AKT1
Apoptosis	(p53   p63   p73   miR200   miR34) & !ZEB2 & !AKT1 & !ERK
EMT	CDH2 & !CDH1
Invasion	(SMAD & CDH2)   CTNNB1
Migration	VIM & AKT2 & ERK & !miR200 & !AKT1 & EMT & Invasion & !p63
Metastasis	Migration

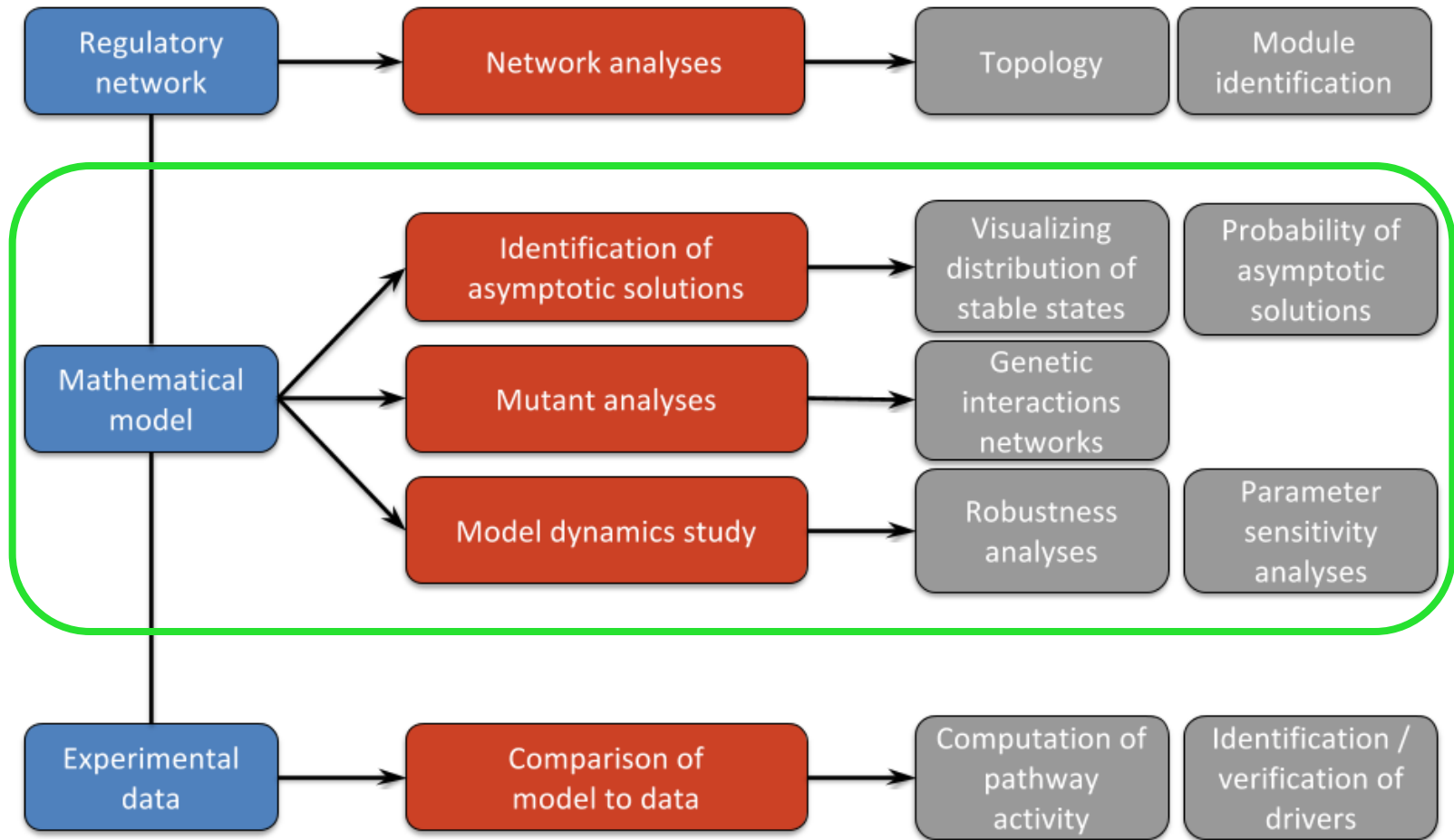


# Several analyses can be done on the model



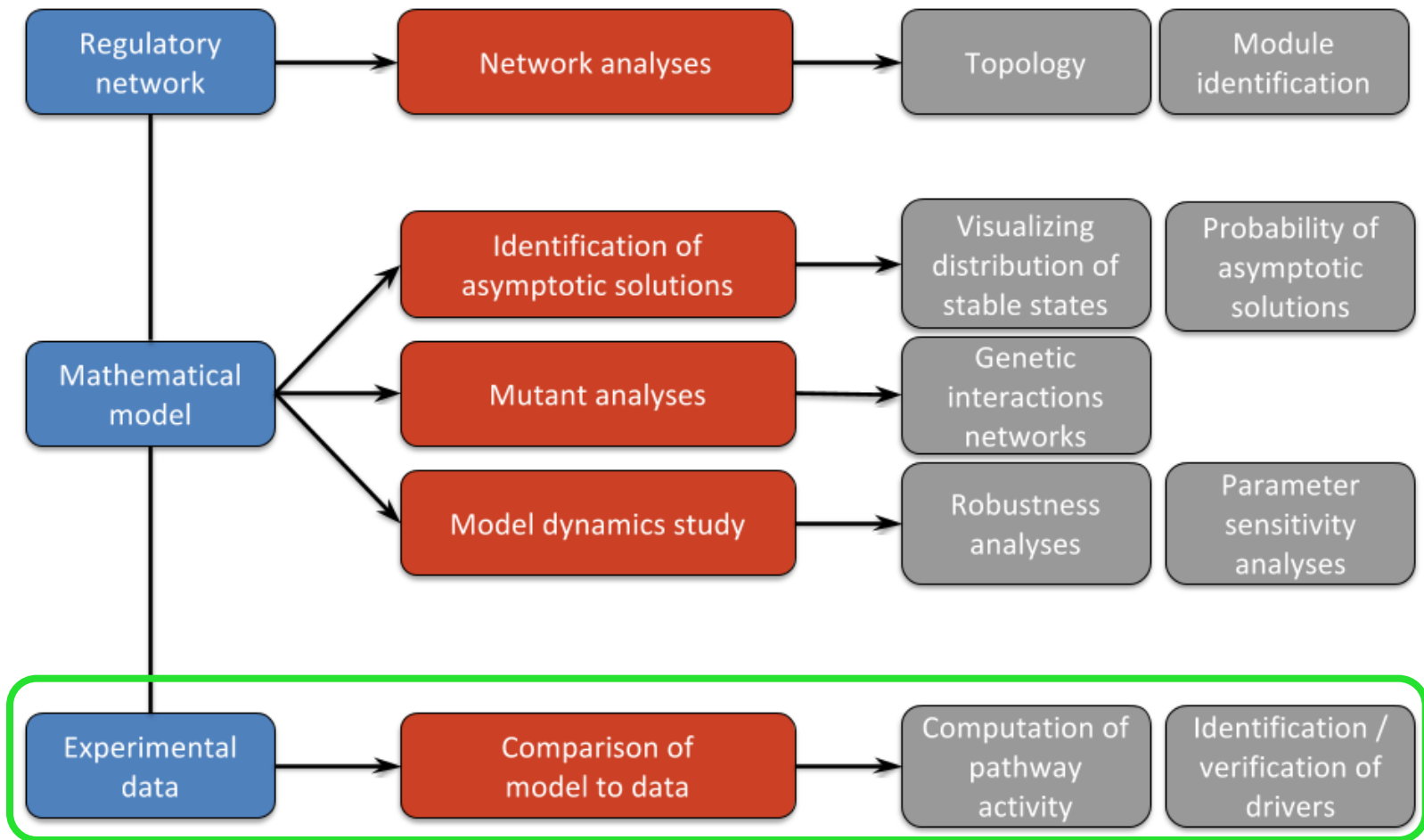
# Several analyses can be done on the model

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# Several analyses can be done on the model

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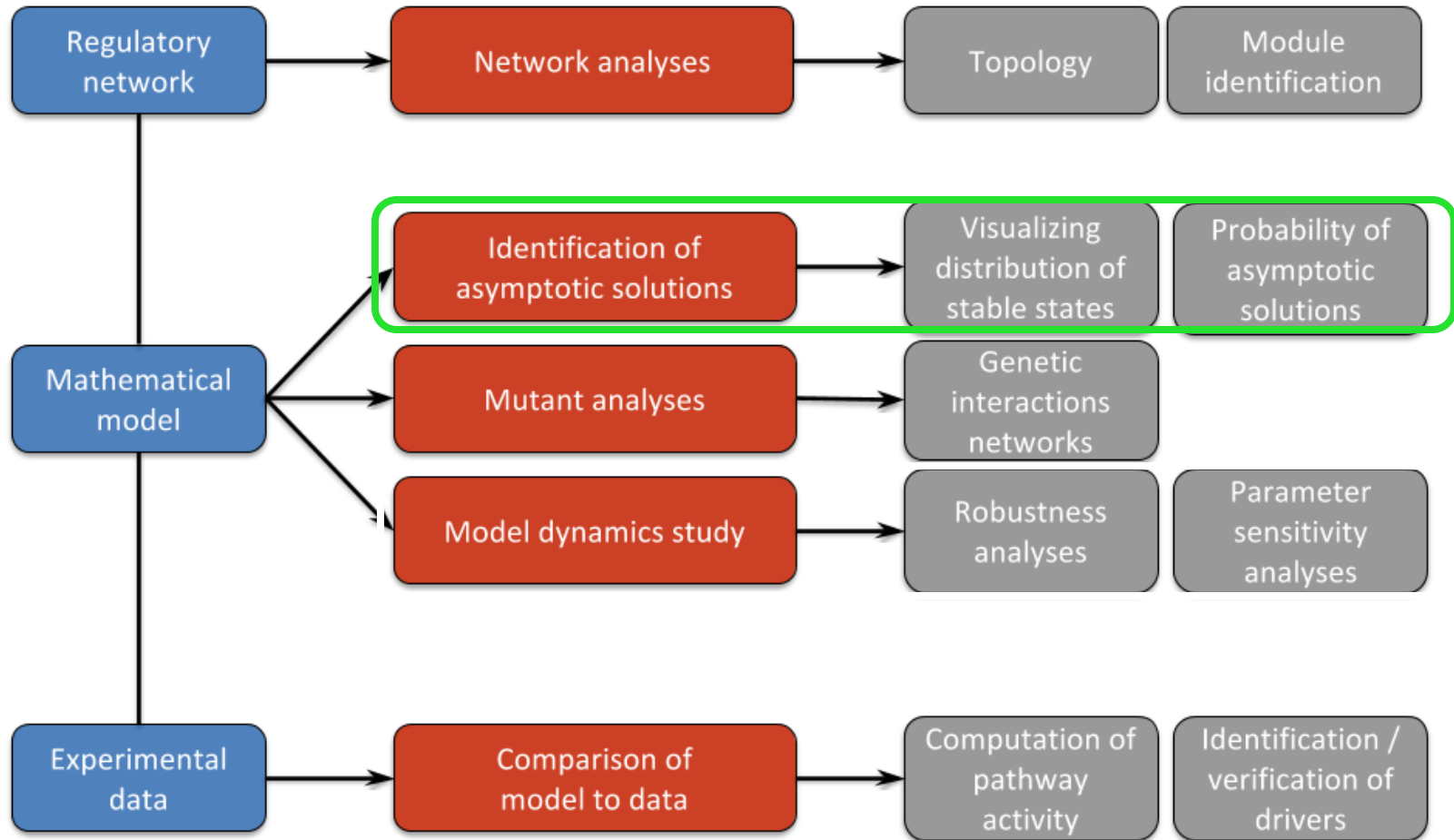
# What insights can we get from the mathematical model

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## Types of questions to be answered

- what are the **solutions of the model** that can be interpreted biologically?
- what are the **important nodes** of the network?
- how **robust/sensitive** is the model?
- can we **predict genetic interactions** (epistasis, synthetic lethality) from the model?
- what nodes are the most **related to a clinical output** (e.g. stage of the tumor or metastasis)?

# Pipeline



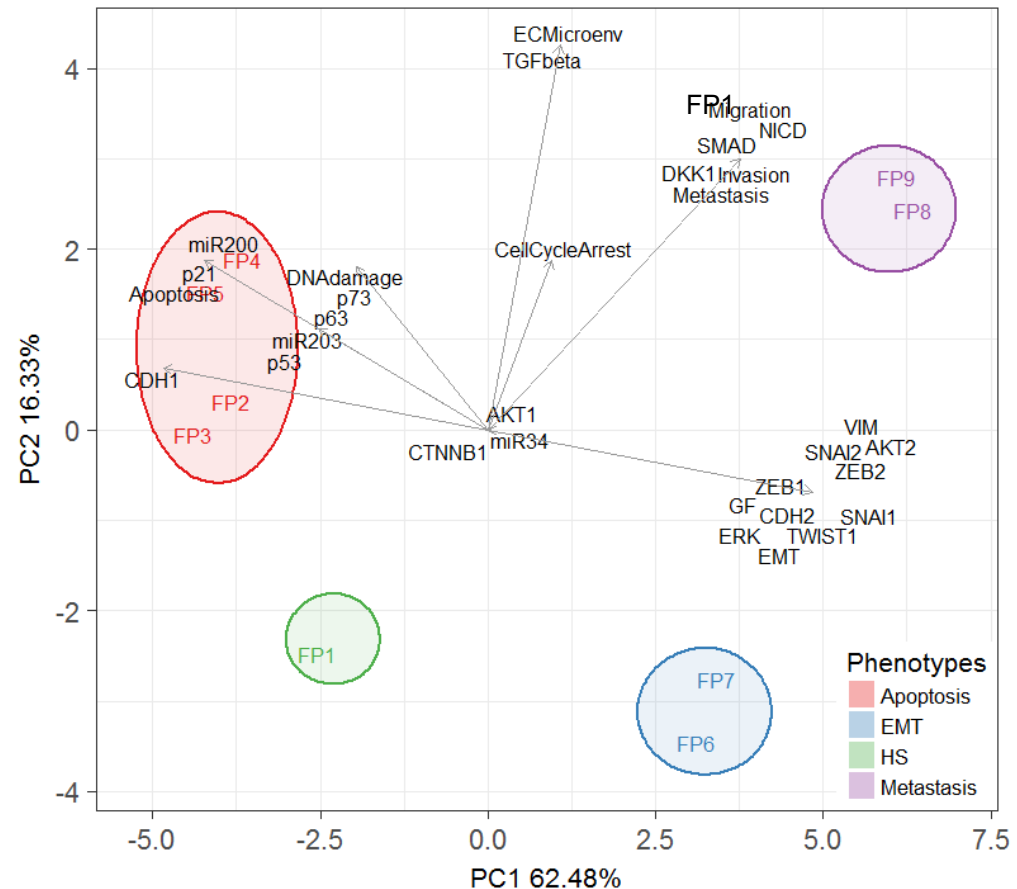


# Visualizing distribution of stable states

FP1 FP2 FP3 FP4 FP5 FP6 FP7 FP8 FP9

	HS	Apop1	Apop2	Apop3	Apop4	EMT1	EMT2	M1	M2
Metastasis	0	0	0	0	0	0	0	1	1
Migration	0	0	0	0	0	0	0	1	1
Invasion	0	0	0	0	0	0	0	1	1
EMT	0	0	0	0	0	1	1	1	1
Apoptosis	0	1	1	1	1	0	0	0	0
CellCycleArrest	0	1	1	1	1	1	1	1	1
ECMicroenv	0	0	0	1	1	0	0	1	1
DNADamage	0	1	1	1	1	1	0	1	0
GF	0	0	0	0	0	1	1	1	1
TGFbeta	0	0	0	1	1	0	0	1	1
p21	0	1	1	1	1	0	0	0	0
CDH1	1	1	1	1	1	0	0	0	0
CDH2	0	0	0	0	0	1	1	1	1
VIM	0	0	0	0	0	1	1	1	1
TWIST1	0	0	0	0	0	1	1	1	1
SNAI1	0	0	0	0	0	1	1	1	1
SNAI2	0	0	0	0	0	1	1	1	1
ZEB1	0	0	0	0	0	1	1	1	1
ZEB2	0	0	0	0	0	1	1	1	1
AKT1	0	0	0	0	0	0	0	0	0
DKK1	0	0	0	0	0	0	0	1	1
CTNNB1	0	0	0	0	0	0	0	0	0
NICD	0	0	0	0	0	0	0	1	1
p63	0	0	1	0	1	0	0	0	0
p53	0	1	0	1	0	0	0	0	0
p73	0	0	1	0	1	0	0	0	0
miR200	0	1	1	1	1	0	0	0	0
miR203	0	1	0	1	0	0	0	0	0
miR34	0	0	0	0	0	0	0	0	0
AKT2	0	0	0	0	0	1	1	1	1
ERK	0	0	0	0	0	1	1	1	1
SMAD	0	0	0	0	0	0	0	1	1

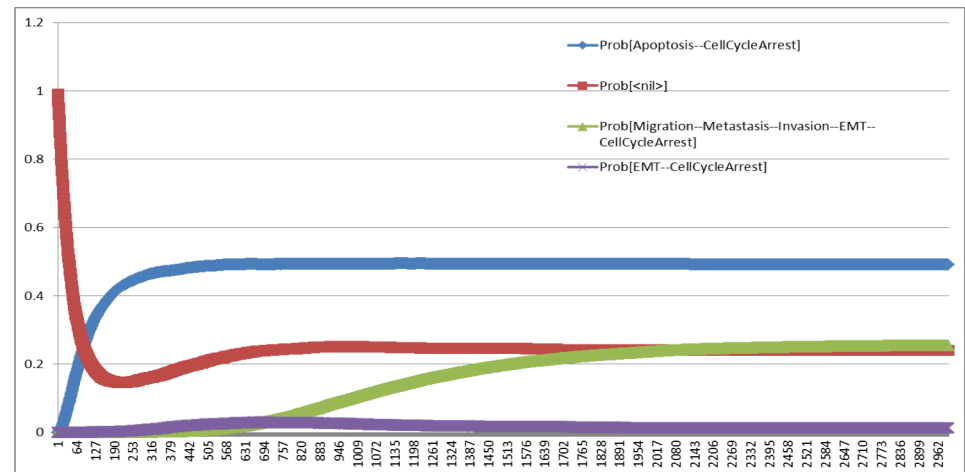
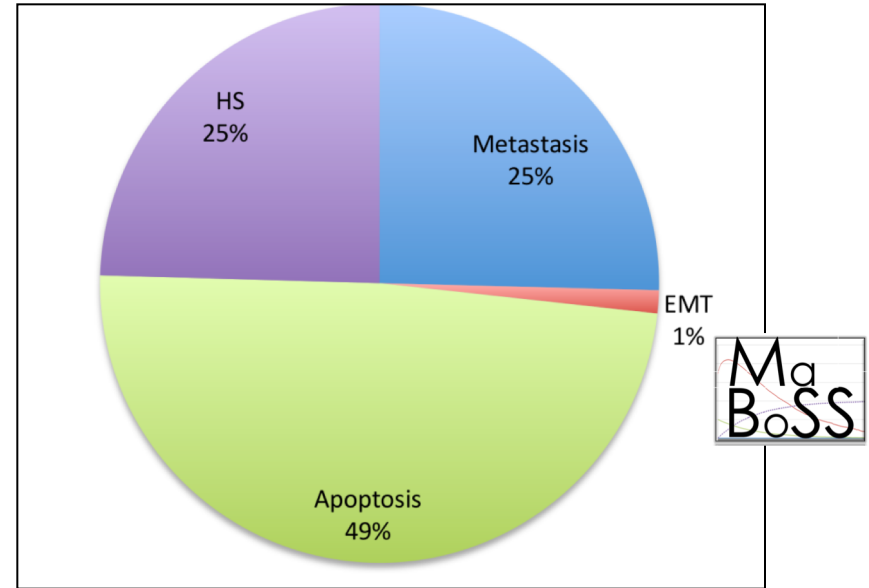
The solutions of the model can be classified using PCA



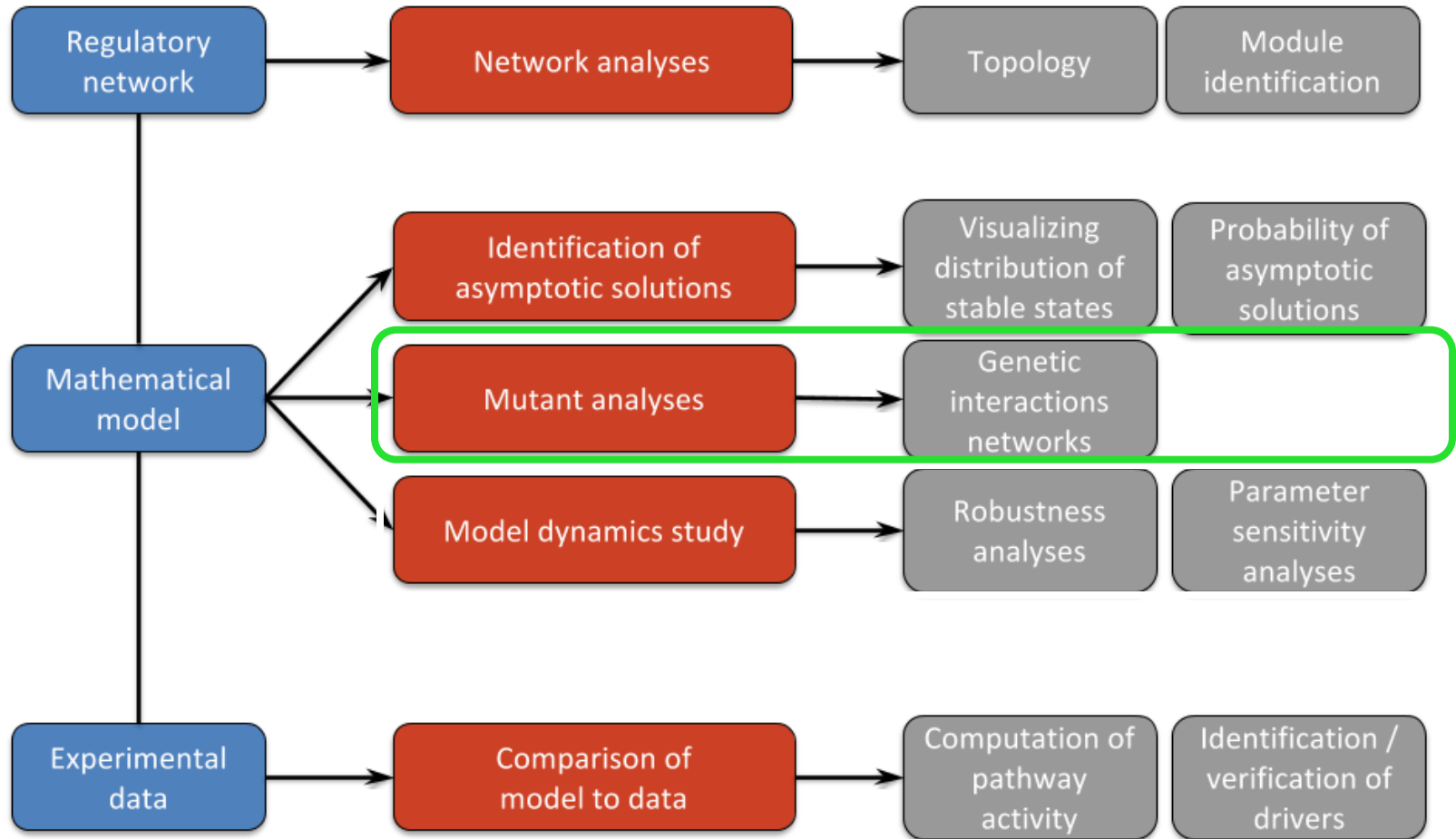
# Probability of asymptotic solutions

FP1 FP2 FP3 FP4 FP5 FP6 FP7 FP8 FP9

	HS	Apop1	Apop2	Apop3	Apop4	EMT1	EMT2	M1	M2
Metastasis	0	0	0	0	0	0	0	1	1
Migration	0	0	0	0	0	0	0	1	1
Invasion	0	0	0	0	0	0	0	1	1
EMT	0	0	0	0	0	1	1	1	1
Apoptosis	0	1	1	1	1	0	0	0	0
CellCycleArrest	0	1	1	1	1	1	1	1	1
ECMicroenv	0	0	0	1	1	0	0	1	1
DNA Damage	0	1	1	1	1	1	0	1	0
GF	0	0	0	0	0	1	1	1	1
TGFbeta	0	0	0	1	1	0	0	1	1
p21	0	1	1	1	1	0	0	0	0
CDH1	1	1	1	1	1	0	0	0	0
CDH2	0	0	0	0	0	1	1	1	1
VIM	0	0	0	0	0	1	1	1	1
TWIST1	0	0	0	0	0	1	1	1	1
SNAI1	0	0	0	0	0	1	1	1	1
SNAI2	0	0	0	0	0	1	1	1	1
ZEB1	0	0	0	0	0	1	1	1	1
ZEB2	0	0	0	0	0	1	1	1	1
AKT1	0	0	0	0	0	0	0	0	0
DKK1	0	0	0	0	0	0	0	1	1
CTNNB1	0	0	0	0	0	0	0	0	0
NICD	0	0	0	0	0	0	0	1	1
p63	0	0	1	0	1	0	0	0	0
p53	0	1	0	1	0	0	0	0	0
p73	0	0	1	0	1	0	0	0	0
miR200	0	1	1	1	1	0	0	0	0
miR203	0	1	0	1	0	0	0	0	0
miR34	0	0	0	0	0	0	0	0	0
AKT2	0	0	0	0	0	1	1	1	1
ERK	0	0	0	0	0	1	1	1	1
SMAD	0	0	0	0	0	0	0	1	1

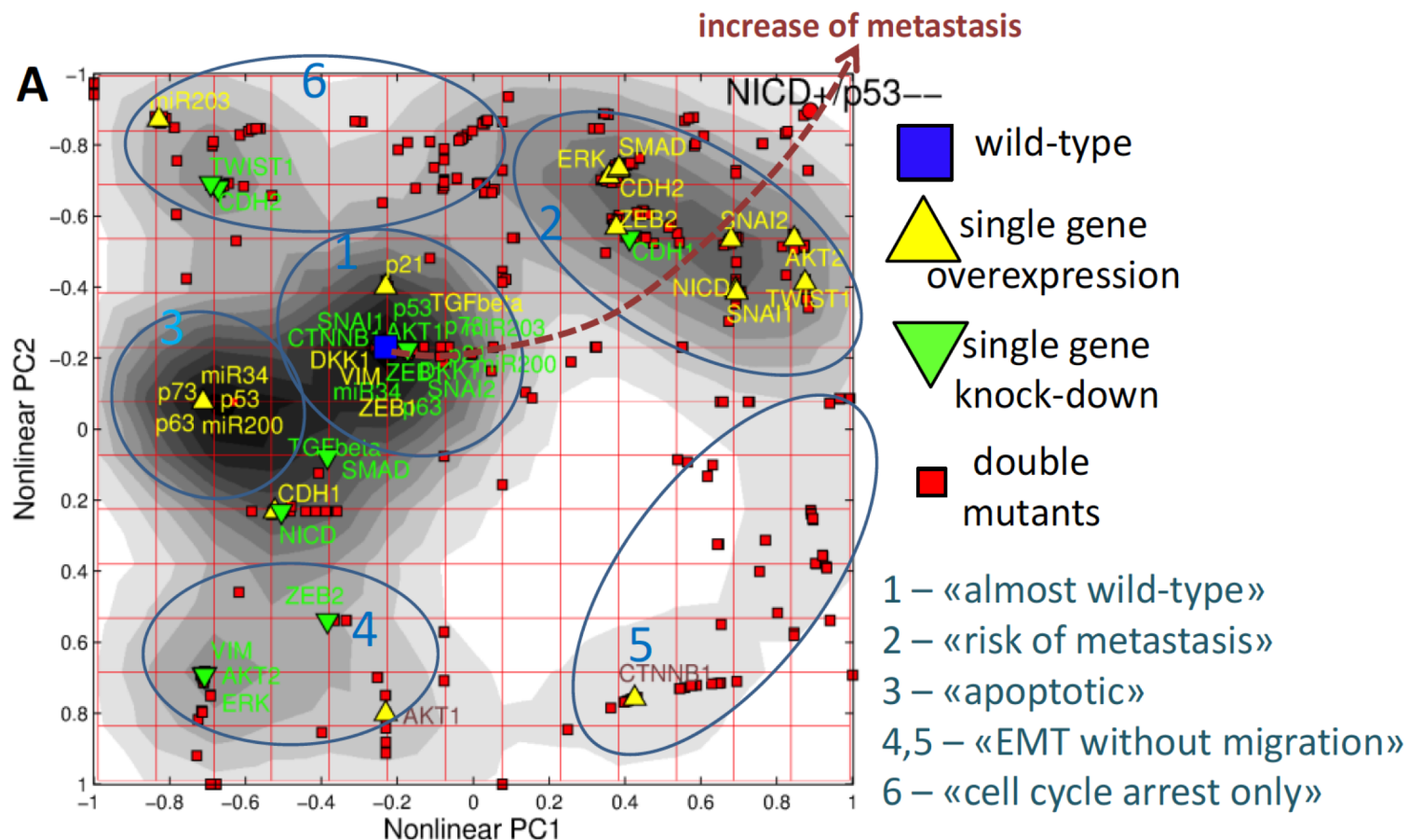


# Pipeline



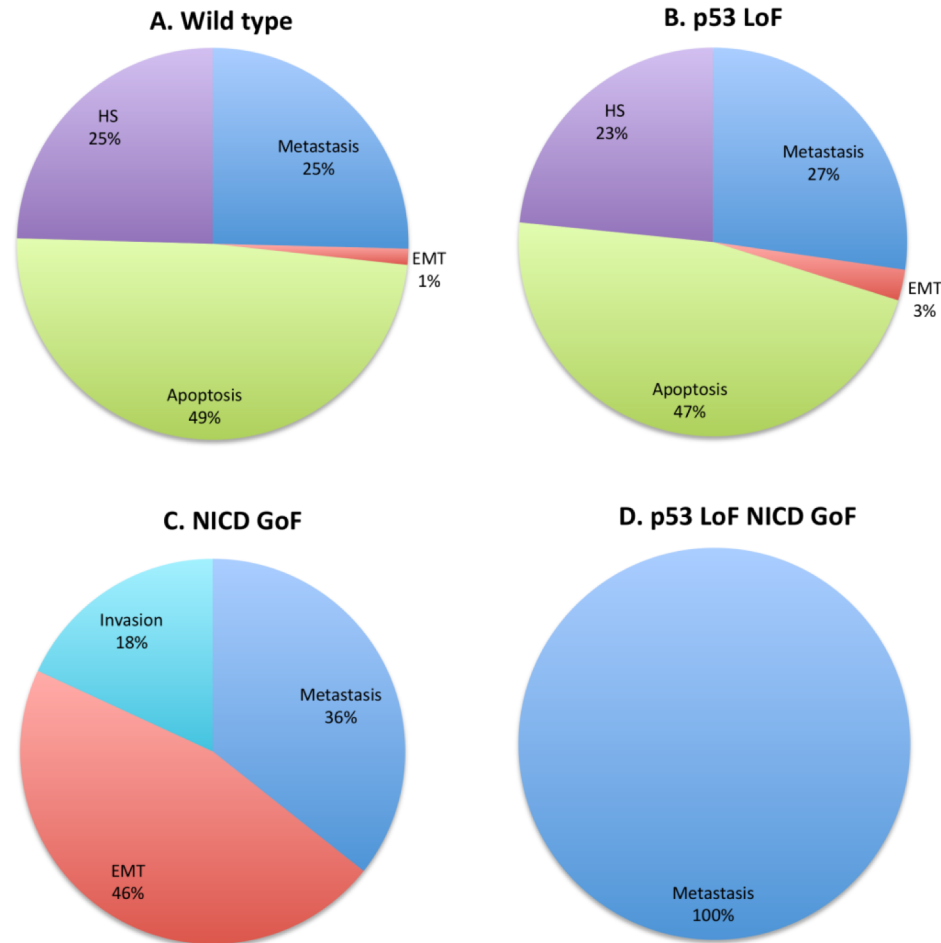
# Map of *in silico* single and double mutations

- Automatic simulation of single and double mutants
- Quantification of probabilities to reach metastasis for all single and double mutants



# What about the double mutant accounting for alterations in the Notch and p53 pathways

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The model confirms the metastatic phenotype in the Notch<sup>+/+</sup>/p53<sup>-/-</sup> double mutant

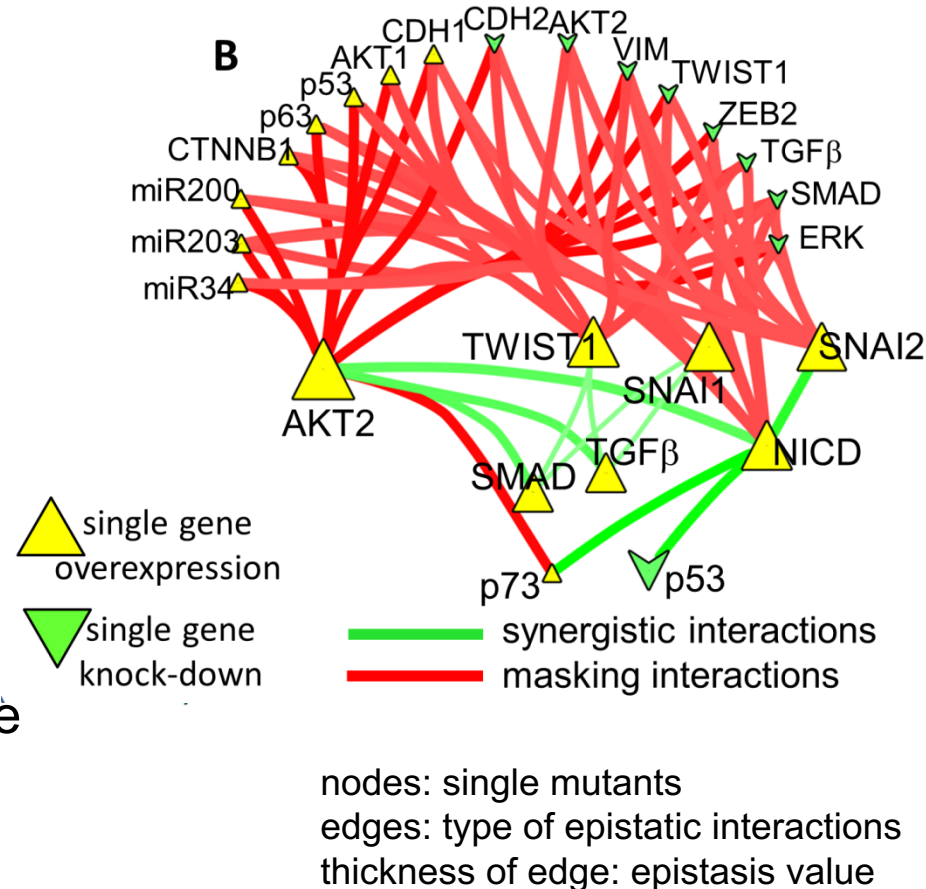
# Predicting **genetic interactions** from the genes of the model with respect to metastasis

4 genetic interactions drastically increase metastasis:

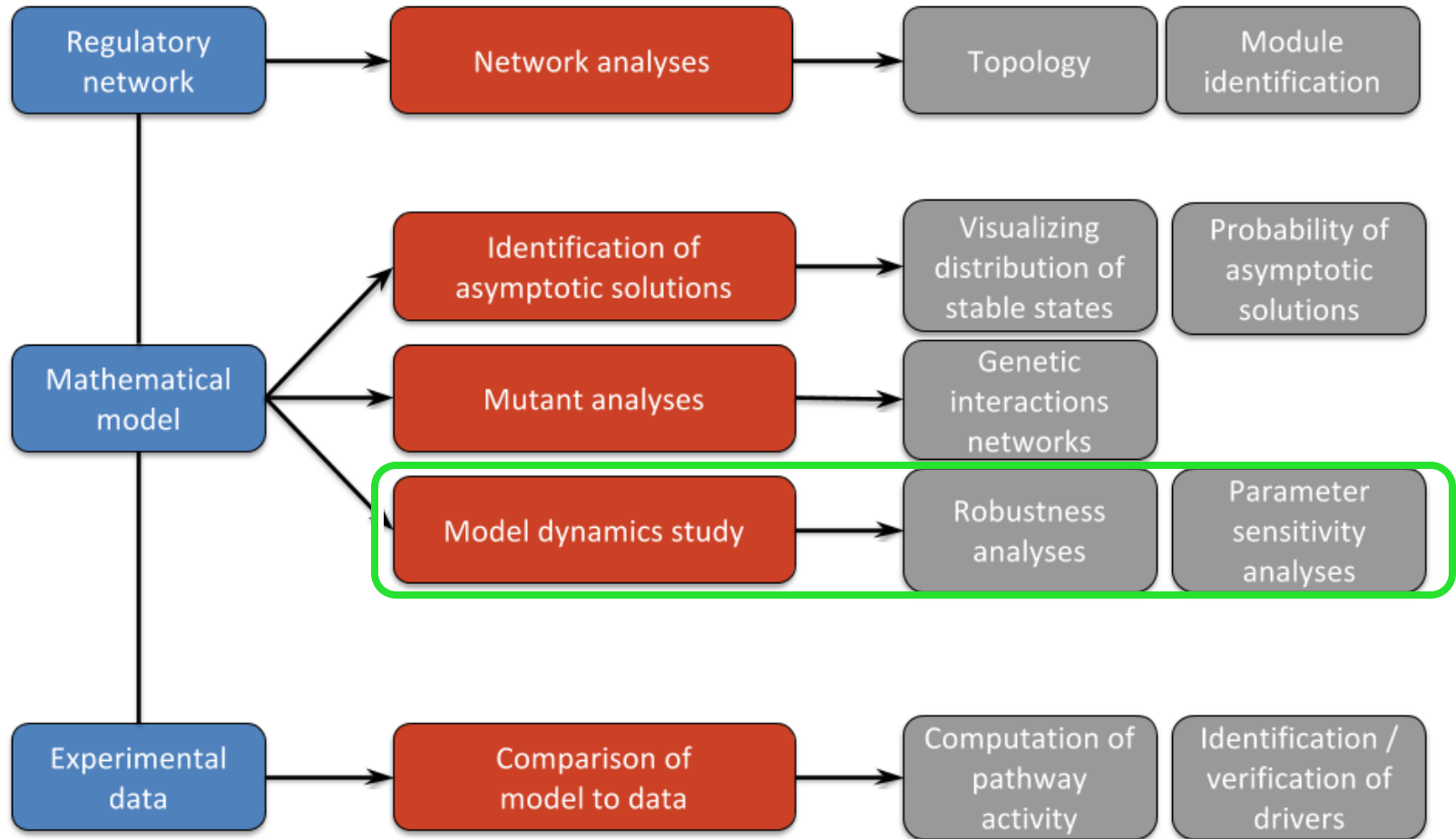
NICD GoF - p53 LoF  
 NICD GoF - p73 GoF

NICD GoF - SNAI2 GoF  
 NICD GoF - AKT2 GoF

⇒ amplifier mechanisms for appearance of metastasis in NICD GoF mutants



# Pipeline



# Robustness analyses

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1. Robustness of a phenotype to mutations  
ex: Does a mutant **enhance or diminish** the probability to reach the *Metastasis* node? Which mutant alters the most the phenotype?
2. **Robustness of logical gates with respect to a phenotype**  
Is the model unique?
3. Robustness of logical gates with respect to stable states  
How does a change in the model affect the stable states?



# Robustness of the logical gates with respect to the phenotype probability

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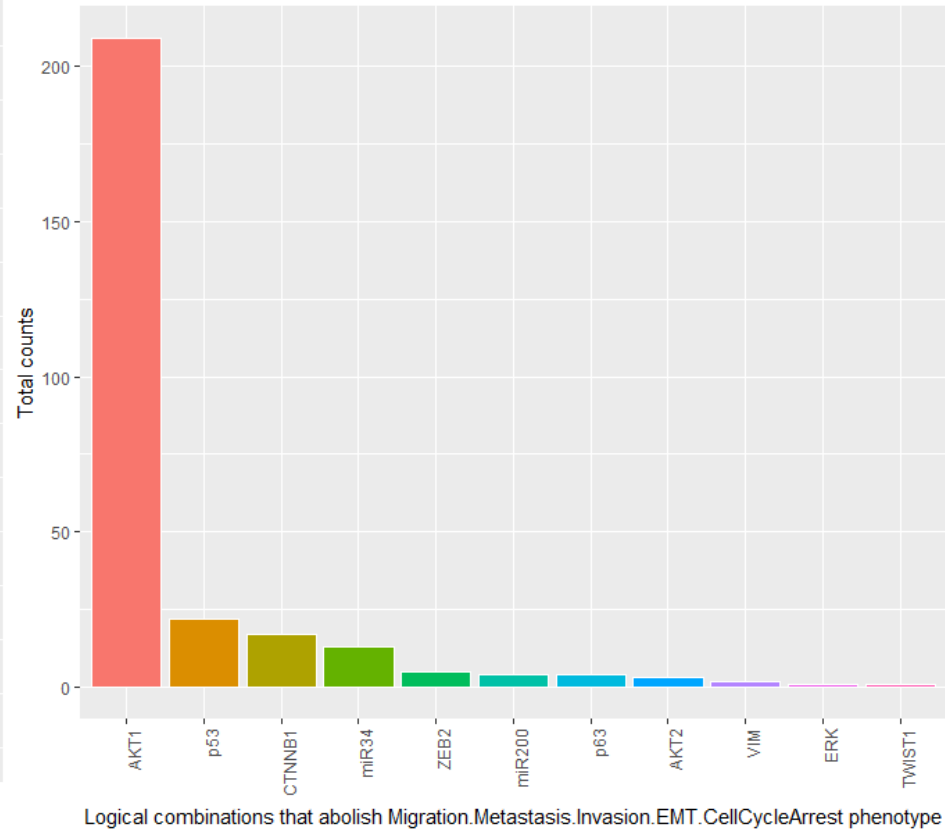
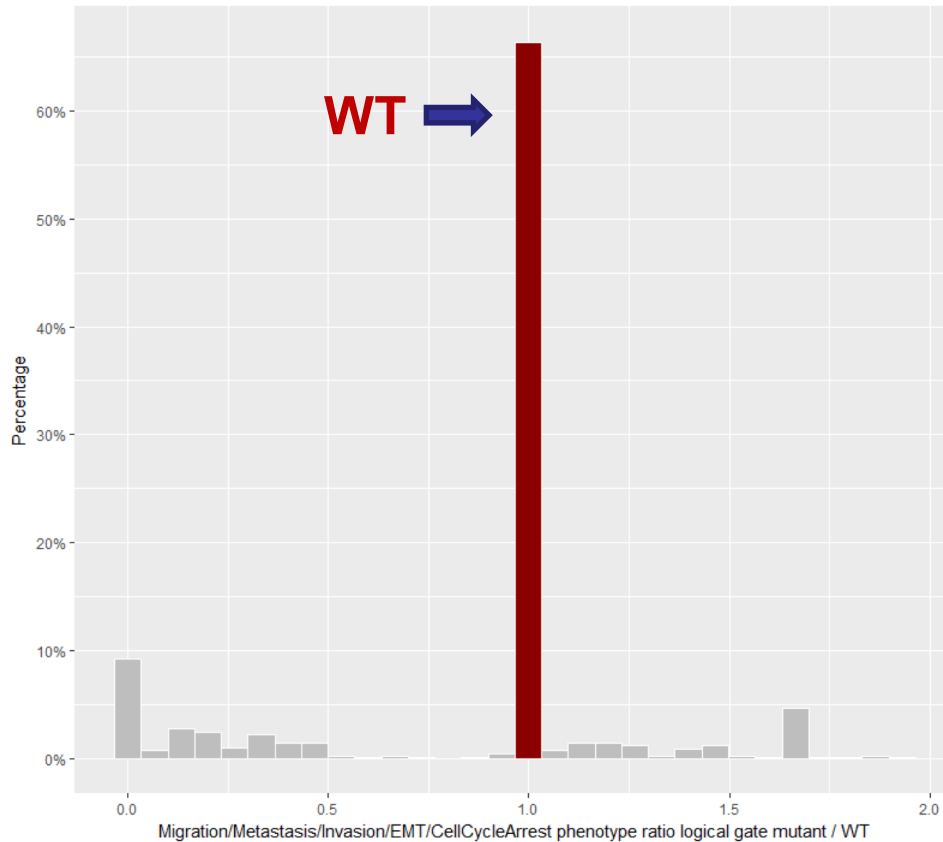
- Can we confirm that the **proposed model is robust** with respect to small changes of logical rules?
- Is there one model or a family of models that could be equivalent?
- Can we identify the **“weak spots”** of the model?

Three tests were performed on logical rules

- **One operator in all rules** was changed (from AND to OR and vice versa)
- **Two operators in one rule** were changed
- **One operator in two rules** was changed

Question: how do these **changes** affect the **probability** to reach a phenotype?

# Robustness of the logical gates with respect to the phenotype probability



- The model is quite robust with respect to all phenotypes
  - Metastasis is the least robust
- The rules of some genes need to be more stringent: **AKT1 and p53 in particular (anti-migratory)**

# [https://github.com/sysbio-curie/Logical\\_modelling\\_pipeline](https://github.com/sysbio-curie/Logical_modelling_pipeline)

sysbio-curie / Logical\_modelling\_pipeline

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Code Issues 0 Pull requests 0 Projects 0 Wiki Insights

Branch: master Logical\_modelling\_pipeline / scripts / Create new file Find file History

ArnaudMontagud corrected Analyses logical gates Latest commit 55ccf0c 8 days ago

..

1 run MaBoSS	BND_CFG file changed	12 days ago
2 PCA on ss	modified stewd in R scripts and new md file in doc folder	28 days ago
3 Displaying asymptotic solutions	modified stewd in R scripts and new md file in doc folder	28 days ago
4 Predicting genetic interactions	updating correct ginsimout	29 days ago
5 Analyses of genetic interactions	modified stewd in R scripts and new md file in doc folder	28 days ago
6 Predicting logical gates interac...	updating correct ginsimout	29 days ago
7 Analyses of logical gates	corrected Analyses of logical gates	8 days ago
8a Using the model as a scaffold ...	Updating ROMA files	28 days ago
8b Using data as priors of model ...	Updating ROMA files	28 days ago
8c Using data as priors of model ...	adding stewardship script to run sections 1 through 7 at once, minor ...	a month ago
run all analyses	corrected Analyses logical gates	8 days ago



## Contributors

Arnaud Montagud  
Pauline Traynard

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Andrei Zinovyev  
Loredana Martignetti  
Gautier Stoll

# Improvements of the pipeline

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- Automatic search for node inhibition:  
suggestion of drug targets (already possible with MaBoSS)
- Automatisation of several tasks:  
choose what to do and launch several tasks in one simulation (already possible but needs optimisation)
- Contextualisation of models to patient data  
in progress
- Integration of logical models into agent-based models  
in progress

# Contextualisation of models to patient data

⇒ Compute the probability of a phenotype per patient (or groups of patients) → specify a model to a patient

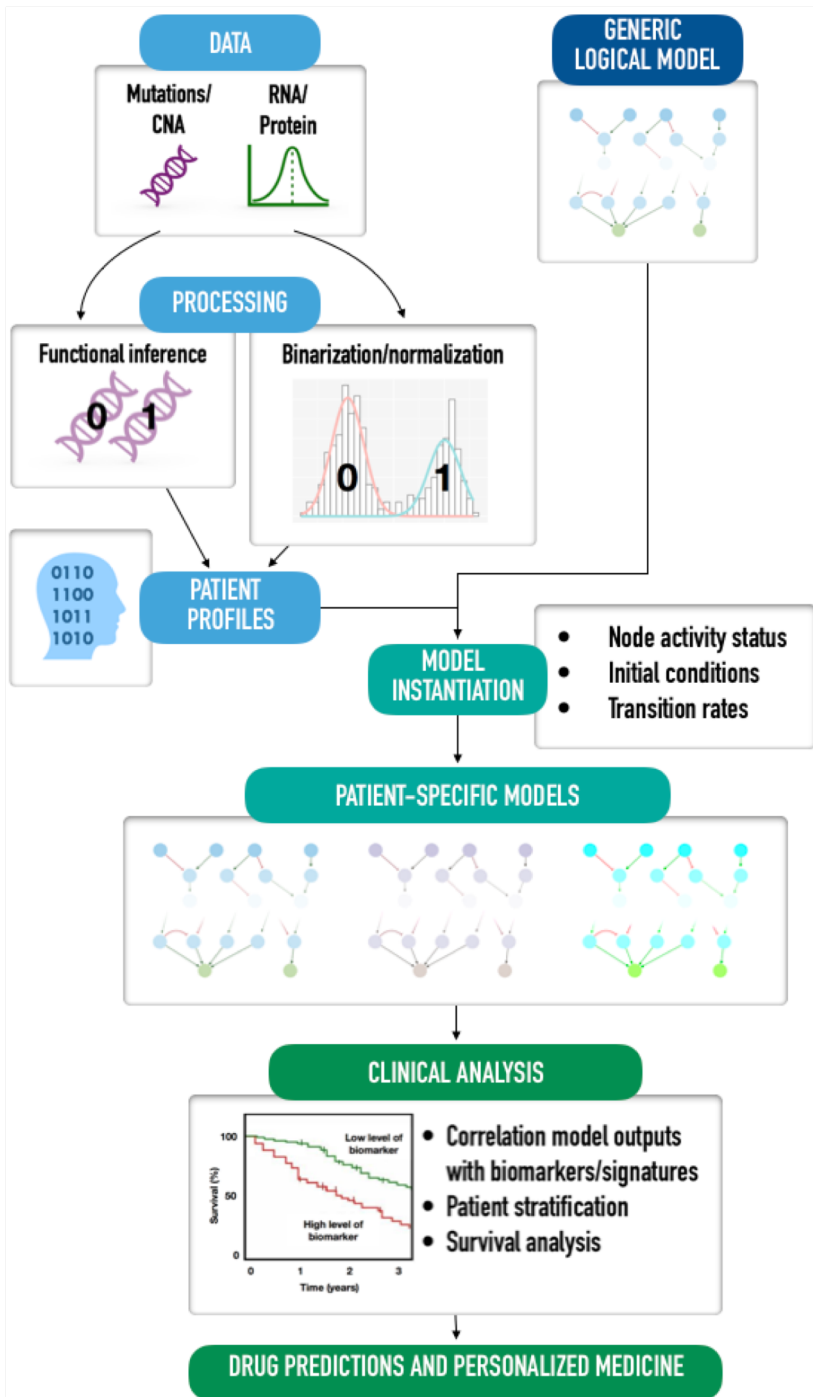
	Patient_1	Patient_2	Patient_3	Patient_4	Patient_5	Patient_6	Patient_7	Patient_8	Patient_9	Patient_10
CDK1	0.34980	-3.63820	-1.64350	-1.12862	-1.48949	-1.14924	-3.13846	-3.97786	-0.77106	-1.08848
CDK2	0.79515	-1.45574	0.21421	-1.22189	-0.28390	-2.77291	-1.71527	-2.04611	0.27713	-0.21242
RB1	1.51308	-1.01982	-0.28808	-0.10028	-0.25528	-0.51715	-0.32806	-0.95599	0.26762	0.02276
NFKB1	0.32836	0.47176	0.45348	0.02632	-0.88051	-0.13897	-1.78039	-0.86474	0.46306	-0.08317
...										



	Patient_1	Patient_2	Patient_3	Patient_4	Patient_5	Patient_6	Patient_7	Patient_8	Patient_9	Patient_10
CDK1	1	*	*	*	0	*	*	*	*	*
CDK2	1	1	1	1	1	*	*	*	*	*
RB1	*	*	*	*	*	*	0	*	0	*
NFKB1	1	*	1	*	*	*	*	*	1	*
...										

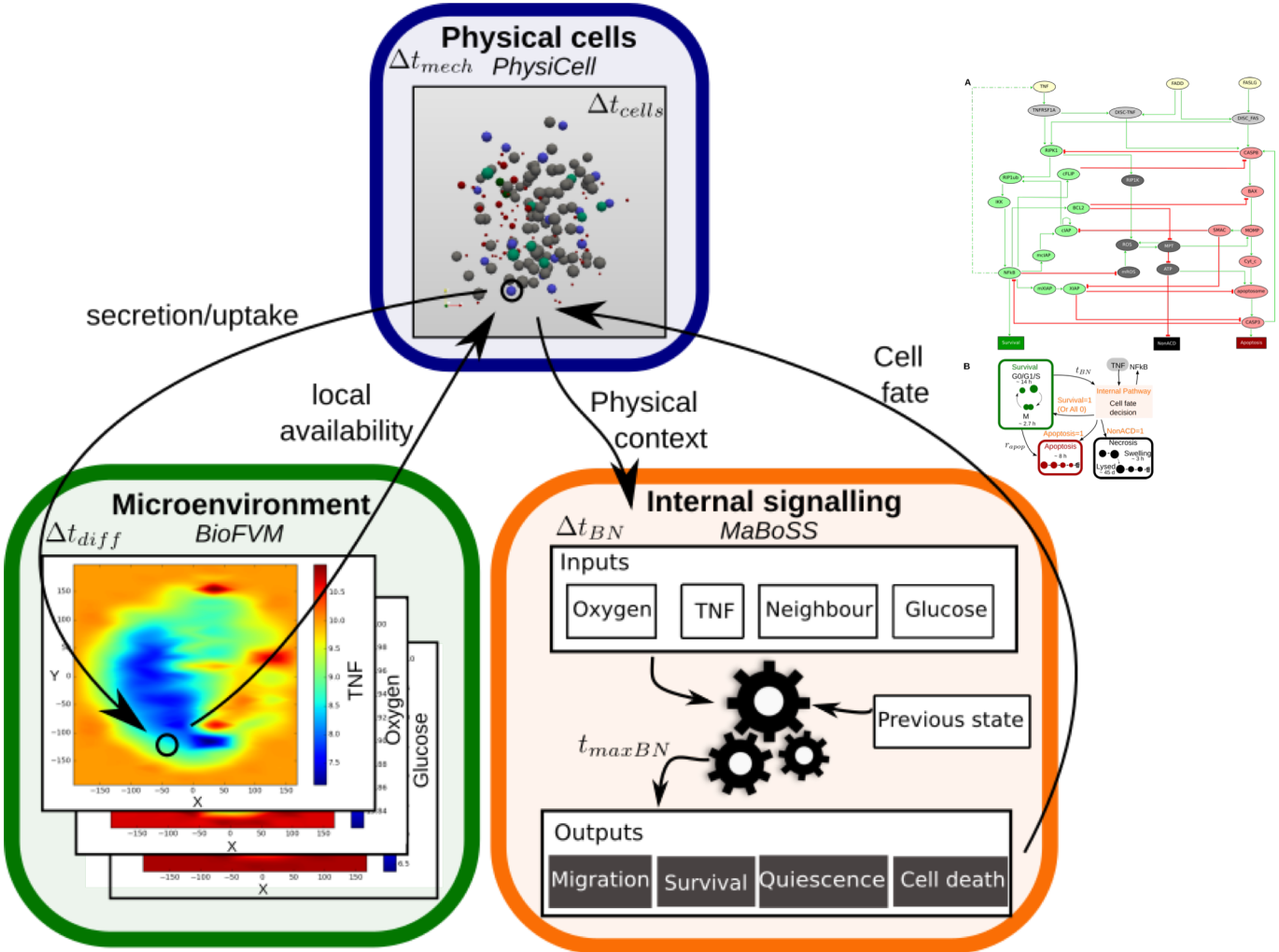


Patient 1: Probability of proliferation increased when compared to normal condition?



1. Start with a model and some patient data
2. Binarize or normalize the data
3. Build individual patient profiles  
 mutations + CNV = mutants  
 expression data = speed of reactions
4. Simulate each patient
5. Correlate results to clinical data  
 (survival curves, proliferation index, size of the tumour, etc.)

# Integration of logical models into agent-based models

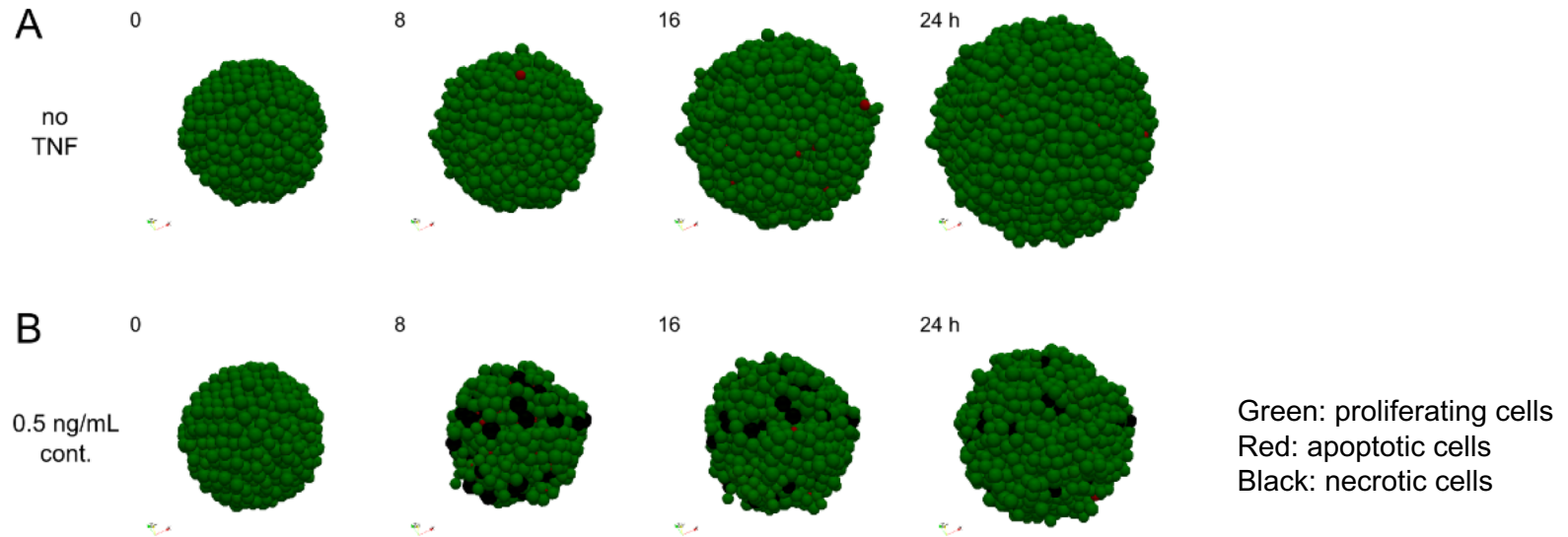


# Integration of a logical (MaBoSS) model into an agent-based tool: PhysiBoSS

Example of model of cell fate decision:

A) in proliferating conditions (cells divide every 16 hours)

B) treated with TNF (Tumor Necrosis Factor) in proliferating conditions



- In silico experiment shows that tumour does not grow as fast when treated with TNF
- Possibility to test effect of treatment on heterogeneous cell population (clonality)
- Possibility to test different types of treatments (pulses or continuous)



# Acknowledgements

## The modelling team



Emmanuel Barillot

Andrei Zinovyev

Arnau Montagud

Loredana Martignetti

Pauline Traynard



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Thank you for your attention