Inference of Drug/Disease targets

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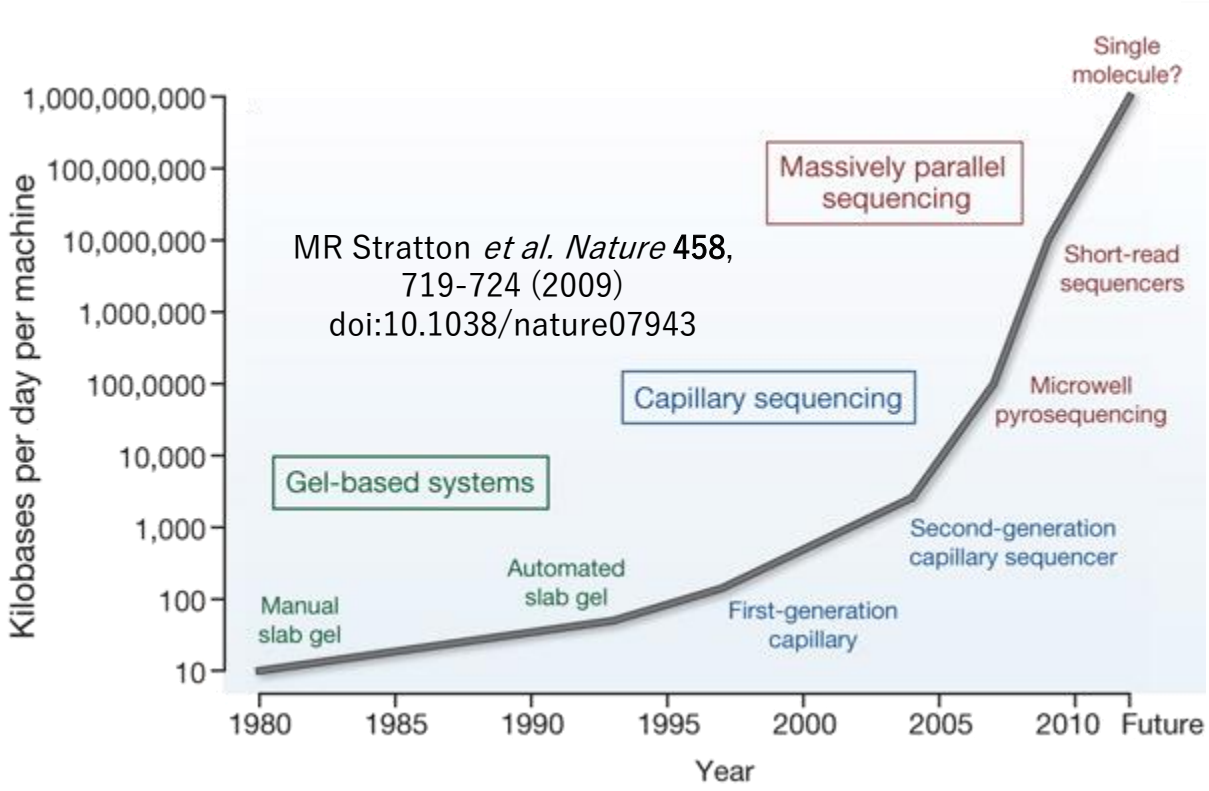
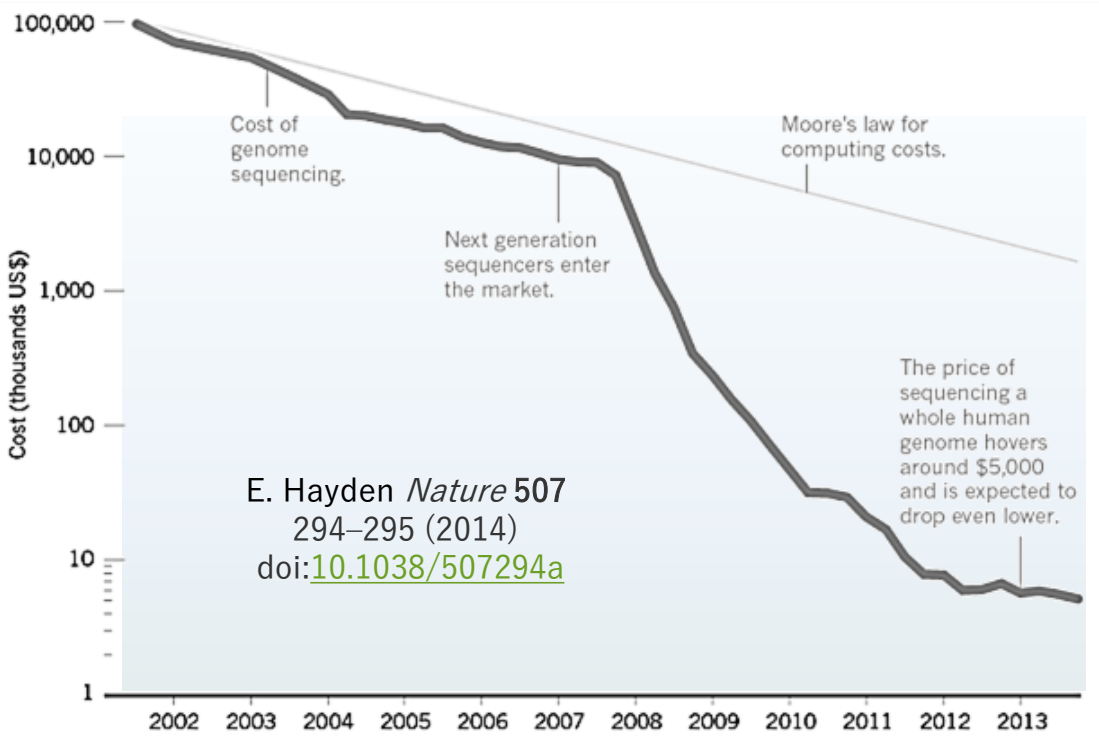
38e Séminaire de la SFBT – SAINT FLOUR - 11-13 juin 2018

Medicine in the Age of Omics Era





- Law of accelerating returns
- Opening avenues to a predictive personalized & precision Medicine
- Based on Omics Big Data : Genomics, Proteomics, Transcriptomics, Epigenomics, …

Omics Analysis in the Age of Precision & Personalized Medicine

Diagnosis

Prognosis

Treatment

Prediction

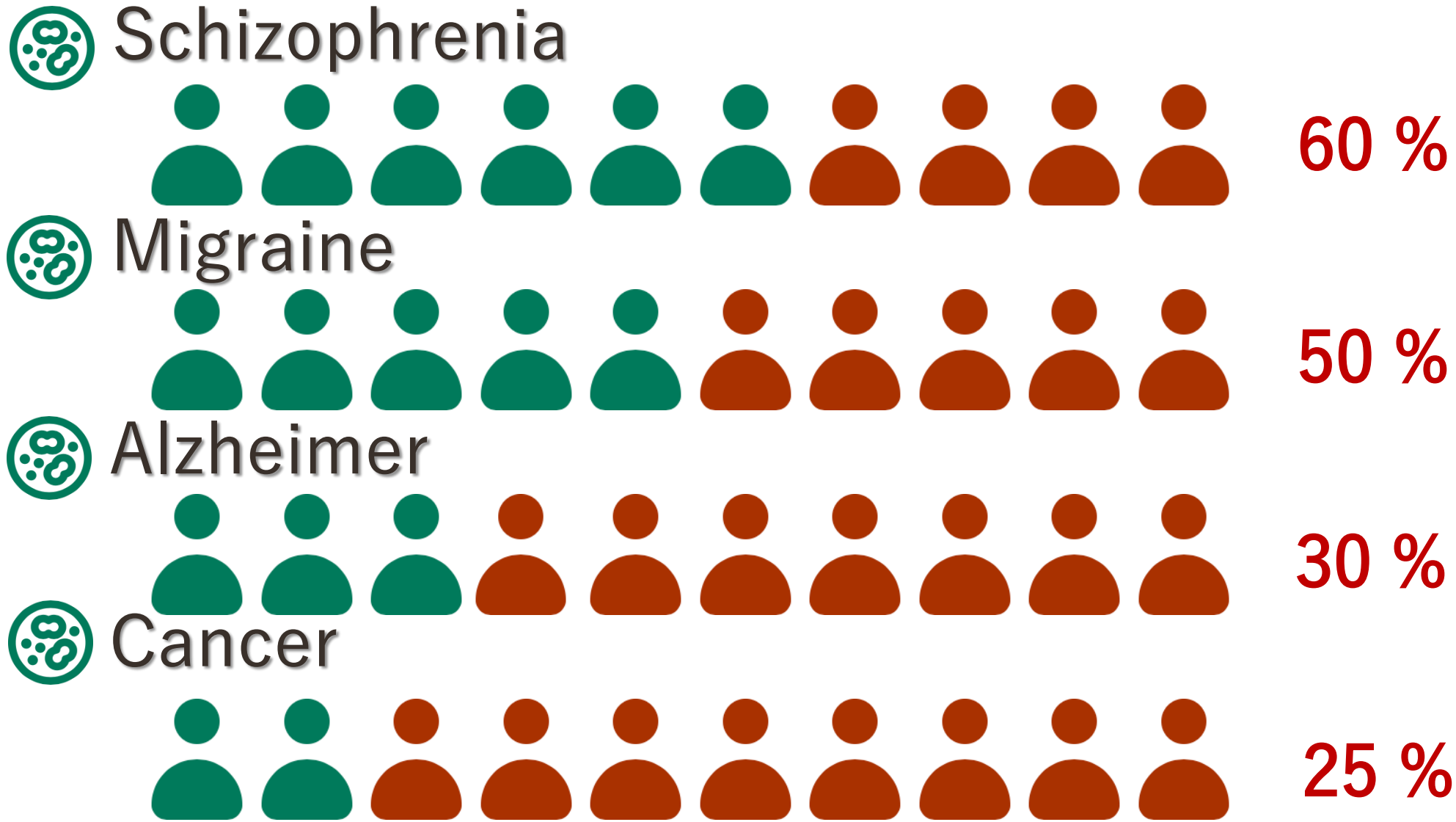
Big Data

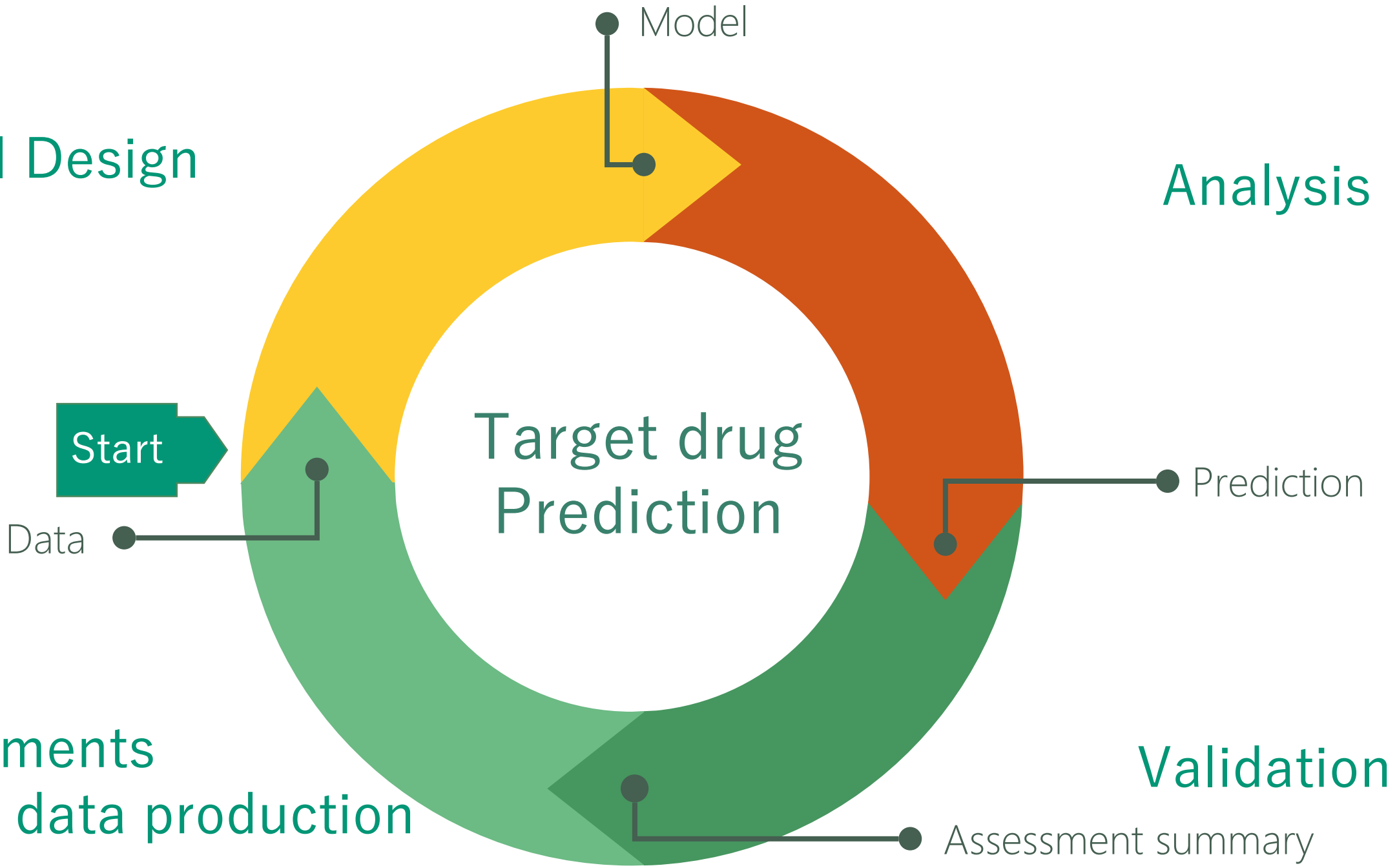
Big to Smart transition

- ✓ Causal analysis
- ✓ Decision Making
- ✓ Risk Management

Drug efficiency

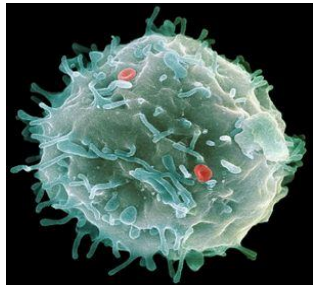
Spear, Brian B., Margo Heath-Chiozzi, and Jeffrey Huff. "Clinical application of pharmacogenetics." *Trends in molecular medicine* 7.5 (2001): 201-204.




Model
Model Design
Analysis
Start
Target drug
Prediction
Data
Prediction
Experiments
Omics data production
Validation
Assessment summary

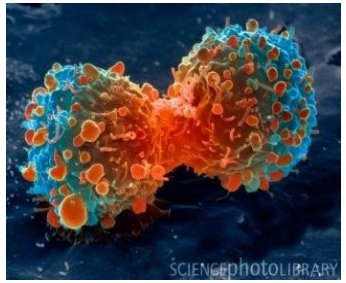
Scenario: Phenotype shift/cell reprogramming

Normal Cell



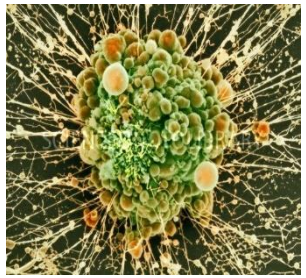
Mutations

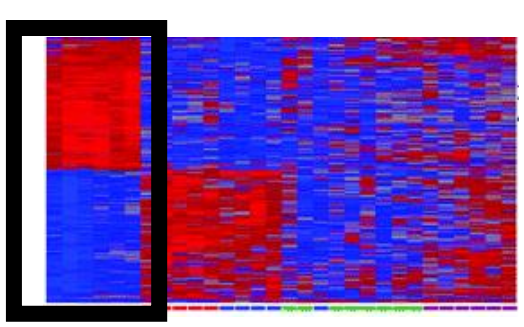
Cancer Cell

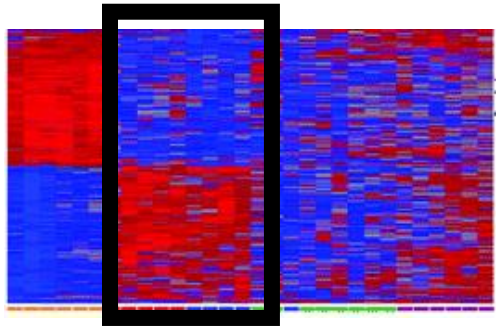


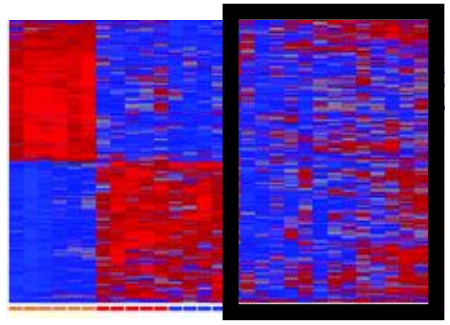
Anti-cancer drugs

Dying Cell







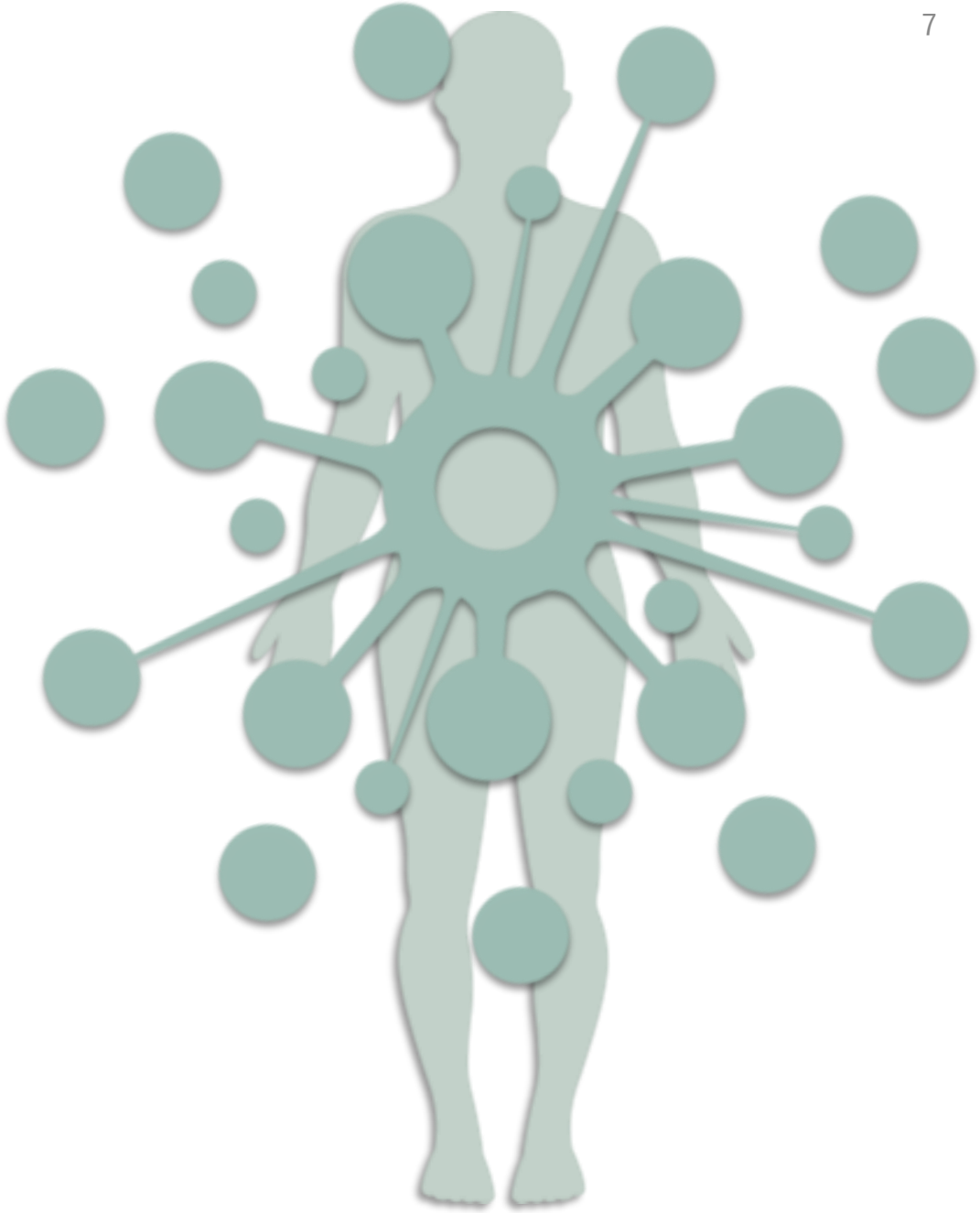


Phenotypic Switch = Observable Biomarker Shift

Modeling analogy

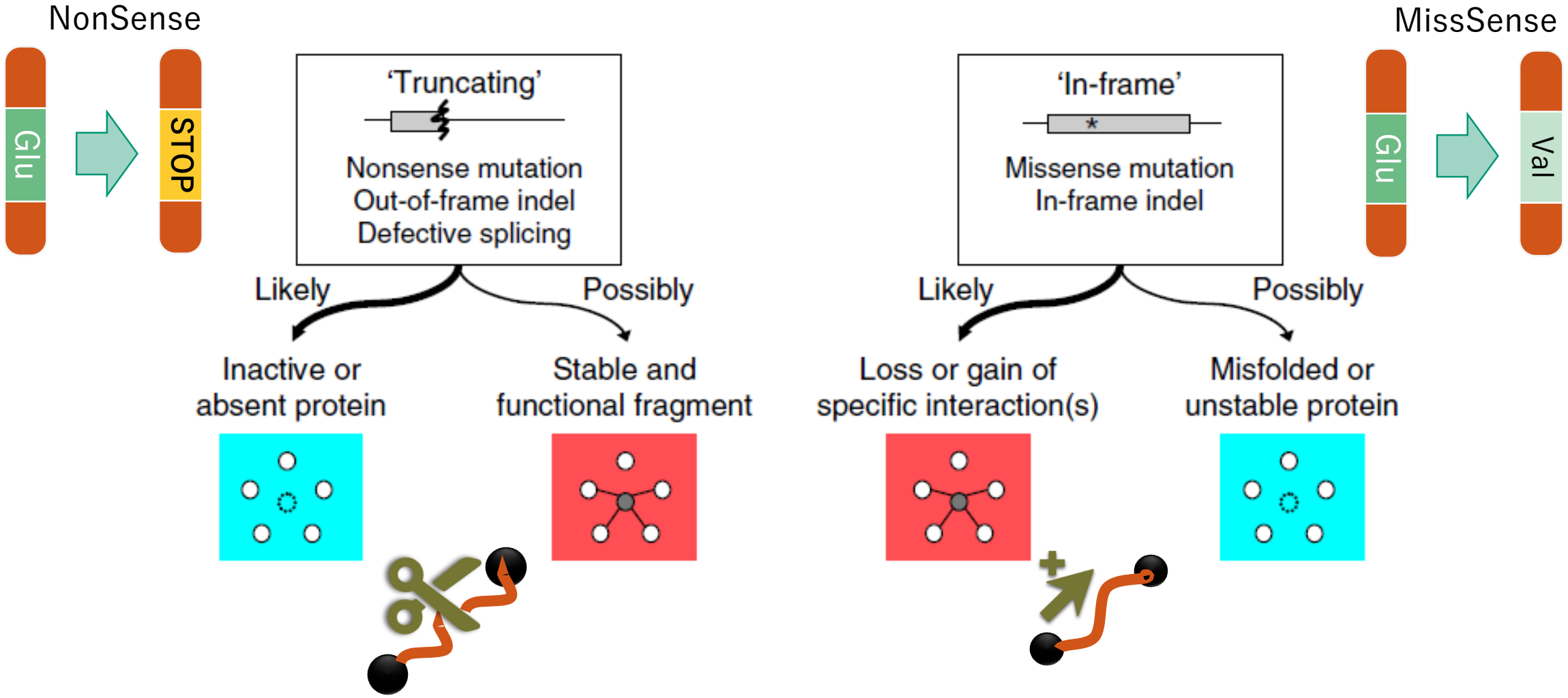
What is a disease model ?

What is a diseased model ?



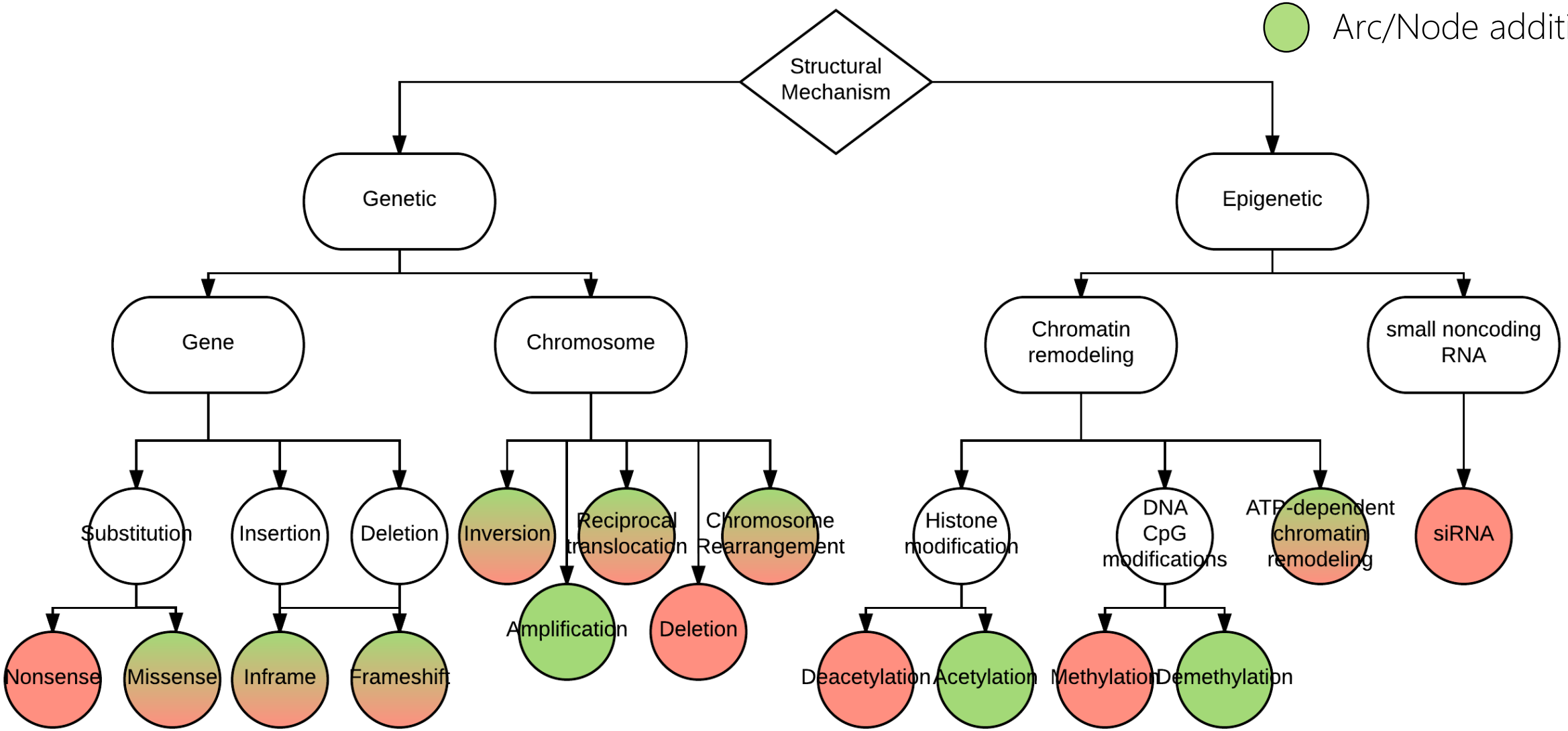
Disease ▶ Interactome perturbation

Zhong et al. 2009. Edgetic perturbation models of human inherited disorders.



Addition & Deletion of arcs and nodes

Causes of Cancer as network actions

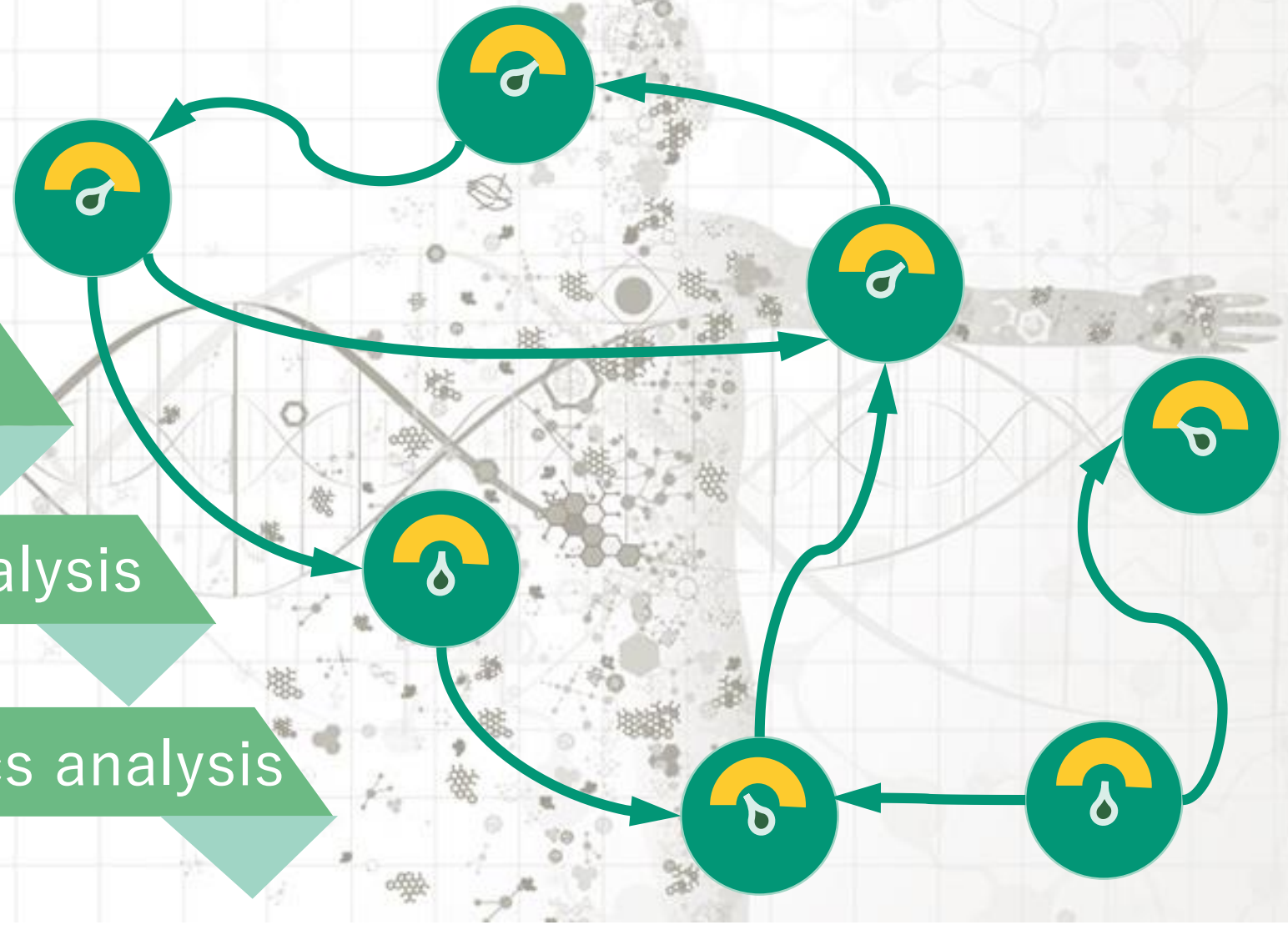


Network Medicine

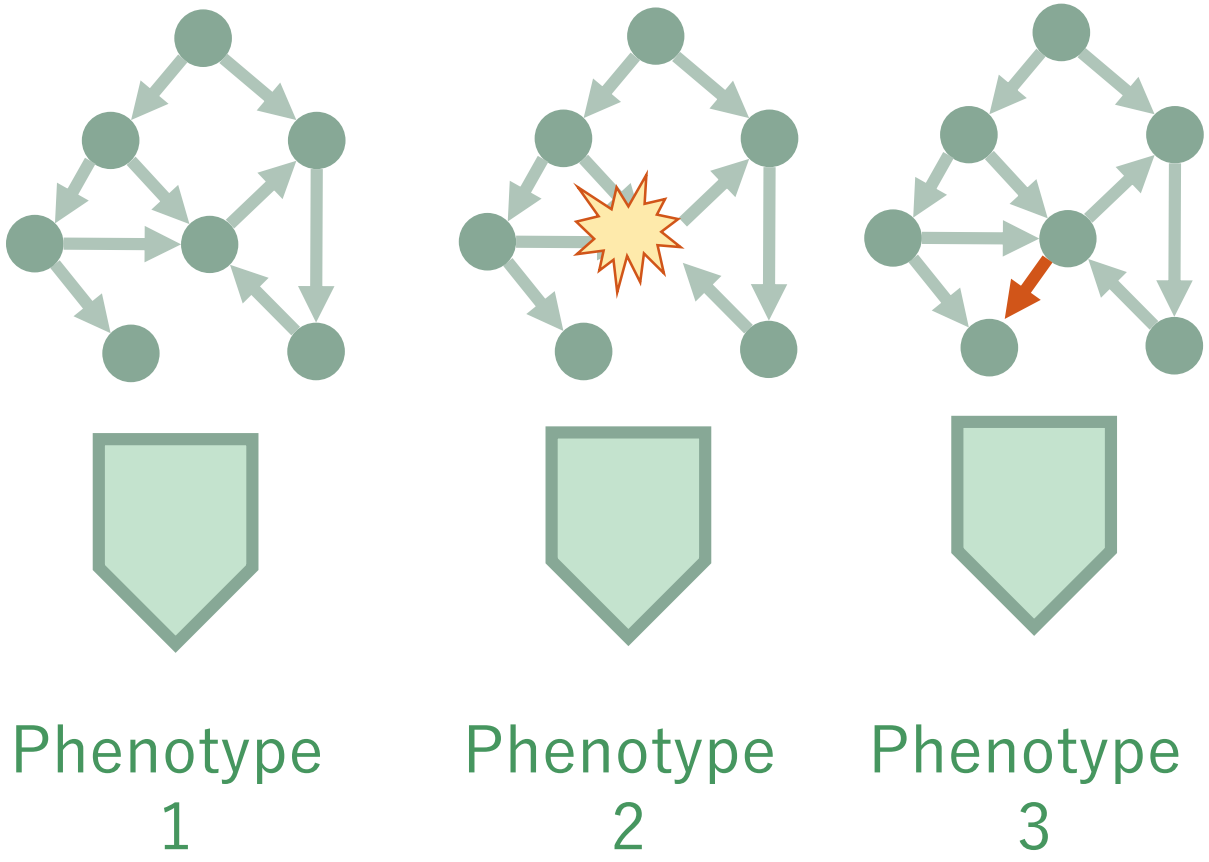
NETWORK SCIENCE

MEDICINE

- Network
- Disease Analysis
- Topology analysis
- Dynamics analysis



Revisiting Genotype-to-Phenotype Relation



Phenotype 1 | Phenotype 2 | Phenotype 3

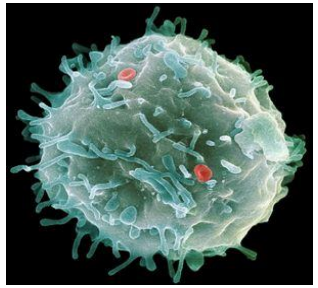
≠ Network Topologies ➔
≠ Phenotypes

Causes of diseases & Therapy prediction based on network actions

Edgotype: a fundamental link between genotype and phenotype
N. Sahni & al. Current Opinion in Genetics & Development 2013, 23

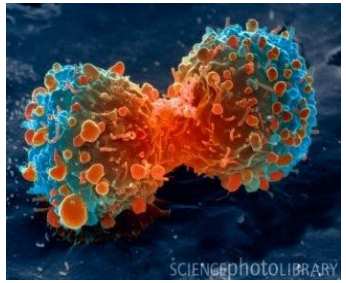
Scenario: action network = perturbation

Normal Cell



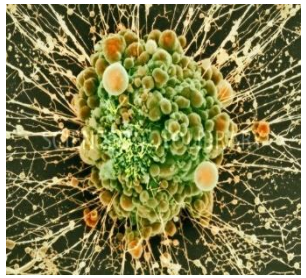
Mutations

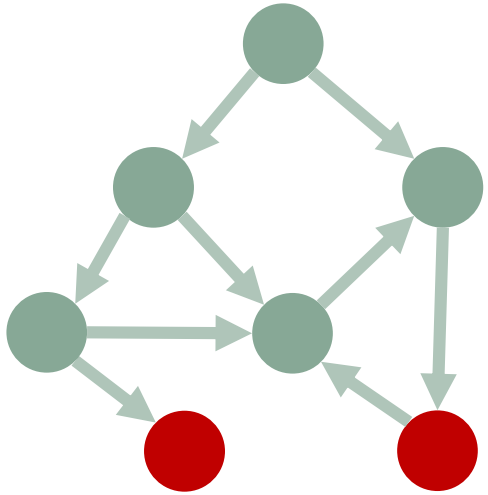
Cancer Cell



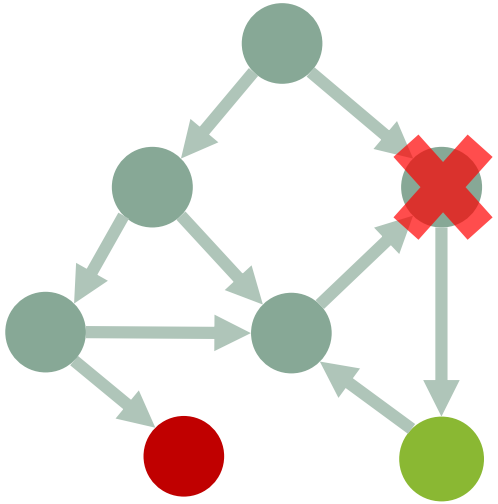
Anti-cancer drugs

Dying Cell

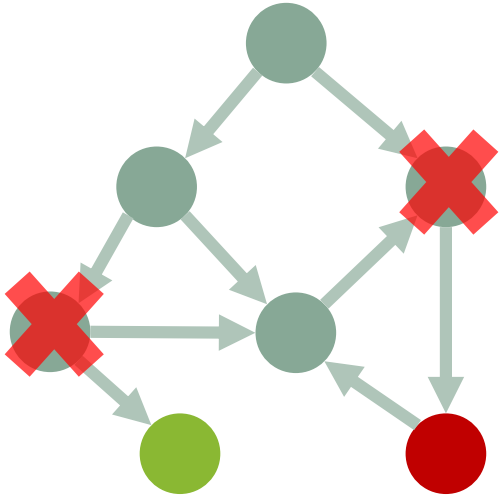




Biomarker 1	Biomarker 2



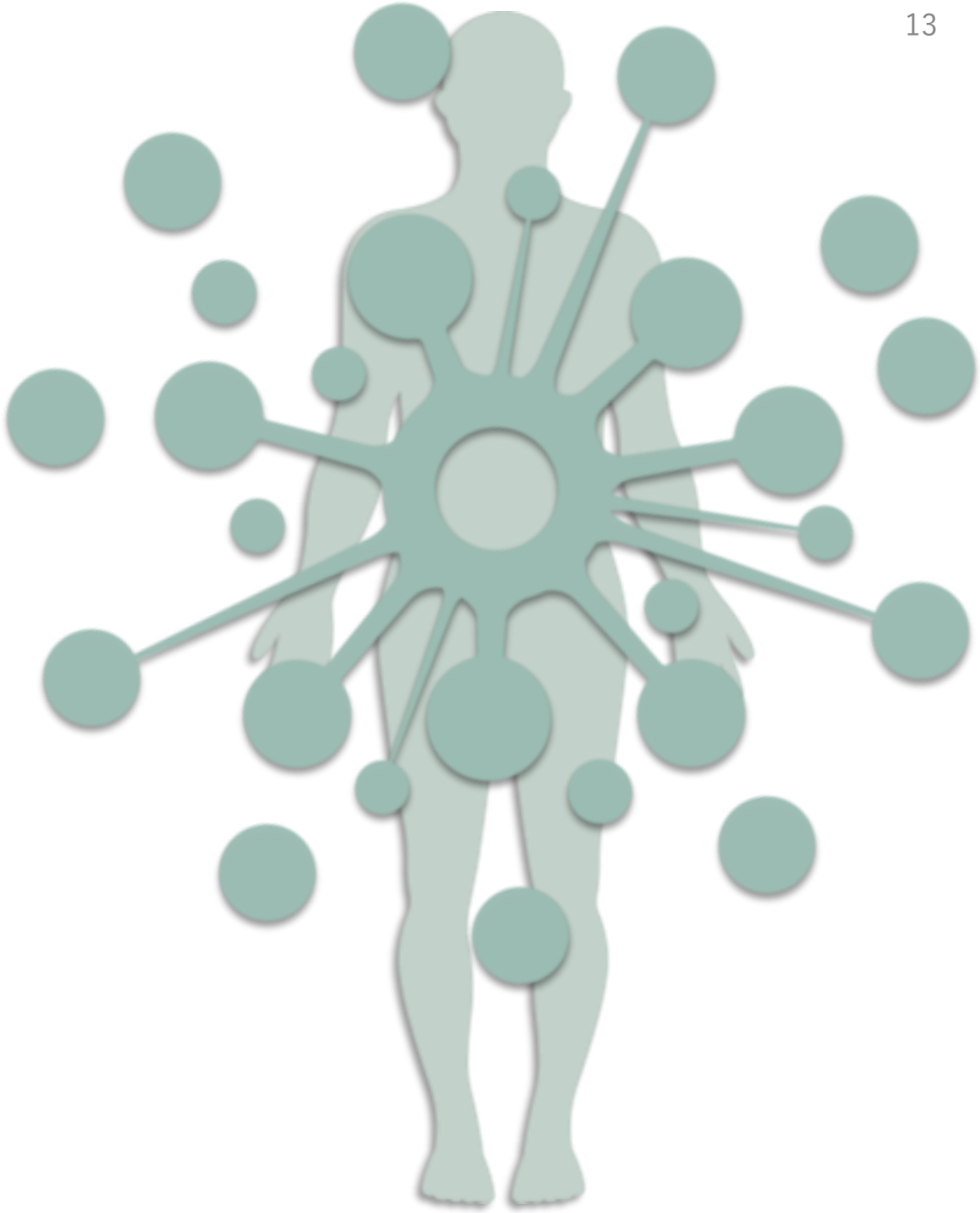
Biomarker 1	Biomarker 2



Biomarker 1	Biomarker 2

Network Action Modelling framework

Theoretical framework



Boolean Network

G1	G2	G
●	●	●
●	○	●
○	●	●
○	○	○

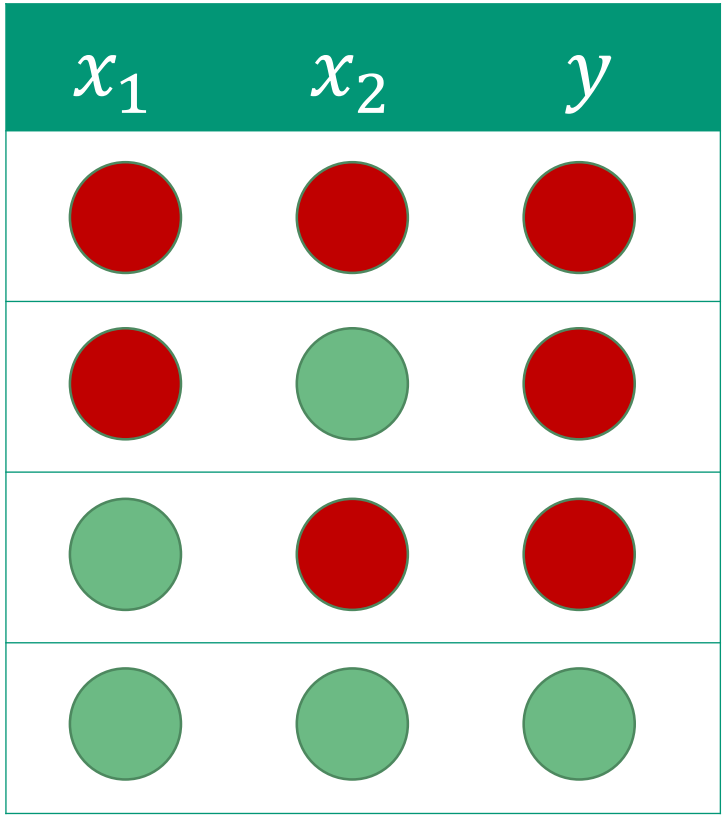
● = 0

○ = 1

$$G_1 \wedge G_2 = G$$

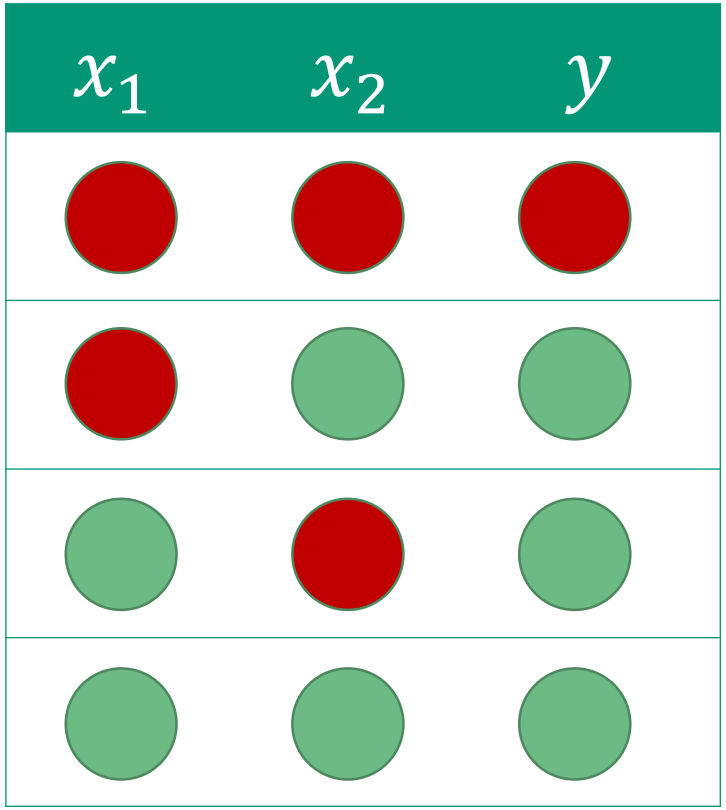
Fundamental operators

$y = x_1 \wedge x_2$



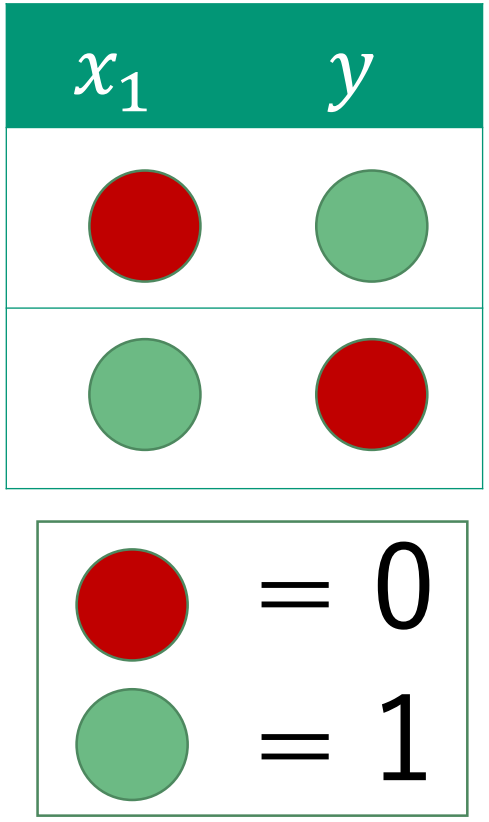
Logical AND

$y = x_1 \vee x_2$



Logical OR

$y = \neg x_1$



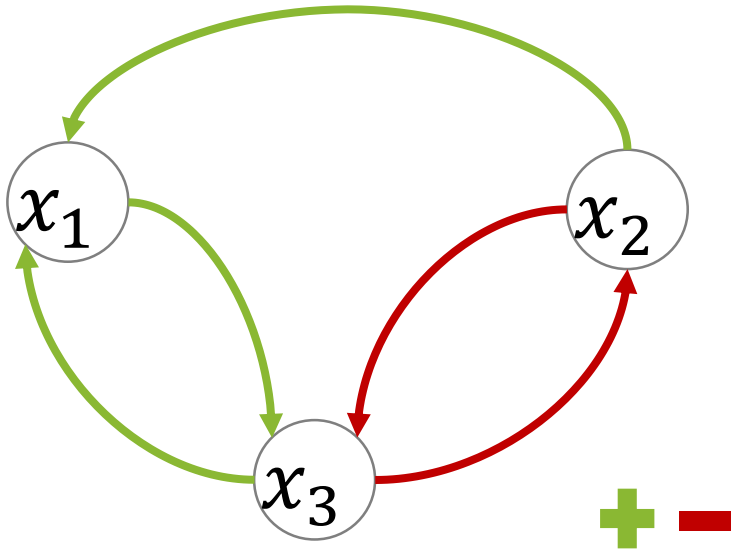
Negation

Boolean Networks – Definition

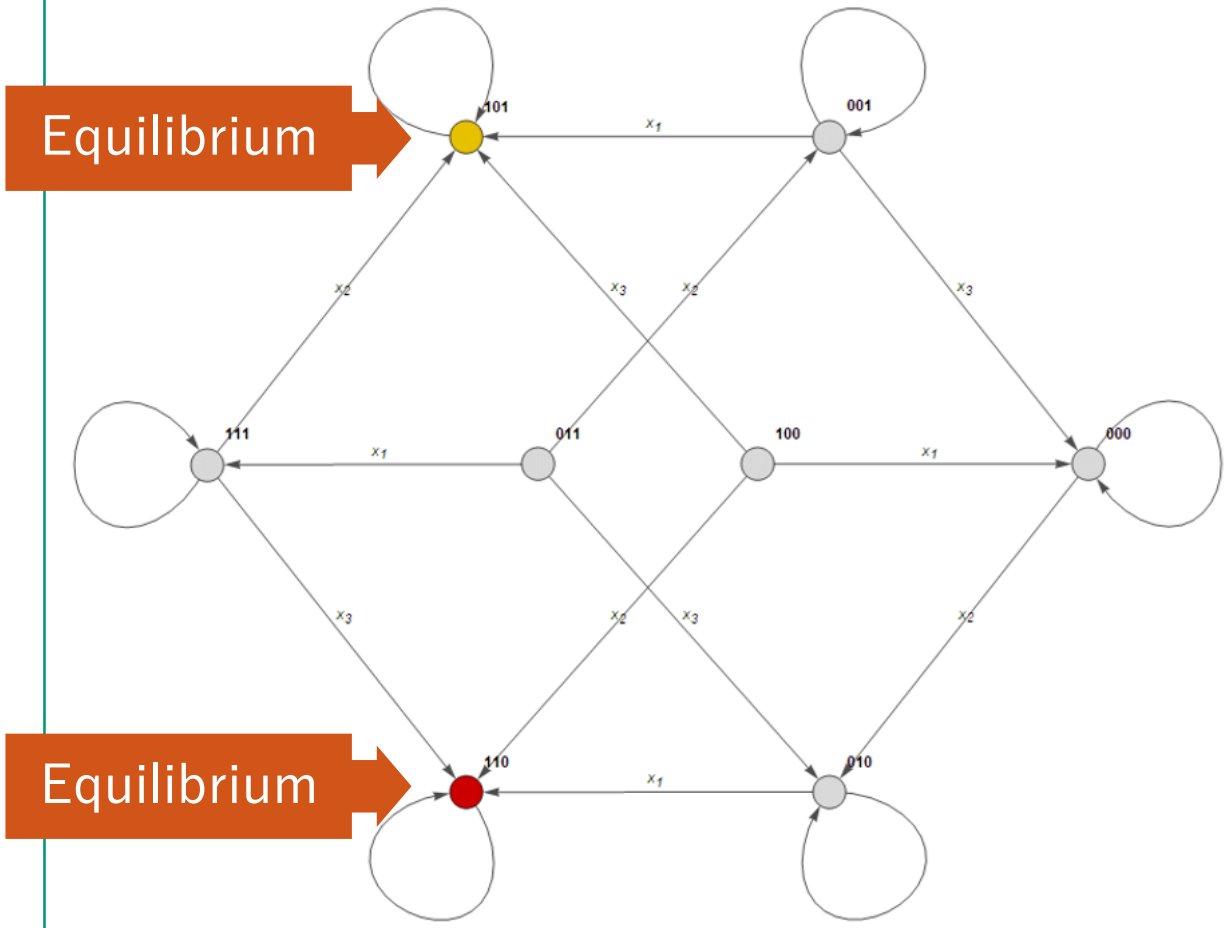
Network = Boolean Dynamical system

$$F = \begin{cases} x_1 = x_2 \vee x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg\, x_2 \wedge x_1 \end{cases}$$

Interaction graph



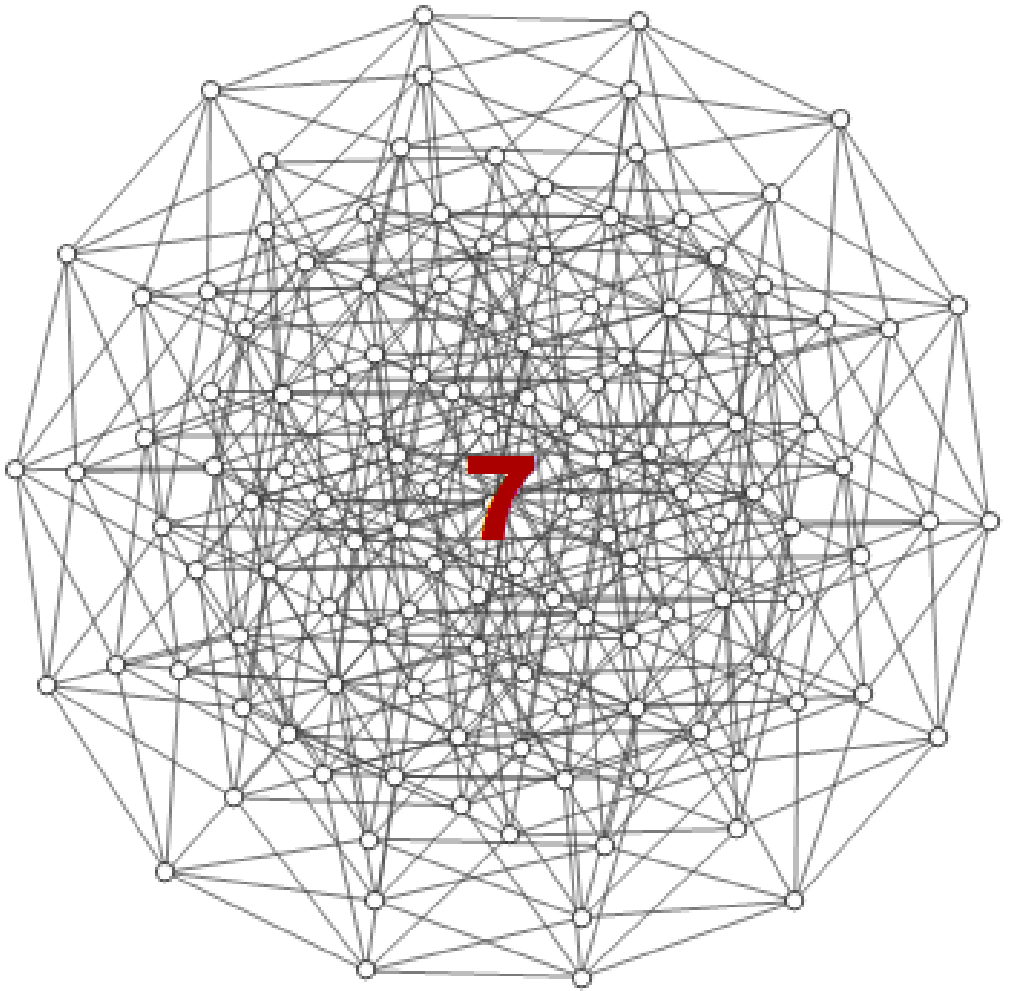
Model of dynamics ➔ $\rightarrow \subseteq S \times X \times S$



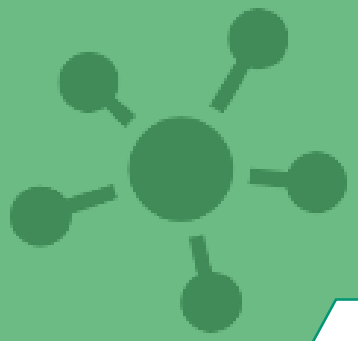
Exponential size of space state

- 2^n states
  n= number of variables
- Reachability problem limitation
  - Cyclic attractor computation
- Require symbolic methods to overcome the state space explosion

Hypercube H_7 = “roads” of trajectories



On Boolean Network



A “classical” modeling framework in system biology

Easy to understand, reliable model,
Integration from ≠scales & sources

Interaction can be modeled by 3 operators

Any formula expressed as a combination of
OR, AND, NOT operators (DNF)

Extension to multi – valued network Integer states

Conversion: Multivalued ➔ Boolean.
Discrete model – Boolean = basic model

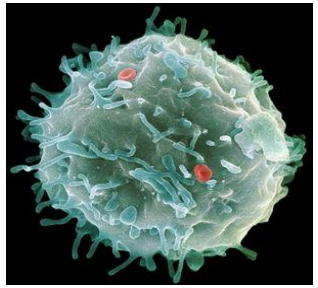
Extension of the updating policy

Updating controlled by a mode defined as a
set of variables set

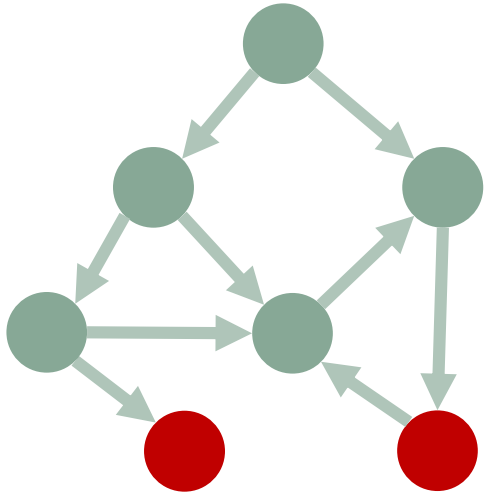
Network action On Boolean Network

Scenario:Dynamical system reprogramming

Normal Cell

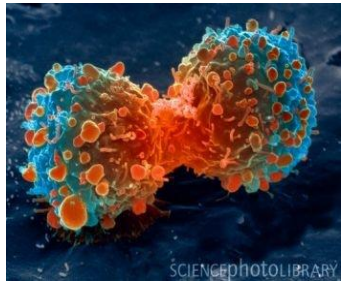


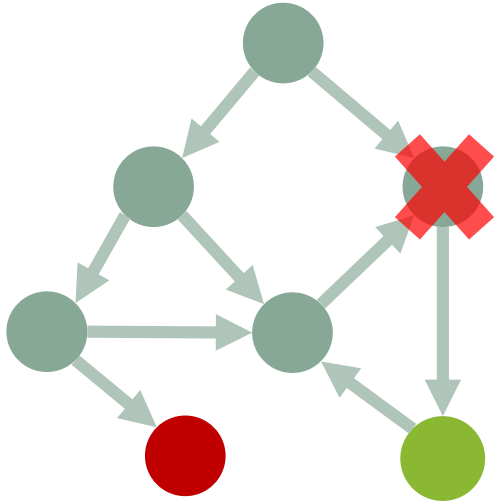
Mutations



$$F = \begin{cases} x_1 = f_1(x_1, \dots, x_n) \\ \dots \\ x_i = f_i(x_1, \dots, x_n) \\ \dots \\ x_n = f_n(x_1, \dots, x_n) \end{cases}$$

Cancer Cell





$$G = \begin{cases} x_1 = g_1(x_1, \dots, x_n) \\ \dots \\ x_i = g_i(x_1, \dots, x_n) \\ \dots \\ x_n = g_n(x_1, \dots, x_n) \end{cases}$$

Computatibility ?

Reprogramming ▶ Boolean control network

$U = \{u_1, \dots u_m\}$: Control parameters

$$F_U = \begin{cases} x_1 = f_1(x_1, \dots, x_n, u_1, \dots, u_m) \\ \dots \\ x_i = f_i(x_1, \dots, x_n, u_1, \dots, u_m) \\ \dots \\ x_n = f_n(x_1, \dots, x_n, u_1, \dots, u_m) \end{cases}$$

Control input

$\mu: U \to \{0,1\}$

A general framework for Boolean system reprogramming

f ⇨ g

$$\equiv F_u = (u \wedge f) \vee (\neg u \wedge g)$$

Network Action Category = Freezing Control

Action on Boolean Network

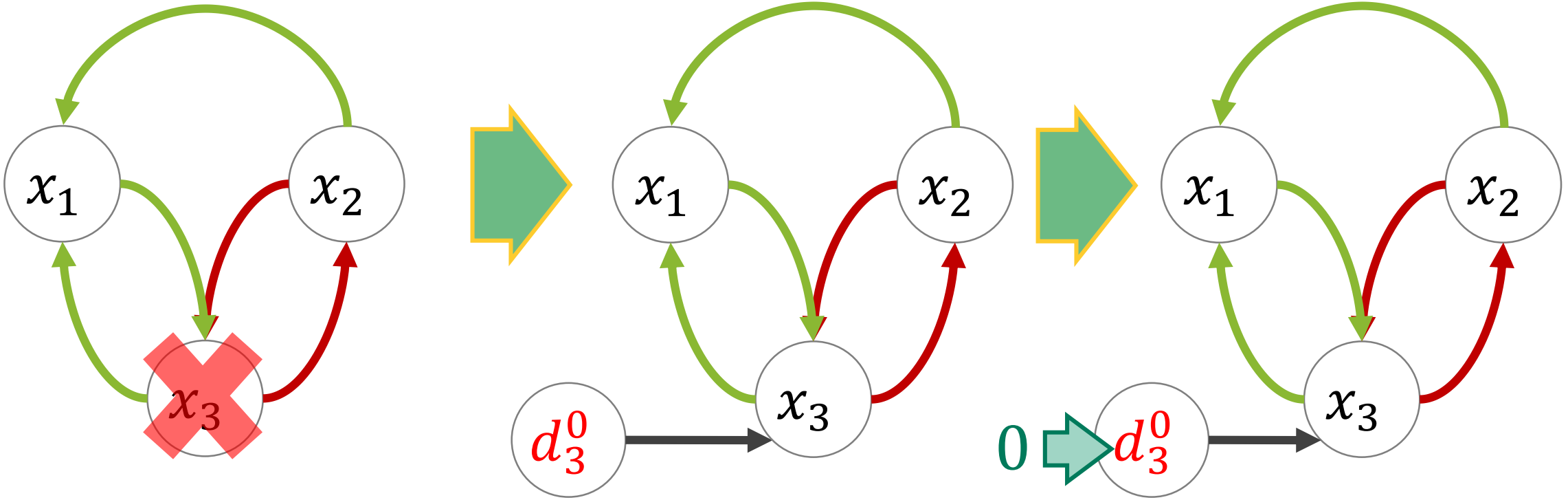
Deleterious mutation

Control Boolean network

Control enhancement

Freezing action

Fix control to 0



$x_3 = (\neg x_2 \wedge x_1)$

$x_3 = (\neg x_2 \wedge x_1) \wedge d_3^0$

$x_3 = 0$

Freezing Control Action

Definition

Freeze=0, Idle =1

Node: DEFINITION freezing

Action	Definition
0	$x_i = f_i(x_1, \dots, x_n) \wedge d_i^0$
1	$x_i = f_i(x_1, \dots, x_n) \vee \neg d_i^1$

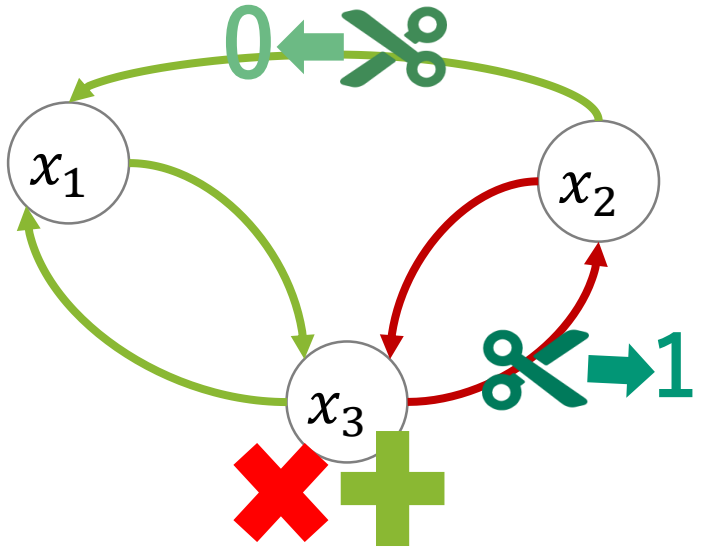
Arc: USE freezing

Action	Definition
0	$x_j = f_j(x_1, \dots, x_i \wedge u_{i,j}^0, \dots, x_n)$
1	$x_j = f_j(x_1, \dots, x_i \vee \neg u_{i,j}^1, \dots, x_n)$

Example

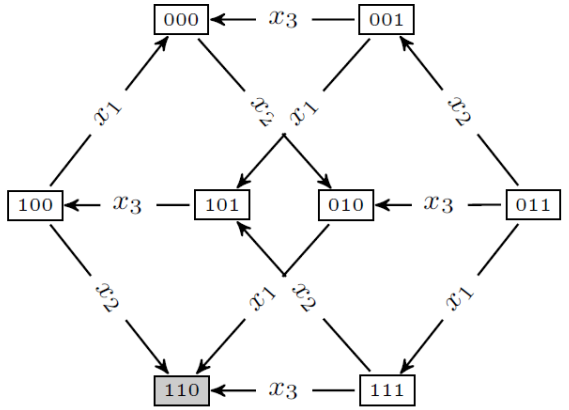
Freeze to 1 & 0

$$\begin{cases} x_1 = (x_2 \wedge u_{2,1}^0) \vee x_3 \\ x_2 = \neg(x_3 \vee \neg u_{3,2}^1) \\ x_3 = \left((\neg\, x_2 \wedge x_1) \vee \neg d_3^1\right) \wedge d_3^0 \end{cases}$$

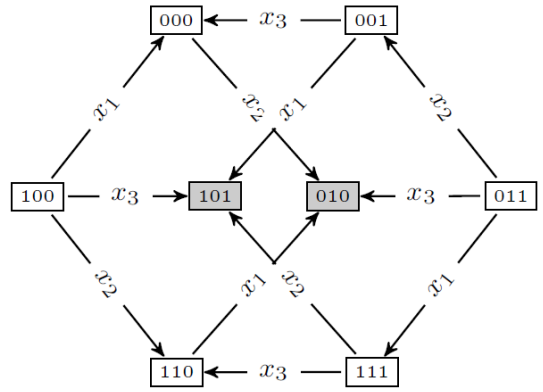


Action impact

Control Acts on Dynamics



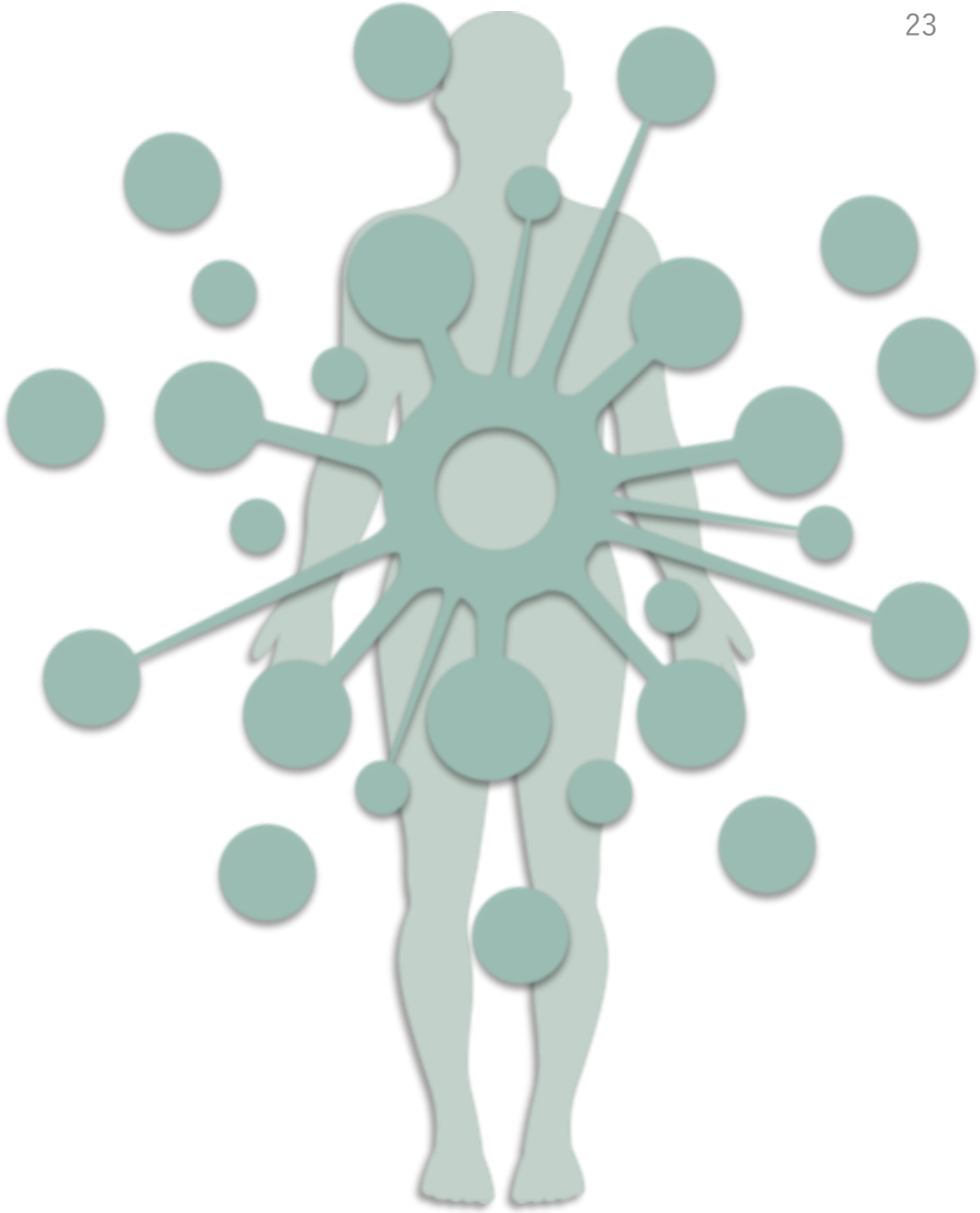
$u_{2,1}^0 = 1, u_{3,2}^1 = 1, d_3^1 = 1, d_3^0 = \mathbf{0}$



$u_{2,1}^0 = \mathbf{0}, u_{3,1}^1 = 1, d_3^1 = 1, d_3^0 = 1$

Boolean Network Action Discovery

Computational Method Principles



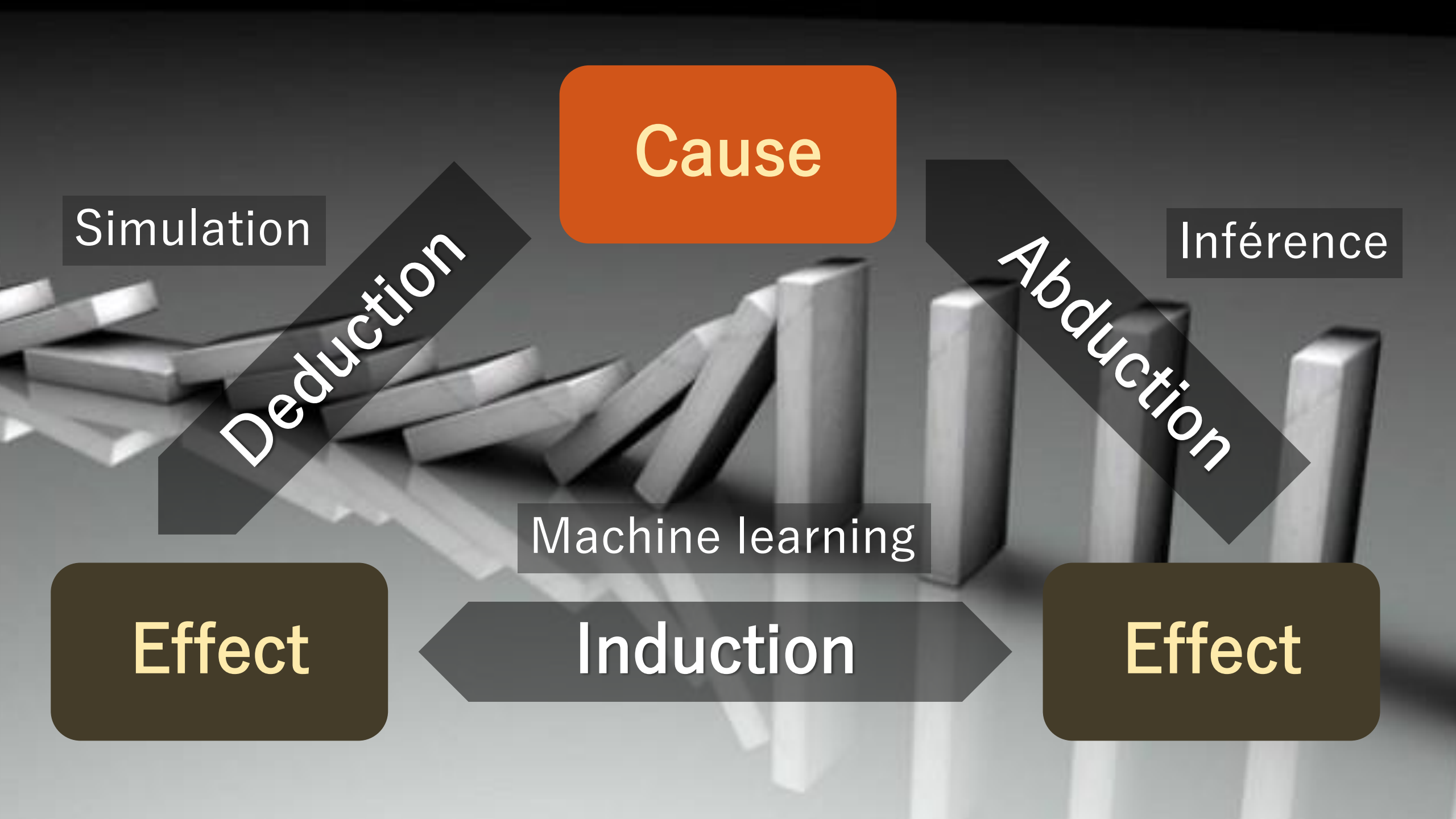
Network action discovery

Network actions inducing biomarker profile switch

Control parameters to freeze inducing equilibrium profile switch

Control discovery

Freezing control as causes.


Cause
Simulation
Deduction
Abduction
Inférence
Machine learning
Effect
Induction
Effect

Exhaustive Simulation by Generate-and-test ?

- Network of 100 genes
- Inhibit 10% of genes at most (0-Freeze)
- Objective: a “healthy” Biomarker profile
- Find the target candidates
- Number of simulation trials ?

Problem statement

Discrete Inverse Problem Category

1 effect ➔ ≠causes : Parsimony

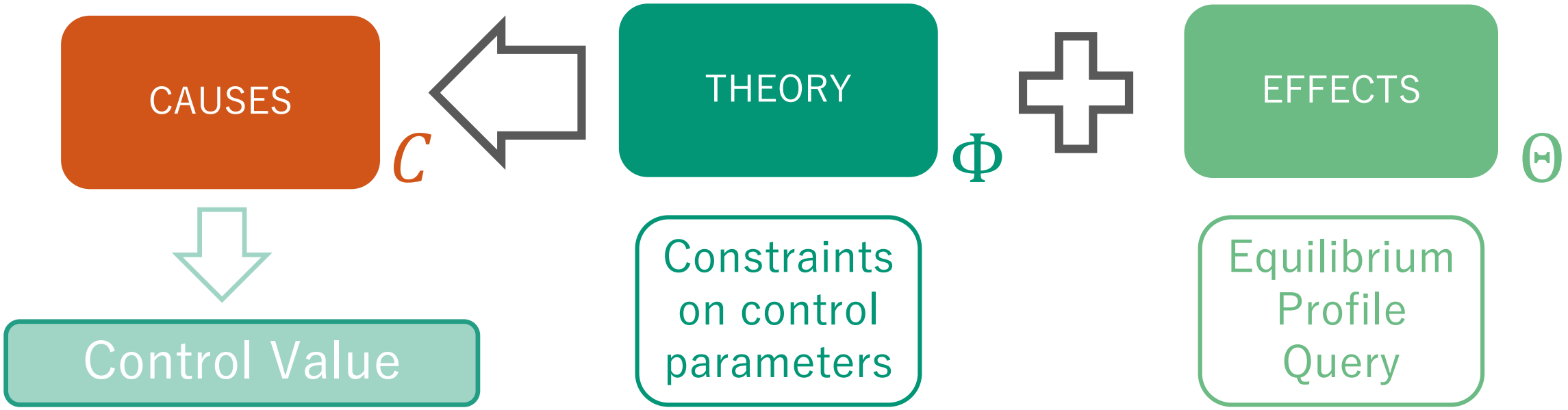
Feed back ➔ Circular causes

Formal approach of cause discovery

Inference
Principles
Discovery

Inference principle = Abduction

$$C \wedge \Phi \models \Theta$$



Parsimonious solutions ⇨ **Cores** = implicants minimizing the freeze

Biological queries formalization

In Some Contexts or Situations

Possibility to meet a property on states at equilibrium

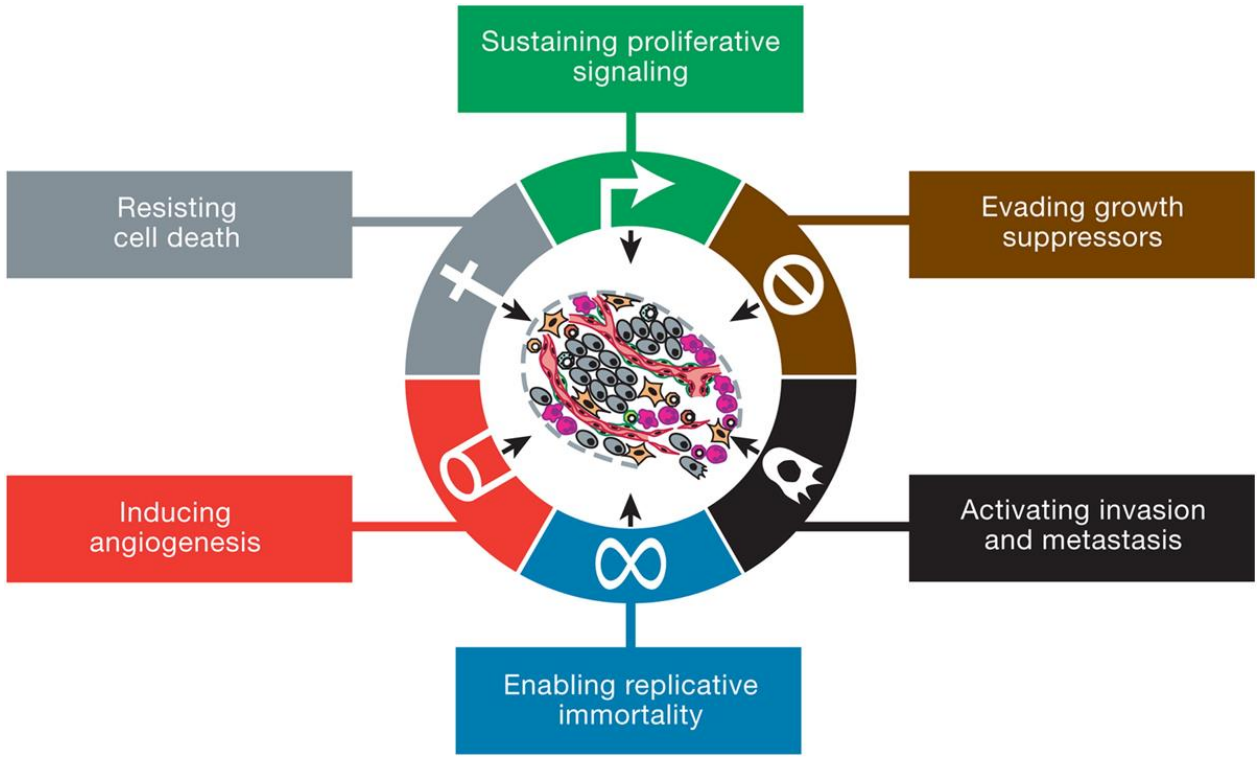
$$\diamond p = \exists s \in S : Stable_{F_\mu}(s) \wedge p(s)$$

In All Contexts or Situations

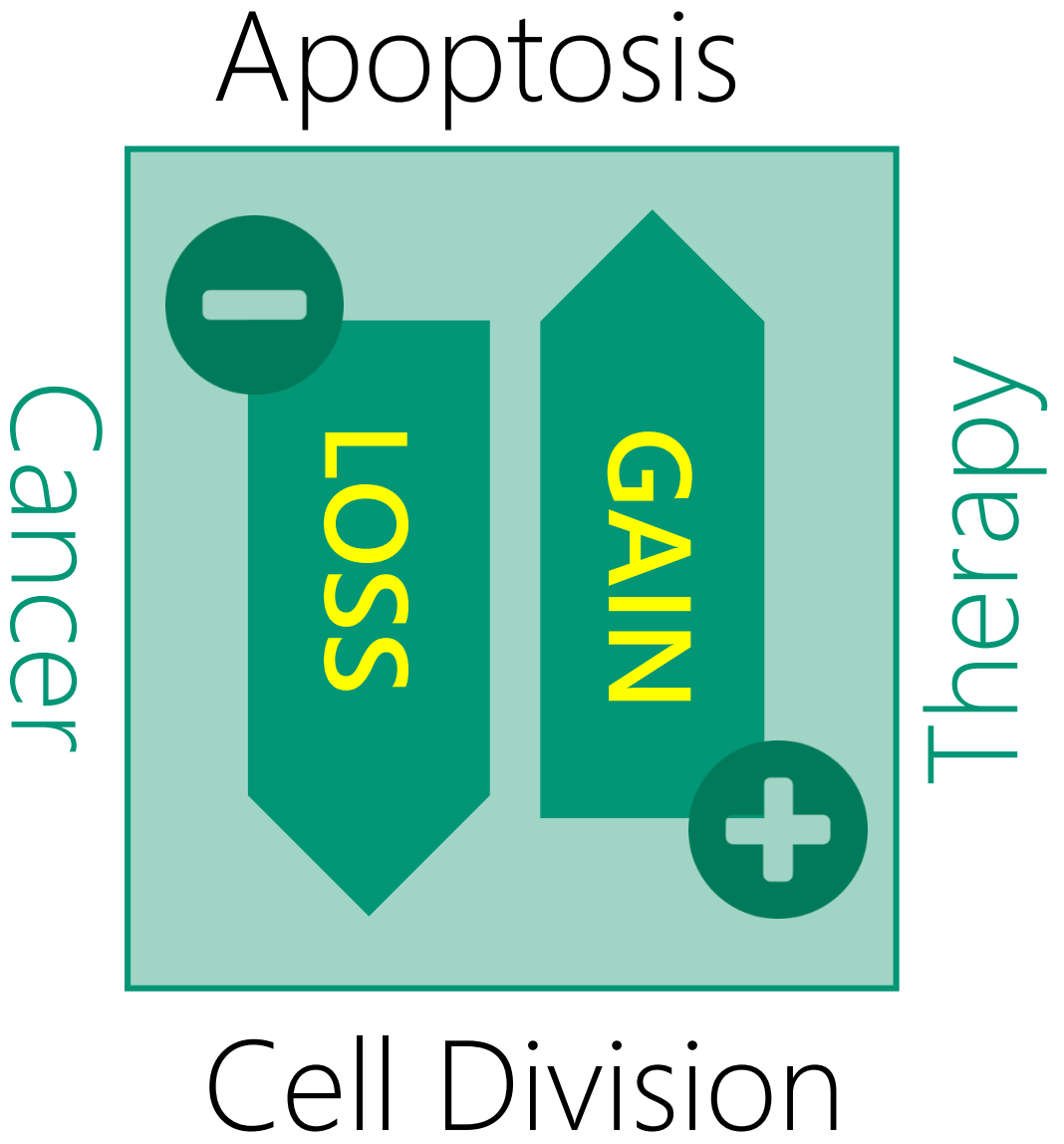
Necessity to meet a property on states at equilibrium

$$\square p = \forall s \in S : Stable_{F_\mu}(s) \Rightarrow \ p(s)$$

Biological Query Examples : Cancer



Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. cell, 144(5), 646-674.



Biological Query Examples

Gain of Apoptosis

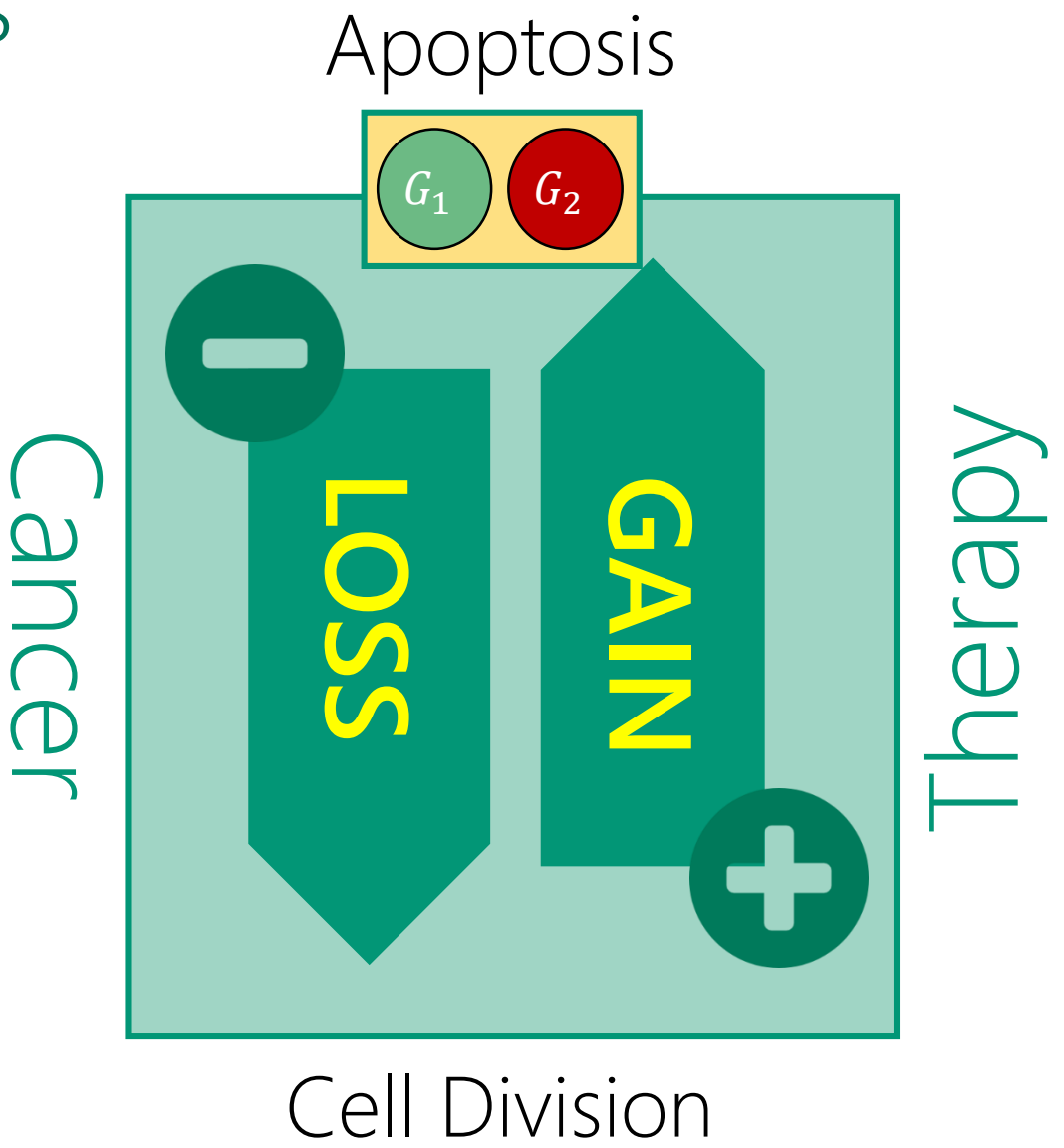
The marking profile may be reached when stabilized

$$\Diamond\,(G_1 \wedge \neg\, G_2)$$

Loss of Apoptosis

Never reach the marking profile when stabilized

$$\Box\neg(G_1 \wedge \neg\, G_2)$$



Inference solver of cores

Boolean Network

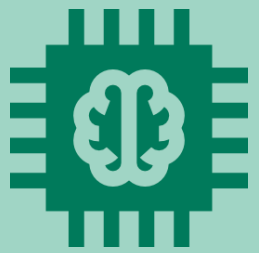
$$F = \begin{cases} x_1 = x_2 \wedge \neg x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg\, x_2 \wedge x_1 \end{cases}$$

Reprogramming query

Possibly

$x_1 = 0$

Abductive Solver



Core

$d_2^0 = \mathbf{0}$

Action

x_2

Result

Parsimonious cause =
Mininal control parameter sets to freeze under the inclusion

Method

Derived from prime implicant computation

Software

Library developed in Mathematica
ActONetLib

Steps of the method (1) : Specification

$$F = \begin{cases} x_1 = x_2 \wedge \neg x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg\, x_2 \wedge x_1 \end{cases}$$

Control Decoration

$$x_1 = x_2 \wedge \neg x_3$$
$$x_2 = (\neg x_3) \vee \neg d^1_{x_2} \wedge d^0_{x_2}$$
$$x_3 = (\neg\, x_2 \wedge x_1) \vee \neg d^1_{x_3} \wedge d^0_{x_2}$$

$\Diamond\,(x_1 = 0)$

Query Specification

$$(x_1 \Leftrightarrow x_2 \wedge \neg x_3) \wedge (\, x_2 \Leftrightarrow \neg x_3 \vee \neg d^1_{x_2} \wedge d^0_{x_2}\,) \wedge (x_3 \Leftrightarrow \neg\, x_2 \wedge x_1 \vee \neg d^1_{x_3} \wedge d^0_{x_2}\,)$$

Stability

$$\wedge$$

$$(\neg x_1)$$

Marking

$$\wedge$$

$$(d^1_{x_2} \vee d^0_{x_2}) \wedge (d^1_{x_3} \vee d^0_{x_3})$$

Control Parcimony

Steps of the method (2): 0-1 ILP

ILP : Minimize $v.w$ subject to $M.v \geq k$ with $v_i \in \{0,1\}$

CNF Form

ILP-based CNF SAT
Terms = Variables

Core
Objective Function
Negative control terms =1

$$\neg x_1 \wedge (\neg x_2 \vee x_3) \wedge (\neg x_2 \vee \neg d^1_{x_2}) \wedge (x_2 \vee d^1_{x_2}) \wedge (\neg x_3 \vee d^0_{x_3}) \wedge (\neg x_3 \vee \neg d^1_{x_3}) \wedge (x_3 \vee \neg d^0_{x_2}) \wedge (x_3 \vee d^1_{x_3}) \wedge (d^0_{x_2} \vee d^1_{x_2})$$

$$\sum_{l_{v_i} \in T_{CNF}} M_{i,*}.l_{v_i} \geq 1$$

$$\min\left(\sum_{l_{v_i} \in T_{Ctrl}} l_{v_i}.w_i\right)$$

$$l_{\neg d^0_{x_2}} = 1 \quad l_{\neg d^1_{x_3}} = 1$$

M

$\neg x_1$	x_2	$\neg x_2$	x_3	$\neg x_3$	$d^0_{x_2}$	$\neg d^0_{x_2}$	$d^1_{x_2}$	$\neg d^1_{x_2}$	$d^0_{x_3}$	$d^1_{x_3}$	$\neg d^1_{x_3}$
1											
		1	1								
	1						1				
				1					1		
				1							1
			1			1					
			1							1	
					1		1				

w

$d^0_{x_2}$	$\neg d^0_{x_2}$	$d^1_{x_2}$	$\neg d^1_{x_2}$	$d^1_{x_3}$	$\neg d^1_{x_3}$
	1		1		1

x_2 x_3

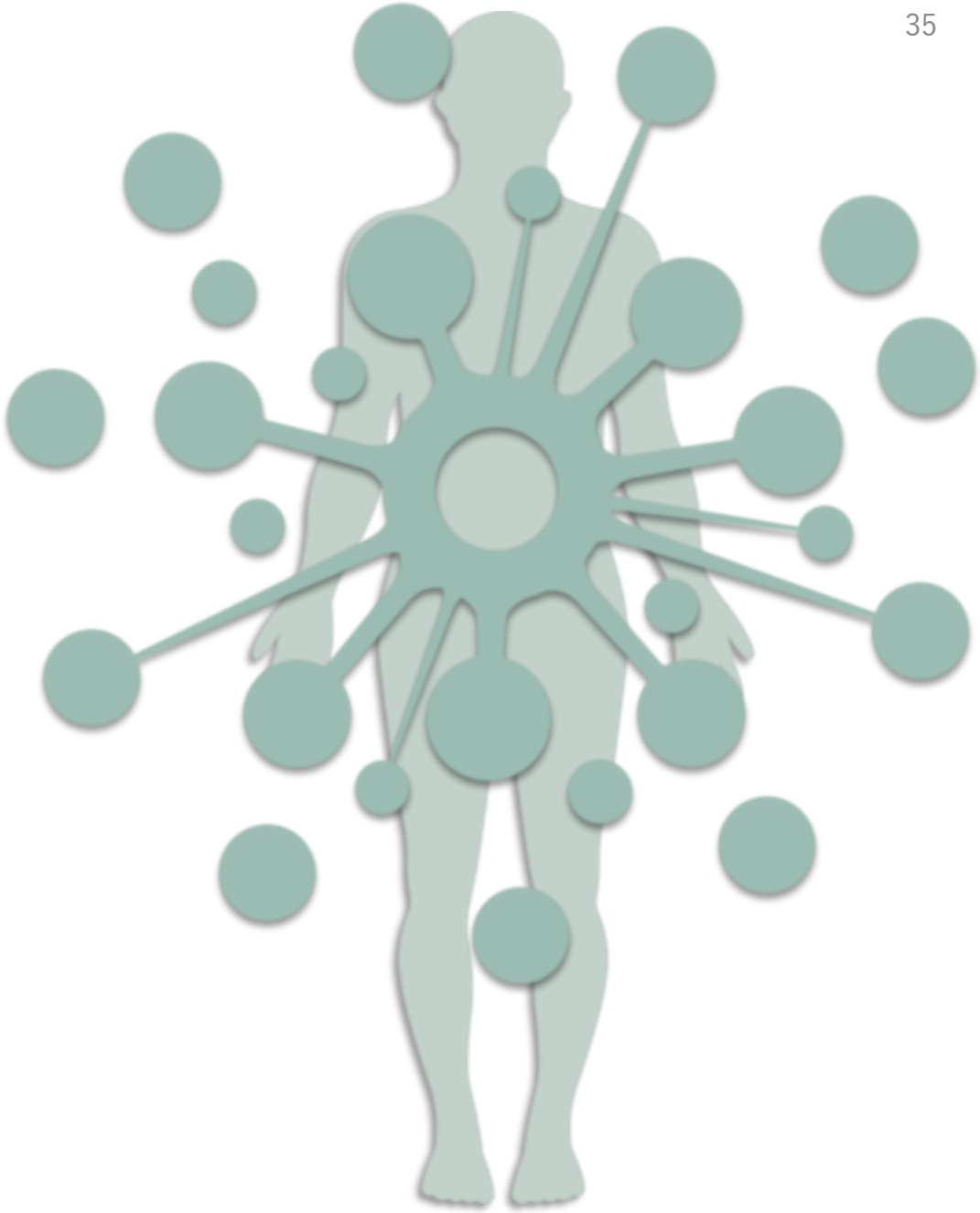
Application

Proof of concepts

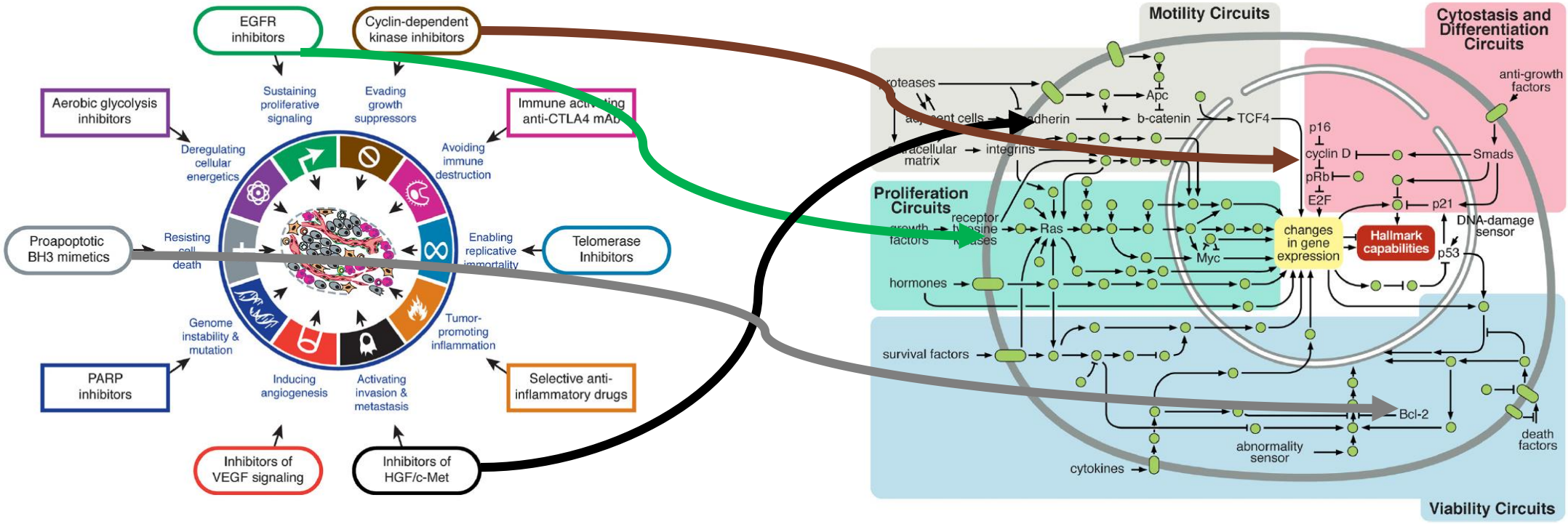
application to Breast cancer

Inference of

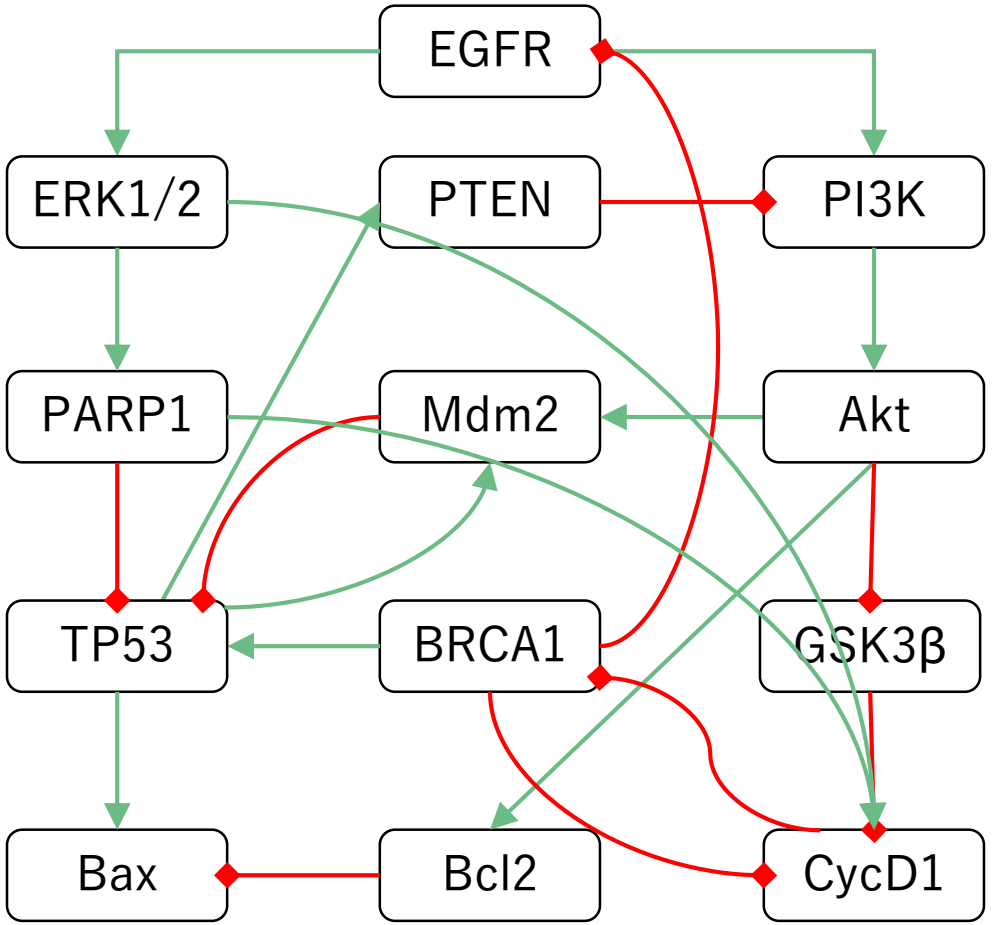
- Drivers
- Drug target



Drug Actions Inference



A Boolean network of apoptosis/proliferation



$$
\begin{cases}
EGFR = \neg BRCA1 \\
ERK1/2 = EGFR \\
PI3K = \neg\ PTEN \wedge EGFR \\
Akt = PI3K \\
GSK3\beta = \neg\ Akt, \\
MDM2 = \ Akt \wedge TP53, \\
TP53 = \neg\ MDM2 \wedge\ (BRCA1 \vee \neg\ PARP1) \\
PTEN = \ TP53 \\
PARP1 = \ ERK1/2 \\
BRCA1 = \ \neg CycD1 \\
Bcl2 = \ Akt \\
Bax = \ \neg Bcl2 \wedge TP53, \\
CycD1 = \neg\ GSK3\beta \vee\ (\neg\ BRCA1 \wedge\ PARP)
\end{cases}
$$

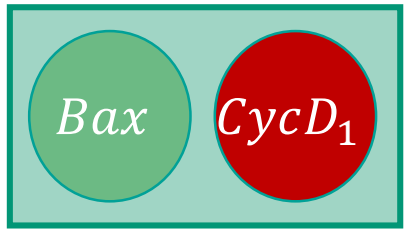
EGFR	ERK1/2	PI3K	Akt	GSK3β	Mdm2	TP53	PTEN	PARP1	BRCA1	Bcl2	Bax	CycD1	Phenotype
													Division
													Apoptosis

Inference of Driver Mutation

Problem statement

Freeze nodes to 0 or 1 except markers
Loss of apoptosis - Bax & CycD1 as markers

Apoptosis signature



Query

$$\square\neg(Bax \wedge \neg CycD_1)$$

Result

1D & 2D-Freezing

Single Frozen Molecule

0	BRCA1
	TP53

Tumor suppressors

	Akt
1	Bcl2
	Mdm2
	PI3K

Oncogenes

Pair of Frozen Molecules

	GSK3 β	EGFR
0	PTEN	EGFR 1
	GSK3 β	ERK1/2

EGFR inhibitors Resistance

Inference of targets in BRCA1-deficient cells

Problem statement

Fix BRCA1 to 0
Gain of apoptosis

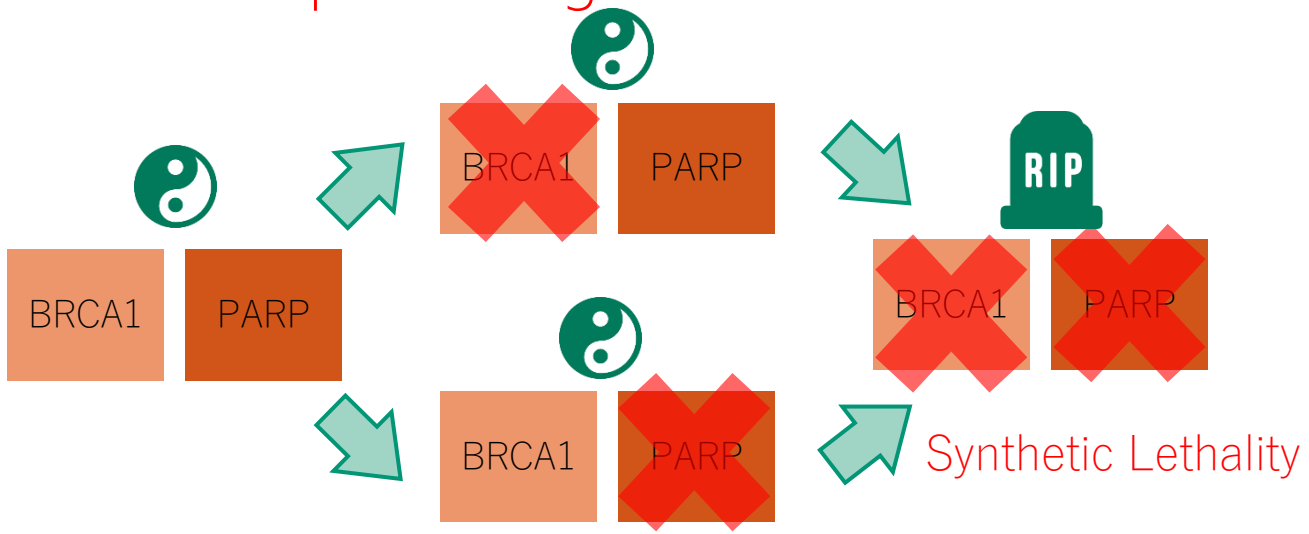
$$
\begin{cases}
EGFR = \neg BRCA1 \\
ERK1/2 = EGFR \\
PI3K = \neg\ PTEN \wedge EGFR \\
Akt = PI3K \\
GSK3\beta = \neg\ Akt, \\
MDM2 = \ Akt \wedge TP53, \\
TP53 = \neg\ MDM2 \wedge\ (BRCA1 \vee \neg\ PARP1) \\
PTEN = \ TP53 \\
PARP1 = \ ERK1/2 \\
BRCA1 = \ 0 \\
Bcl2 = \ Akt \\
Bax = \ \neg Bcl2 \wedge TP53, \\
CycD1 = \neg\ GSK3\beta \vee\ (\neg\ BRCA1 \wedge\ PARP)
\end{cases}
$$

Query

- $(Bax \wedge \neg CycD_1)$

Result

1D Freezing only



Notebook Example

⋆ Boolean Network Definition

```
F = {EGFR → ! BRCA1, ERK12 → EGFR, PIK3CA → ! PTEN && EGFR, Akt → PIK3CA, GSK3 → ! Akt, MDM2 → Akt && p53, p53 → ! MDM2 && (BRCA1 || ! PARP1), PTEN → p53, PARP1 → ERK12, BRCA1 → ¬ CycD1, Bcl2 → Akt, Bax → ! Bcl2 && p53, CycD1 → (! GSK3 && ERK12) || (! BRCA1 && PARP1)};
```

```
In[30]:= Fact = ActNet[F, {BRCA1 → False}];
In[31]:= AttractorToTable@First@StableStates[Fact]
```

Out[31]=

Akt	Bax	Bcl2	BRCA1	CycD1	EGFR	ERK12	GSK3	MDM2	p53	PARP1	PIK3CA	PTEN
1	0	1	0	1	1	1	0	0	0	1	1	0

Mutation

Original network

★ Marking definition and satisfiability test

```
In[32]:= markers = {CycD1, Bax}
Out[32]= {CycD1, Bax}

In[33]:= marking = {CycD1 → False, Bax → True}
Out[33]= {CycD1 → False, Bax → True}
```

★ List of variables that are allowed to be frozen either True or False

```
In[34]:= frozenfalse = Complement[Agents[Fact], markers]
Out[34]= {Akt, Bcl2, BRCA1, EGFR, ERK12, GSK3, MDM2, p53, PARP1, PIK3CA, PTEN}

In[35]:= frozentrue = Complement[Agents[Fact], markers]
Out[35]= {Akt, Bcl2, BRCA1, EGFR, ERK12, GSK3, MDM2, p53, PARP1, PIK3CA, PTEN}
```

Frozen variables

Core

```
In[36]:= Highlighted[TableForm[Timing[TableForm@CoreForm[cores = Destify[Fact, Nothing, MarkingToFormula[marking], frozenfalse, frozentrue, ControlType → controltype]]]], Frame → True]
Out[36]=
0.03125
EGFR
PARP1
ERK12
BRCA1
```

Abductive Solver

Validation

```
In[41]:= Fcure = ActNet[Fact, {PARP1 → False}]
Out[41]= {EGFR → ! BRCA1, ERK12 → EGFR, PIK3CA → ! PTEN && EGFR, Akt → PIK3CA, GSK3 → ! Akt, MDM2 → Akt && p53, p53 → ! MDM2 && (BRCA1 || ! PARP1), PTEN → p53, PARP1 → False, BRCA1 → False, Bcl2 → Akt, Bax → ! Bcl2 && p53, CycD1 → (! GSK3 && ERK12) || (! BRCA1 && PARP1)}
In[40]:= AttractorToTable@First@StableStates[Fcure]
```

Out[40]=

Akt	Bax	Bcl2	BRCA1	CycD1	EGFR	ERK12	GSK3	MDM2	p53	PARP1	PIK3CA	PTEN
0	1	0	0	0	1	1	1	0	1	0	0	1

New Stable states

Conclusion & Perspective

Conclusion

- Network based analysis: symmetrical analysis for disease & therapy
- Boolean control network to model cell reprogramming
- Biological validation provides seemingly **promising outcome**
- Dynamics analysis enlarges target inference ability ➔ Synthetic lethal partner discovery
- Computational method improvement : **BDD based Core inference**

Perspective

- Application to prediction of targets – DMD - ISTEM
- Extensions to other disease process
- Design of models for therapeutic prediction

Thank You

- Célia Biane, Franck Delaplace:
  Abduction Based Drug Target Discovery Using Boolean Control Network. CMSB 2017: 57-73
  https://tel.archives-ouvertes.fr/IBISC/hal-01522072

- Célia Biane, Franck Delaplace, Hanna Klaudel:
  Networks and games for precision medicine. Biosystems 150: 52-60 (2016)