



Inference of Drug/Disease targets

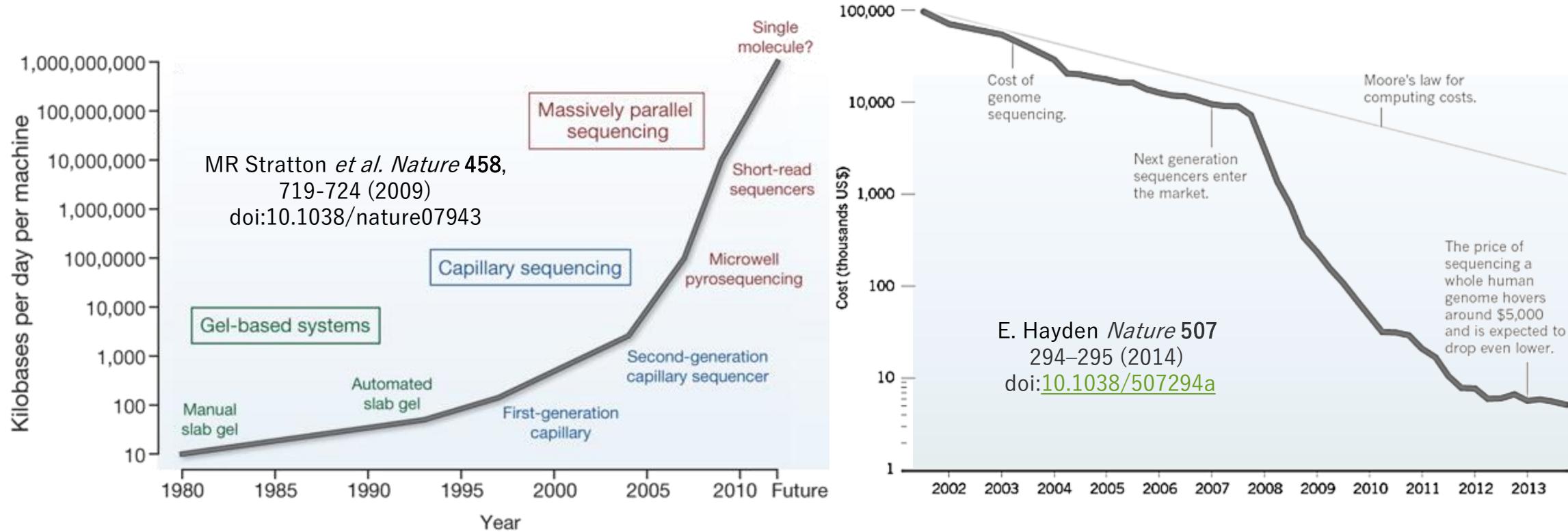
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IBISC – Paris Saclay University, Univ Evry



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

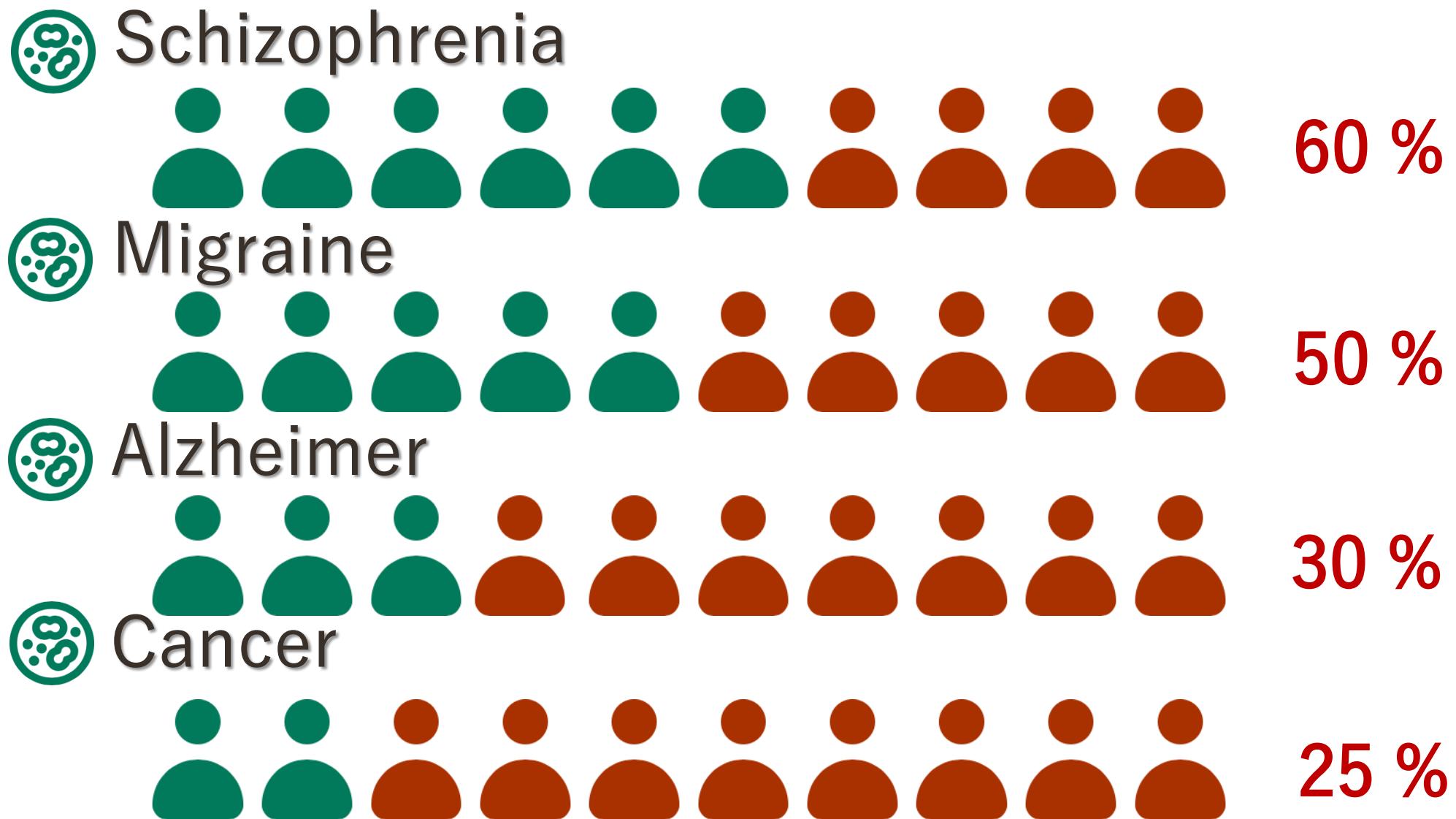
Big to Smart
transition

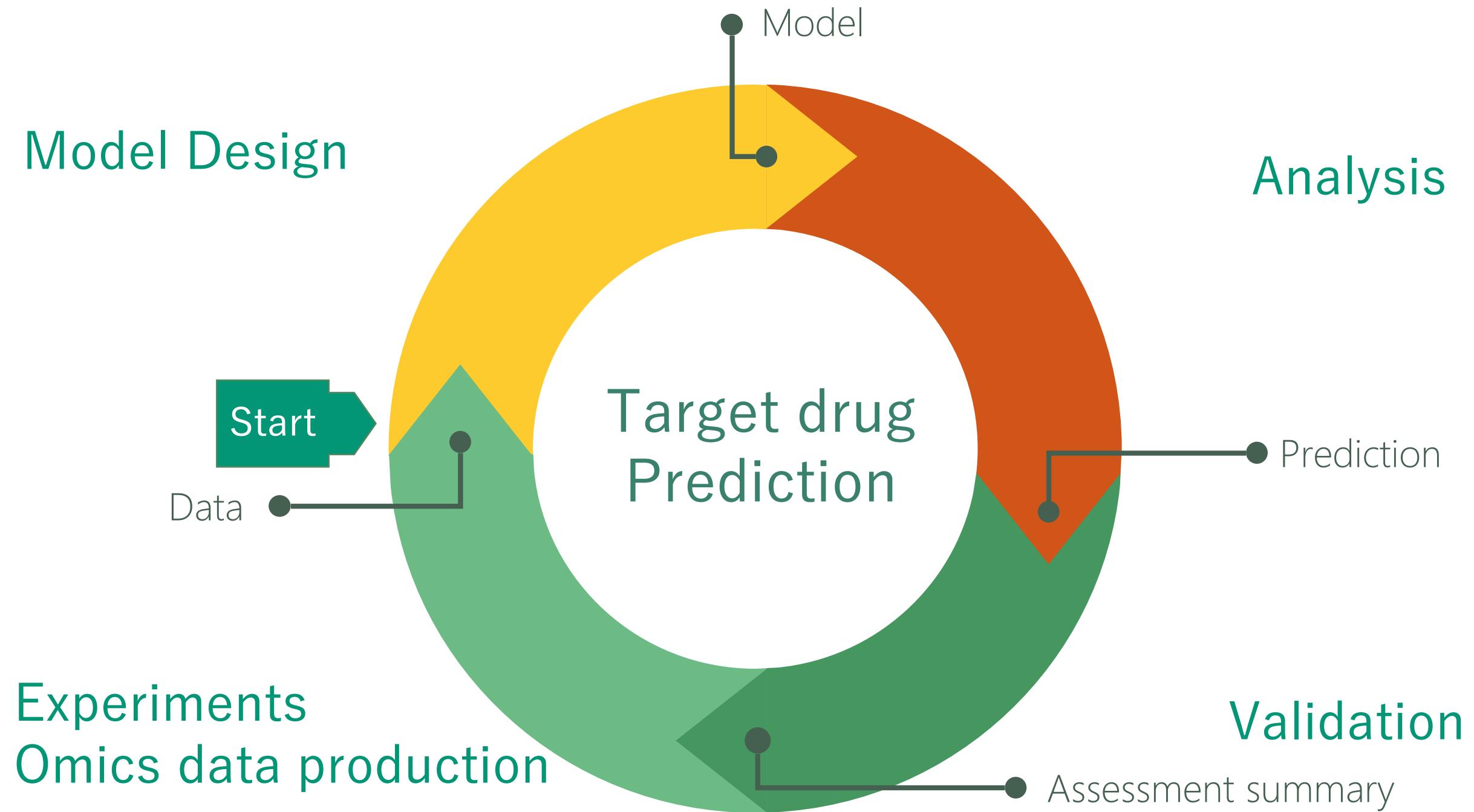
- ✓ Causal analysis
- ✓ Decision Making
- ✓ Risk Management



Drug efficiency

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

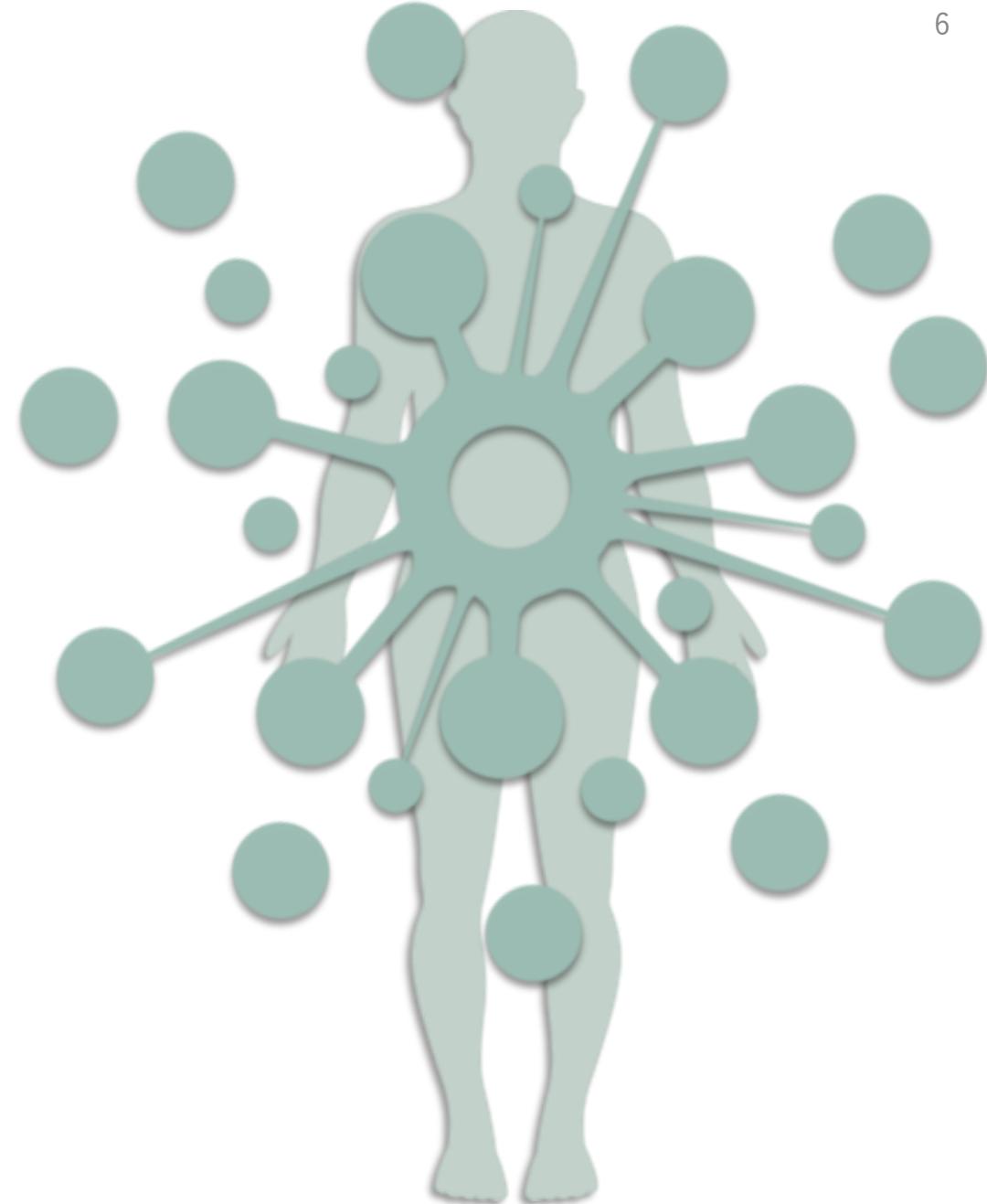




Modeling Framework

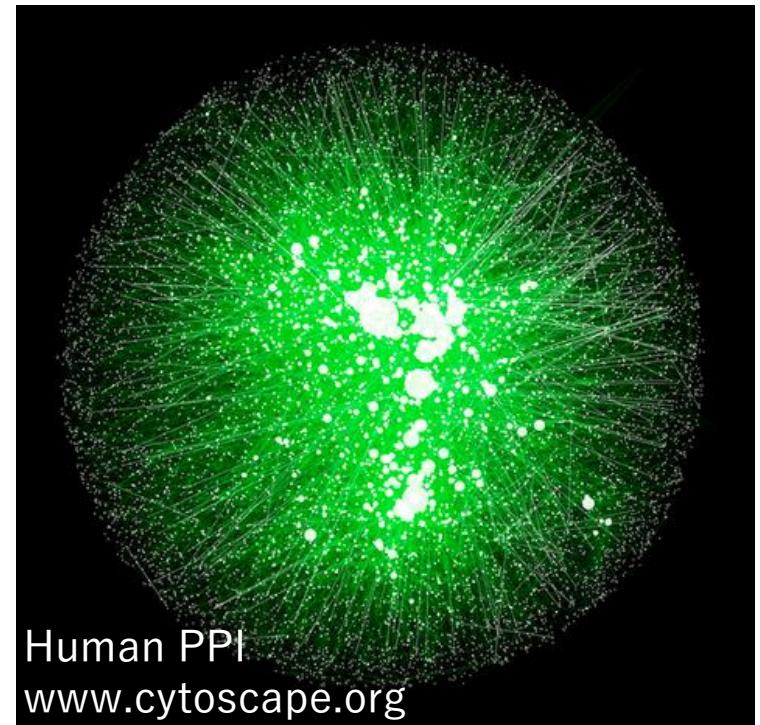
What is a disease model ?

What is a diseased model ?



Object of analysis: Interactome

- Whole set of molecular interactions in a cell
- Functional/Integrative approach of interactions
- Originally coined by Bernard Jacq - 1999



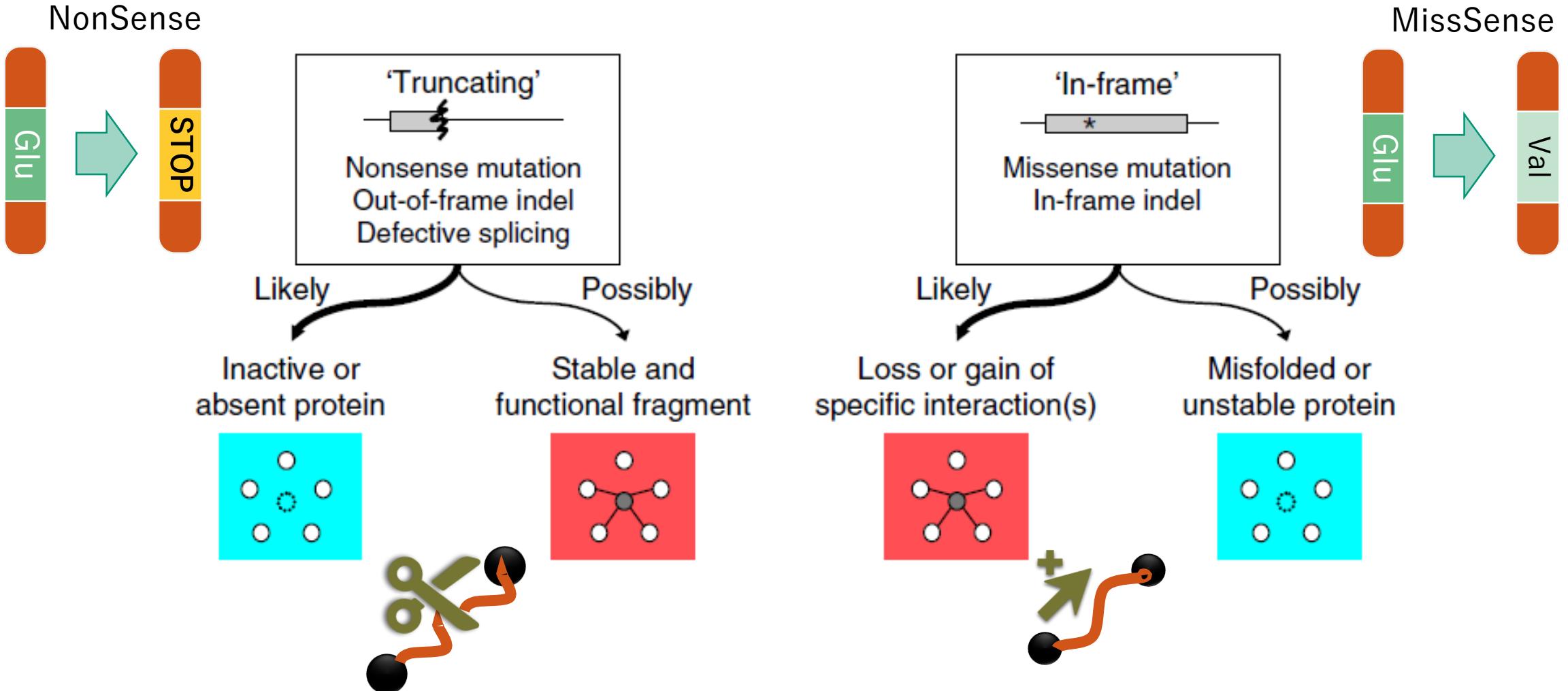
Type of interactions

Name	Nature of the interactions	Type
Protein-Protein	Specific physical contact between protein steered by electrostatic forces	↔
Signaling	Signal transduction mechanism	→
Regulation	mechanisms between genes regulating the production of specific gene product	→

Disease ► Interactome perturbation

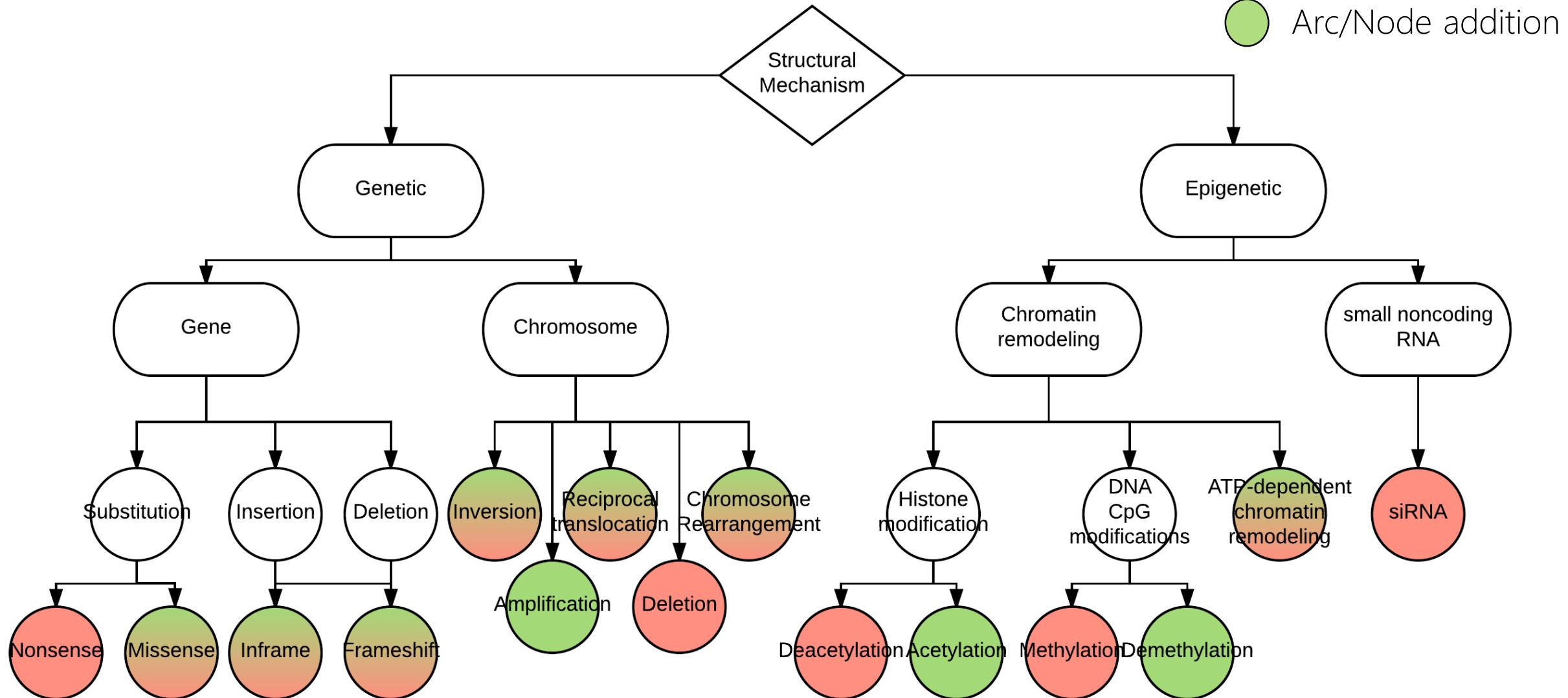
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Zhong et al. 2009. Edgetic perturbation models of human inherited disorders.

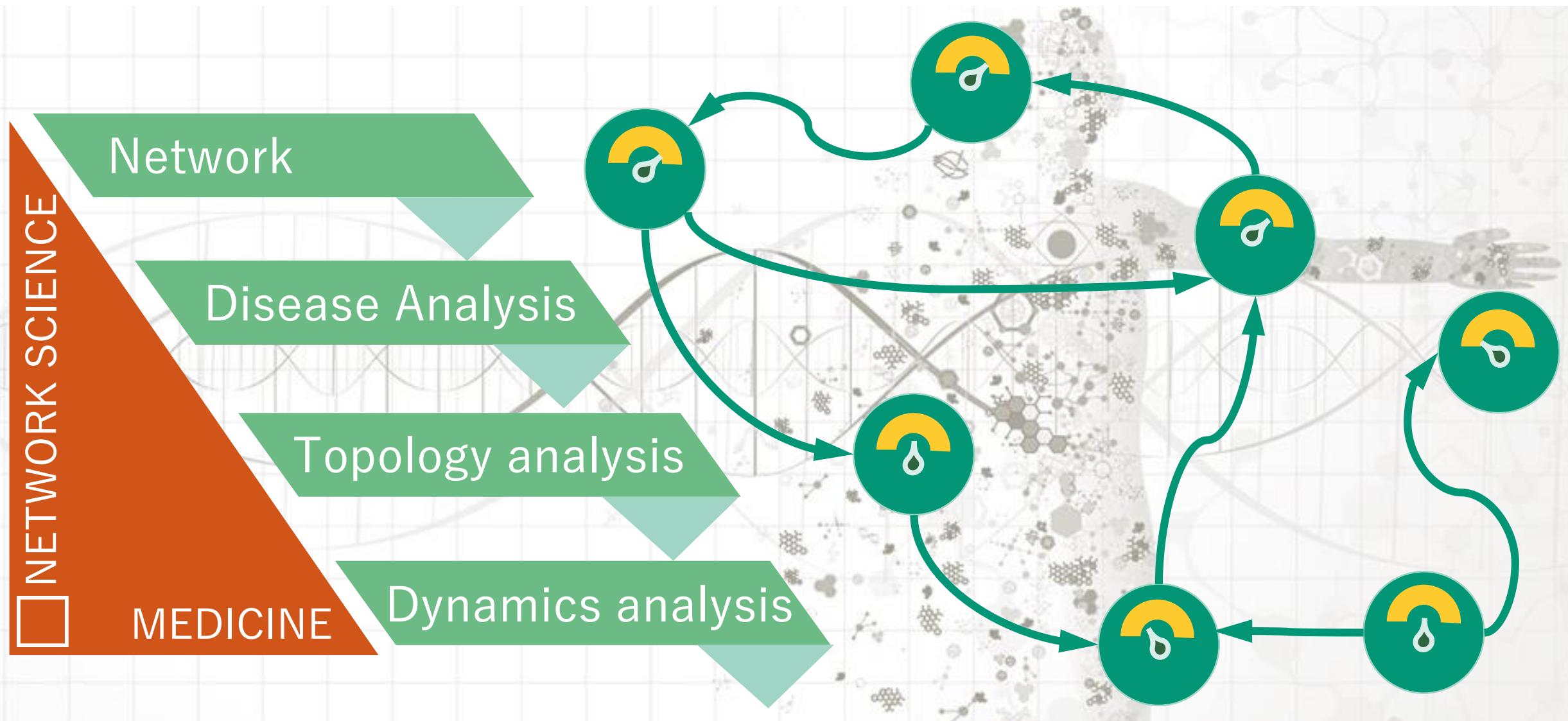


Addition & Deletion of arcs and nodes

Causes of Cancer as network actions



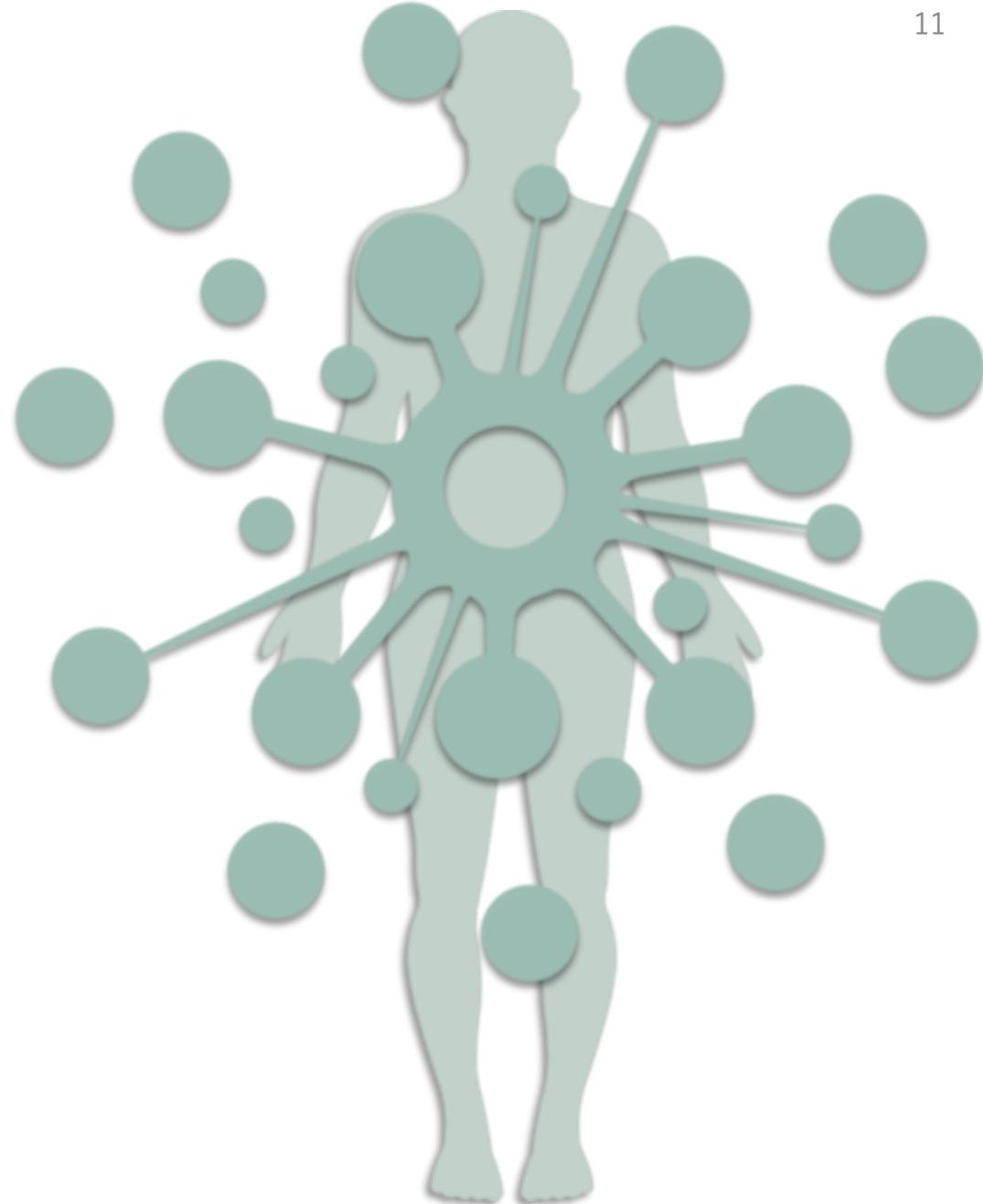
Network Medicine



Modeling analogy

What is a disease model ?

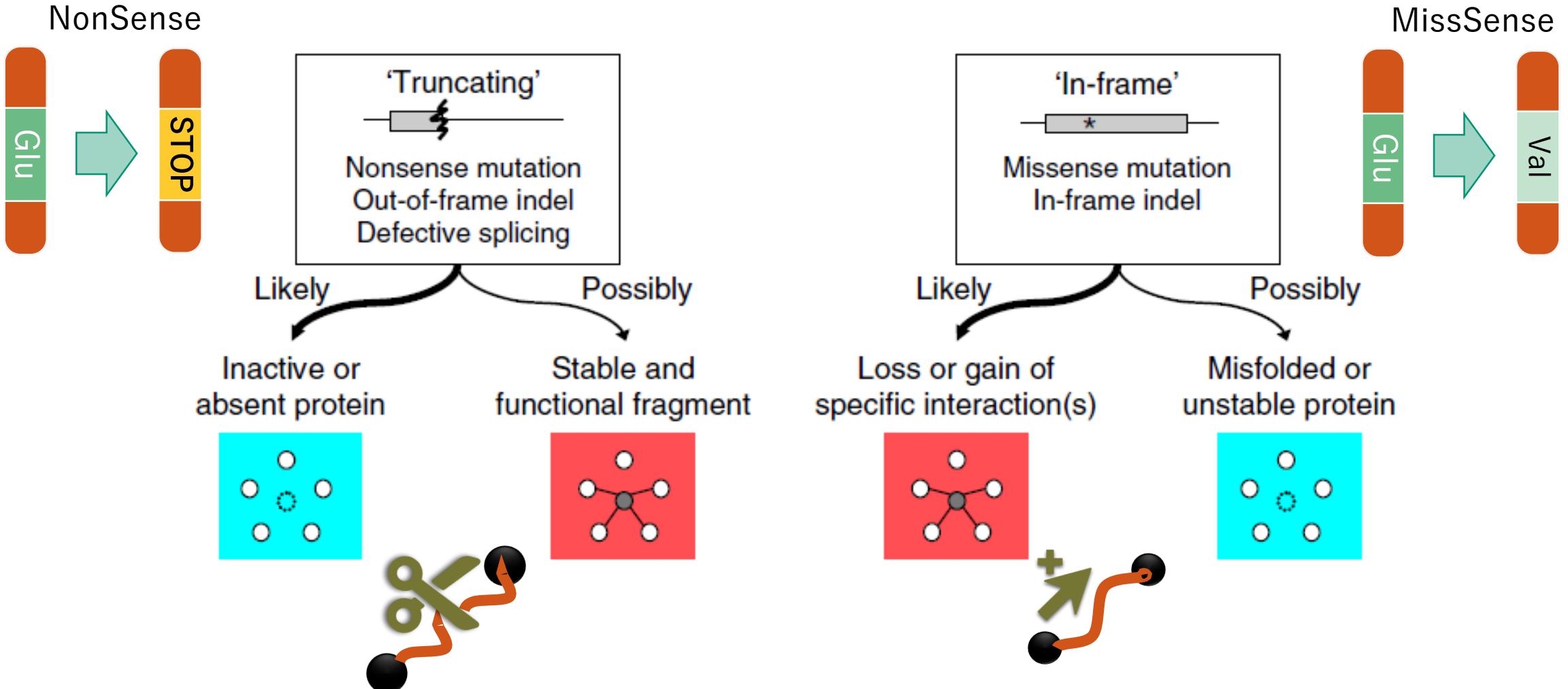
What is a diseased model ?



Disease ► Interactome perturbation

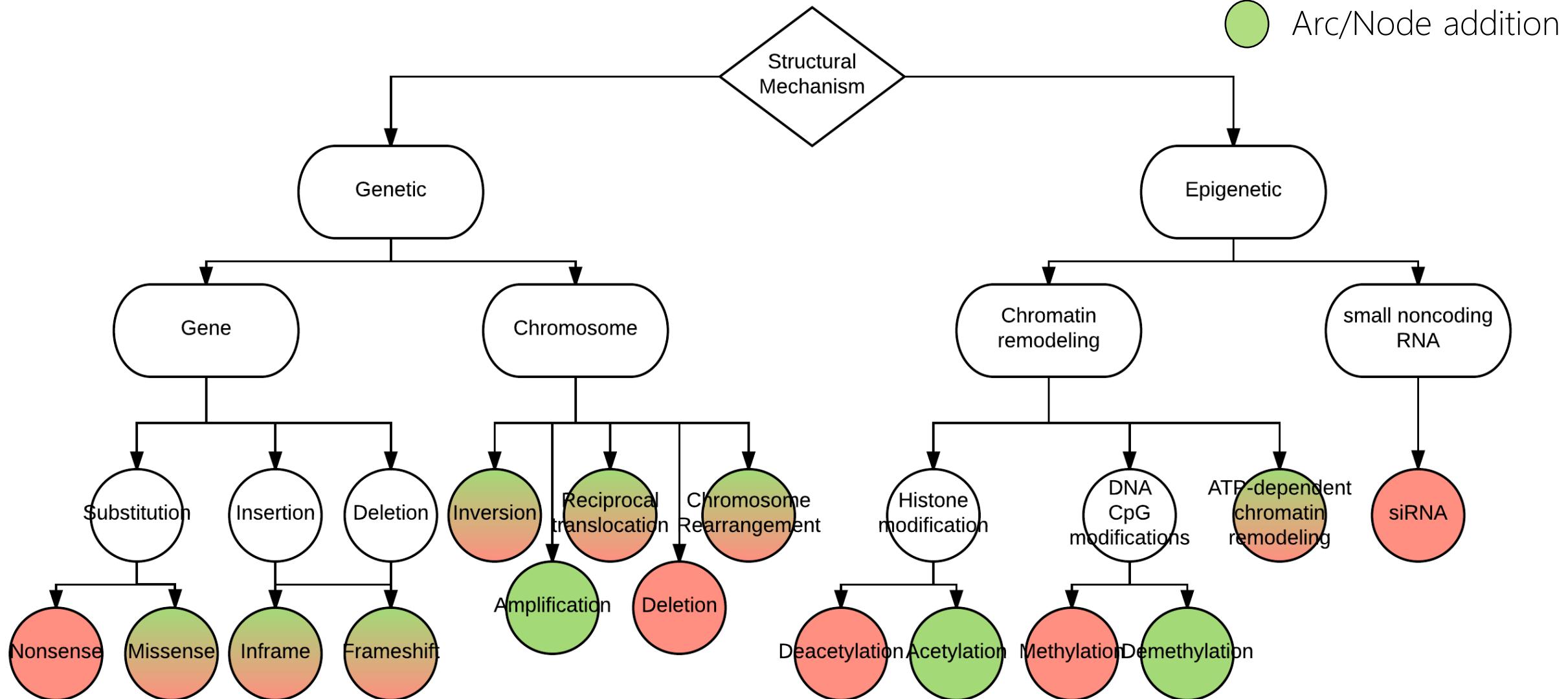
12

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

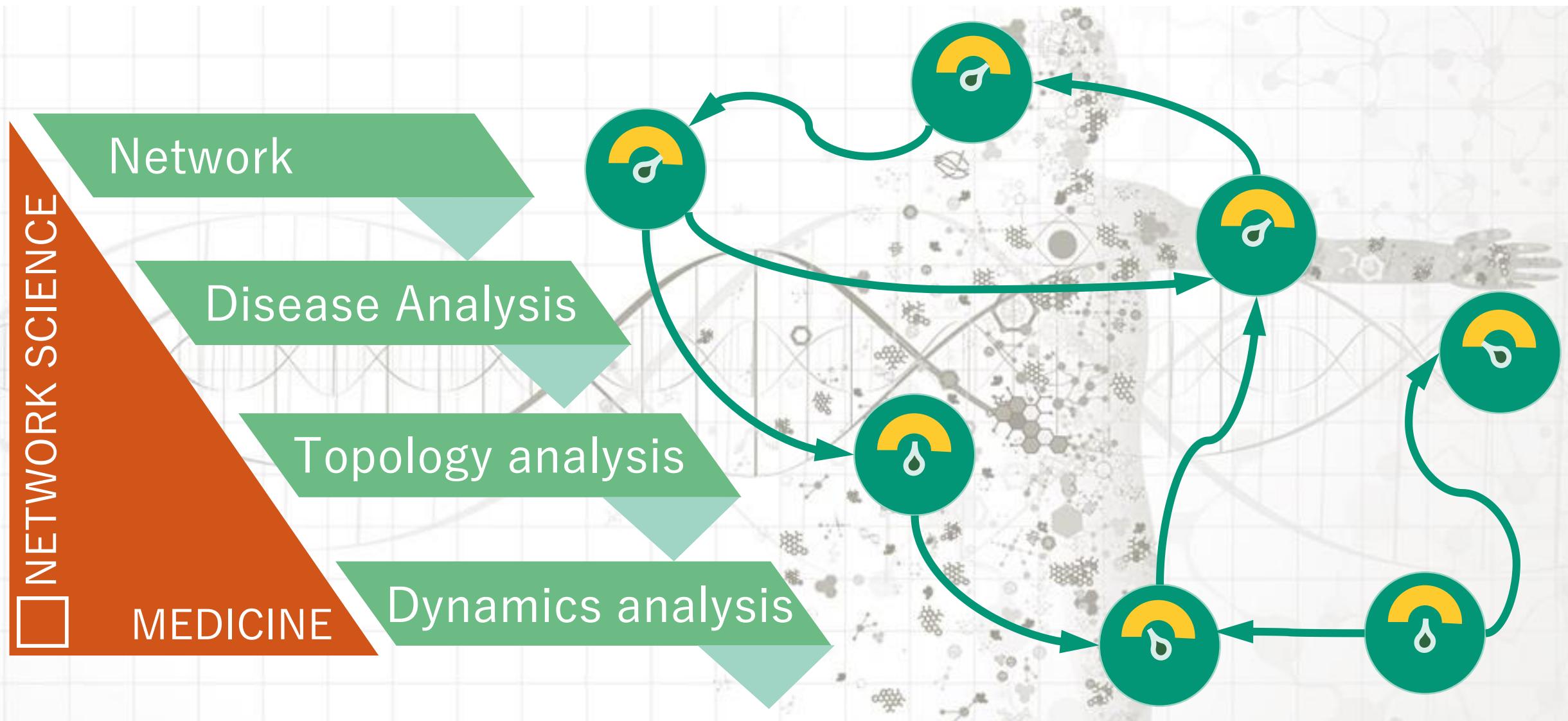


Addition & Deletion of arcs and nodes

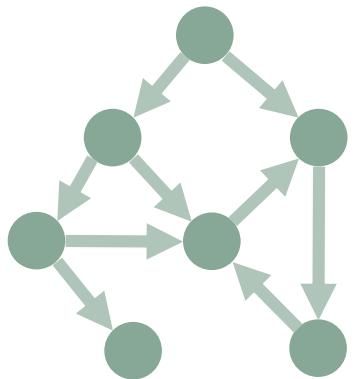
Causes of Cancer as network actions



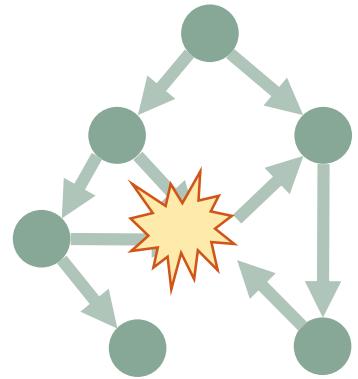
Network Medicine



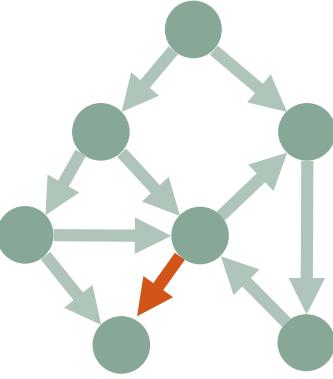
Revisiting Genotype-to-Phenotype Relation



Phenotype
1



Phenotype
2

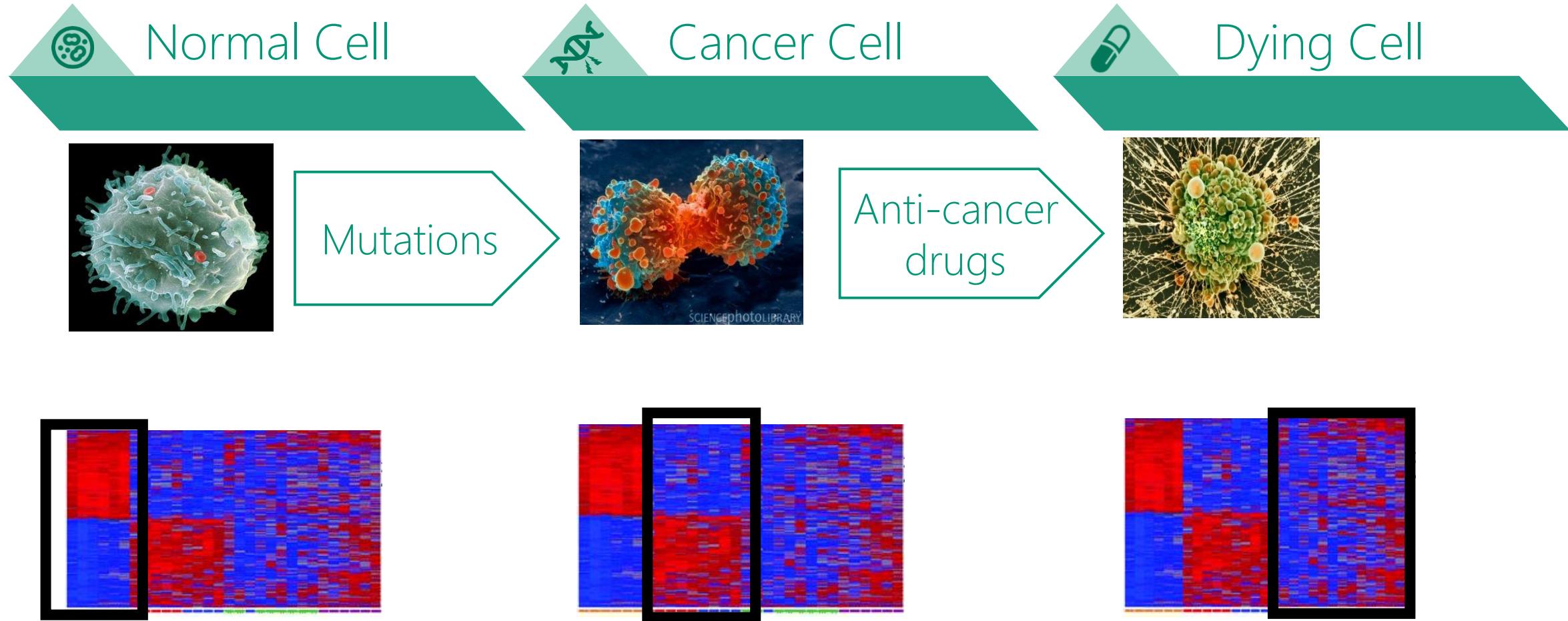


Phenotype
3

≠ Network Topologies →
≠ Phenotypes

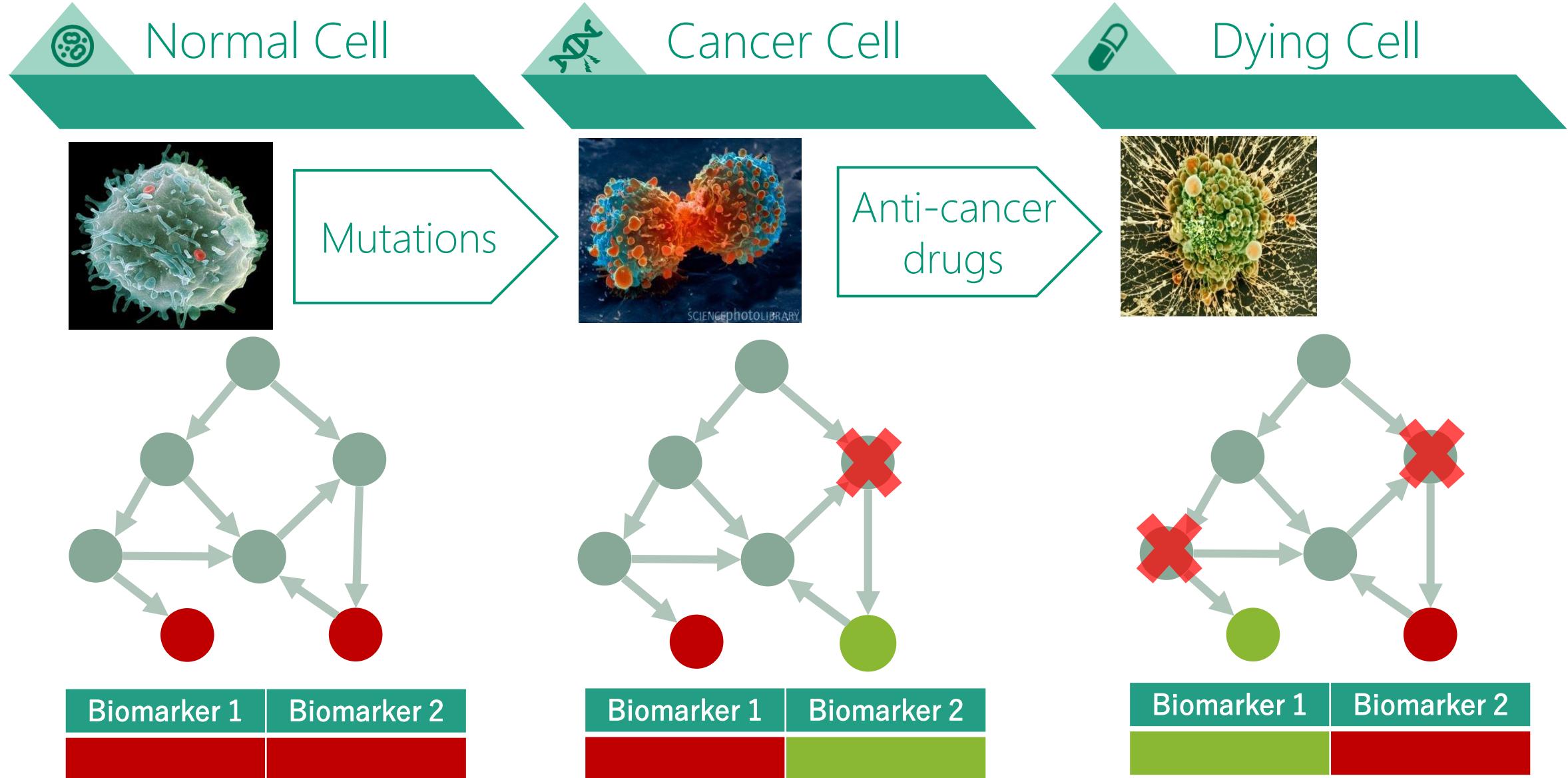
Causes of diseases & Therapy prediction based on network actions

Scenario: Phenotype shift/cell reprogramming



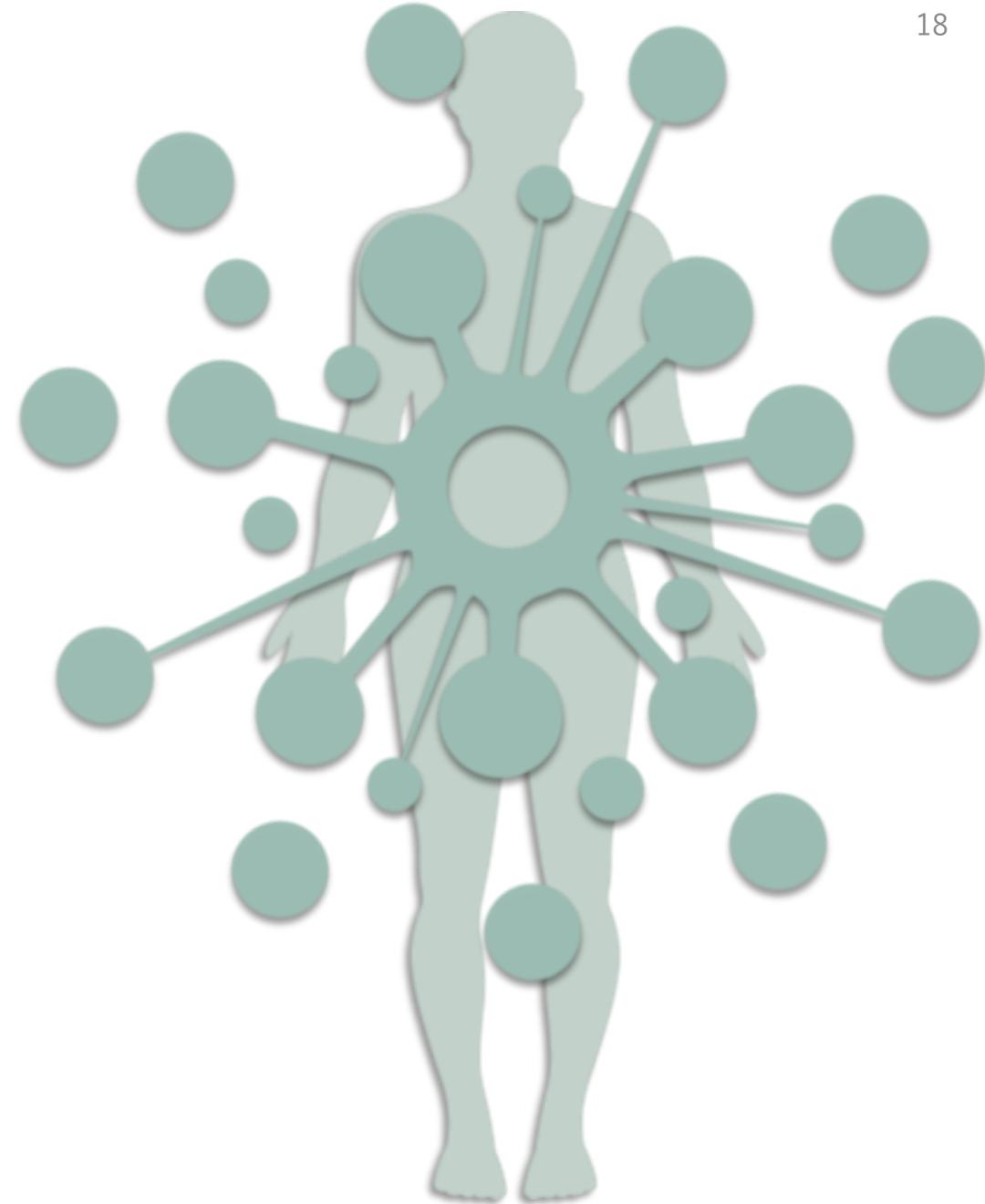
Phenotypic Switch = Observable Biomarker Shift

Scenario: action network = perturbation



Network Action Modelling framework

Theoretical framework

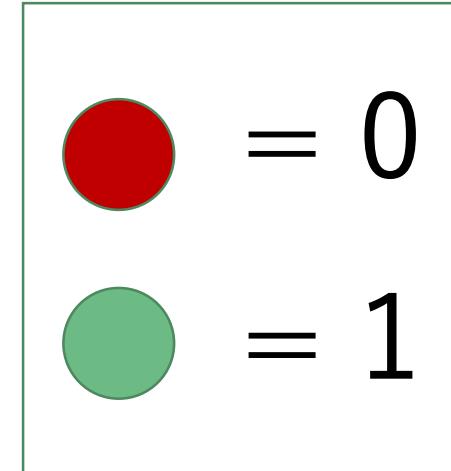


Boolean Network



G_1	G_2	G
Red	Red	Red
Red	Green	Red
Green	Red	Red
Green	Green	Green

$$G_1 \wedge G_2 = G$$



Fundamental operators

$$y = x_1 \wedge x_2$$

x_1	x_2	y

Logical AND

$$y = x_1 \vee x_2$$

x_1	x_2	y

Logical OR

$$y = \neg x_1$$

x_1	y

$= 0$
 $= 1$

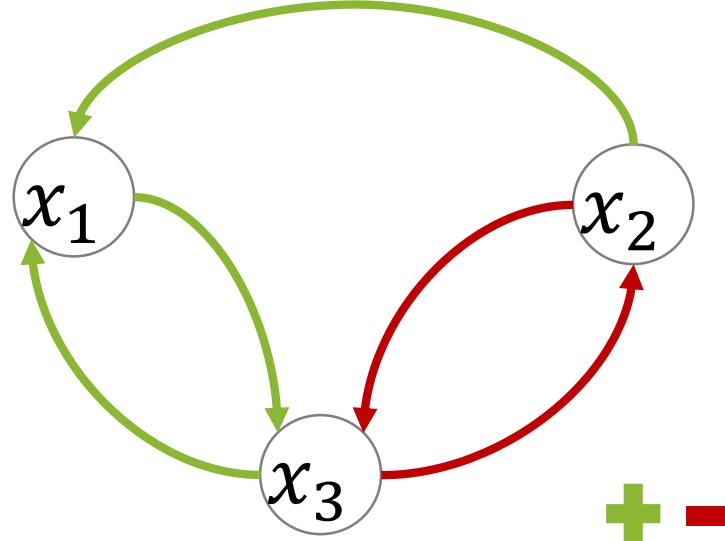
Negation

Boolean Networks – Definition

Network = Boolean Dynamical system

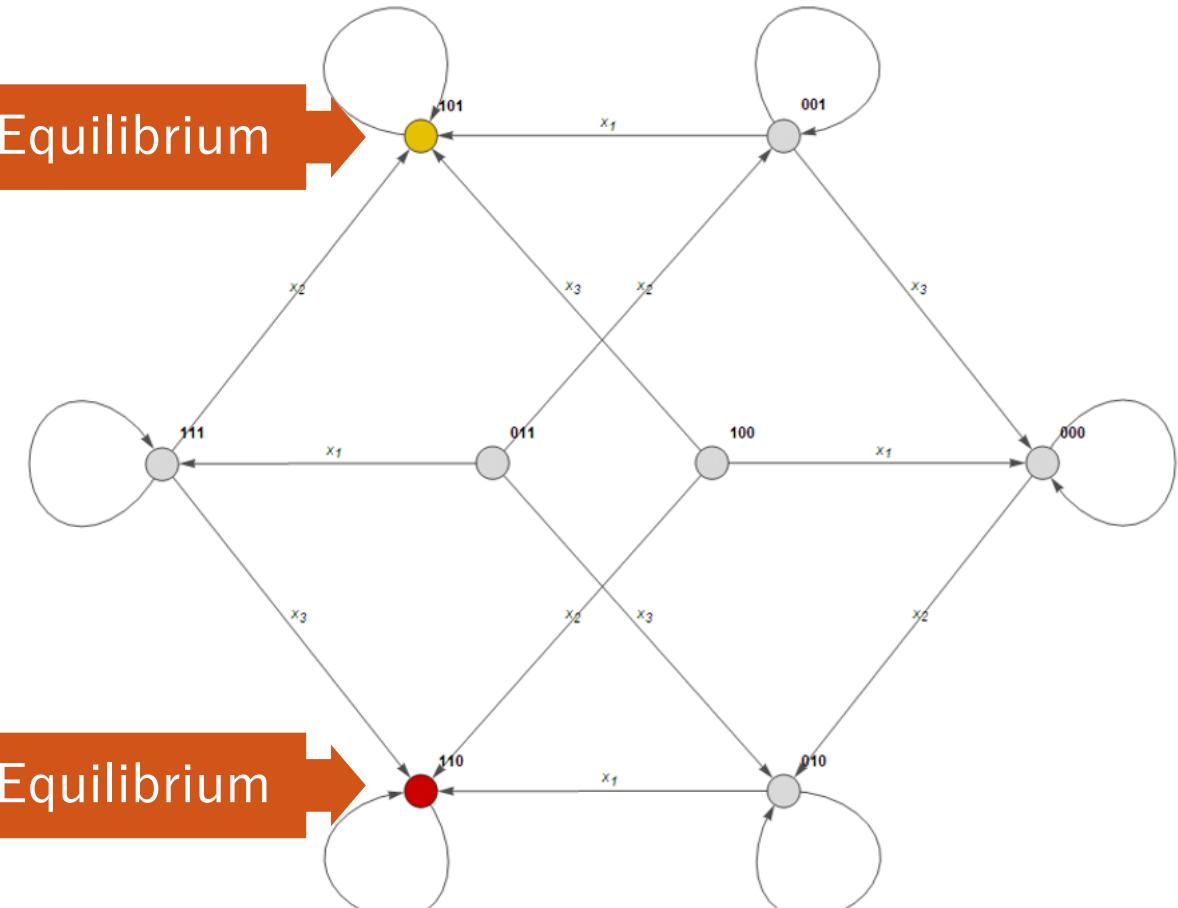
$$F = \begin{cases} x_1 = x_2 \vee x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg x_2 \wedge x_1 \end{cases}$$

Interaction graph



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

Equilibrium

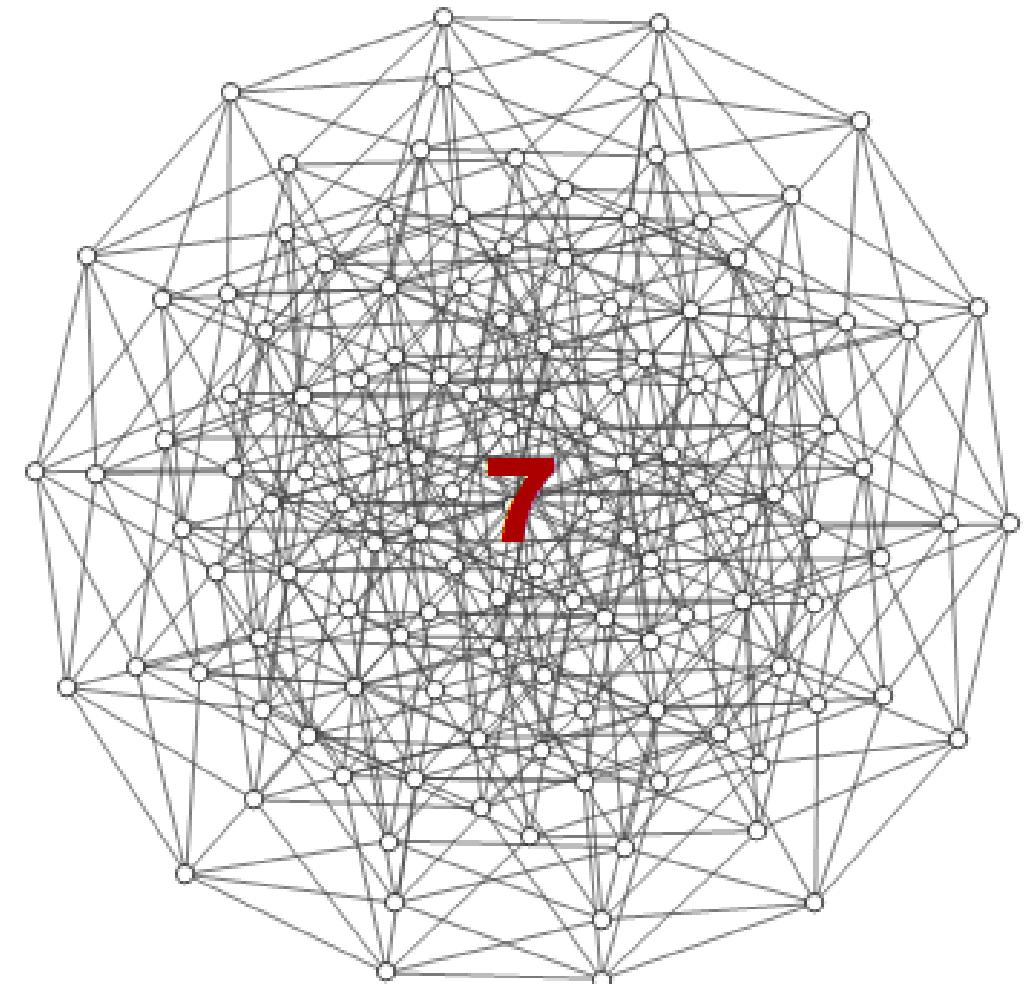


Equilibrium

Exponential size of space state

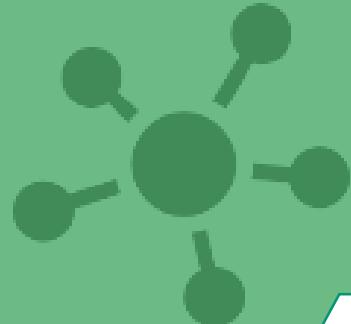
Hypercube H_7 = “roads” of trajectories

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



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

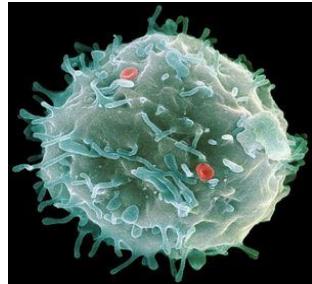
Extension of the updating policy

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

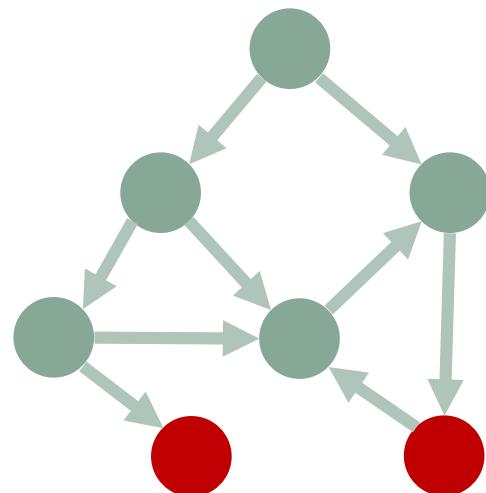
Network
action
On
Boolean Network



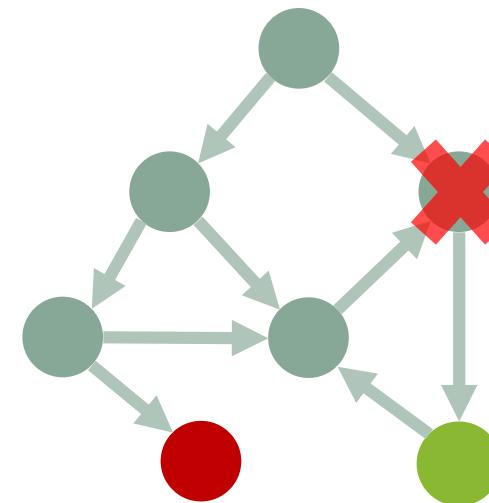
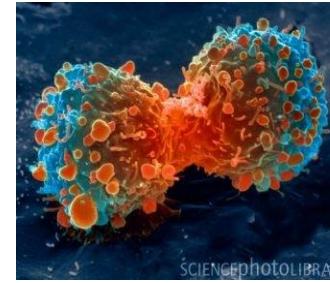
Scenario:Dynamical system reprogramming



Mutations



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



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

Computability ?

Reprogramming ▶ Boolean control network

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

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

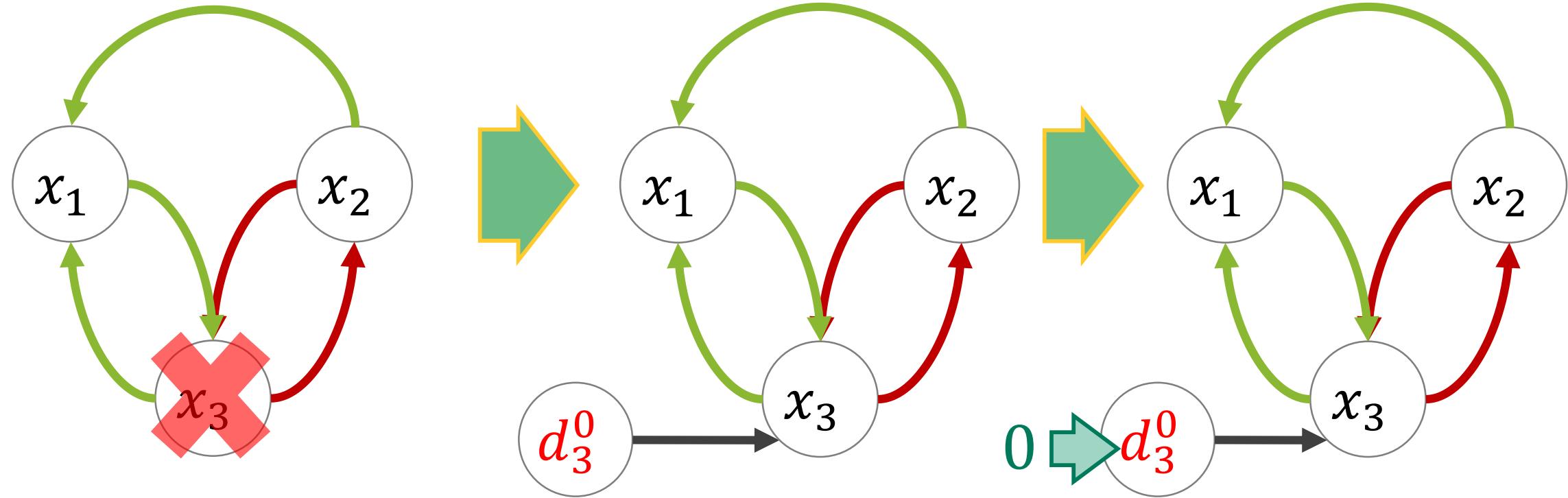
Control input
 $\mu: U \rightarrow \{0,1\}$

A general framework for Boolean system reprogramming

$$f \quad \xrightarrow{\hspace{1cm}} \quad g$$

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

Network Action Category = Freezing Control



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

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

$$x_3 = 0$$

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

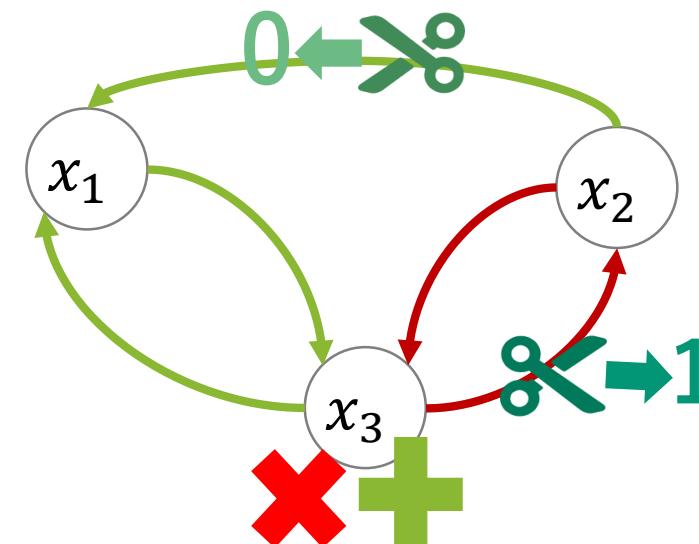
✗ 1 $x_j = f_j(x_1, \dots, x_i \vee \neg u_{i,j}^1, \dots, x_n)$



Example

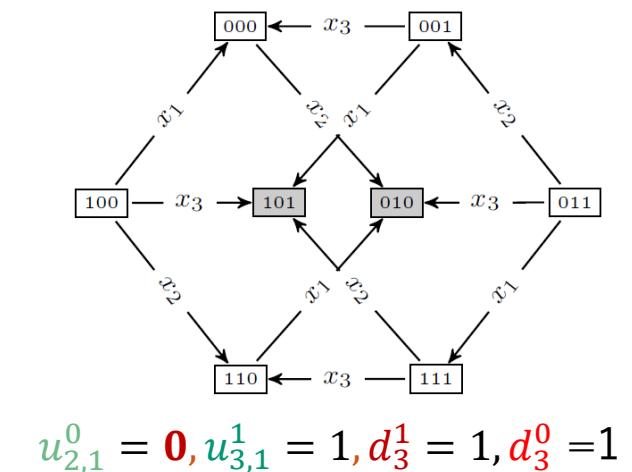
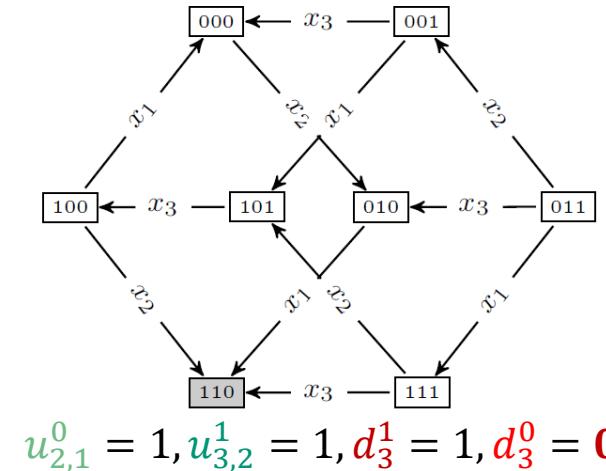
Freeze to 1 & 0

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



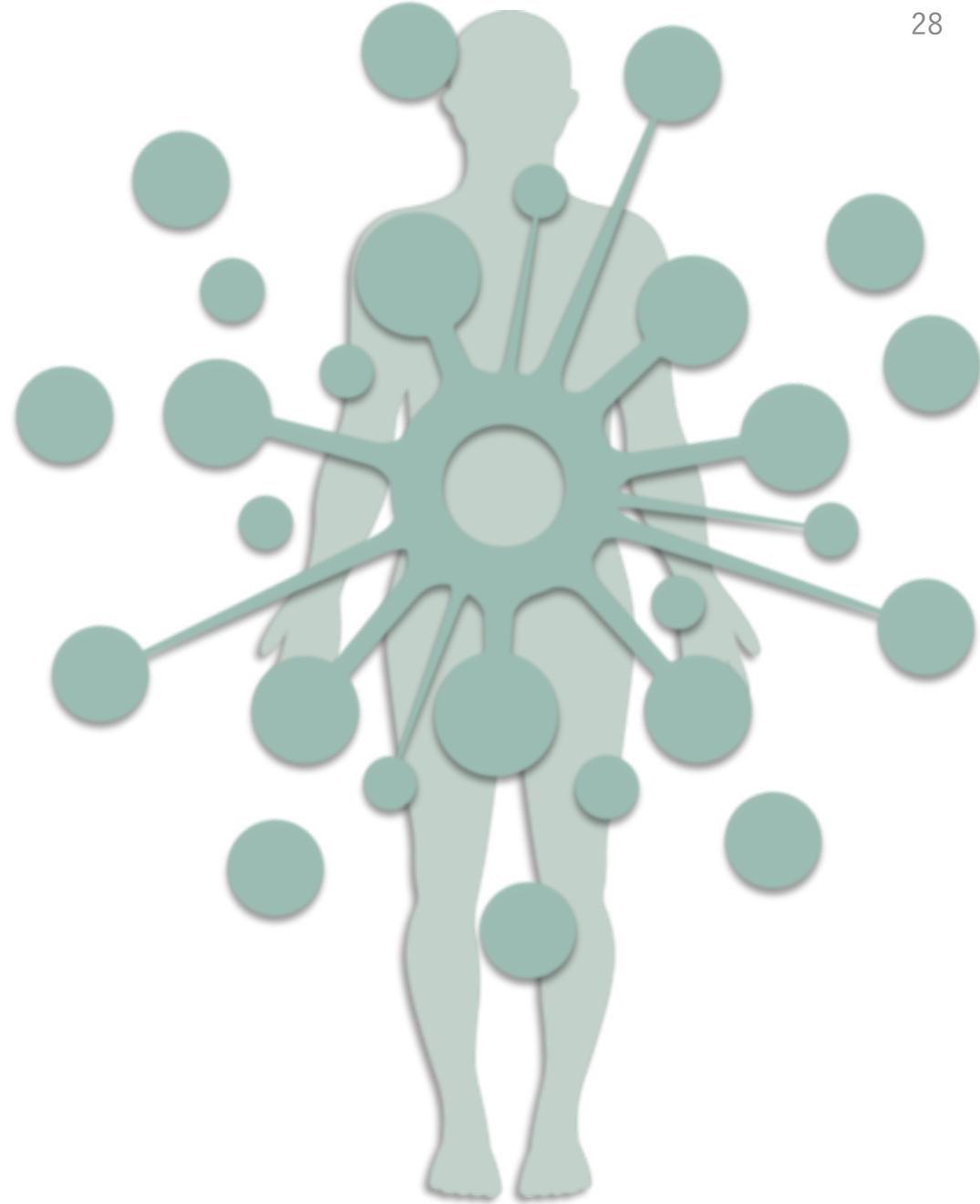
Action impact

Control Acts on Dynamics



Boolean Network Action Discovery

Computational Method Principles



Network action discovery



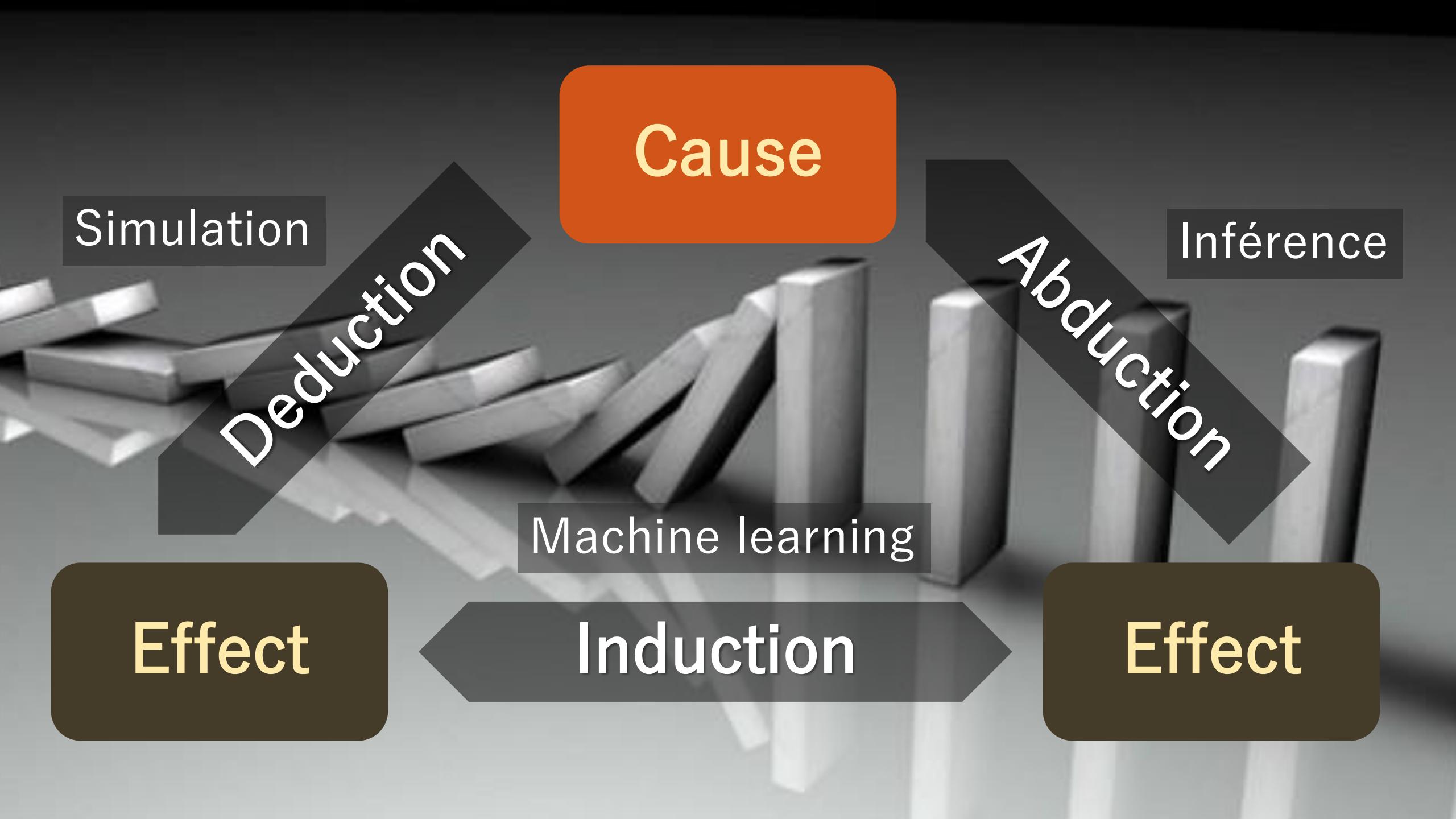
Network actions inducing biomarker profile switch

Control parameters to freeze inducing equilibrium profile switch



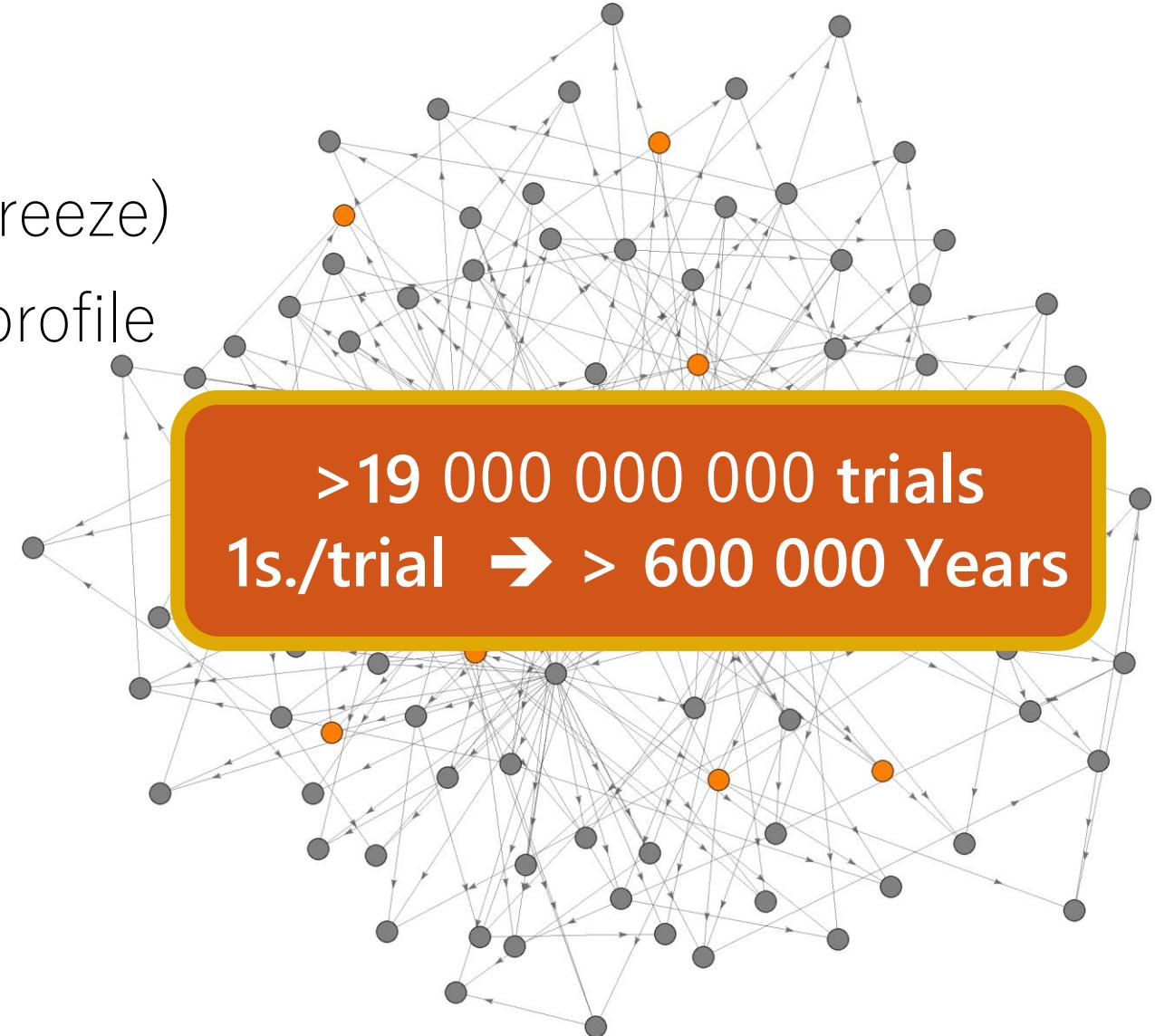
Control discovery

Freezing control as causes.



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 \rightarrow \neq causes : Parsimony

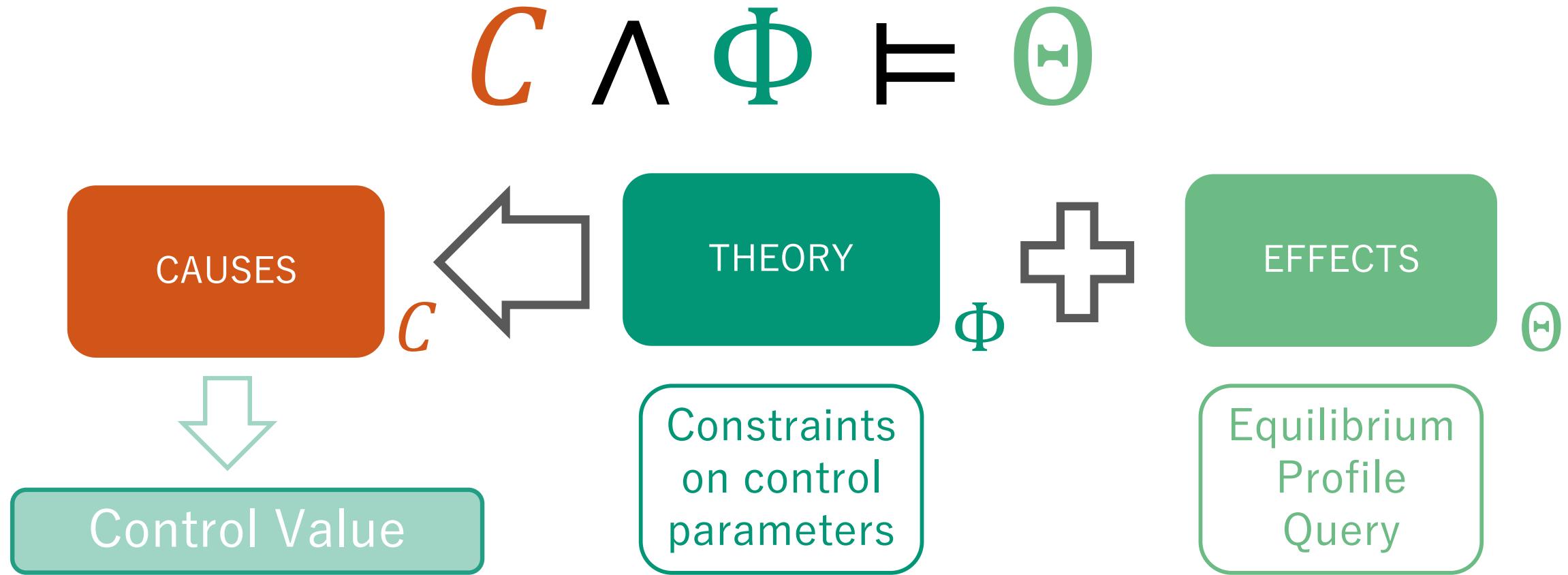
Feed back \rightarrow Circular causes

Formal approach of cause discovery

Inference
Principles
Discovery



Inference principle = Abduction



Parsimonious solutions \Rightarrow Cores = implicants minimizing the freeze

Biological queries formalization



In Some Contexts or Situations

Possibility to meet a property on states at equilibrium

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

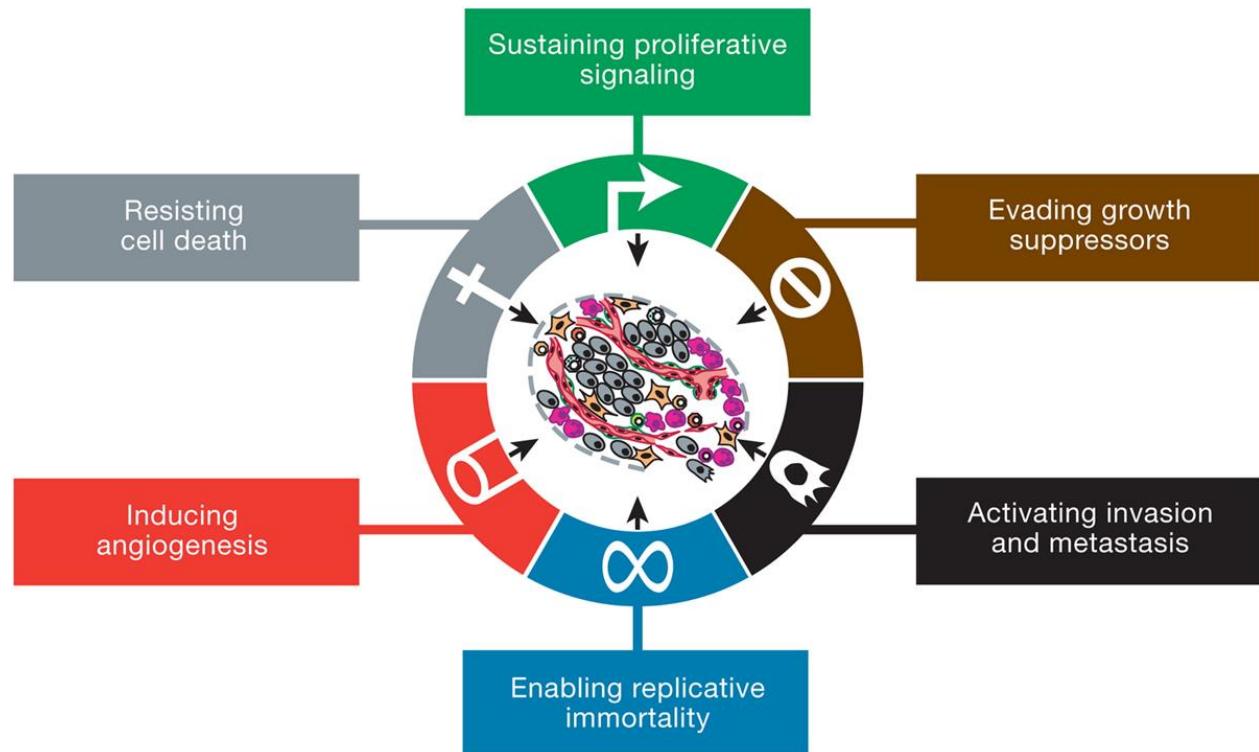


In All Contexts or Situations

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

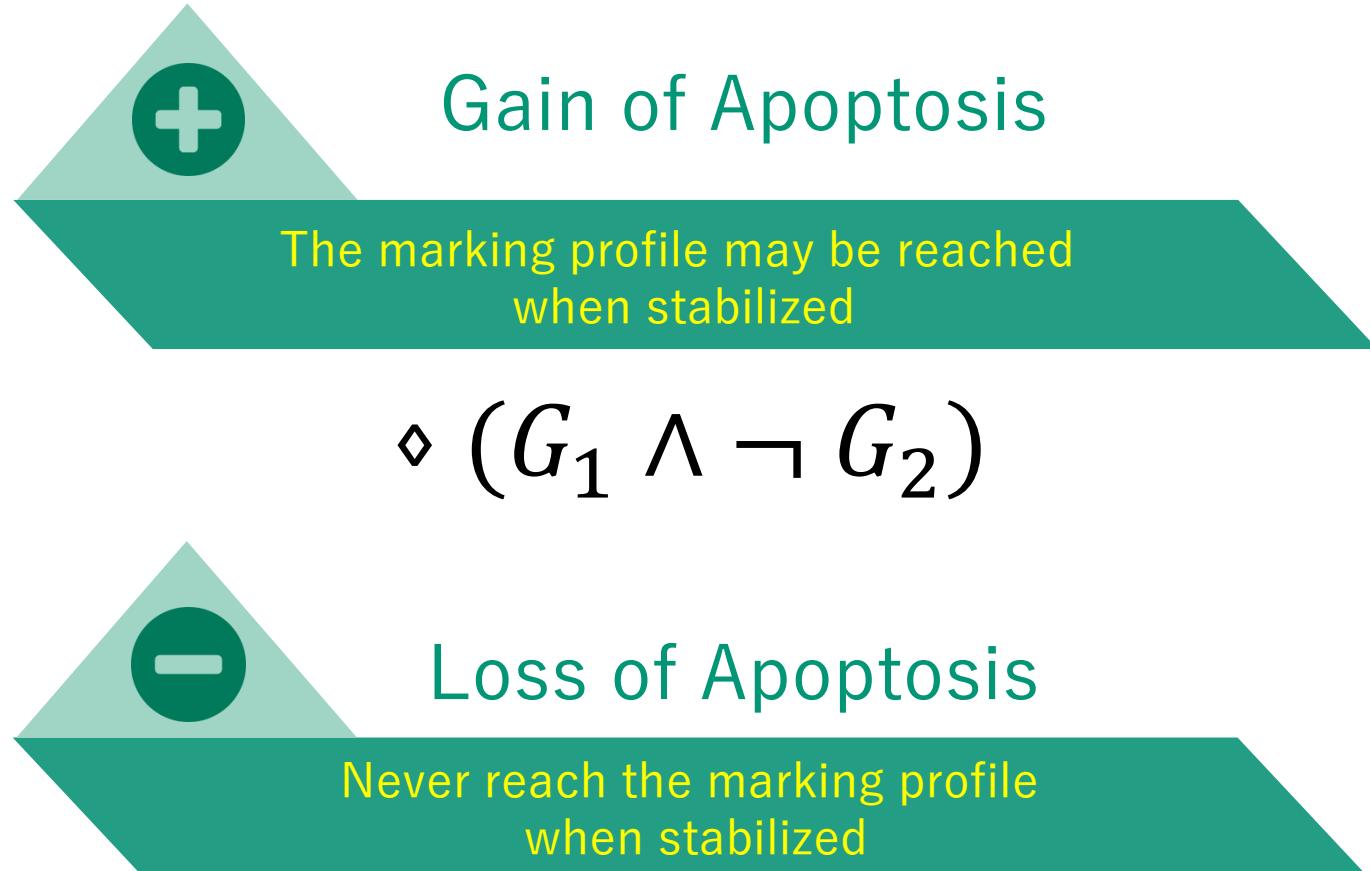


Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *cell*, 144(5), 646-674.

Apoptosis

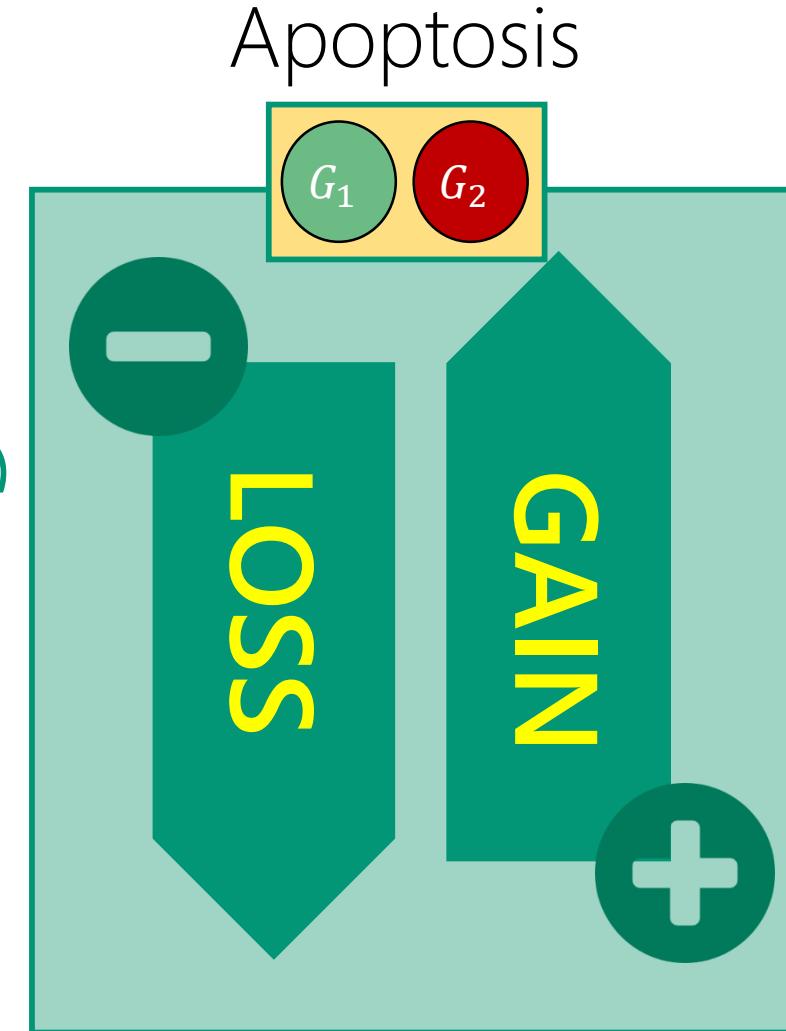


Biological Query Examples

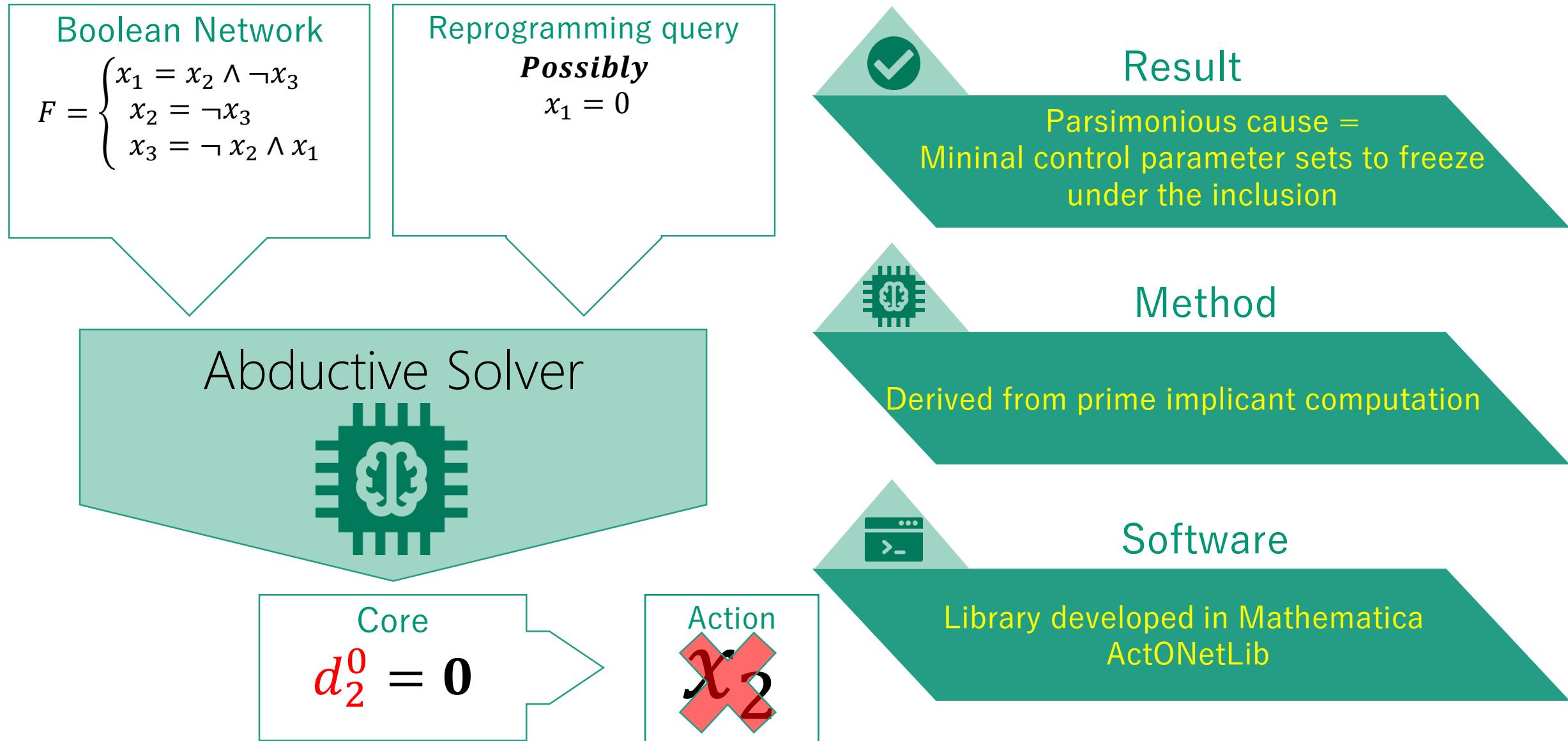


$$\square \neg (G_1 \wedge \neg G_2)$$

Cancer



Inference solver of cores



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

$$\begin{cases} x_1 = x_2 \wedge \neg x_3 \\ x_2 = (\neg x_3) \vee \neg d_{x_2}^1 \wedge d_{x_2}^0 \\ x_3 = (\neg x_2 \wedge x_1) \vee \neg d_{x_3}^1 \wedge d_{x_2}^0 \end{cases}$$

$$\diamond (x_1 = 0)$$

Query
Specification

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

Stability

$$\wedge \\ (\neg x_1) \\ \wedge$$

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

Marking

Control
Parcimony

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

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

CNF Form

$$\begin{aligned} & \neg x_1 \wedge (\neg x_2 \vee x_3) \wedge (\neg x_2 \vee \neg d_{x_2}^1) \\ & \wedge (x_2 \vee d_{x_2}^1) \wedge (\neg x_3 \vee d_{x_3}^0) \\ & \wedge (\neg x_3 \vee \neg d_{x_3}^1) \wedge (x_3 \vee \neg d_{x_2}^0) \\ & \wedge (x_3 \vee d_{x_3}^1) \wedge (d_{x_2}^0 \vee d_{x_2}^1) \end{aligned}$$

ILP-based CNF SAT

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

Core
Objective Function
Negative control
terms =1

$$\min\left(\sum_{l_{v_i} \in T_{ctrl}} l_{v_i} \cdot w_i\right)$$

2

x3

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

M

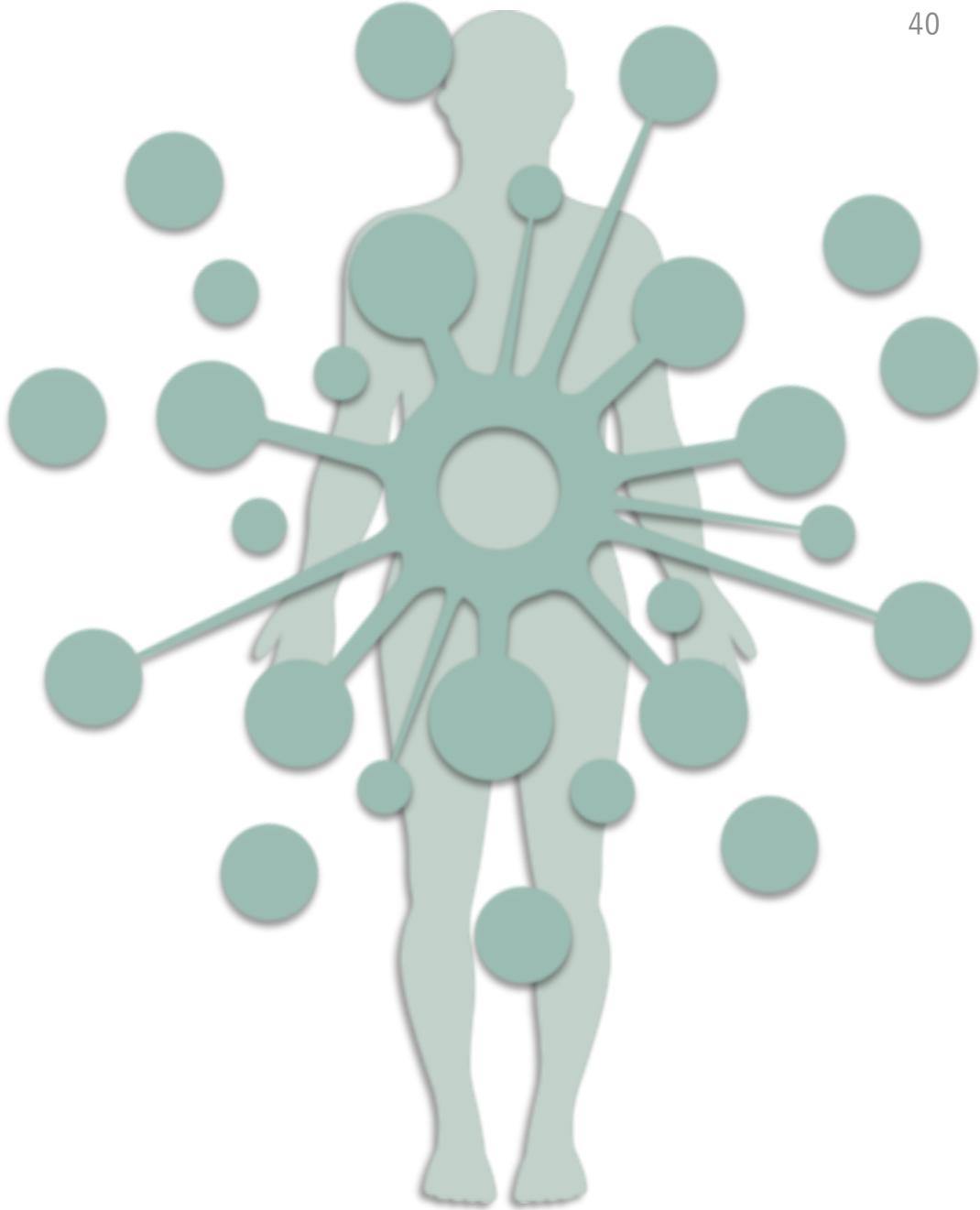
W

$\neg x_1$	x_2	$\neg x_2$	x_3	$\neg x_3$	$d_{x_2}^0$	$\neg d_{x_2}^0$	$d_{x_2}^1$	$\neg d_{x_2}^1$	$d_{x_3}^0$	$d_{x_3}^1$	$\neg d_{x_3}^1$
1											
		1	1								
	1							1			
				1						1	
				1							1
			1				1				
			1							1	
					1			1			
						1					
$d_{x_2}^0$	$\neg d_{x_2}^0$	$d_{x_2}^1$	$\neg d_{x_2}^1$	$d_{x_3}^1$	$\neg d_{x_3}^1$						
		1					1				1

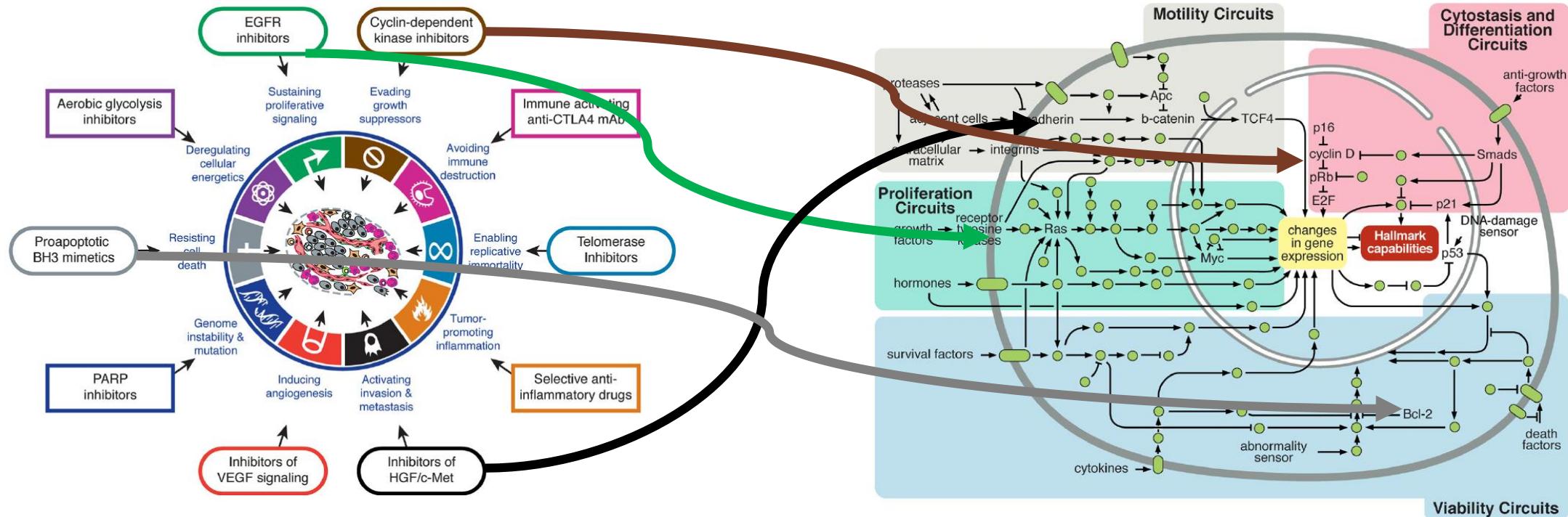
Application

Proof of concepts
application to Breast cancer
Inference of

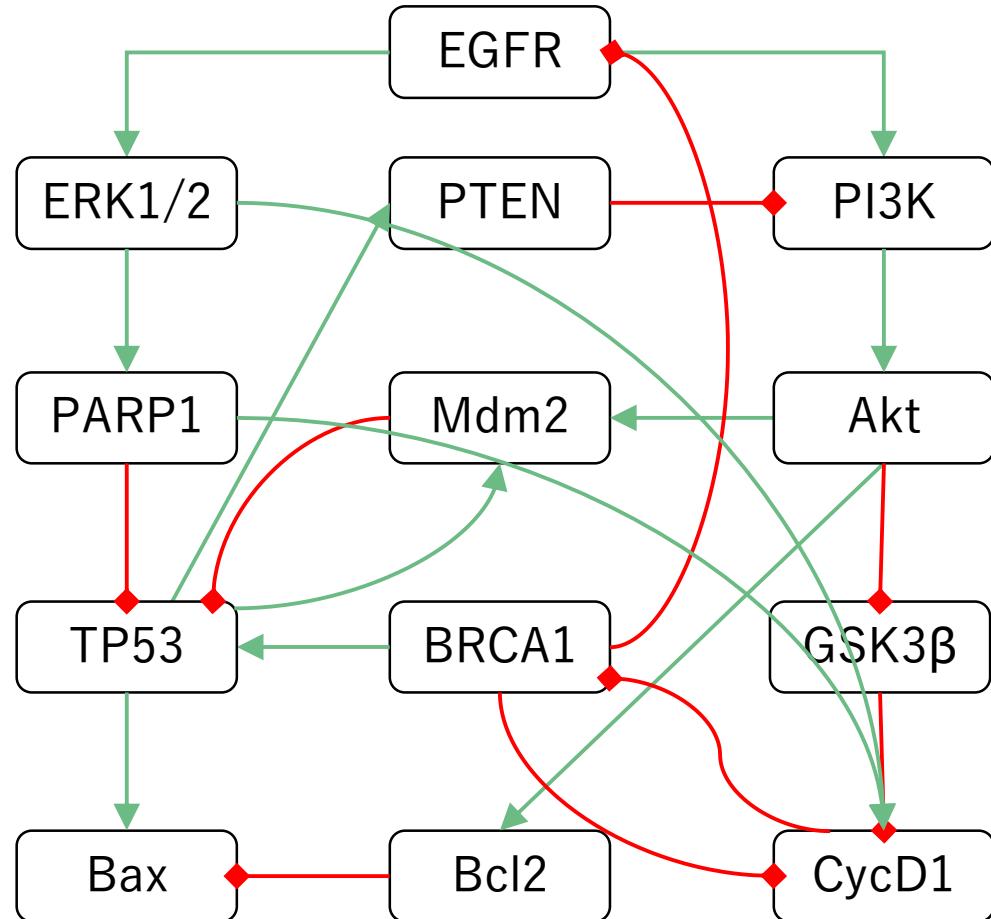
- Drivers
- Drug target



Drug Actions Inference



A Boolean network of apoptosis/proliferation



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

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

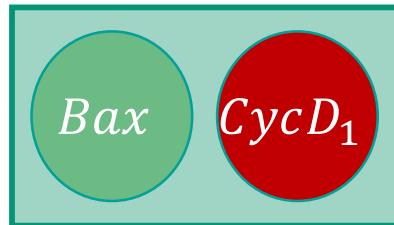
Inference of Driver Mutation



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
Bcl2
Mdm2
PI3K

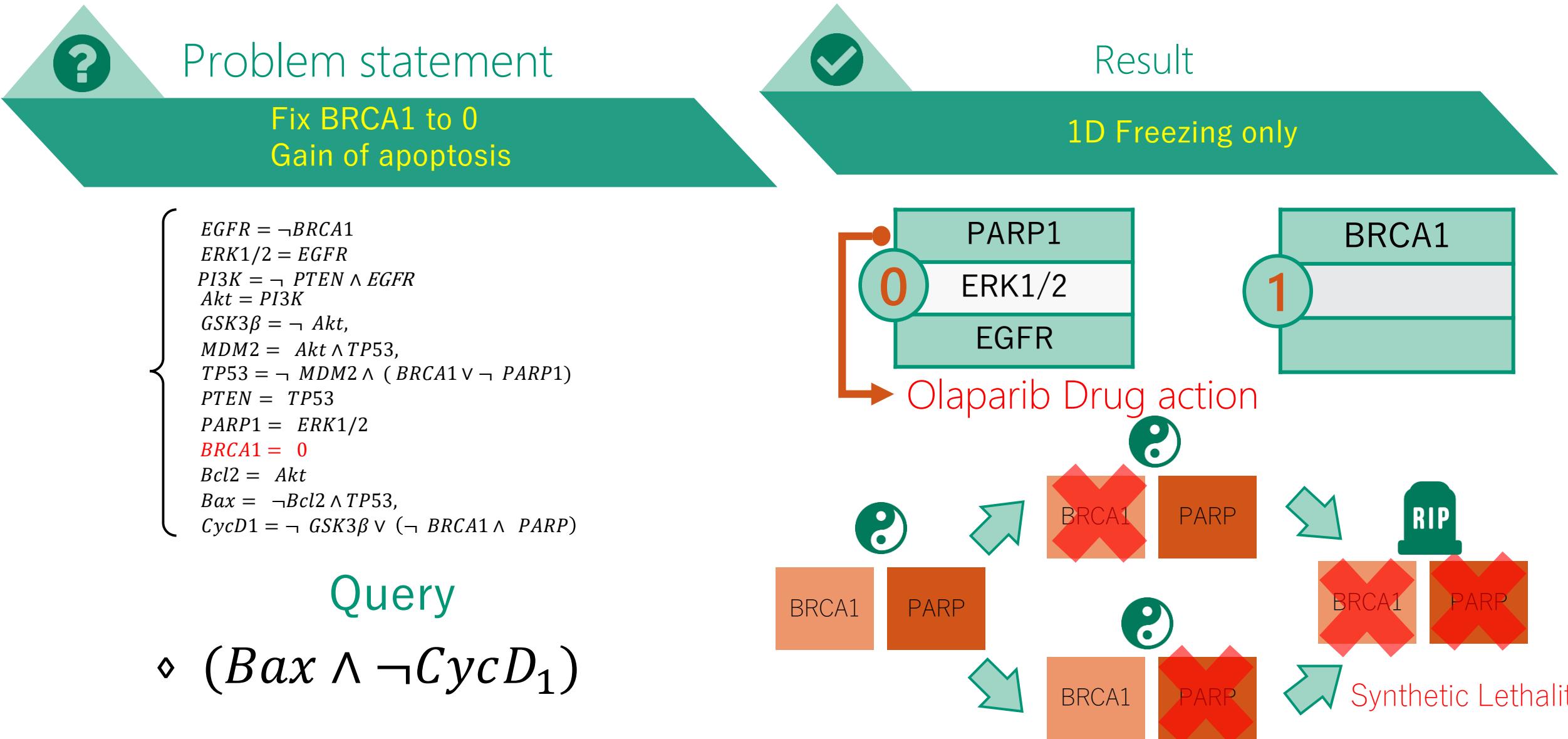
Oncogenes

Pair of Frozen Molecules

GSK3 β	EGFR
0	PTEN
GSK3 β	ERK1/2

EGFR inhibitors
 Resistance

Inference of targets in BRCA1-deficient cells



* 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]
```

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



* 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}
```

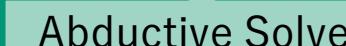
```
In[35]:= frozentru = Complement[Agents[Fact], markers]
```

```
Out[35]:= {Akt, Bcl2, BRCA1, EGFR, ERK12, GSK3, MDM2, p53, PARP1, PIK3CA, PTEN}
```

Core

```
In[36]:= Highlighted[TableForm[Timing[TableForm@CoreForm[cores = Destify[Fact, Nothing, MarkingToFormula[marking], frozenfalse, frozentru, ControlType → controltype]]]], Frame → True]
```

0.03125
EGFR
PARP1
ERK12
BRCA1



Frozen variables

Notebook Example

Validation

```
In[41]:= Fcore = 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[Fcore]
```

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



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)

