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Combinatorial Interventions for Control Tasks in Large-Scale Signaling Networks

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Cell Biology Department
Institute for Systems Genomics

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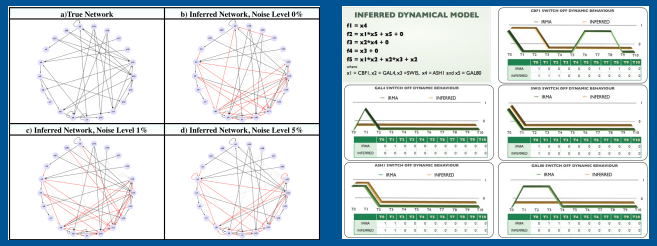
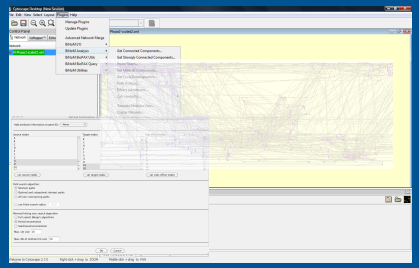
Data-Driven Static and Dynamical Modelling (Reverse Engineering)



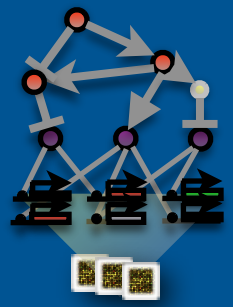
Controllability of Large Scale Networks

- Cascading Failures
- Optimal Combinations of Intervention



Algorithm Development and Software Implementation

Target Identification (Breast Cancer, GPCR proteins and infertility)



Mathematics & Computational Biology

- Graph theory
- Combinatorics
- Polynomial dynamical systems
- Optimization methods
- Network Theory

Group website: http://compsysmed.org

Outline of Presentation

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Part I: Breaking down the title of this talk

- Signal transduction networks
- Network controllability
- Targeted network controllability

Part II: Let's solve the problem together!

- Little example

Part III: OCSANA

- Introduction
- What does combinatorics and algebra got to do with it?
- How OCSANA works

Part IV: Application Example to breast cancer

- Intro
- Results

Conclusions and Future Work

Part I: Breaking down the title of this talk

Signaling Networks

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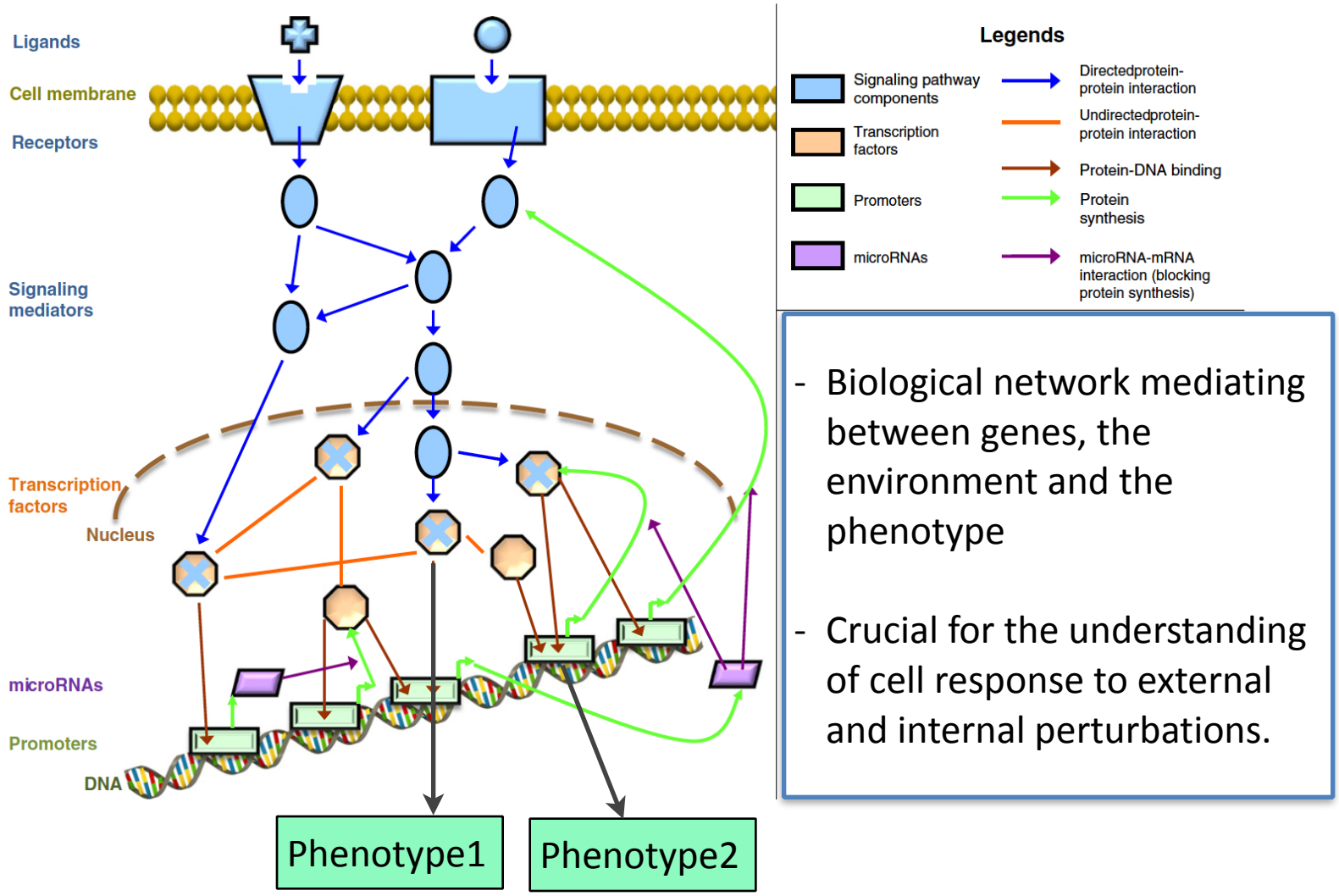
P. Csermely et al. / Pharmacology & Therapeutics 138 (2013) 333–408



- Biological network mediating between genes, the environment and the phenotype

- Crucial for the understanding of cell response to external and internal perturbations.

Controllability of Complex Systems

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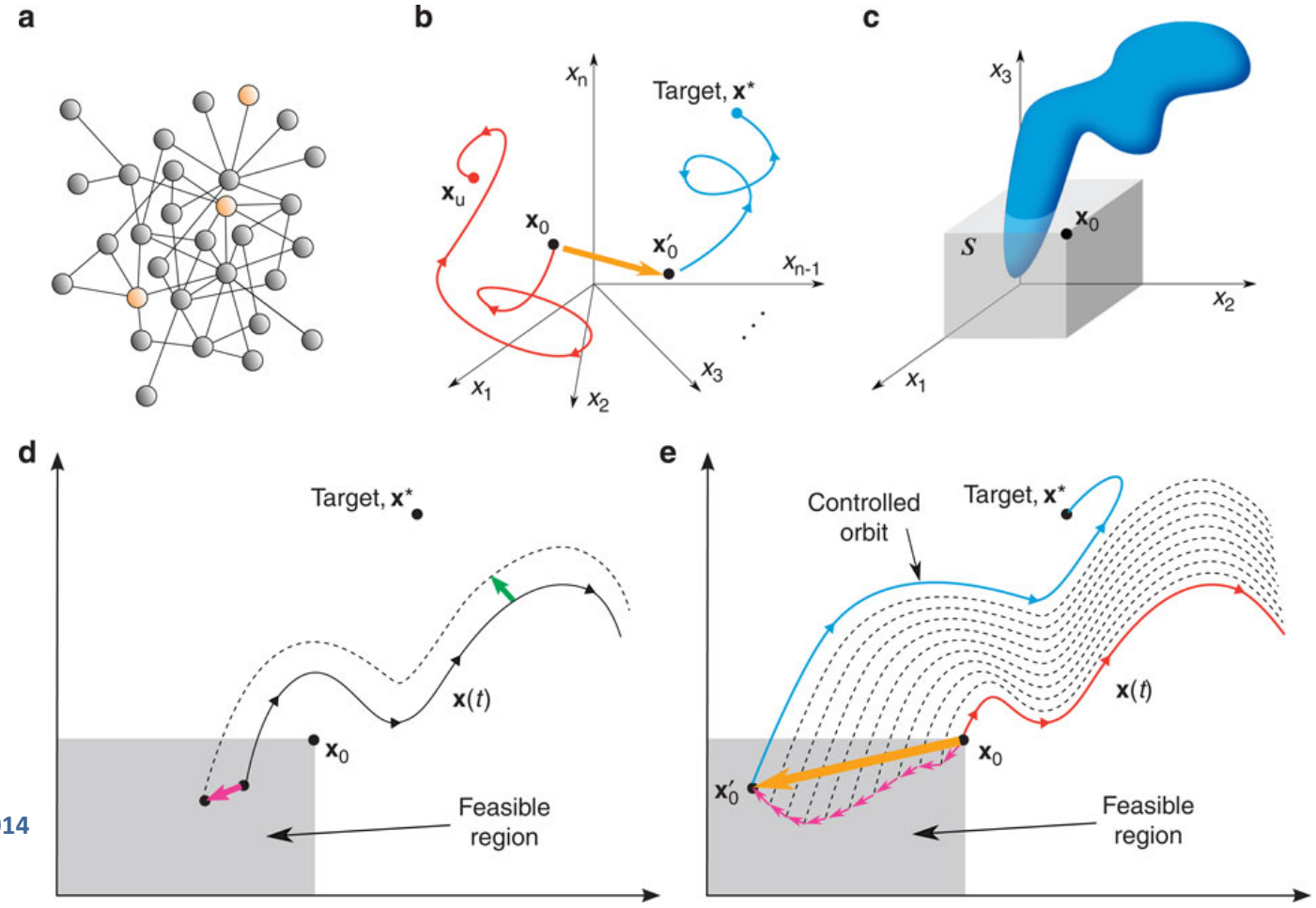

Cornelius *et al.* Realistic control of network dynamics. Nature Comms., 2014

(**a)** Network portrait. The goal is to drive the network to a desired state by perturbing nodes in a control set. **(b)** State space portrait. In the absence of control, the network at an initial state x_0 evolves to an undesirable equilibrium x_u in the n-dimensional state space (red curve). By perturbing the initial state (orange arrow), the network reaches a new state that evolves to the desired target state x* (blue curve). **(c)** Constraints. In general, there will be constraints on the types of compensatory perturbations that one can make. **(d, e)** Iterative construction of compensatory perturbations.

Signaling Networks

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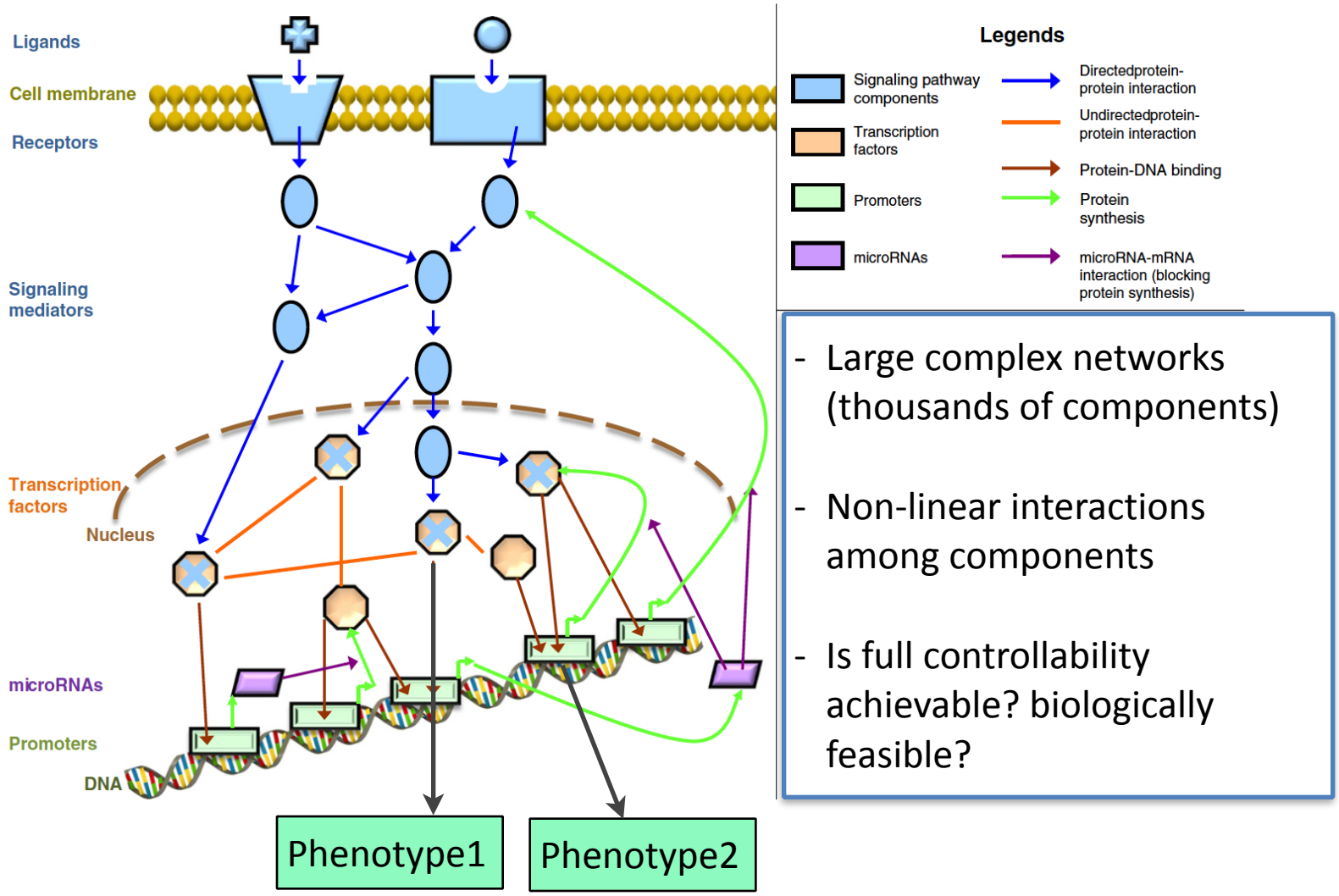

- Large complex networks (thousands of components)
- Non-linear interactions among components
- Is full controllability achievable? biologically feasible?

Signaling Networks

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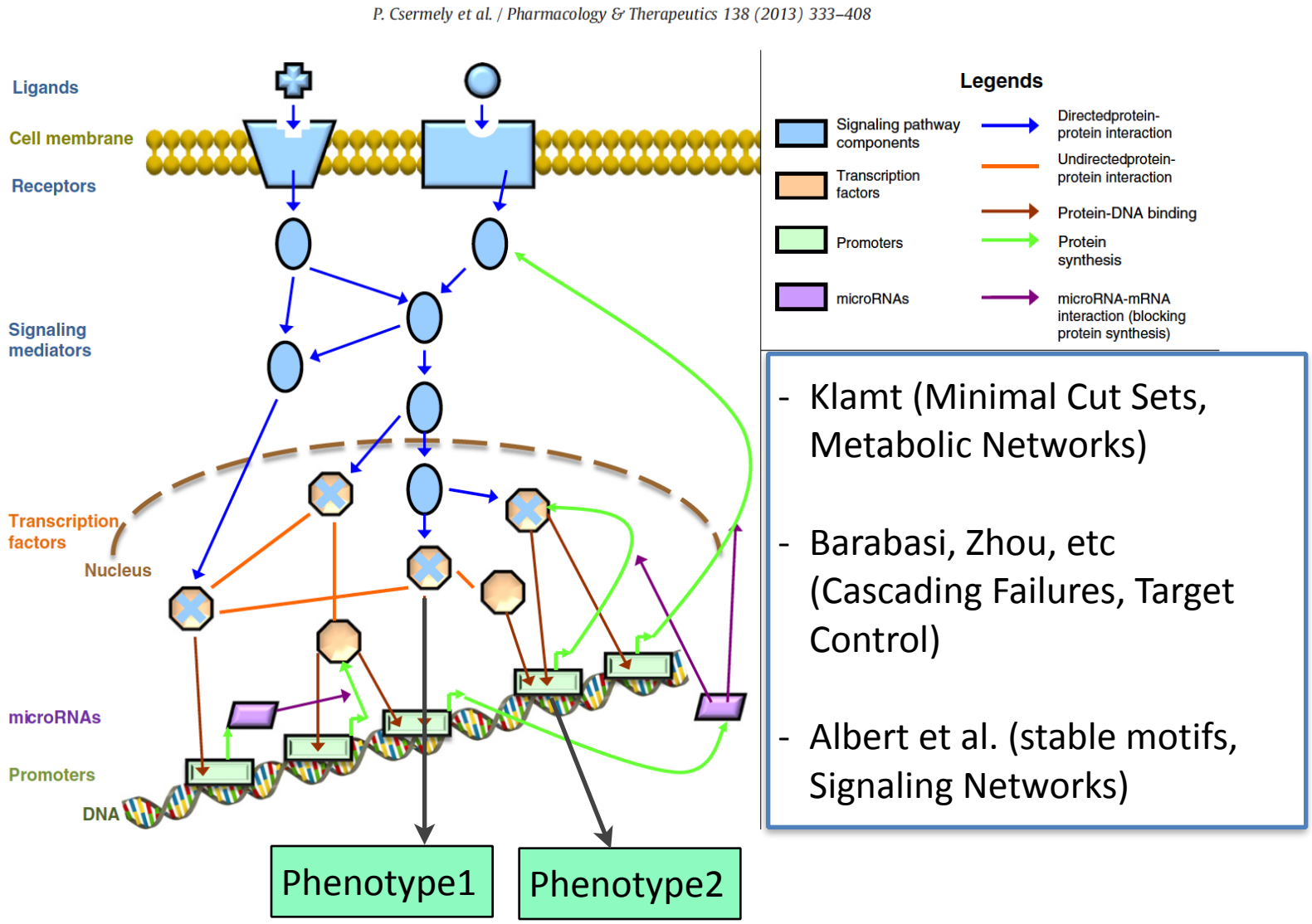

- Klamt (Minimal Cut Sets, Metabolic Networks)
- Barabasi, Zhou, etc (Cascading Failures, Target Control)
- Albert et al. (stable motifs, Signaling Networks)

Targeted Control Tasks in Signaling Networks

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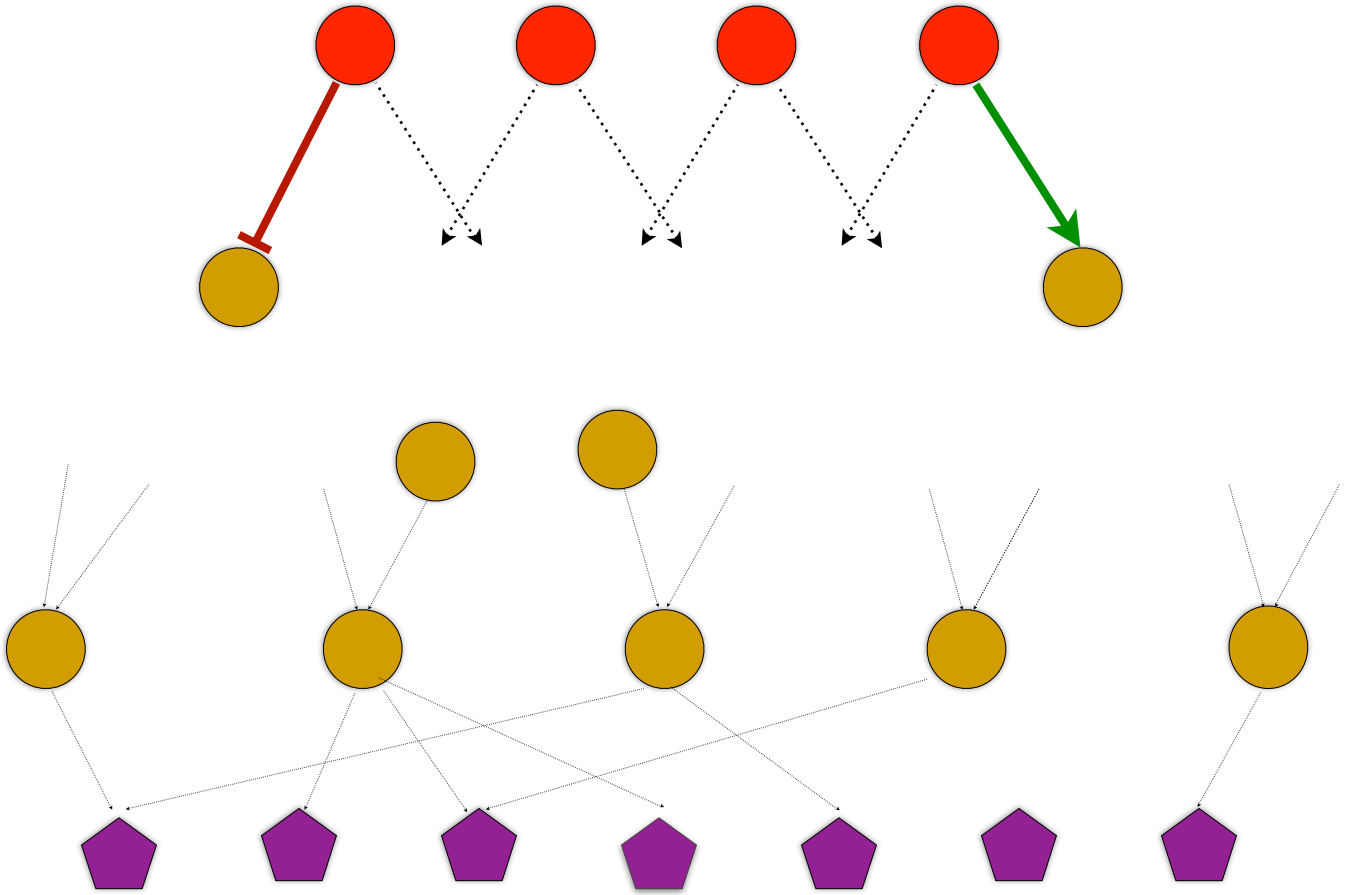

Vera-Licona *et al.* Institut Curie & Servier Scientific Report, 2013.

Targeted Control Tasks in Signaling Networks

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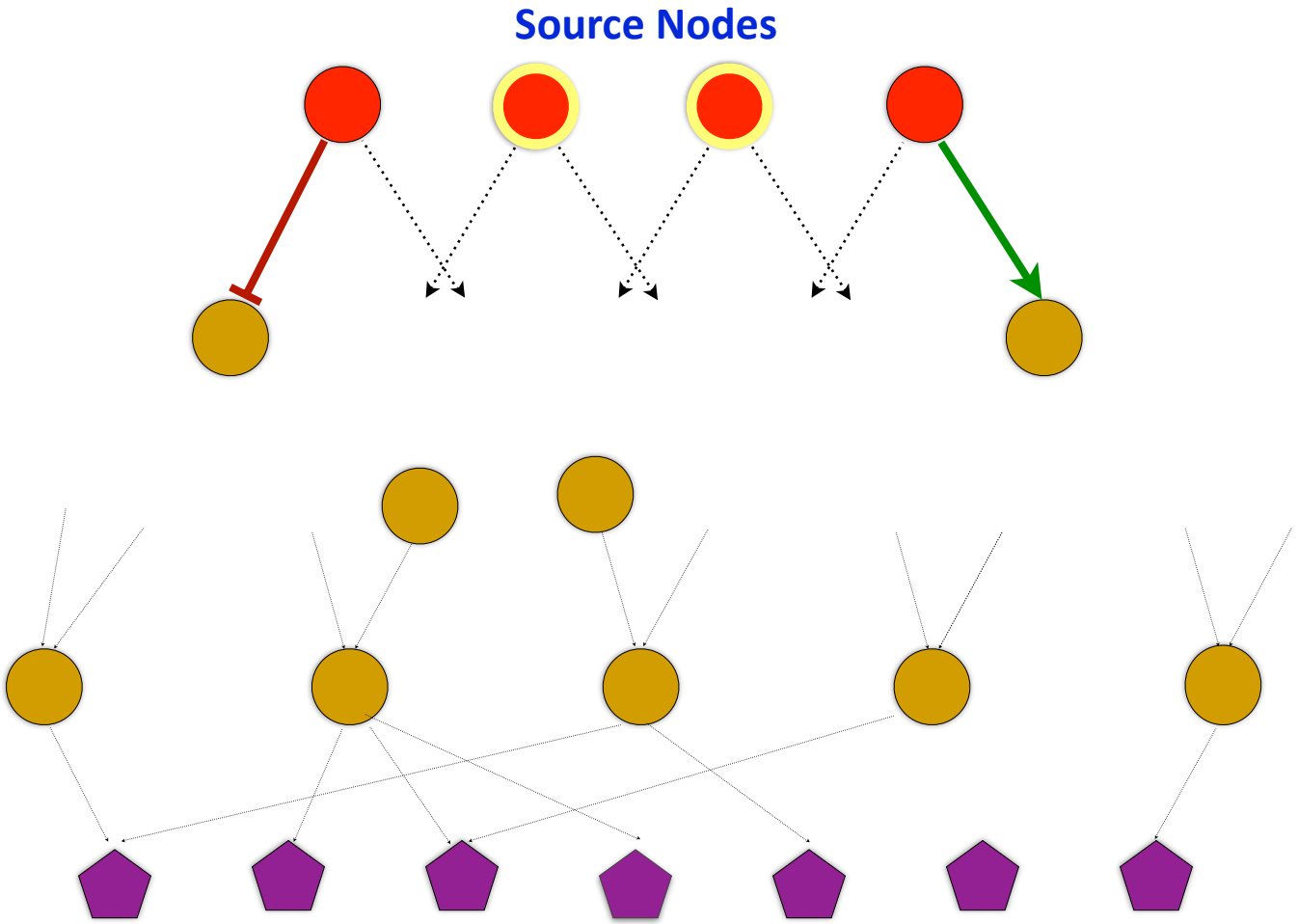

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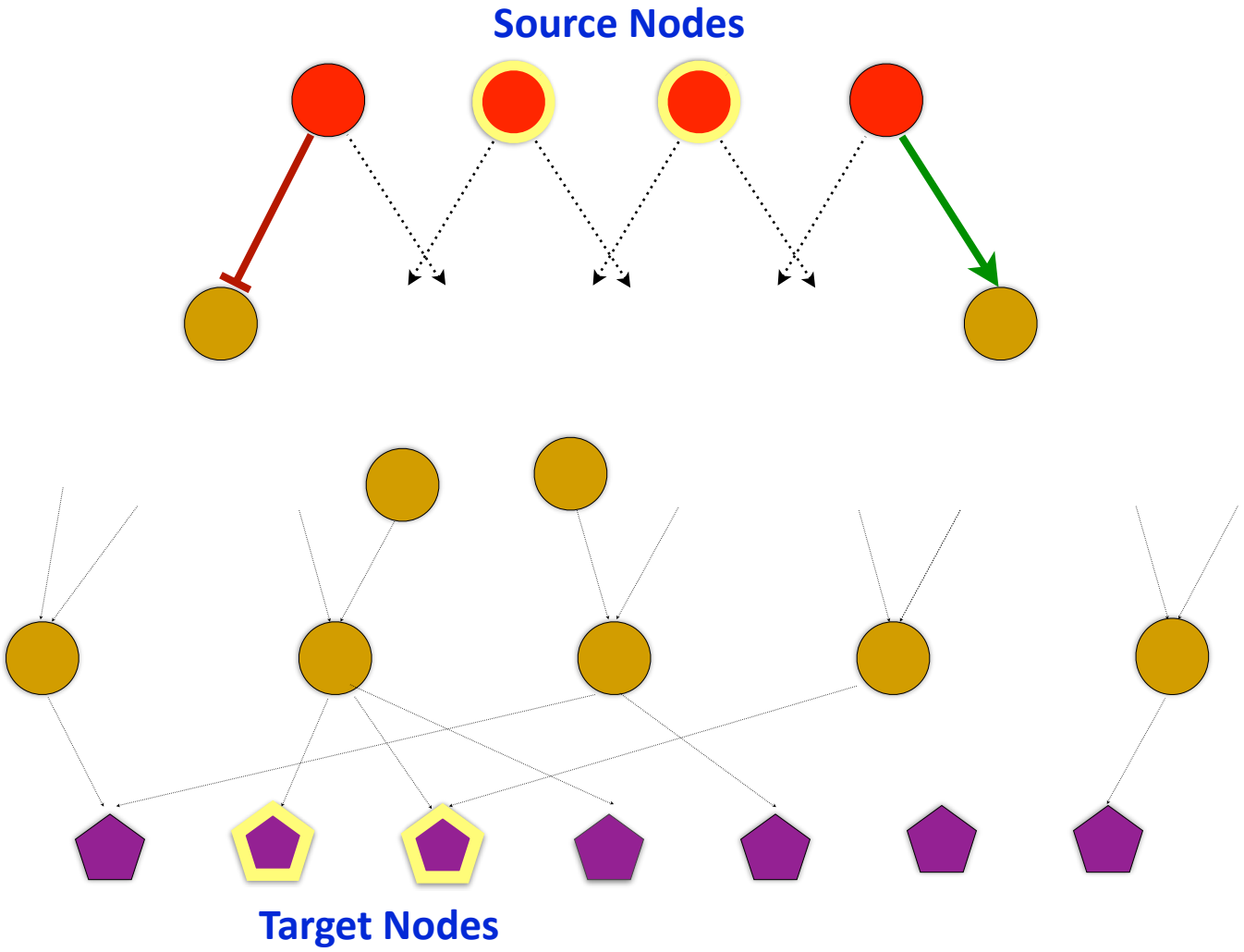

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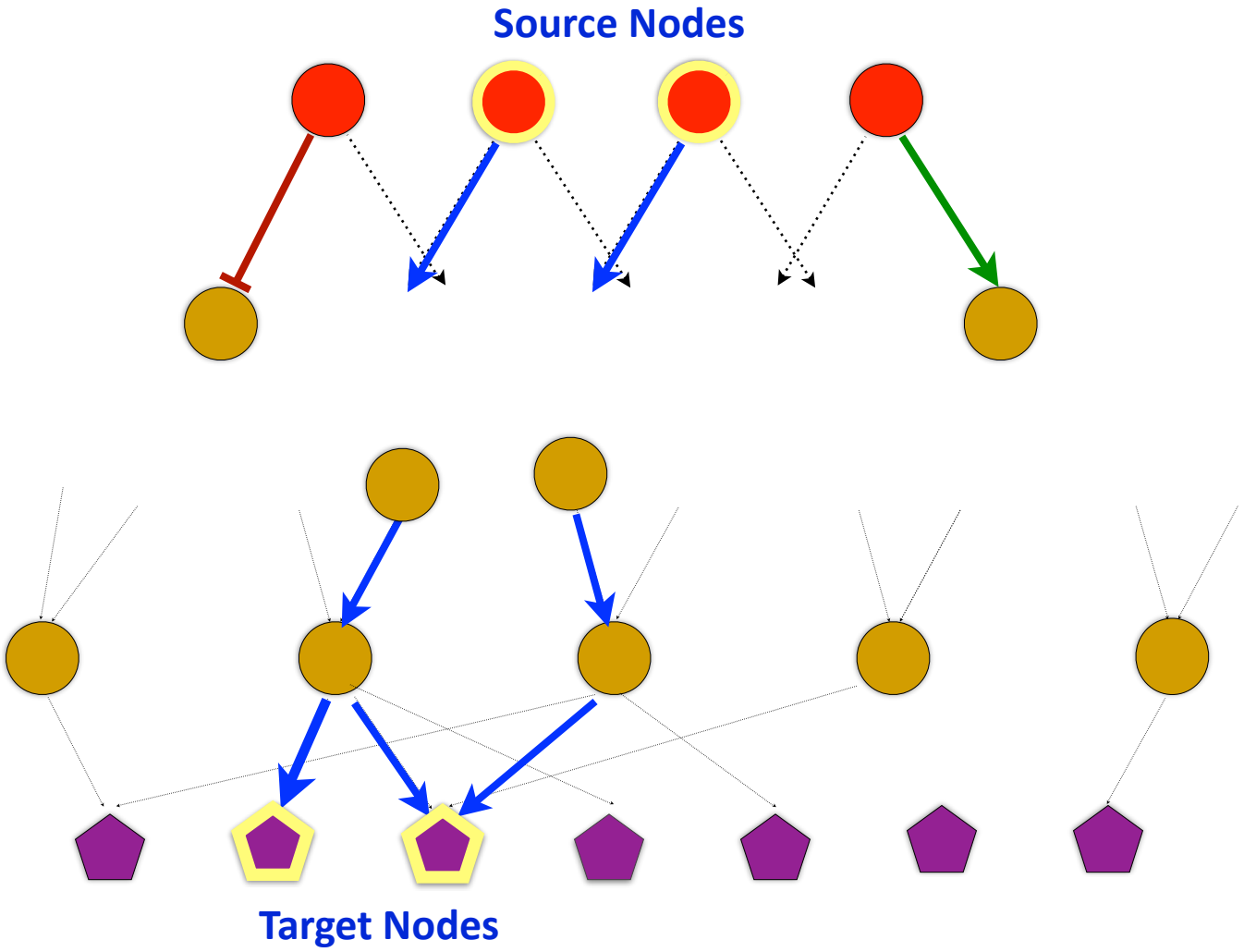

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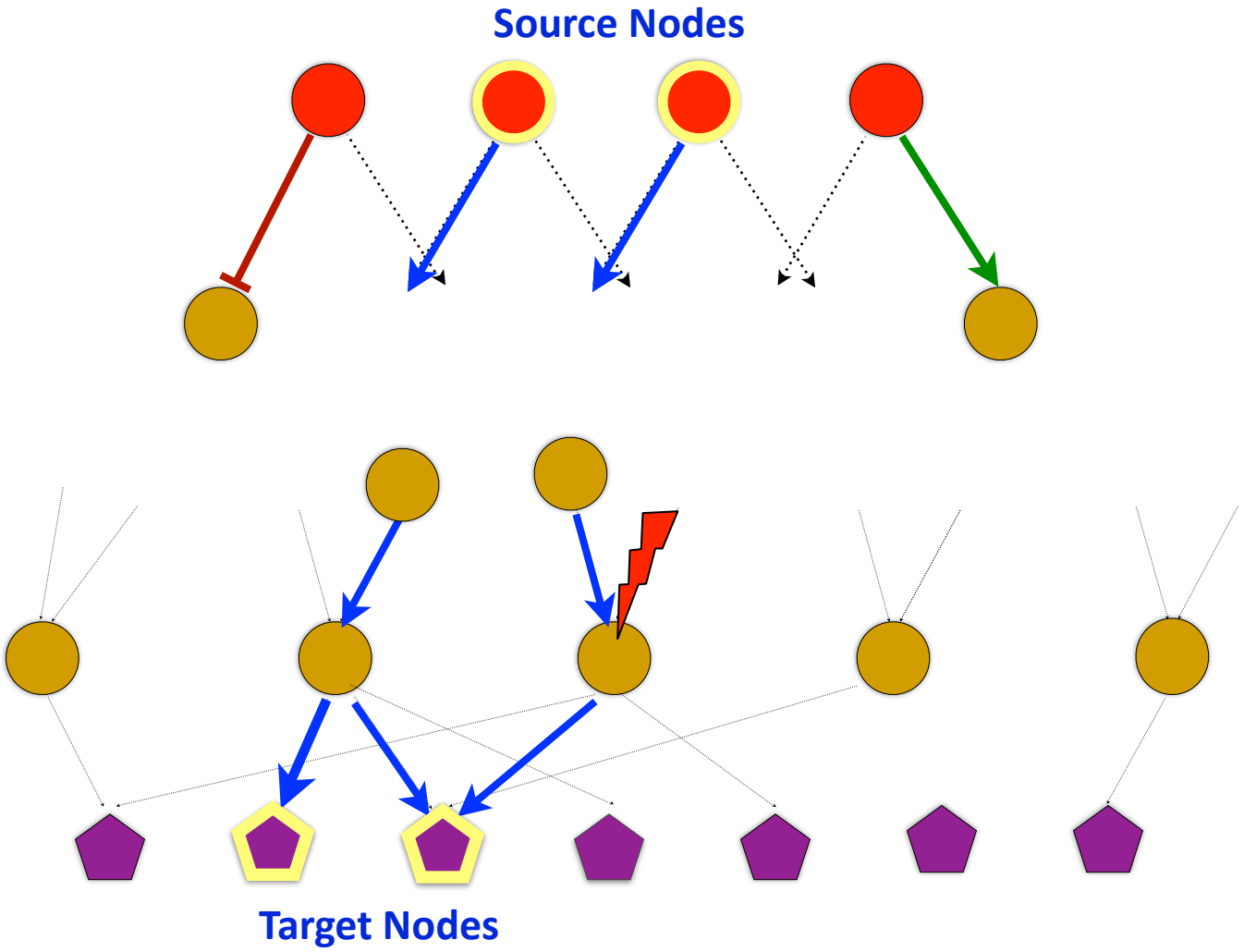

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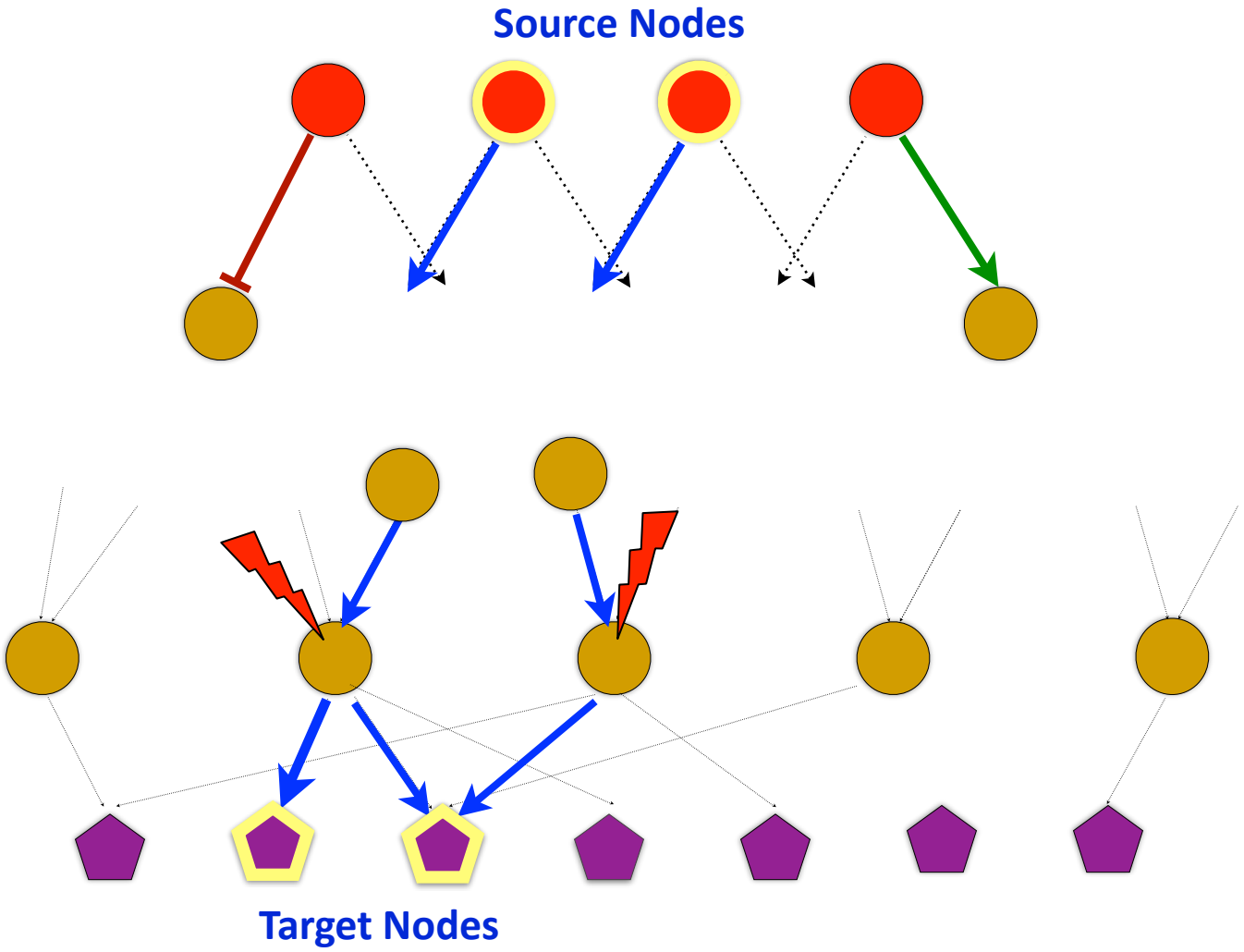

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Targeted Control Tasks in Signaling Networks

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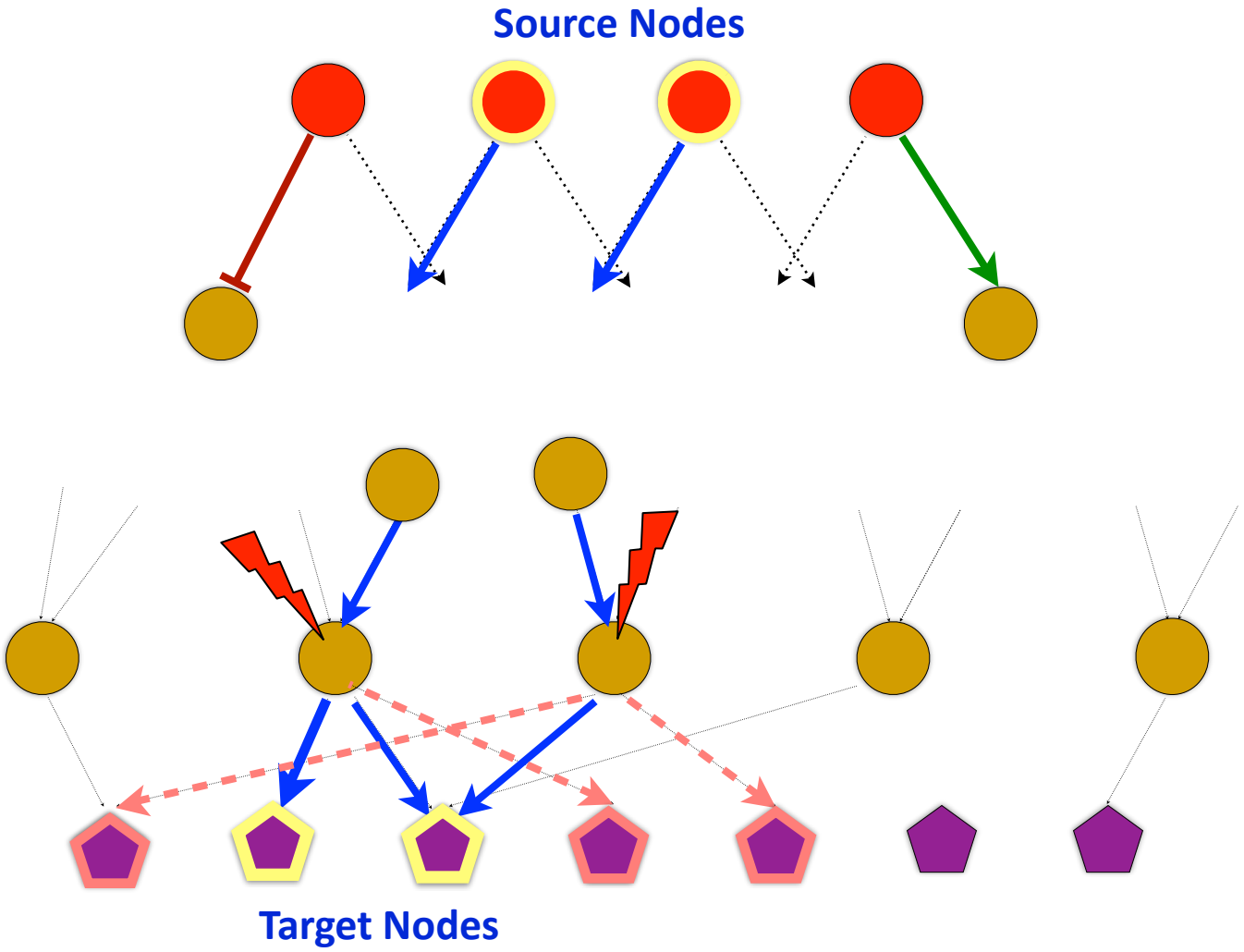

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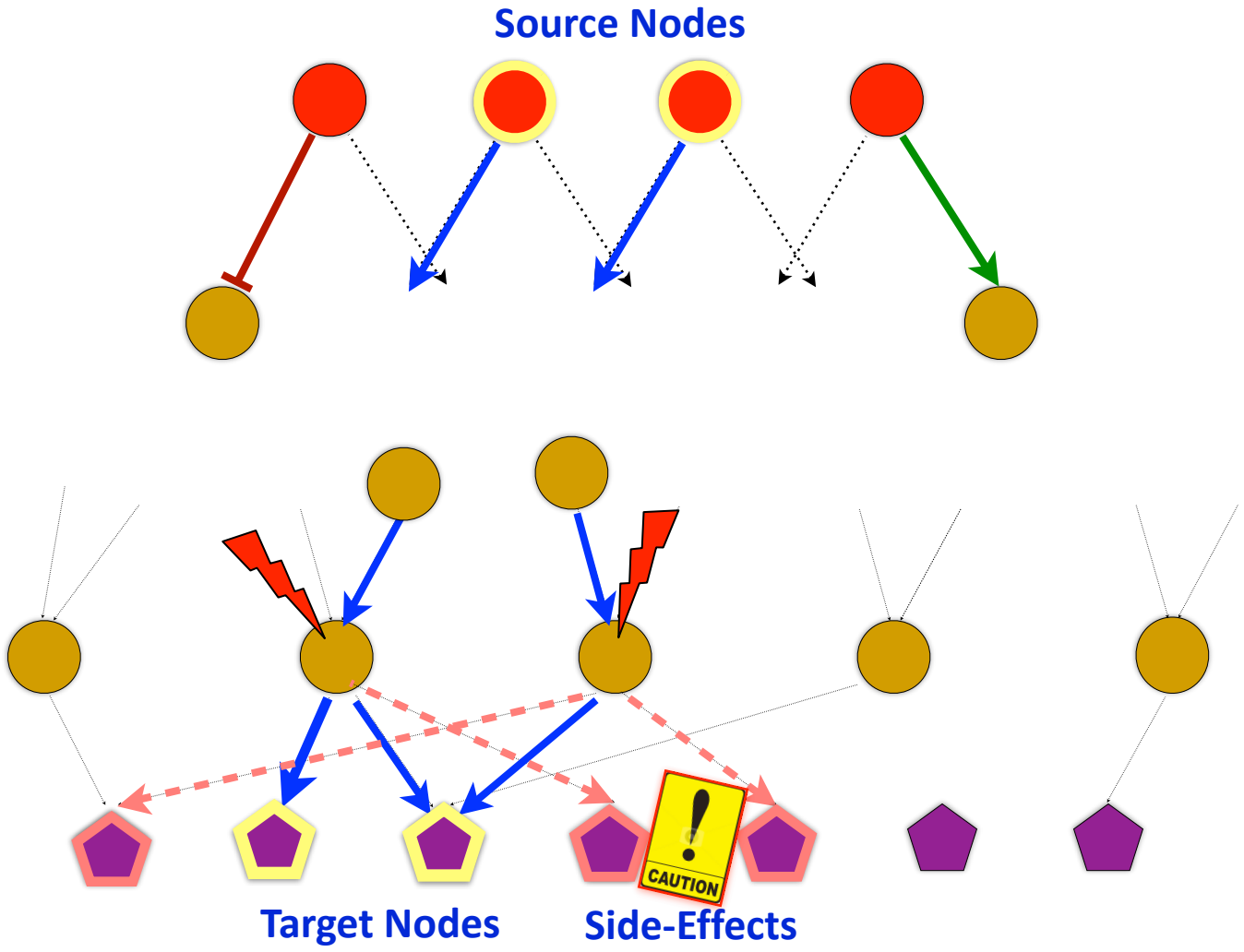

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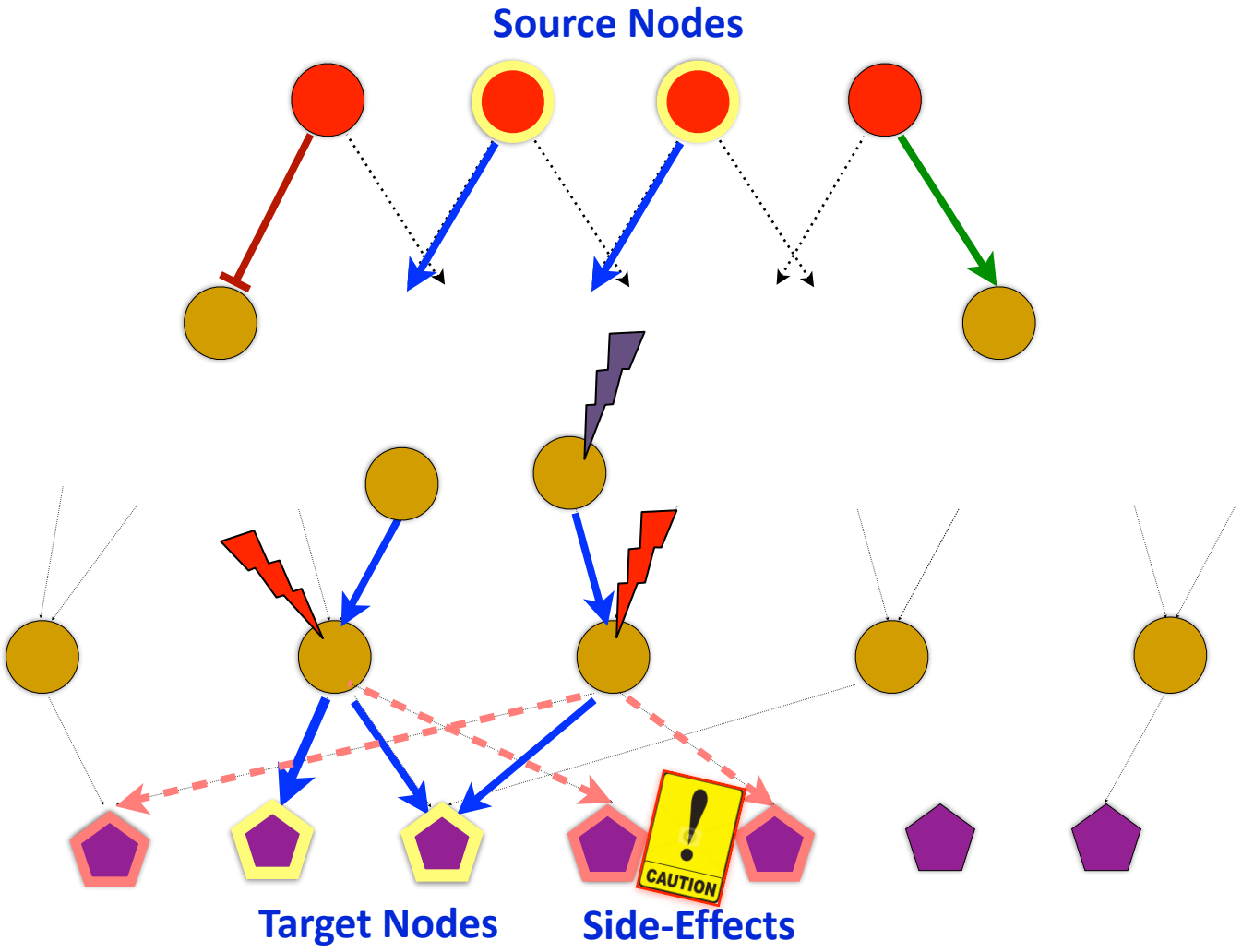

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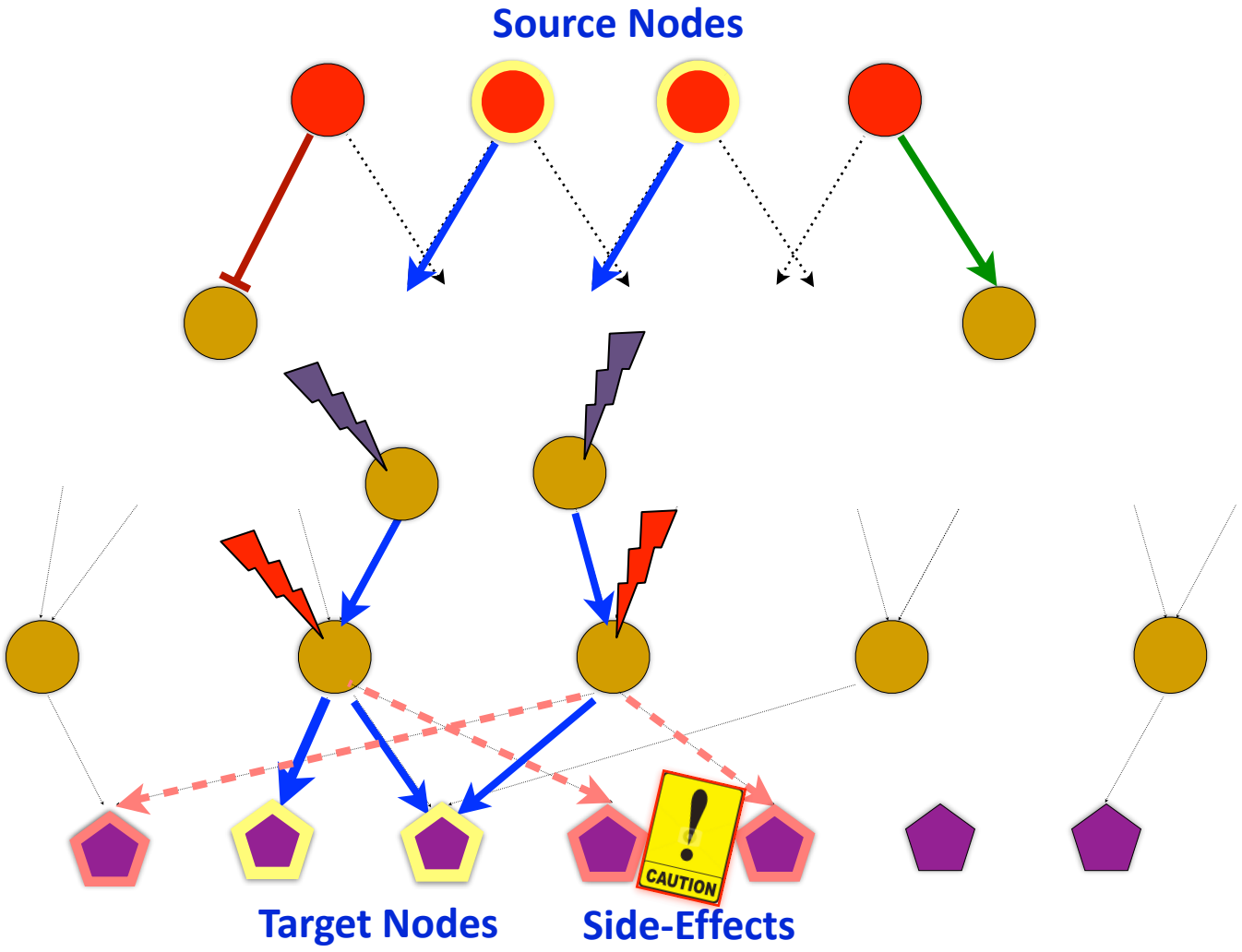

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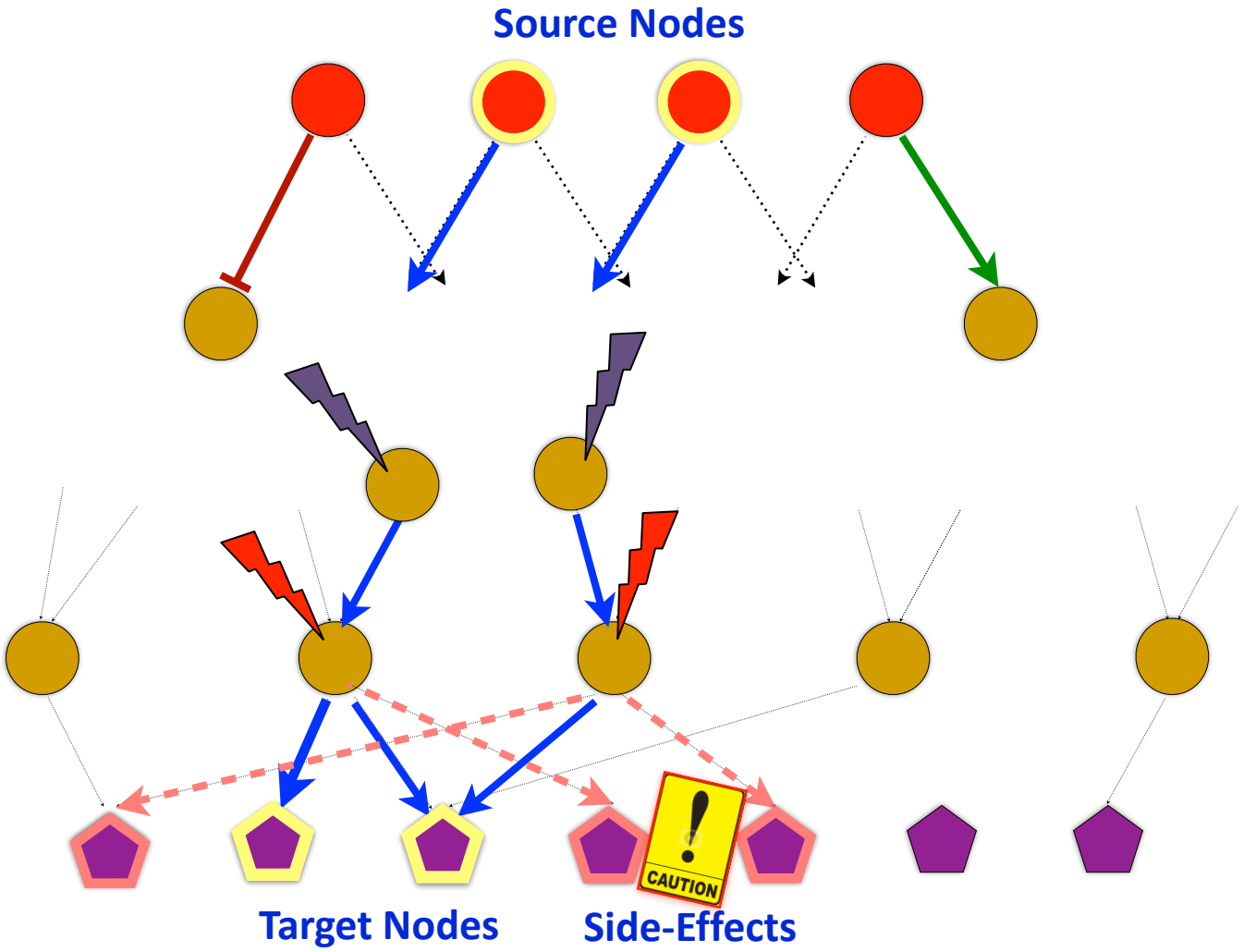

Vera-Licona *et al.* Institut Curie & Servier Scientific Report, 2013.

- Which Combination of Interventions (CI) is more optimal? **Prioritization of CIs**

Part II: Let's solve the problem together!

Minimal Combinations of Interventions (Signed Digraphs)

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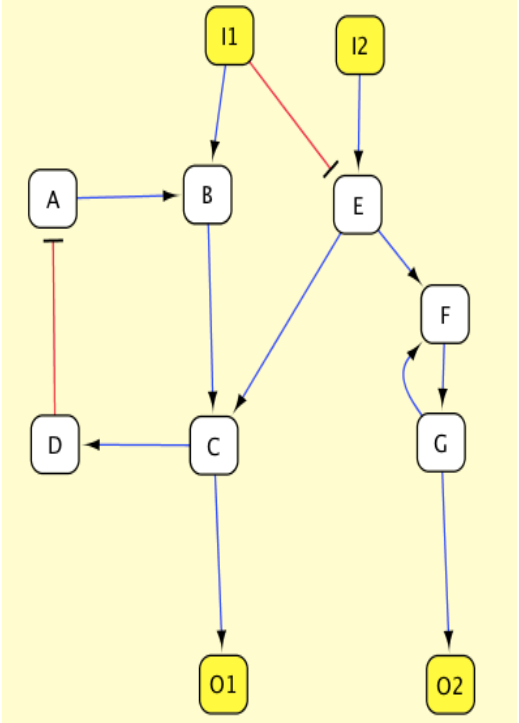

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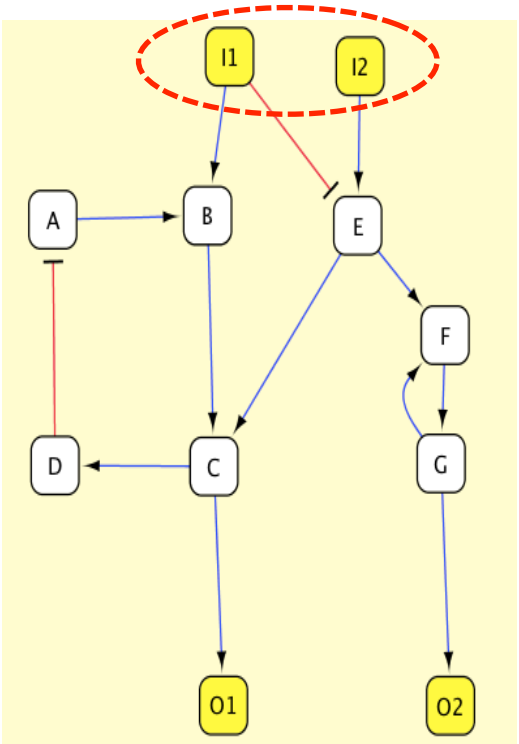

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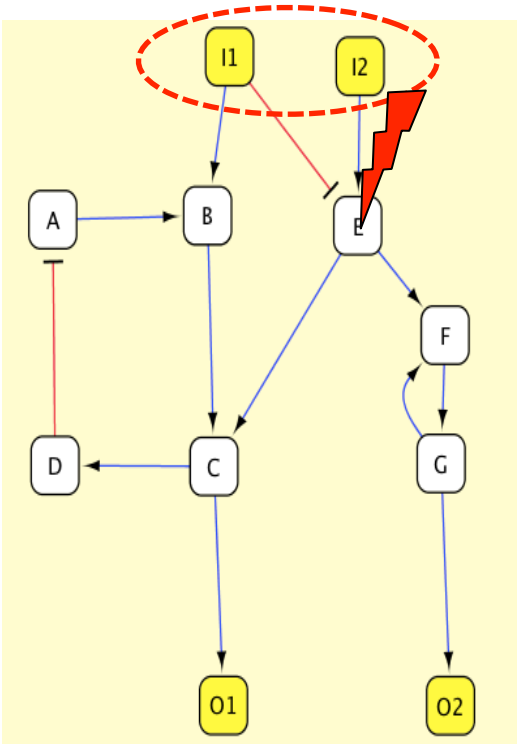

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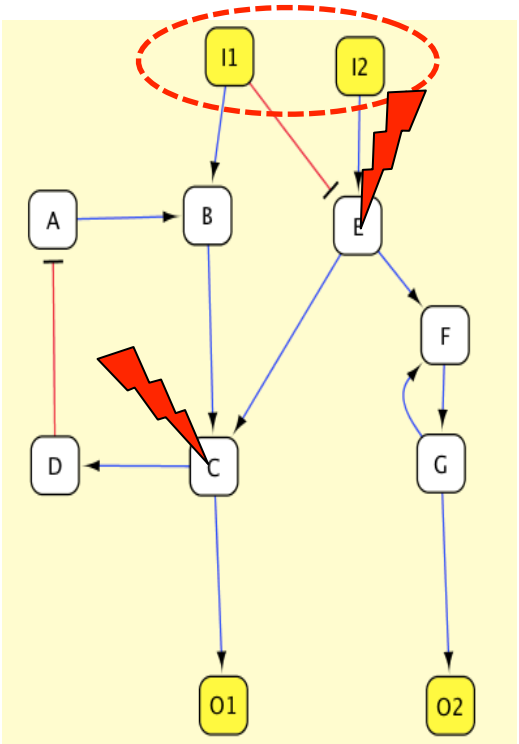

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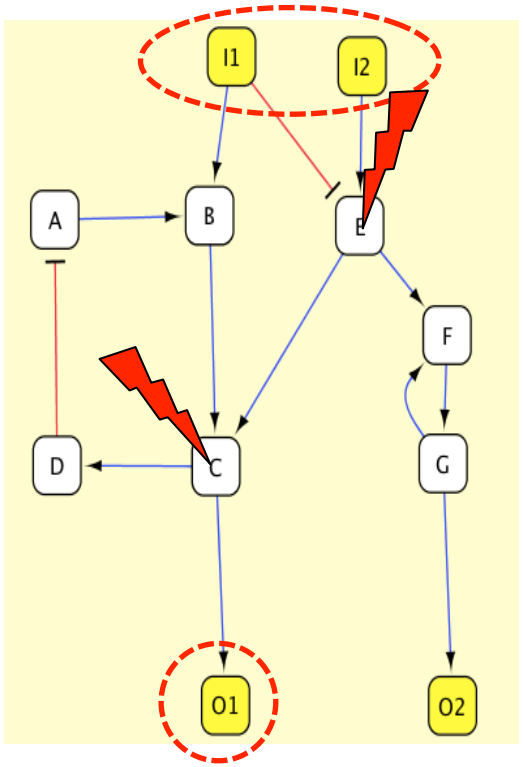

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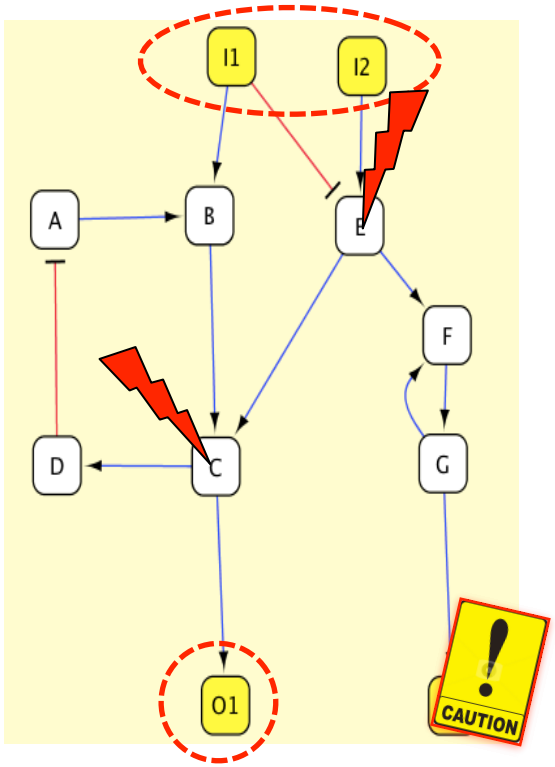

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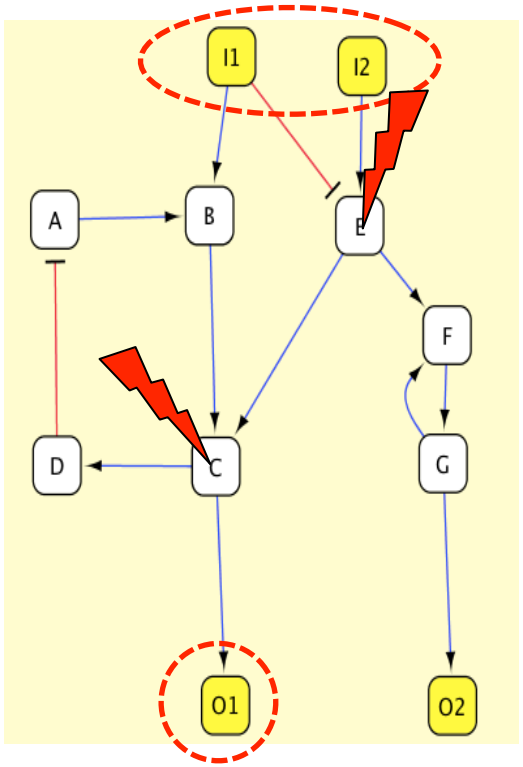

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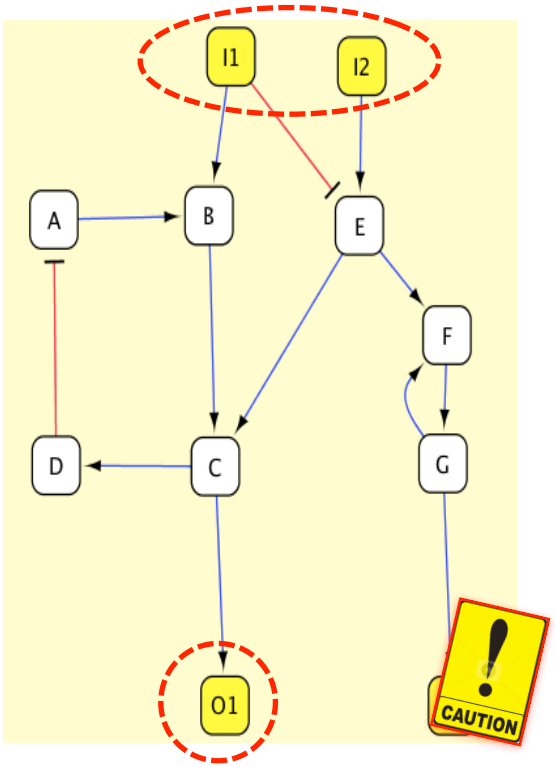

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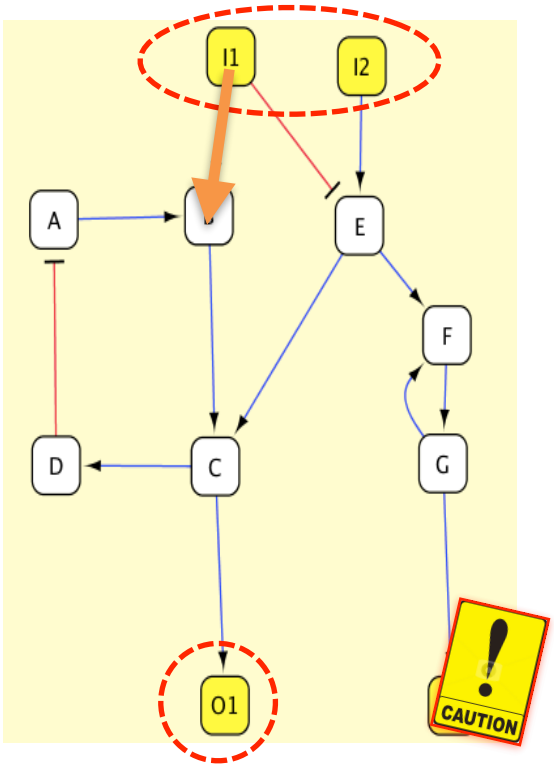

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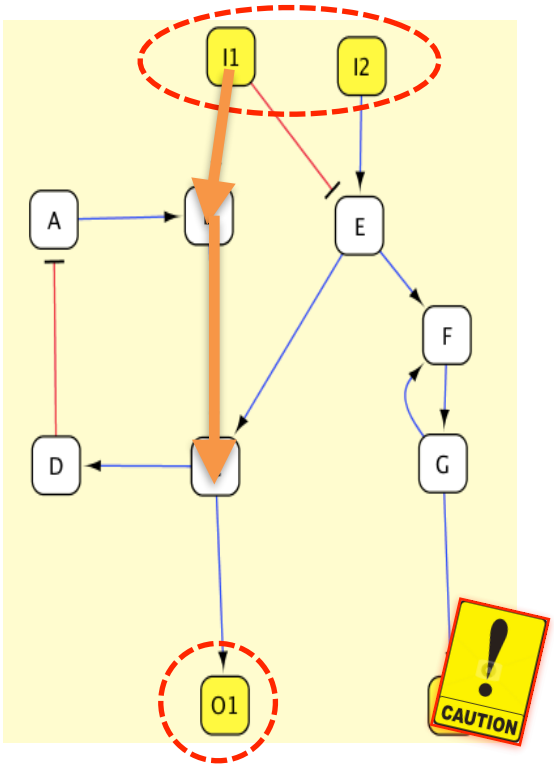

Minimal Combinations of Interventions

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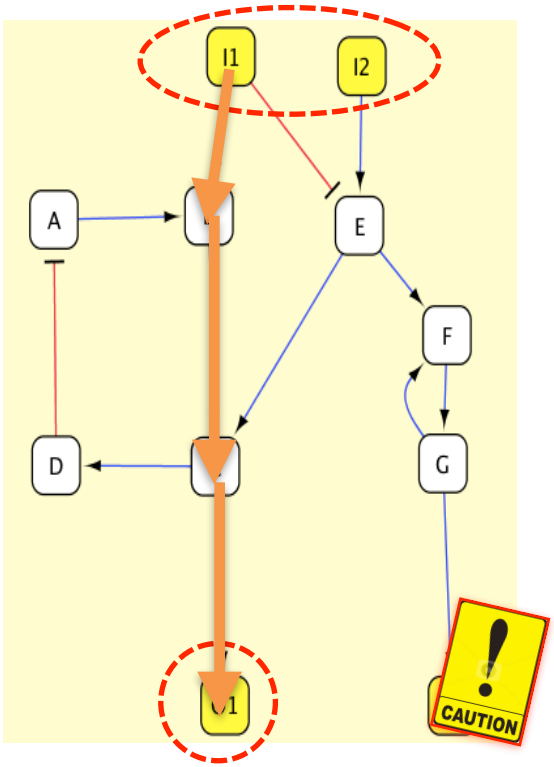

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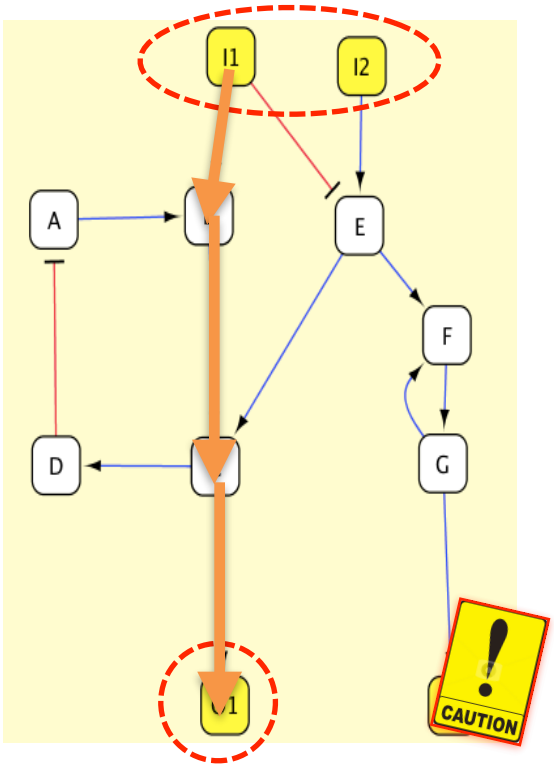
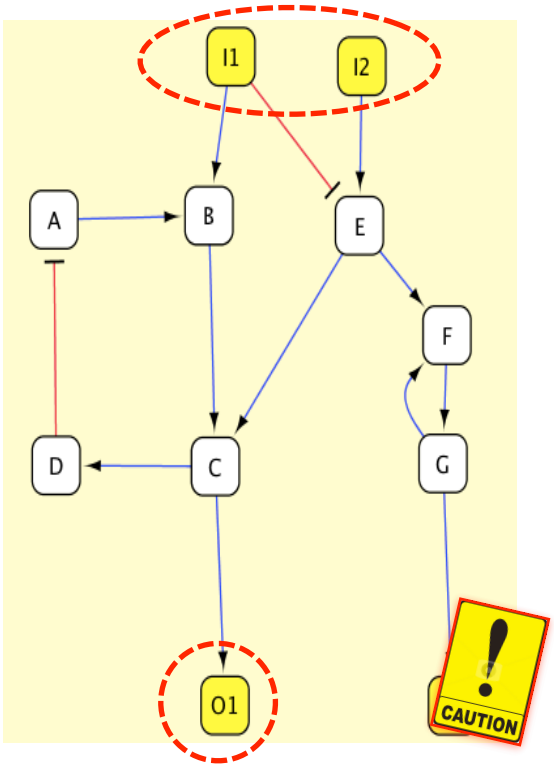


I1-> B-> C -> O1

Minimal Combinations of Interventions



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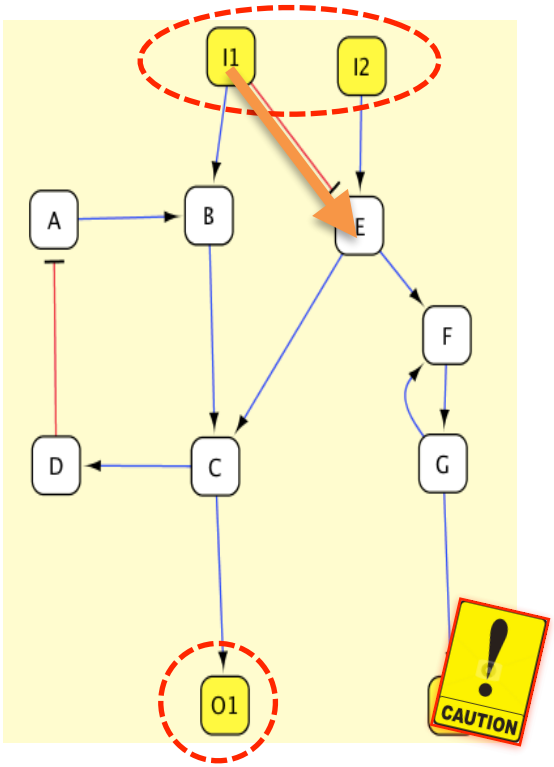

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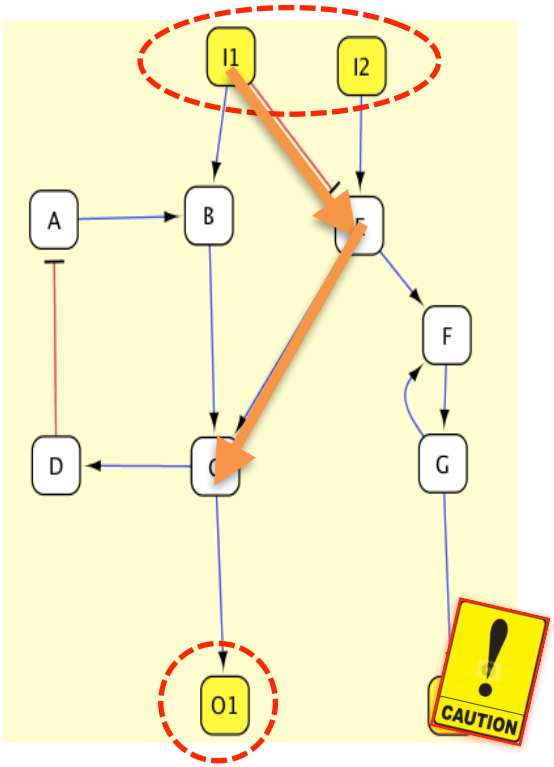

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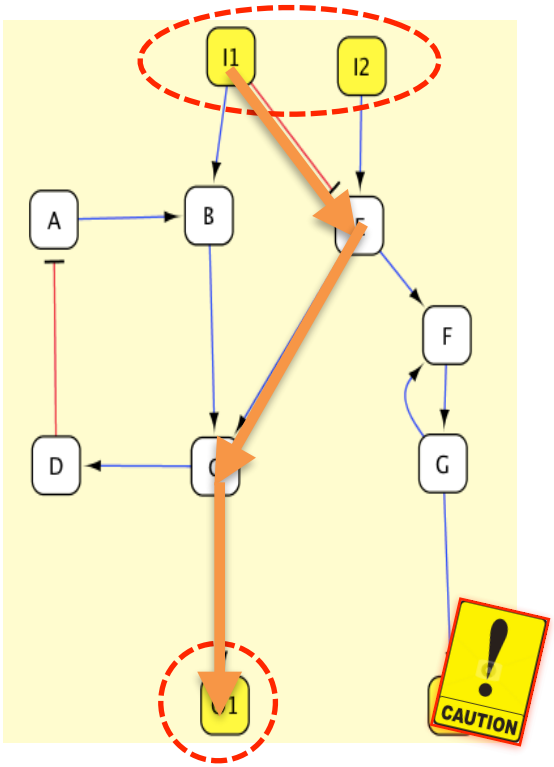

I1-> B-> C -> O1

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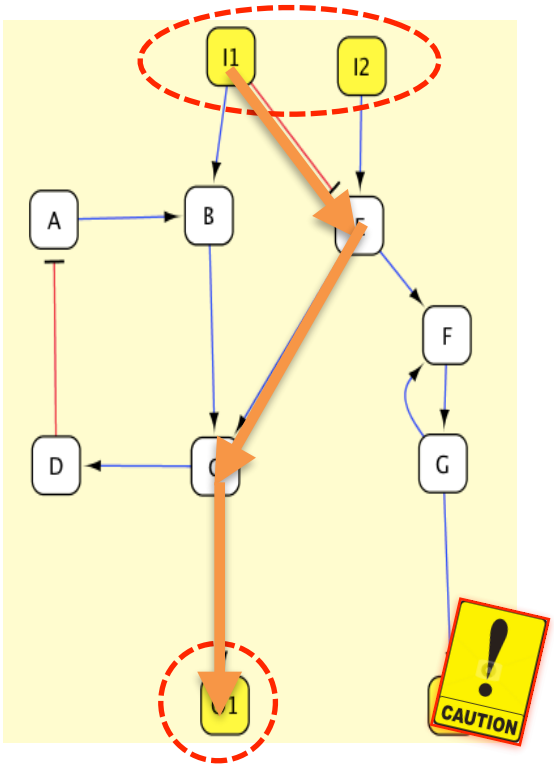
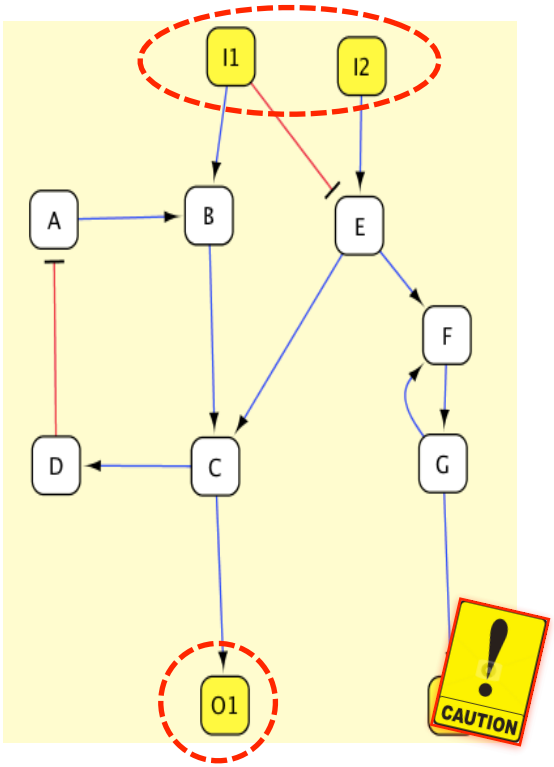


I1-> B-> C -> O1

I1-| E -> C -> O1

Minimal Combinations of Interventions



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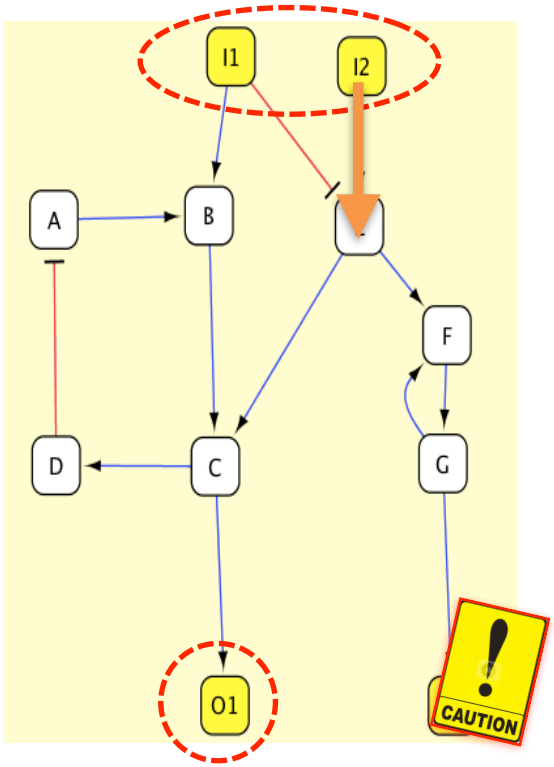

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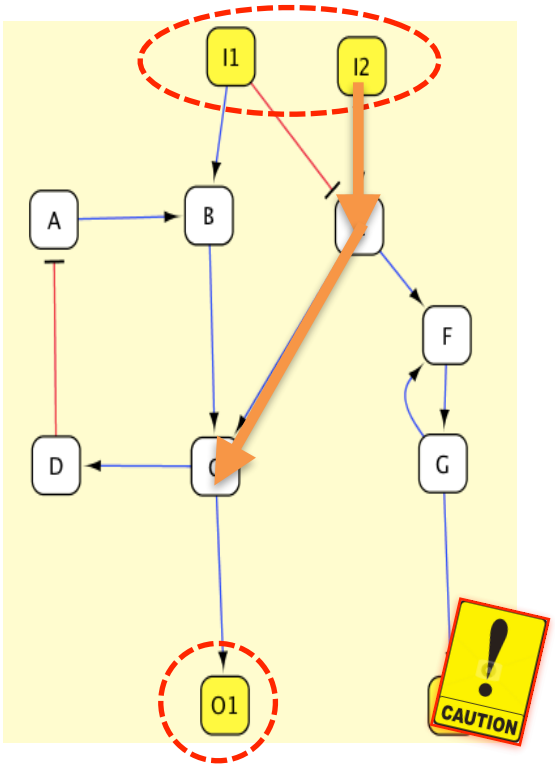

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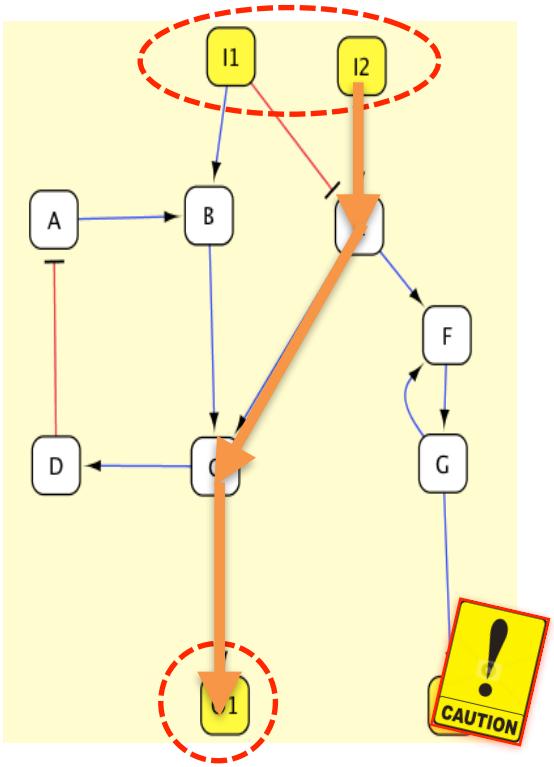

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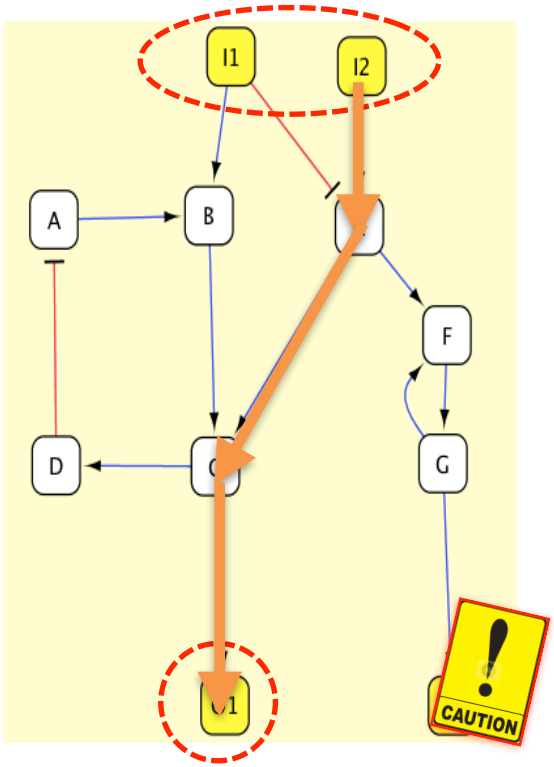
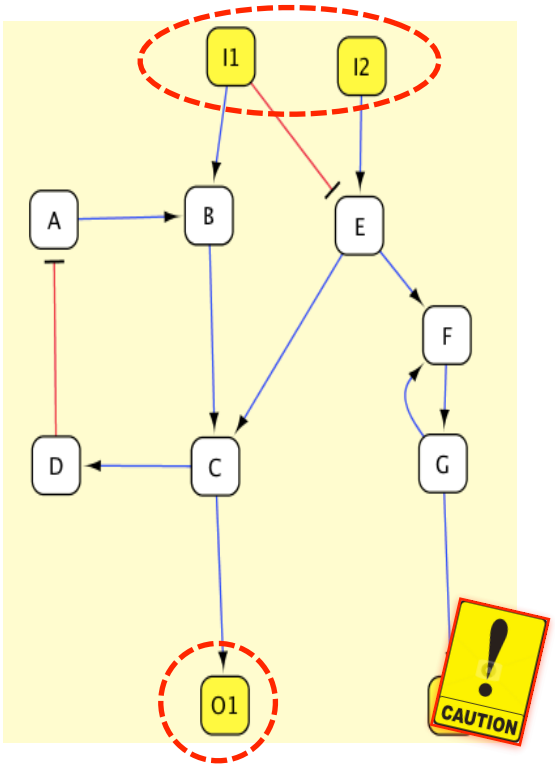


I1-> B-> C -> O1

I1-| E -> C -> O1

I2-> E -> C -> O1

Minimal Combinations of Interventions (CIs)



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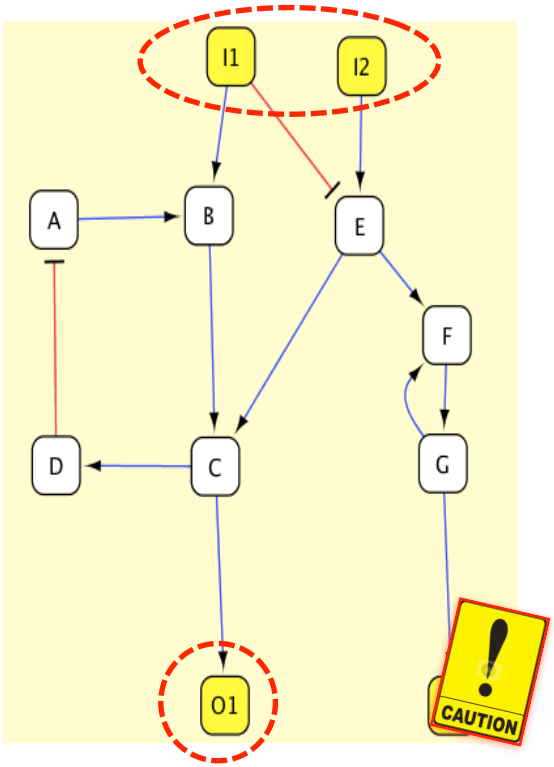


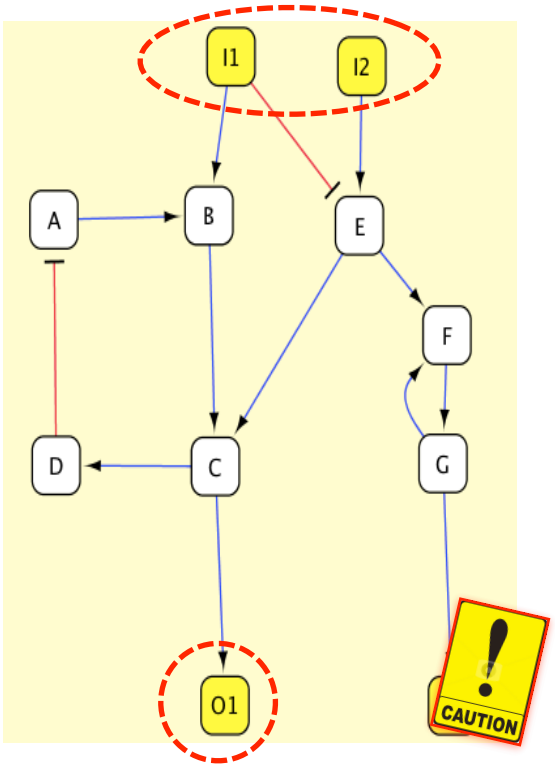
I1-> B-> C -> O1

I1-| E -> C -> O1

I2-> E -> C -> O1

Intervene (Knockout or Over-express) <u>at least one</u> time each one of these elementary paths

Minimal Combinations of Interventions (CIs)



I1-> B-> C -> O1

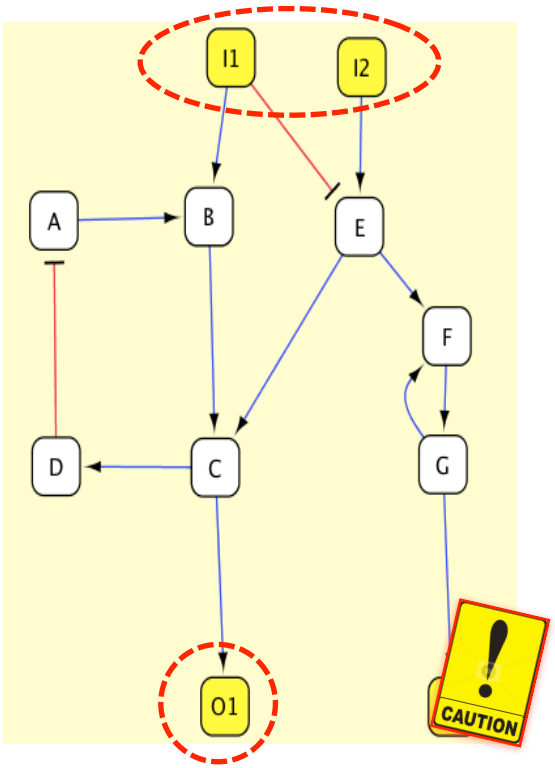
I1-| E -> C -> O1

I2-> E -> C -> O1

Intervene (Knockout or Over-express) <u>at least one</u> time each one of these elementary paths

Interventions of size 1: {C}

Minimal Combinations of Interventions (CIs)



I1-> B-> C -> O1

I1-| E -> C -> O1

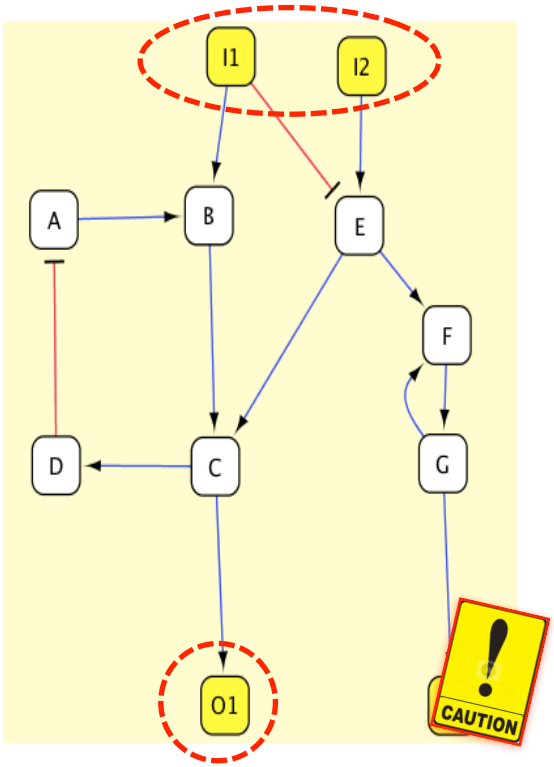
I2-> E -> C -> O1

Intervene (Knockout or Over-express) <u>at least one</u> time each one of these elementary paths

Interventions of size 1: {C}

Interventions of size 2: {B,E},
{I1, E},
{I2,B}, {I1,I2}

Minimal Combinations of Interventions (CIs)



I1-> B-> C -> O1

I1-| E -> C -> O1

I2-> E -> C -> O1

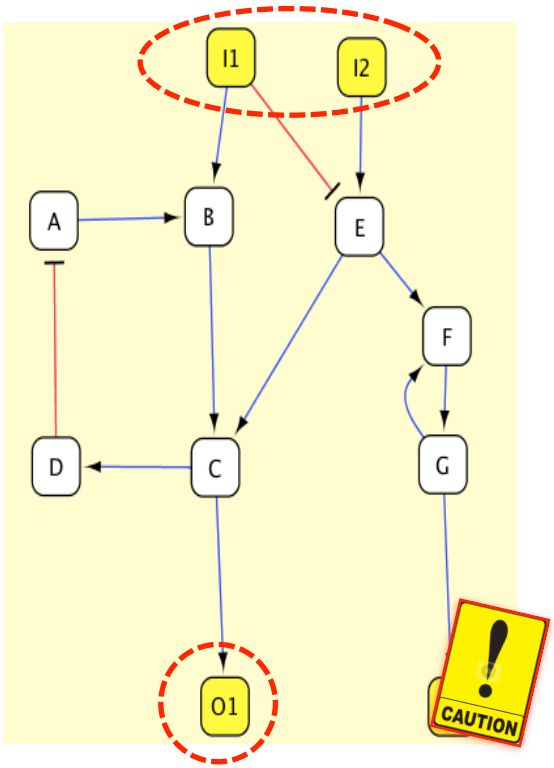
Intervene (Knockout or Over-express) <u>at least one</u> time each one of these elementary paths

Interventions of size 1: {C}

Interventions of size 2: {B,E},
{I1, E},
{I2,B}, {I1,I2}

"*Minimal*" in the sense that no subset of an intervention set can be an intervention set itself.

Minimal Combinations of Interventions (CIs)



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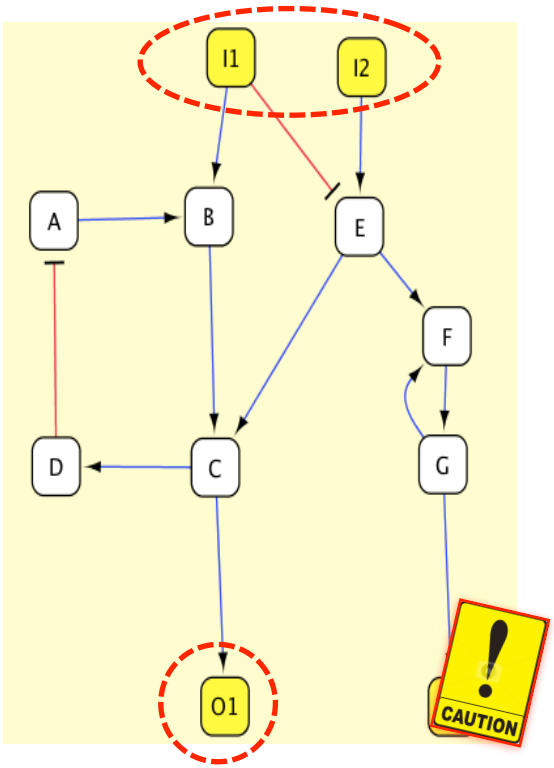

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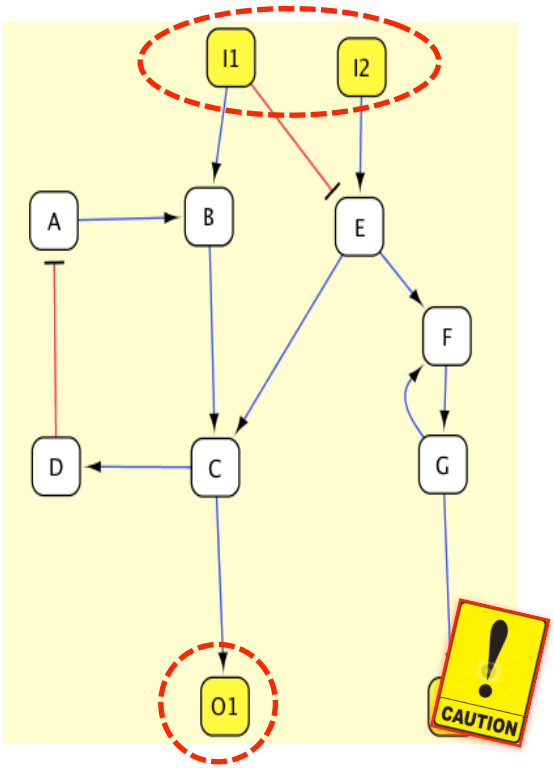

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Minimal Combinations of Interventions

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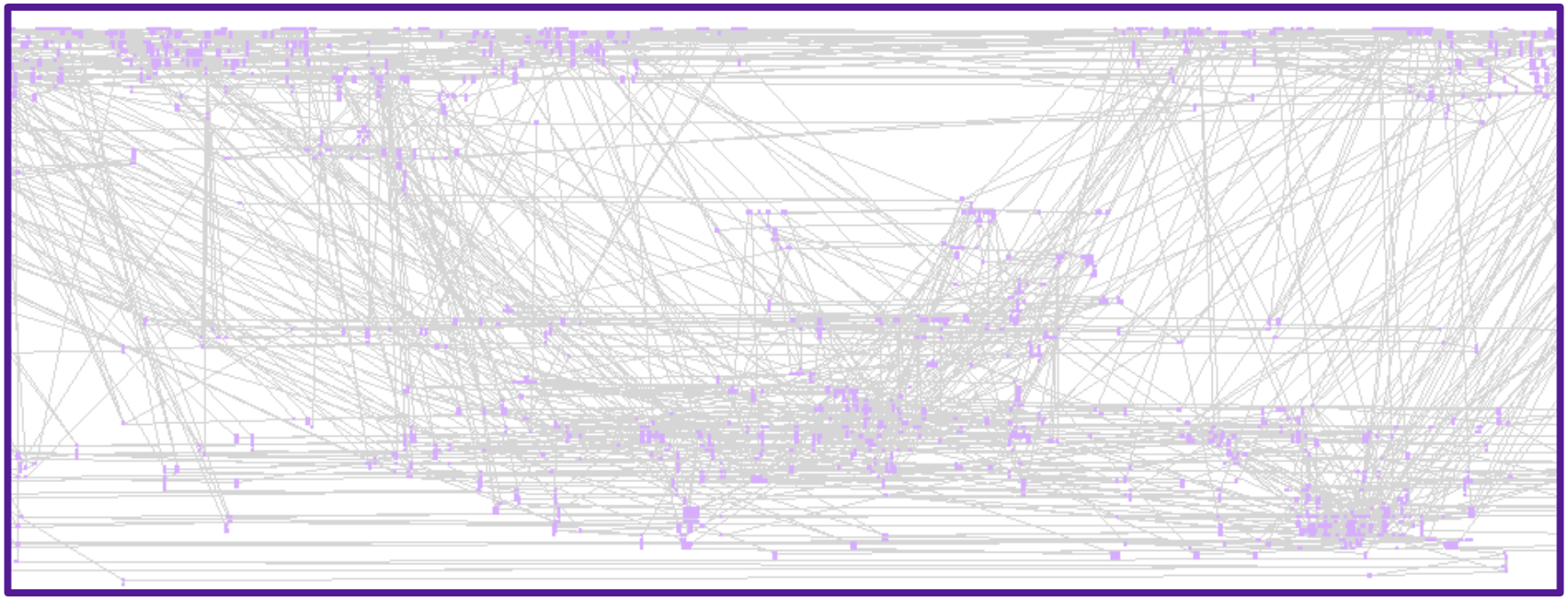

Part III: OCSANA

BIOINFORMATICS

Vol. 29 no. 12 2013, pages 1571–1573
doi:10.1093/bioinformatics/btt195

Systems biology

Advance Access publication April 26, 2013

OCSANA: optimal combinations of interventions from network analysis

Paola Vera-Licona[1,2,3,*], Eric Bonnet[1,2,3], Emmanuel Barillot[1,2,3] and Andrei Zinovyev[1,2,3]

[1]Institut Curie, Paris F-75248, France, [2]INSERM, U900, Paris F-75248, France and [3]Mines Paris Tech, Fontainebleau F-77300, France

Associate Editor: Martin Bishop

ABSTRACT

Targeted therapies interfering with specifically one protein activity are promising strategies in the treatment of diseases like cancer. However, accumulated empirical experience has shown that targeting multiple proteins in signaling networks involved in the disease is often necessary. Thus, one important problem in biomedical research is the design and prioritization of optimal combinations of interventions to repress a pathological behavior, while minimizing side-effects. OCSANA (optimal combinations of interventions from network analysis) is a new software designed to identify and prioritize optimal and minimal combinations of interventions to disrupt the paths between source nodes and target nodes. When specified by the user, OCSANA seeks to additionally minimize the side effects that a combination of interventions can cause on specified off-target nodes. With the crucial ability to cope with very large networks, OCSANA includes an exact solution and a novel selective enumeration approach for the combinatorial interventions' problem.

Availability: The latest version of OCSANA, implemented as a plugin for Cytoscape and distributed under LGPL license, is available together with source code at http://bioinfo.curie.fr/projects/ocsana.

implies that intervening molecules that play a central role in the cell may cause side effects, requiring alternative points of intervention (Samaga *et al.*, 2010). Some methods have been proposed to address some aspects of this problem (Hädicke and Klamt, 2011; Haus *et al.*, 2008; Klamt *et al.*, 2006). However, limited scalability of the methods and the lack of a prioritization criterion are hindering factors for their applicability to large biological networks. We introduce OCSANA, a software for the identification and prioritization of optimal minimal combinations of interventions (CIs). We define a CI as a set of nodes such that each elementary path (a path from source to target node) contains at least one node from this set. This CI set indicates the nodes to be intervened to disrupt all the identified elementary paths. The interventions can be knock outs (deletion of genes/proteins) and knock ins (overexpressions of genes/proteins). A CI is minimal if no proper subset of the CI is a CI itself, and its optimality is defined in terms of a heuristic scoring (see Section 2). To ensure the method's scalability, OCSANA includes an EXACT SOLUTION via an adaptation of Berge's algorithm (Berge, 1989) and a novel SELECTIVE ENUMERATION approach based on a weighted-

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Minimal Combinations of Interventions

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Although some *in silico* strategies have been proposed [1,2,3,4], scalability and prioritization of the CIs remain as important limitations to their full applicability.

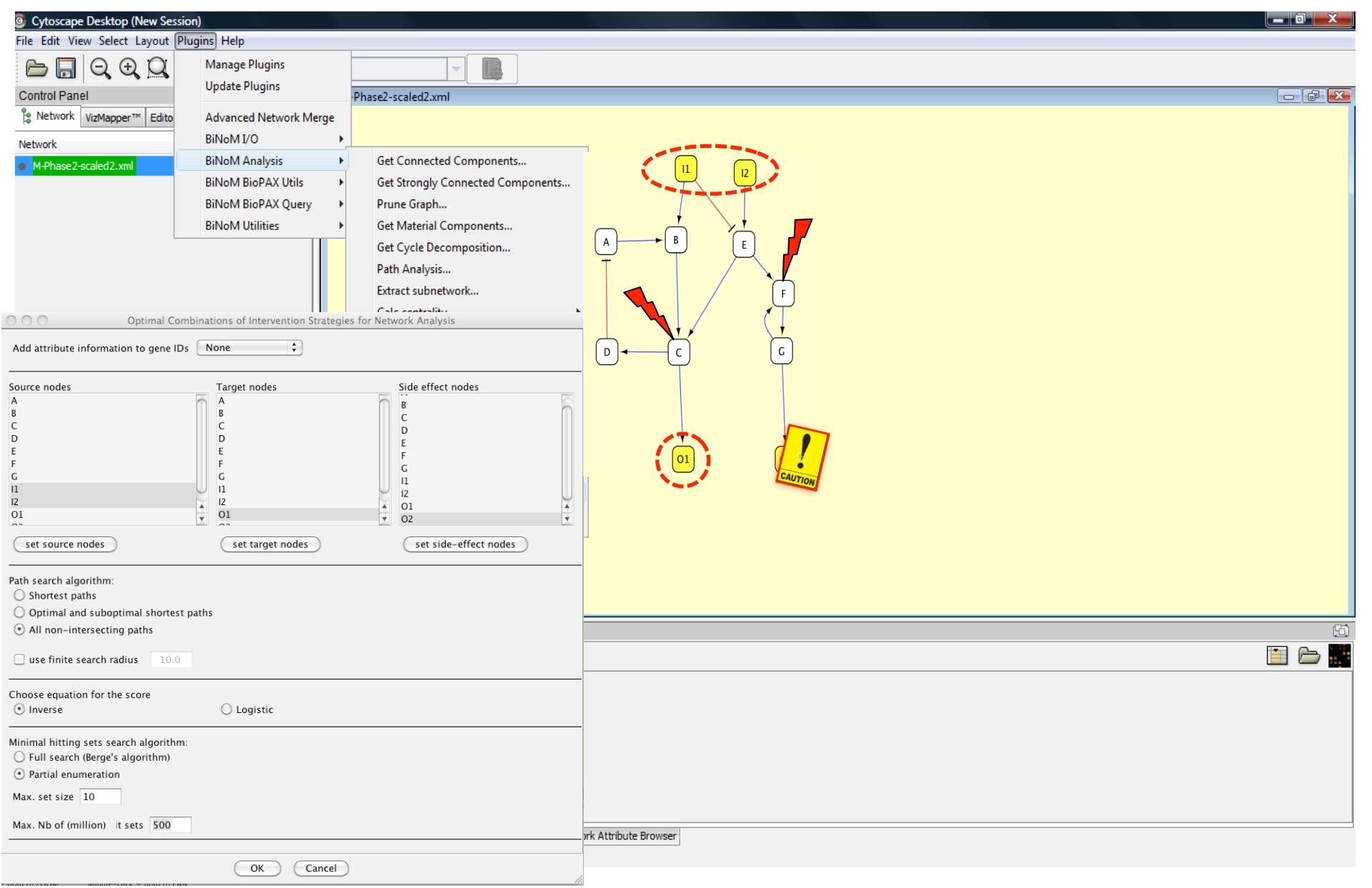
OCSANA has been designed as a systemic method designed to **identify and rank** optimal combinations of interventions (CIs) that intervene, the elementary path between specified source and targets nodes to obtain a desired behavior in the network while minimizing side-effects on pre-specified non-target paths for large size signal transduction networks.

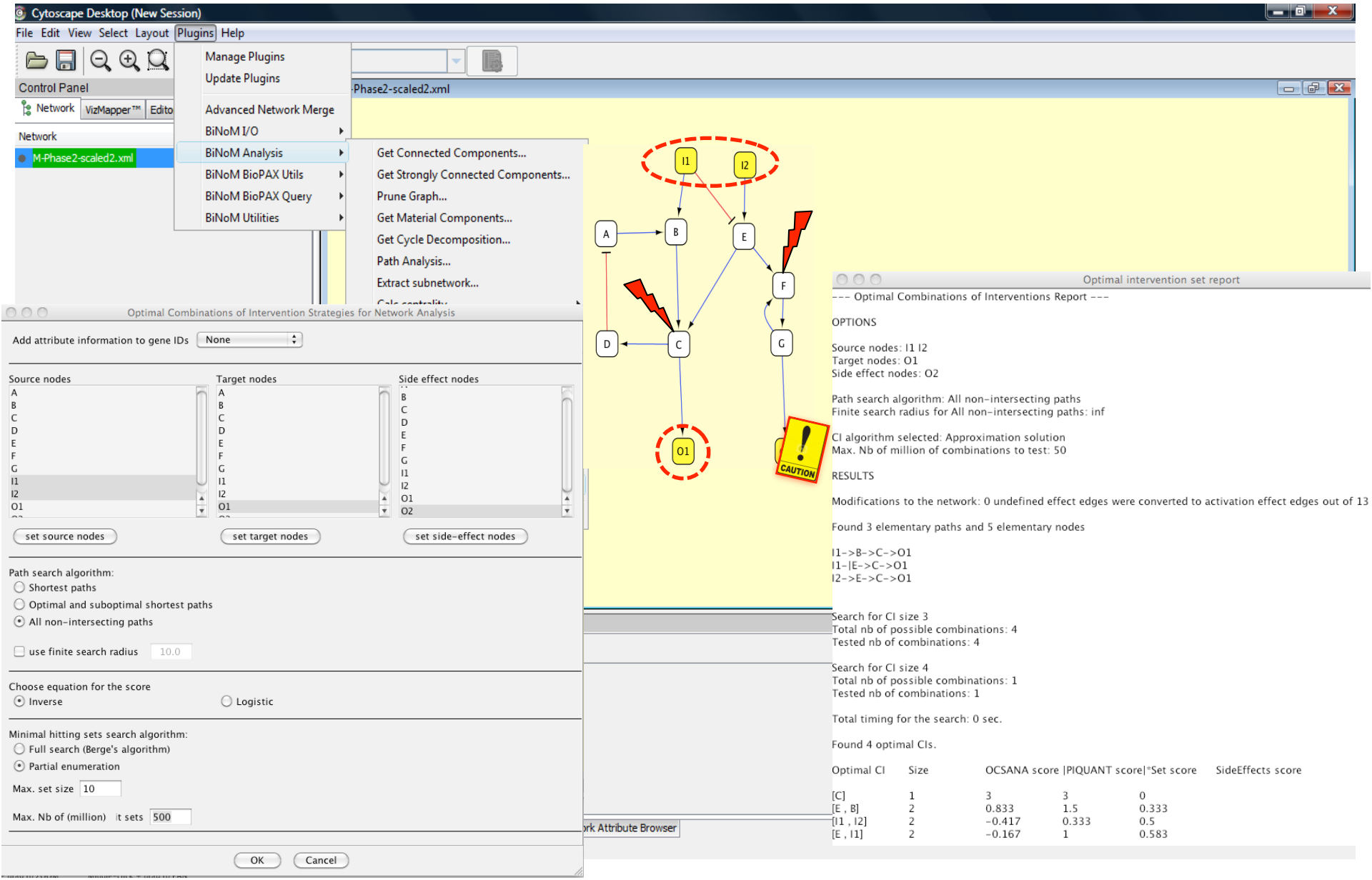
[1] Klamt, S., Saez-Rodriguez, J., Lindquist, J.A., Sorger P. (2006) A methodology for the structural and functional analysis of signaling and regulatory networks. BMC Bioinformatics, 7(56).

[2] Haus UU, Klamt S, Stephen T (2008) Computing knock-out strategies in metabolic networks, J. Comput Biol, 15, 259-268.

[3]Samaga, R., Von Kamp, A., Klamt S. (2010) Computing Combinatorial Intervention Strategies and Failure Modes in Signaling Networks. Journal of Computational Biology, 17(1): 39-53.

[4]Yan, H., Zhang, B., Li, S., Zhao, Q. (2010) A formal model for analyzing drug combination effects and its application in TNF-alpha-induced NFkappaB pathway. BMC Syst Biol, 4:50


Cytoscape Desktop (New Session)
File Edit View Select Layout Plugins Help
Manage Plugins
Update Plugins
Advanced Network Merge
BiNoM I/O
BiNoM Analysis
BiNoM BioPAX Utils
BiNoM BioPAX Query
BiNoM Utilities
Get Connected Components...
Get Strongly Connected Components...
Prune Graph...
Get Material Components...
Get Cycle Decomposition...
Path Analysis...
Extract subnetwork...
Control Panel
Network
VizMapper™
Network
M-Phase2-scaled2.xml
Phase2-scaled2.xml
I1
I2
A
B
E
F
D
C
G
O1
CAUTION
Optimal Combinations of Intervention Strategies for Network Analysis
Add attribute information to gene IDs
None
Source nodes
Target nodes
Side effect nodes
A
B
C
D
E
F
G
I1
I2
O1
O2
set source nodes
set target nodes
set side-effect nodes
Path search algorithm:
Shortest paths
Optimal and suboptimal shortest paths
All non-intersecting paths
use finite search radius
10.0
Choose equation for the score
Inverse
Logistic
Minimal hitting sets search algorithm:
Full search (Berge's algorithm)
Partial enumeration
Max. set size
10
Max. Nb of (million) it sets
500
OK
Cancel
ork Attribute Browser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File Edit View Select Layout Plugins Help
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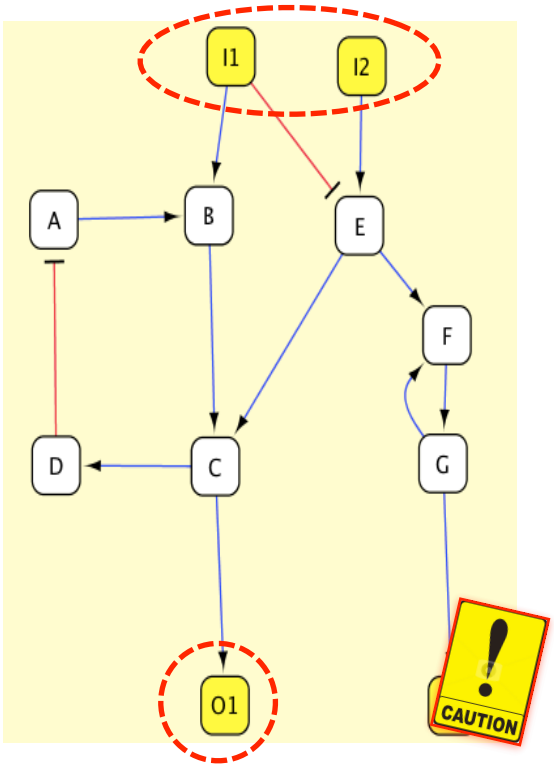
BiNoM Analysis
BiNoM BioPAX Utils
BiNoM BioPAX Query
BiNoM Utilities
Get Connected Components...
Get Strongly Connected Components...
Prune Graph...
Get Material Components...
Get Cycle Decomposition...
Path Analysis...
Extract subnetwork...
Control Panel
Network
VizMapper™
M-Phase2-scaled2.xml
Phase2-scaled2.xml
I1
I2
A
B
E
F
D
C
G
O1
CAUTION
Optimal Combinations of Intervention Strategies for Network Analysis
Add attribute information to gene IDs
None
Source nodes
Target nodes
Side effect nodes
set source nodes
set target nodes
set side-effect nodes
Path search algorithm:
Shortest paths
Optimal and suboptimal shortest paths
All non-intersecting paths
use finite search radius
10.0
Choose equation for the score
Inverse
Logistic
Minimal hitting sets search algorithm:
Full search (Berge's algorithm)
Partial enumeration
Max. set size
10
Max. Nb of (million) it sets
500
OK
Cancel
Optimal intervention set report
--- Optimal Combinations of Interventions Report ---
OPTIONS
Source nodes: I1 I2
Target nodes: O1
Side effect nodes: O2
Path search algorithm: All non-intersecting paths
Finite search radius for All non-intersecting paths: inf
CI algorithm selected: Approximation solution
Max. Nb of million of combinations to test: 50
RESULTS
Modifications to the network: 0 undefined effect edges were converted to activation effect edges out of 13
Found 3 elementary paths and 5 elementary nodes
I1->B->C->O1
I1-|E->C->O1
I2->E->C->O1
Search for CI size 3
Total nb of possible combinations: 4
Tested nb of combinations: 4
Search for CI size 4
Total nb of possible combinations: 1
Tested nb of combinations: 1
Total timing for the search: 0 sec.
Found 4 optimal CIs.
Optimal CI Size OCSANA score |PIQUANT score|*Set score SideEffects score
[C] 1 3 3 0
[E , B] 2 0.833 1.5 0.333
[I1 , I2] 2 -0.417 0.333 0.5
[E , I1] 2 -0.167 1 0.583

Minimal Combinations of Interventions



I1-> B-> C -> O1

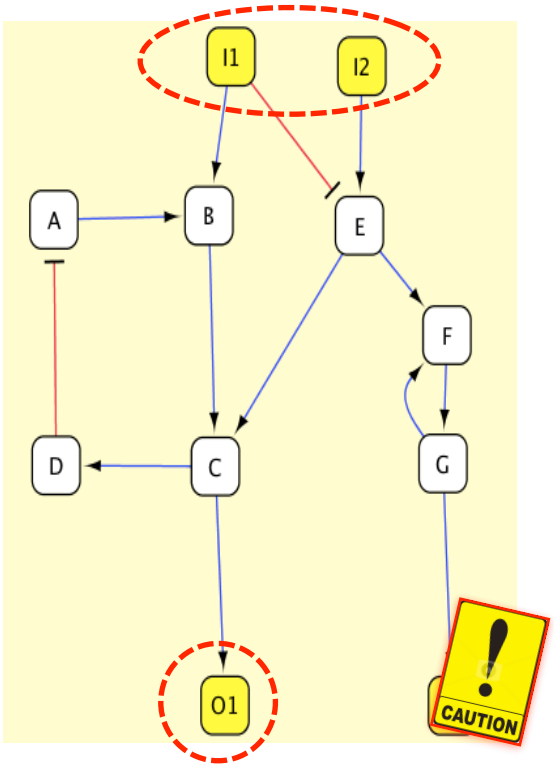
I1-| E -> C -> O1

I2-> E -> C -> O1

Interventions of size 1: {C}

Interventions of size 2: {B,E},
{I1, E},
{I2,B}, {I1,I2}

Minimal Combinations of Interventions



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I1-| E -> C -> O1

I2-> E -> C -> O1

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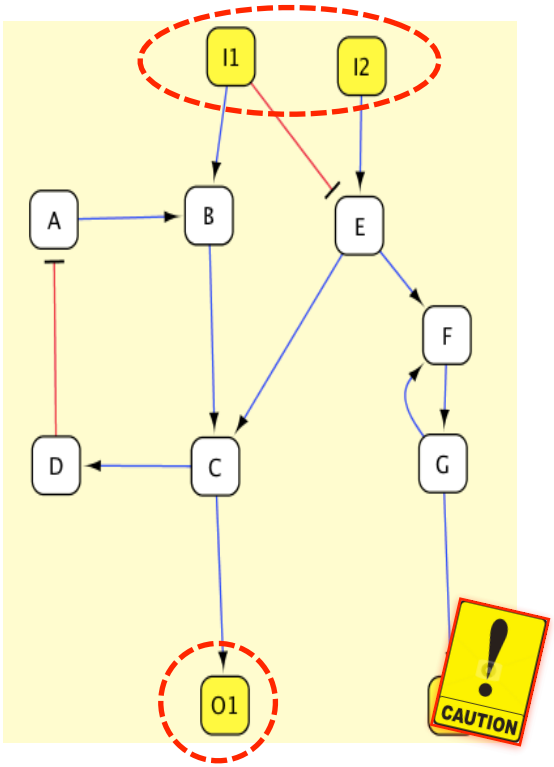
Interventions of size 2: {B,E},
{I1, E},
{I2,B}, {I1,I2}

Minimal Combinations of Interventions



I1-> B-> C -> O1

I1-| E -> C -> O1

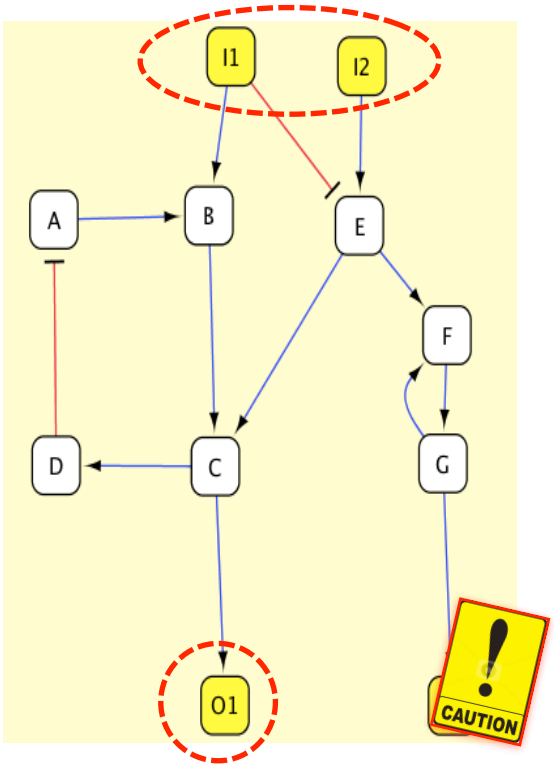
I2-> E -> C -> O1

Find Elementary Paths

Interventions of size 1: {C}

Interventions of size 2: {B,E},
{I1, E},
{I2,B}, {I1,I2}

Minimal Combinations of Interventions



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Find Elementary Paths

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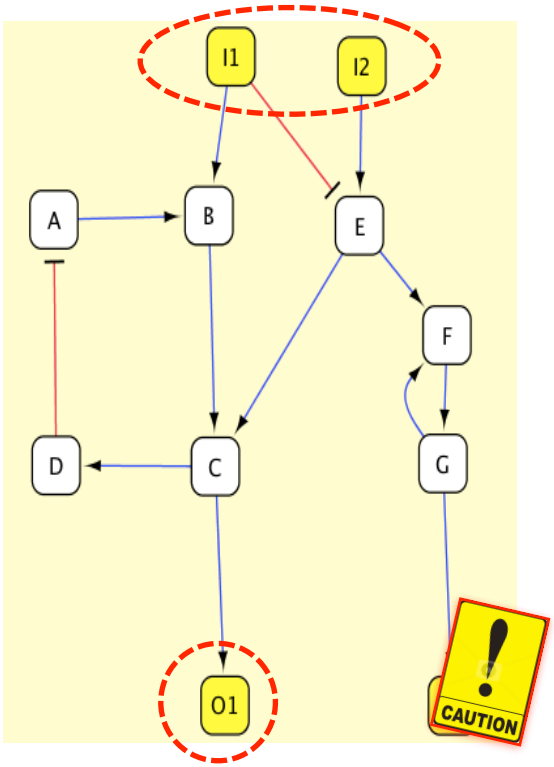
Minimal Combinations of Interventions



I1-> B-> C -> O1

I1-| E -> C -> O1

I2-> E -> C -> O1

Find Elementary Paths

Interventions of size 1: {C}

Interventions of size 2: {B,E},
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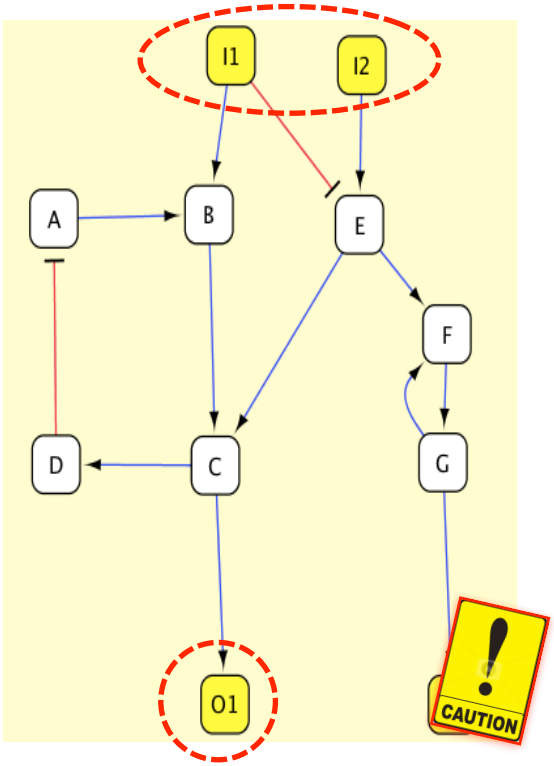
Minimal Intervention Sets

Minimal Combinations of Interventions



I1-> B-> C -> O1

I1-| E -> C -> O1

I2-> E -> C -> O1

Interventions of size 1: {C}

Interventions of size 2: {B,E},
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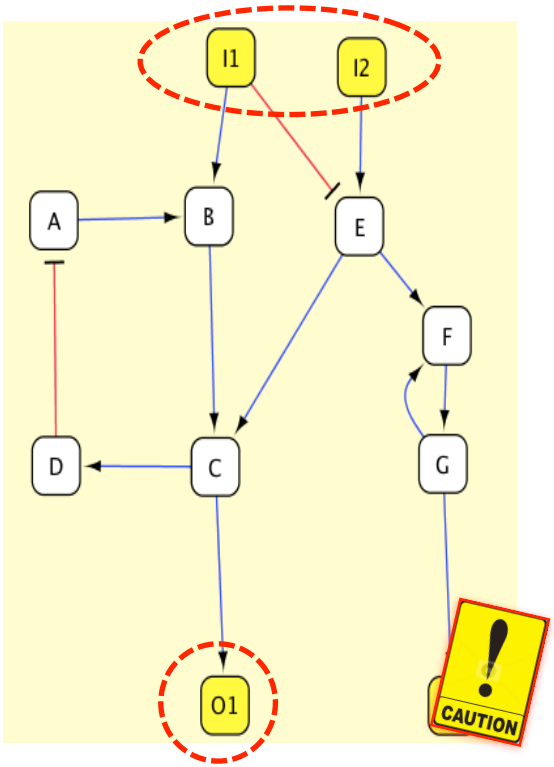
{I2,B}, {I1,I2}

Minimal Intervention Sets

Minimal Combinations of Interventions

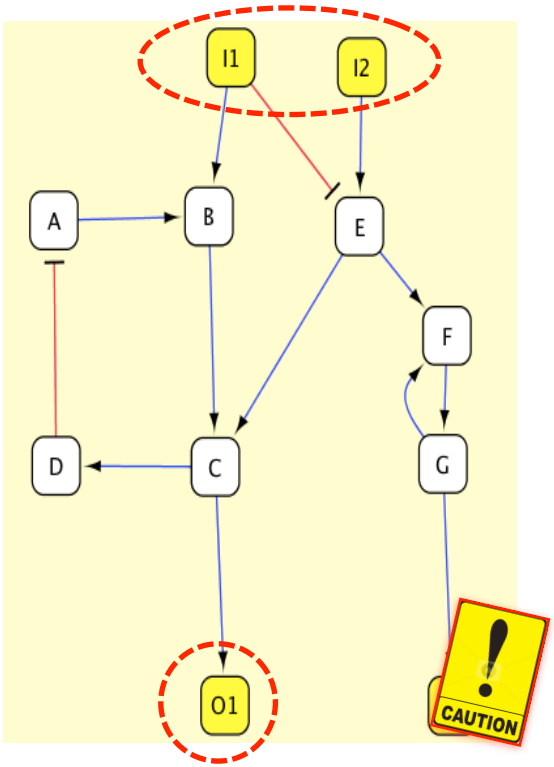


I1-> B-> C -> O1 === {I1, B, C, O1}

I1-| E -> C -> O1 === {I1, E, C, O1}

I2-> E -> C -> O1 === {I2, E, C, O1}

Minimal Combinations of Interventions



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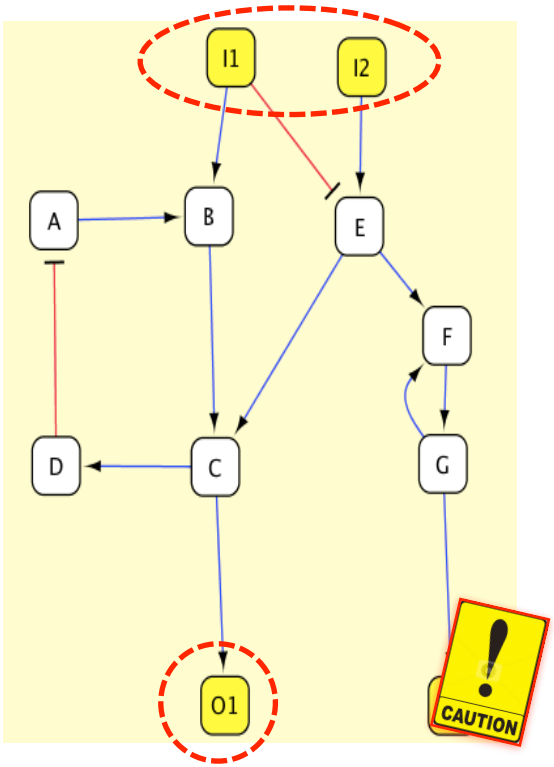
I1-| E -> C -> O1 === {I1, E, C, O1}

I2-> E -> C -> O1 === {I2, E, C, O1}

"**Hit" (intersect)** at least one time each one of these elementary paths

Minimal Combinations of Interventions



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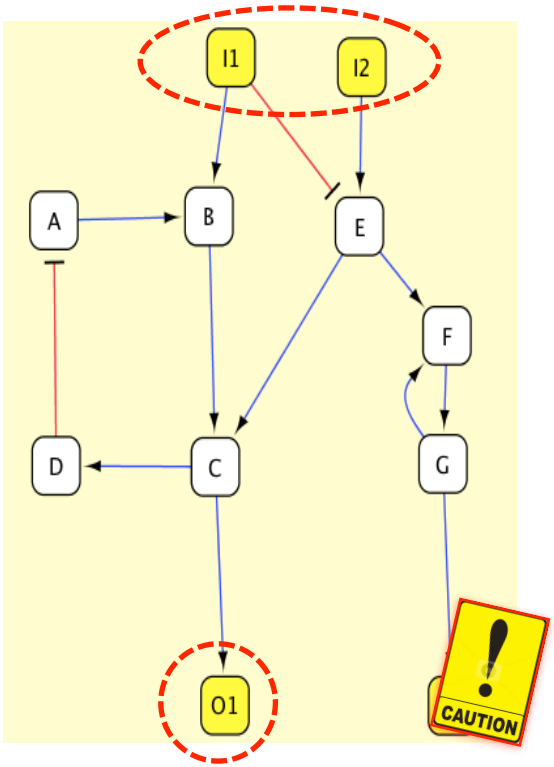
I2-> E -> C -> O1 === {I2, E, C, O1}

"**Hit" (intersect)** at least one time each one of these elementary paths

Interventions of size 1: {C}

Minimal Combinations of Interventions



I1-> B-> C -> O1 === {I1, B, C, O1}

I1-| E -> C -> O1 === {I1, E, C, O1}

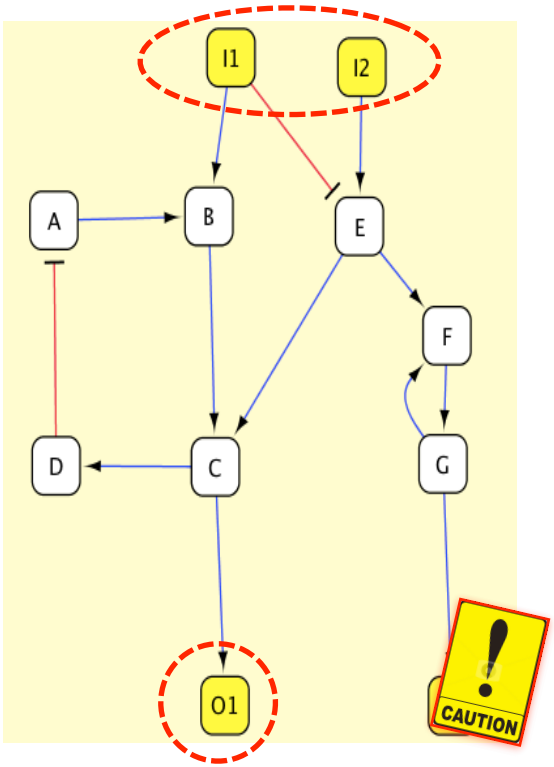
I2-> E -> C -> O1 === {I2, E, C, O1}

"**Hit" (intersect)** at least one time each one of these elementary paths

Interventions of size 1: {C}

Interventions of size 2: {B,E},
{I1, E},
{I2,B}, {I1,I2}

Minimal Combinations of Interventions



I1-> B-> C -> O1 === {I1, B, C, O1}

I1-| E -> C -> O1 === {I1, E, C, O1}

I2-> E -> C -> O1 === {I2, E, C, O1}

"**Hit" (intersect)** <u>at least one</u> time each one of these elementary paths

Minimal Hitting Set Problem

Interventions of size 1: {C}

Interventions of size 2: {B,E},
{I1, E},
{I2,B}, {I1,I2}

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Minimal Hitting Set Problem

Boolean Dualization

Minimal Transversal for Hypergraphs

Maximal Elements

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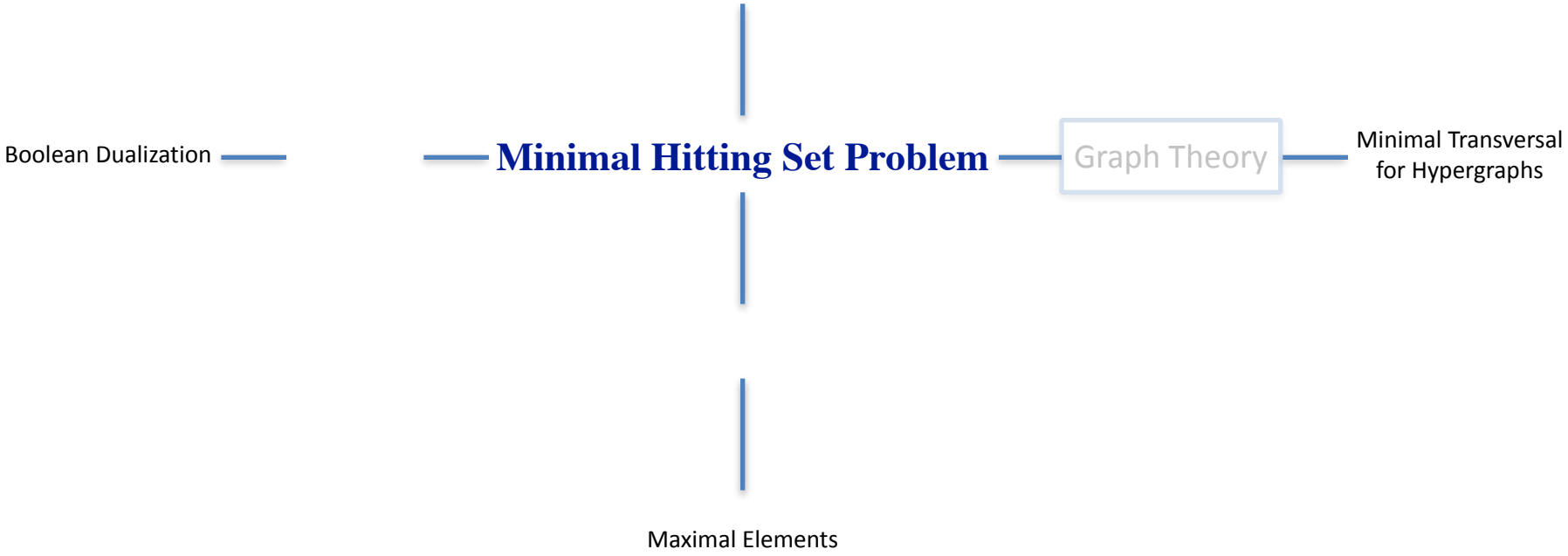

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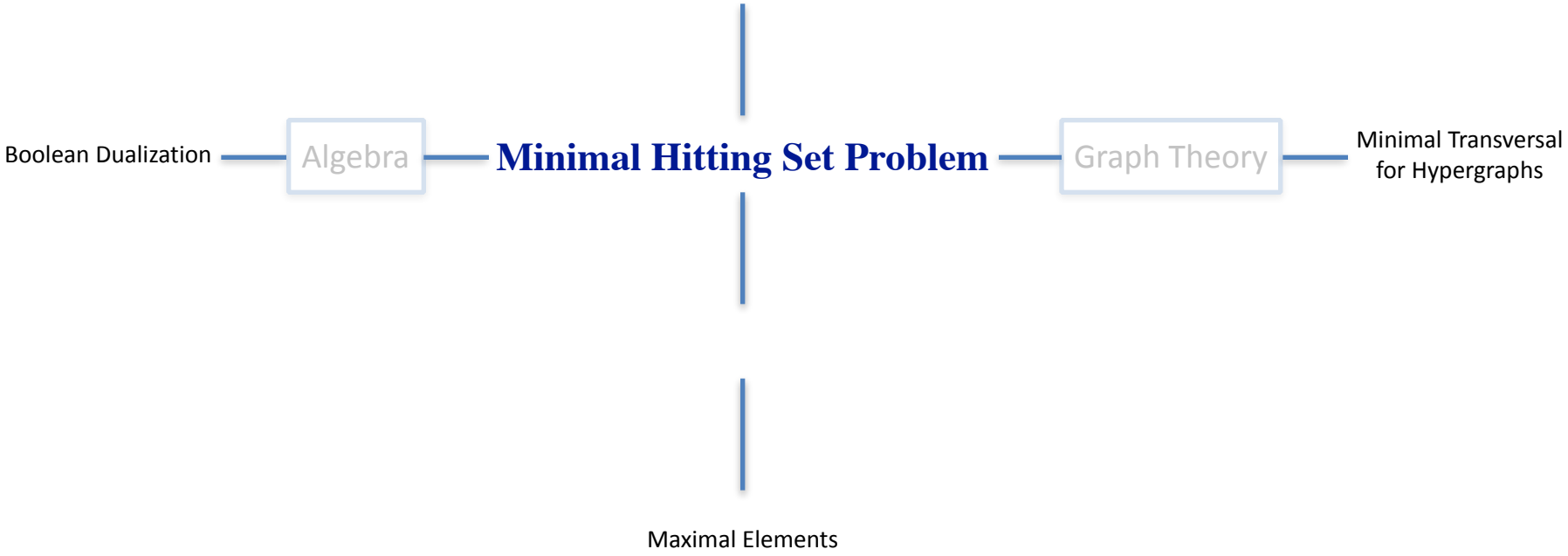

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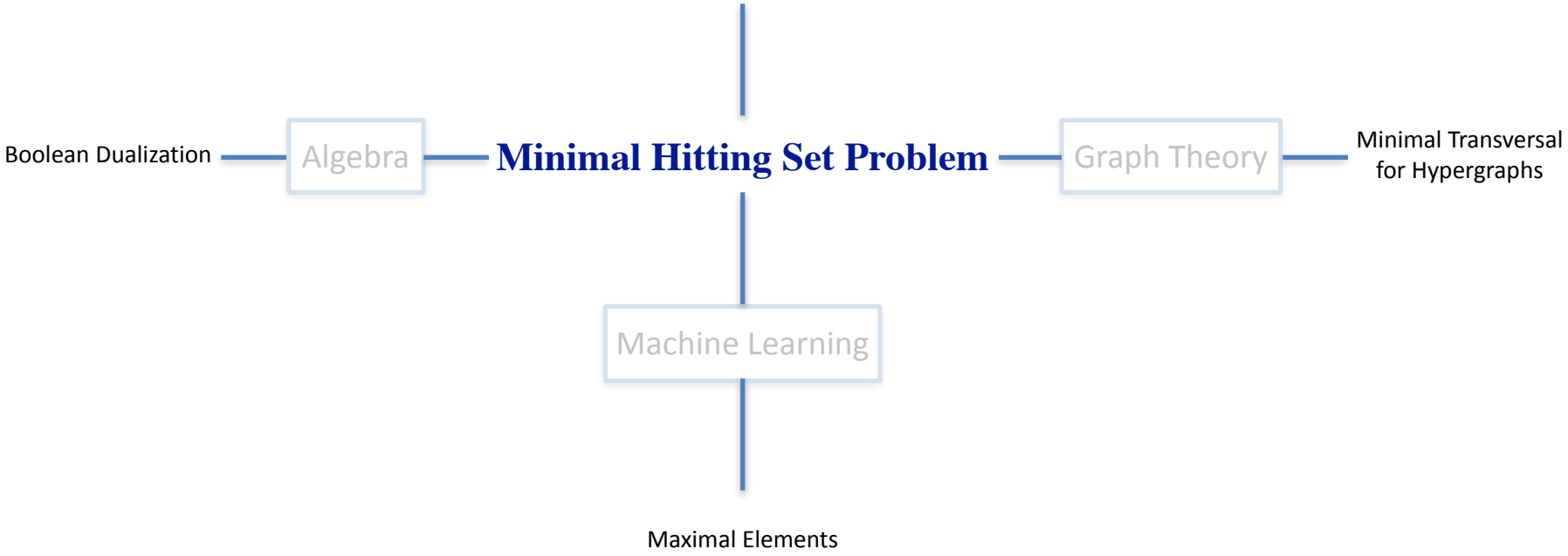

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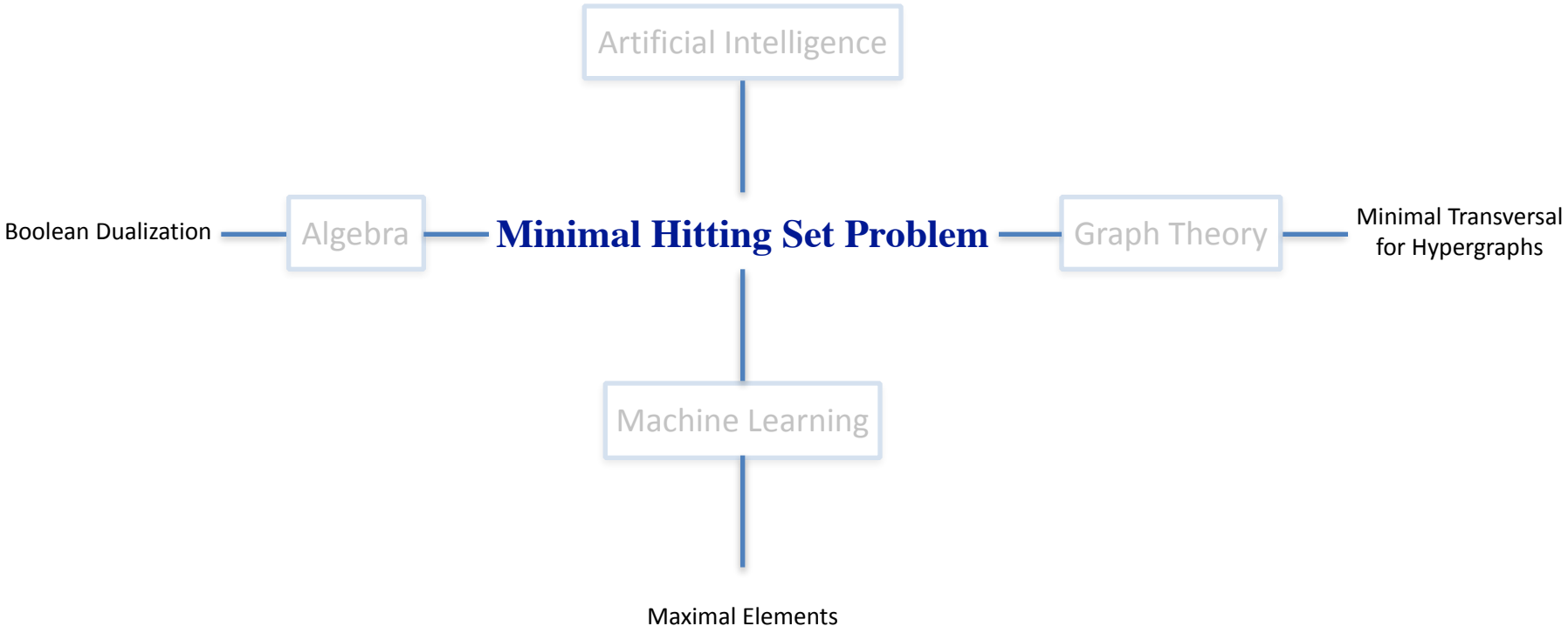

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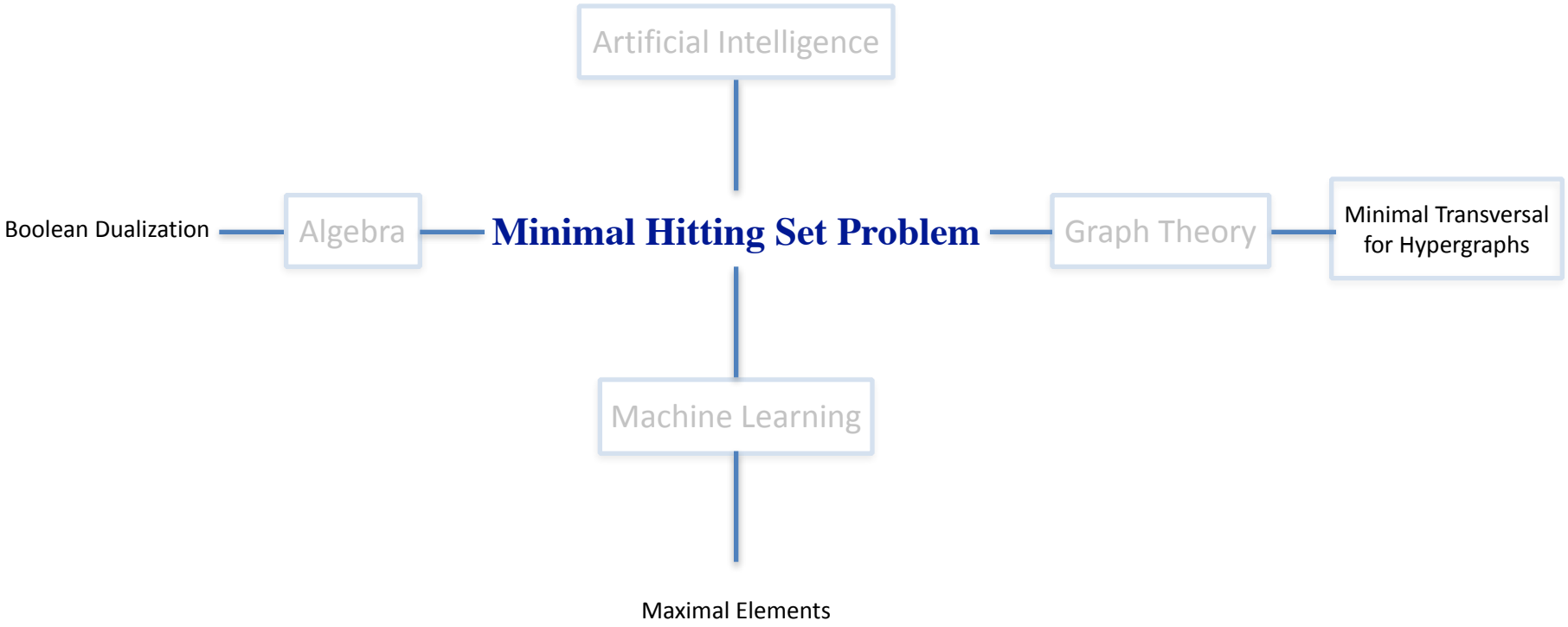

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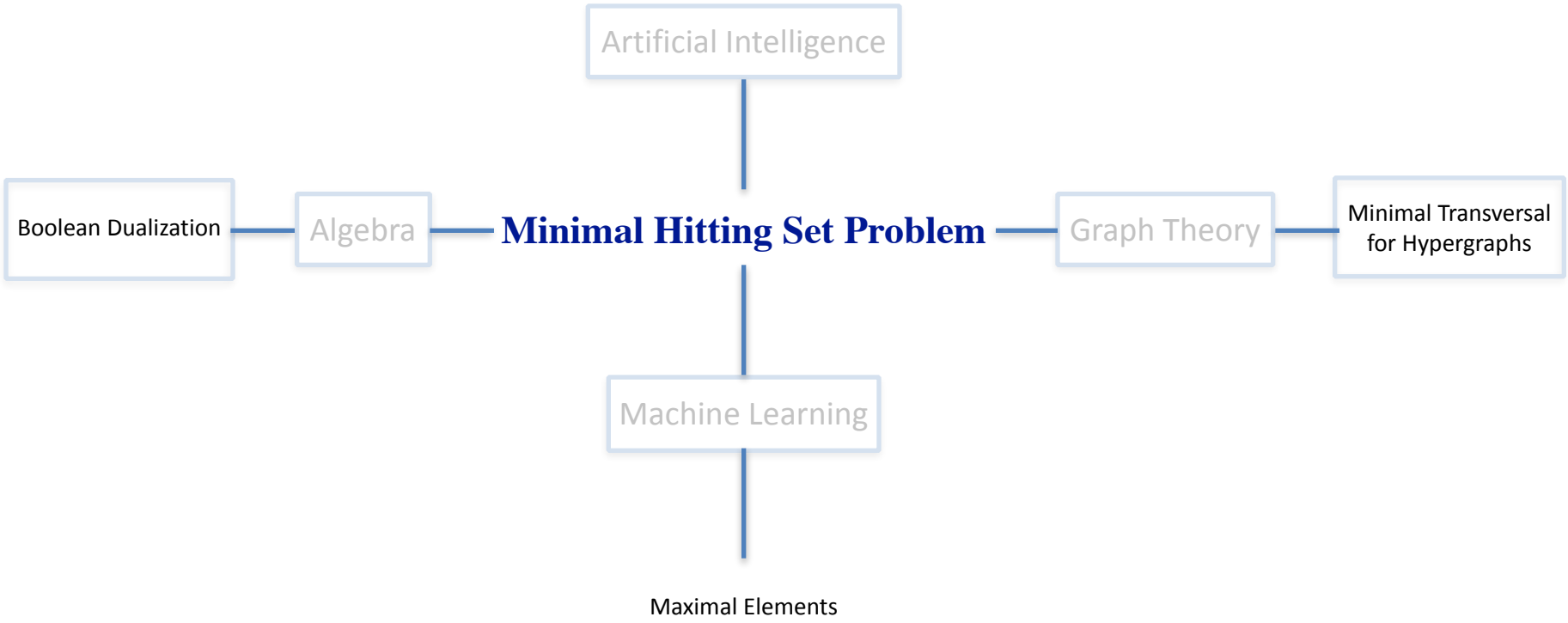

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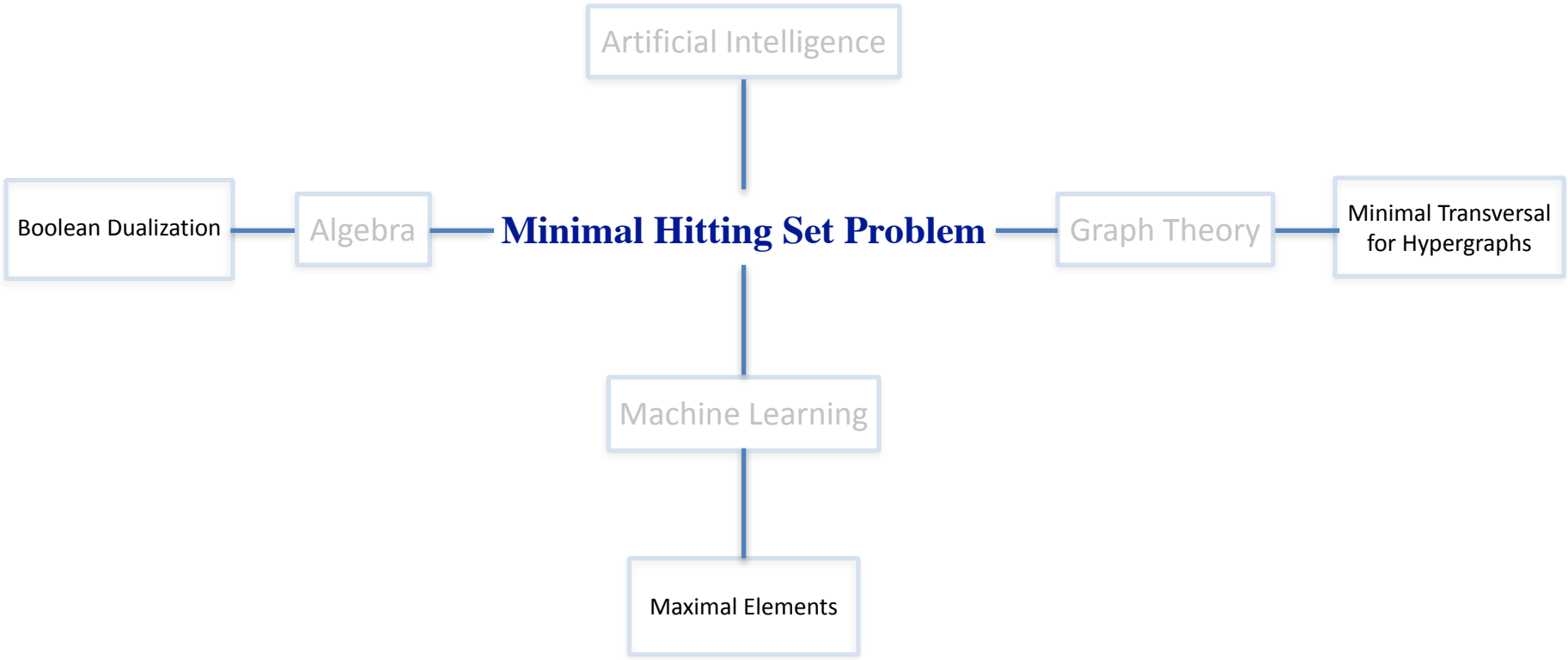

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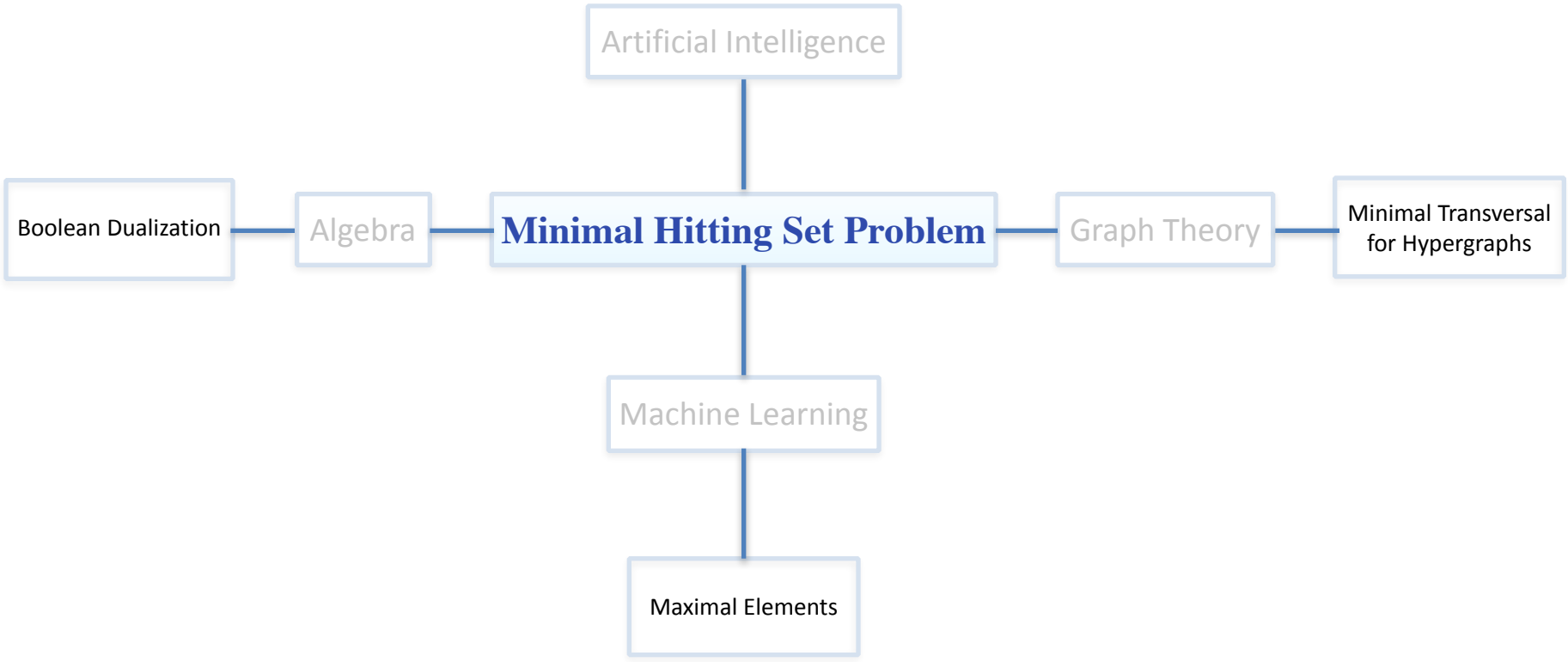
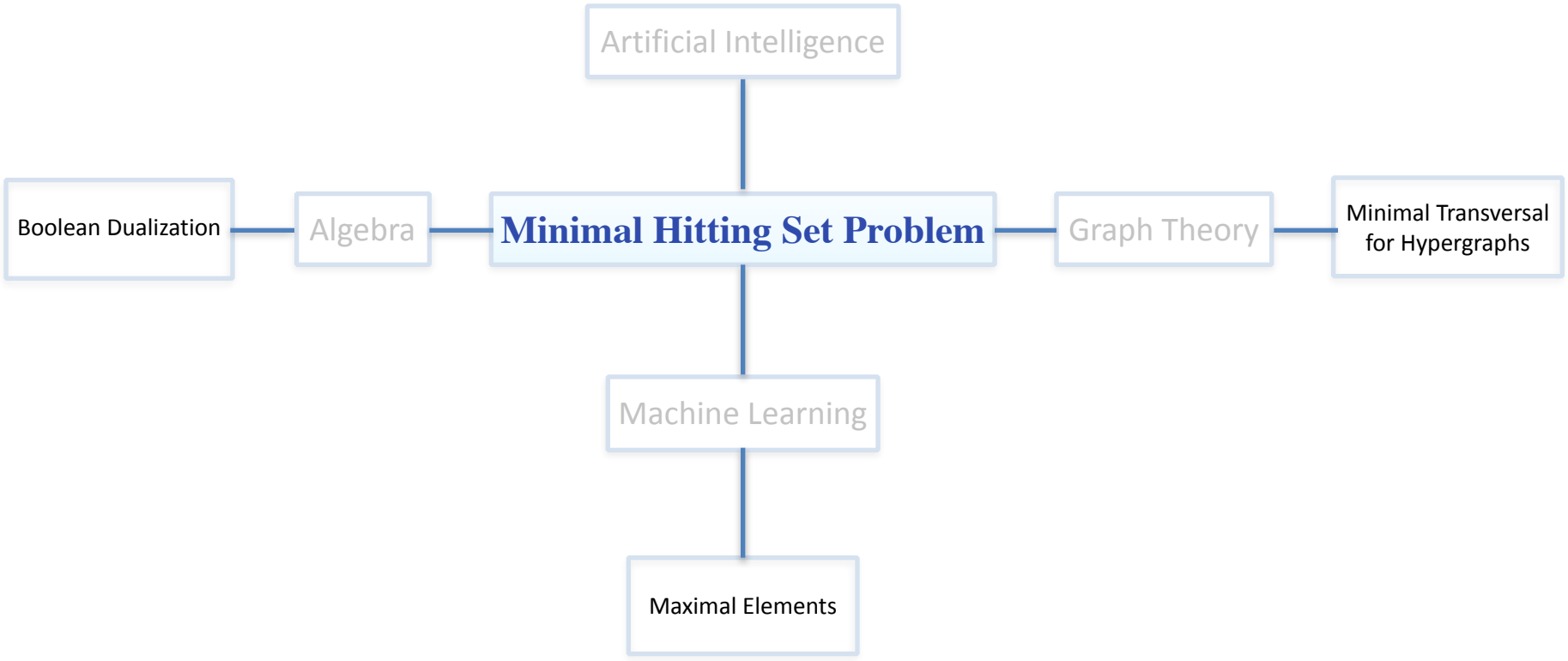


Given a collection of sets $\mathscr{C}$, to find minimal hitting sets ""H_i" is a classical problem in Combinatorics called "The Minimal Hitting Set Problem". This is an NP-Complete problem



Minimal Hitting Set Problem

Problem 1: Finding Minimal Hitting Sets

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Several known algorithms:

- Sequential Method [Berge 1989]
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Problem 2: How to choose from the identified MIs? Which one(s) is better and why?

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We score MHSs by first, scoring each one of its nodes.

The scoring is based on:

(i) The lengths of the paths from the node of interest to the targets,

(ii) The type of effect on target nodes (e.g. activation/inhibition effect),

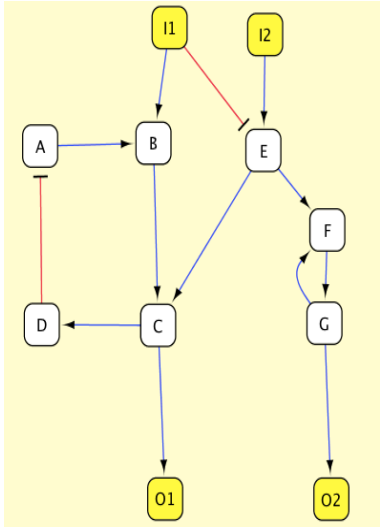
(iii) Side effects with respect to off-target nodes,

(iv) The number of elementary paths in which the node participates and

(v) The number of targets that such node can reach simultaneously.

Problem 2: How to choose from the identified MIs? Which one(s) is better and why?

We introduce a score for nodes according to the effect on the target node O1. Let's suppose that we have *m* source paths sinking in O1.



$$s_{O1}(n) = \sum_{i=1,m} \sigma(i) \frac{1}{\text{length of path } i}, \text{ where } \sigma(i) \text{ is the sign of the } i^{th} \text{ path starting from node } n$$

$$s_{O1}(C) = (+)\frac{1}{1} = 1$$

$$s_{O1}(B) = (+)\frac{1}{2} = 0.5$$

$$s_{O1}(E) = (+)\frac{1}{2} = 0.5$$

$$s_{O1}(I1) = (+)\frac{1}{3} + (-)\frac{1}{3} = 0$$

$$s_{O1}(I2) = (+)\frac{1}{3} = 0.33$$

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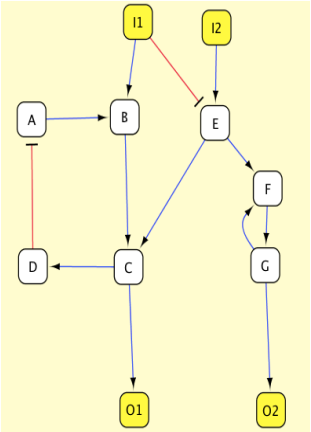


Additionally, we introduce a penalty score for the source nodes, according to their effect on all unwanted target nodes:

$$p_{\overline{O1}}(n) = \frac{1}{r}\sum_{i=1}^{r} s_{U_i}(x), \text{ where } U_i \text{ is the set of unwanted targeted nodes and } r = |U_i| \text{ path starting from node } n$$

$$p_{\overline{O2}}(C) = 0$$
$$p_{\overline{O2}}(B) = 0$$
$$p_{\overline{O2}}(E) = 1/3 = 0.33$$
$$p_{\overline{O2}}(I1) = -1/4$$
$$p_{\overline{O2}}(I2) = +1/4$$

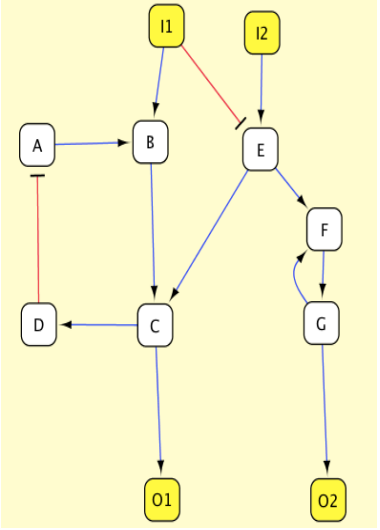
Thus the total score of each one of the source nodes *x* to *O1* are scored as $S_{O1}(x) = s_{U_i}(x) - p_{\overline{O1}}(x)$

$$S_{O1}(C) = 1 - 0 = 1$$
$$S_{O1}(B) = 1/2 - 0 = 0.5$$
$$S_{O1}(E) = 1/2 - 1/3 = .166$$
$$S_{O1}(I1) = 0 - (-)1/4 = .25$$
$$S_{O1}(I2) = 1/3 - 1/4 = 0.083$$

Problem 2: How to choose from the identified MIs? Which one(s) is better and why?

Optimal minimal intervention sets according to their score is:

Size	Optimal Cut Sets for O1 $OCS(O1)$
1	$S_{O1}(\{C\}) = 1$
2	$S_{O1}(\{I2, B\}) = 0.083 + 0.5 = 0.583$ $S_{O1}(\{I1, E\}) = .25 + .166 = 0.316$ $S_{O1}(\{I1, I2\}) = .25 + 0.083 = 0.333$



Minimal Hitting Set Problem

Problem 3: Scalability of the Method

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Exact Solution

Selective Enumeration
(Greedy Algorithm)

Minimal Hitting Set Problem

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Outline of Algorithm to Compute Minimal Combinations of Interventions

Input/mandatory: A network (signed digraph), a set of source nodes, target nodes and a set of parameters.
Input/optional: A set of complementary nodes assigned as off-target nodes (i.e. side effects).

Output: Prioritized list of optimal CIs.

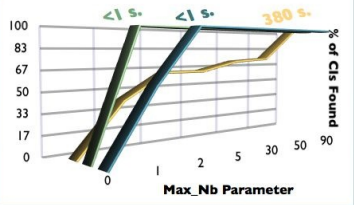
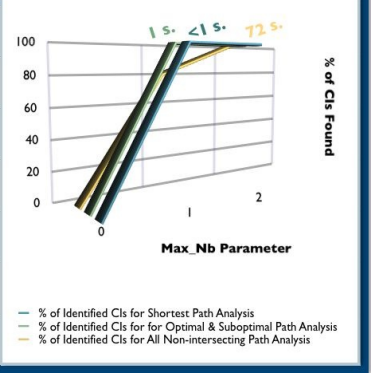
1. Pre-processing step: Compute the collection of elementary paths, that is, paths from source nodes to target nodes according to the selected parameters for the path analysis.

2. Score the nodes present in the elementary paths and sort them in a descending order.

3. Compute the so-called minimal hitting sets (MHSs) for the elementary paths according to the selected algorithm approach and sort them according to OCSANA's score.

This sorted list ofMHSs is the sought list of prioritized optimal CIs.

Outline of Algorithm to Compute Minimal Combinations of Interventions

		Path Analysis Selected			
		Shortest Paths	Optimal & Suboptimal Shortest Paths	All Non Self-intersecting Paths	Graphs on the % of CIs Up to Size 5 identified by Selective Enumeration/ Optimal Solutions
(A1)	EGFR Network (144 Nodes, 266 Edges)				
(A2)	[No. Elementary Paths, No. Elementary Nodes]	[125, 49]	[234, 55]	[11050, 63]	N/A (The search space is too small to require selective enumeration)
(A3)	Time to find all CIs up to Size 5 by Exact Sol. (Berge's alg.)	< 1s.	< 1s.	< 1s.	
(A4)	Time to find all CIs up to Size 5 by Full Enumeration/Exhaustive Search	< 1s.	< 1s.	< 1s.	
(A5)	Time to find all of CIs up to Size 5 by Selective Enumeration/Optimal Sols.	< 1s.	< 1s.	< 1s.	
(B1)	ErbB Family Breast Cancer Network (336 Nodes, 492 Edges)				
(B2)	[No. Elementary Paths, No. Elementary Nodes]	[158, 77]	[473, 103]	[23668, 160] (All paths up to length 20)	
(B3)	Time to find all CIs up to Size 5 by Exact Sol. (Berge's alg.)	78 s.	66 s.	965 s.	
(B4)	Time to find all CIs up to Size 5 by Full Enumeration/Exhaustive Search	6 s.	25 s.	3401 s.	
(B5)	[Time to find all of CIs up to Size 5 by Selective Enumeration /Optimal Sols., % of search space needed]	[<1 s., 9.47%]	[<1 s., 2.29%]	[380 s., 11.19%]	
(C1)	HER2+ Breast Cancer Network (2753 Nodes, 3812 Edges)				
(C2)	[No. Elementary Paths, No. Elementary Nodes]	[534, 121]	[2538, 170]	[69805, 317] (All paths up to length 20)	
(C3)	Time to find all CIs up to Size 5 by Exact Sol. (Berge's alg.)	741 s.	133 s.	696 s.	
(C4)	Time to find all CIs up to Size 5 by Full Enumeration/Exhaustive Search	59 s.	753 s.	N/A (> 43000 s.)	
(C5)	[Time to find all of CIs up to Size 5 by Selective Enumeration /Optimal Sols., % of search space needed]	[<1 s., 1.07%]	[1 s., 0.57%]	[72 s., 0.76%]	
(C6)	Time to find all CIs up to Size 5 by Exact Sol. (Berge's alg.)	36610 s.	9965 s.	N/A (> 43000 s.)	
(C7)	Time to find all CIs up to Size 5 by Full Enumeration/Exhaustive Search	1274 s.	21786 s.	N/A (> 43000 s.)	
(C8)	[Time to find all of CIs up to Size 6 by Selective Enumeration /Optimal Sols., % of search space needed]	[484 s., 36.40%]	[1633 s., 7.36%]	N/A (> 43000 s.) 95 s. to compute 40% of CIs	

Part IV: Application Example to breast cancer

Introduction: HER2-positive Breast Cancer

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- **HER2** (also known as **ErbB2** or **Her2/neu**) stands for Human Epidermal Growth Factor Receptor 2.

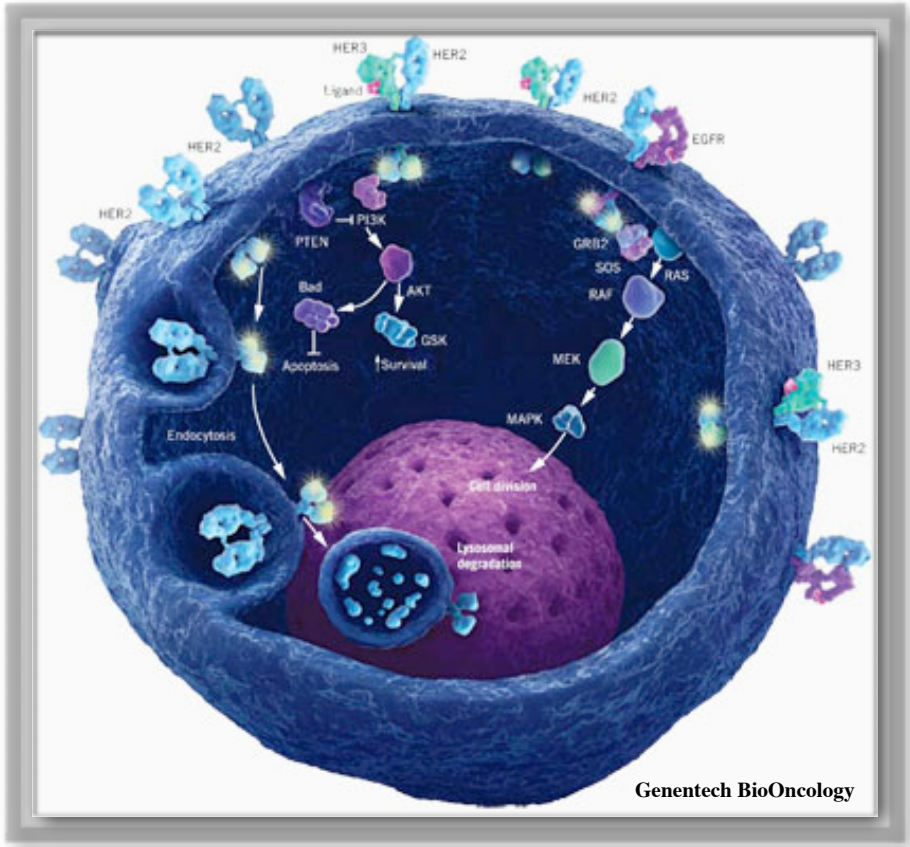
- Each normal breast cell contains copies of the HER2 gene which encodes the HER2 protein (also called **HER2 receptor**).

- **HER2** is a member of the **HER receptor tyrosine kinase family**, which includes three other members: Epidermal growth factor receptor (**EGFR** or **HER1**), **HER3** and **HER4**.

- HER2, the preferred heterodimerization partner of the other HER receptors, does not have a ligand and is **activated** by

  - **overexpression** and **homodimerization**, or

  - **ligand-mediated stimulation of another HER receptor by heterodimerization**.



Introduction: HER2-positive Breast Cancer

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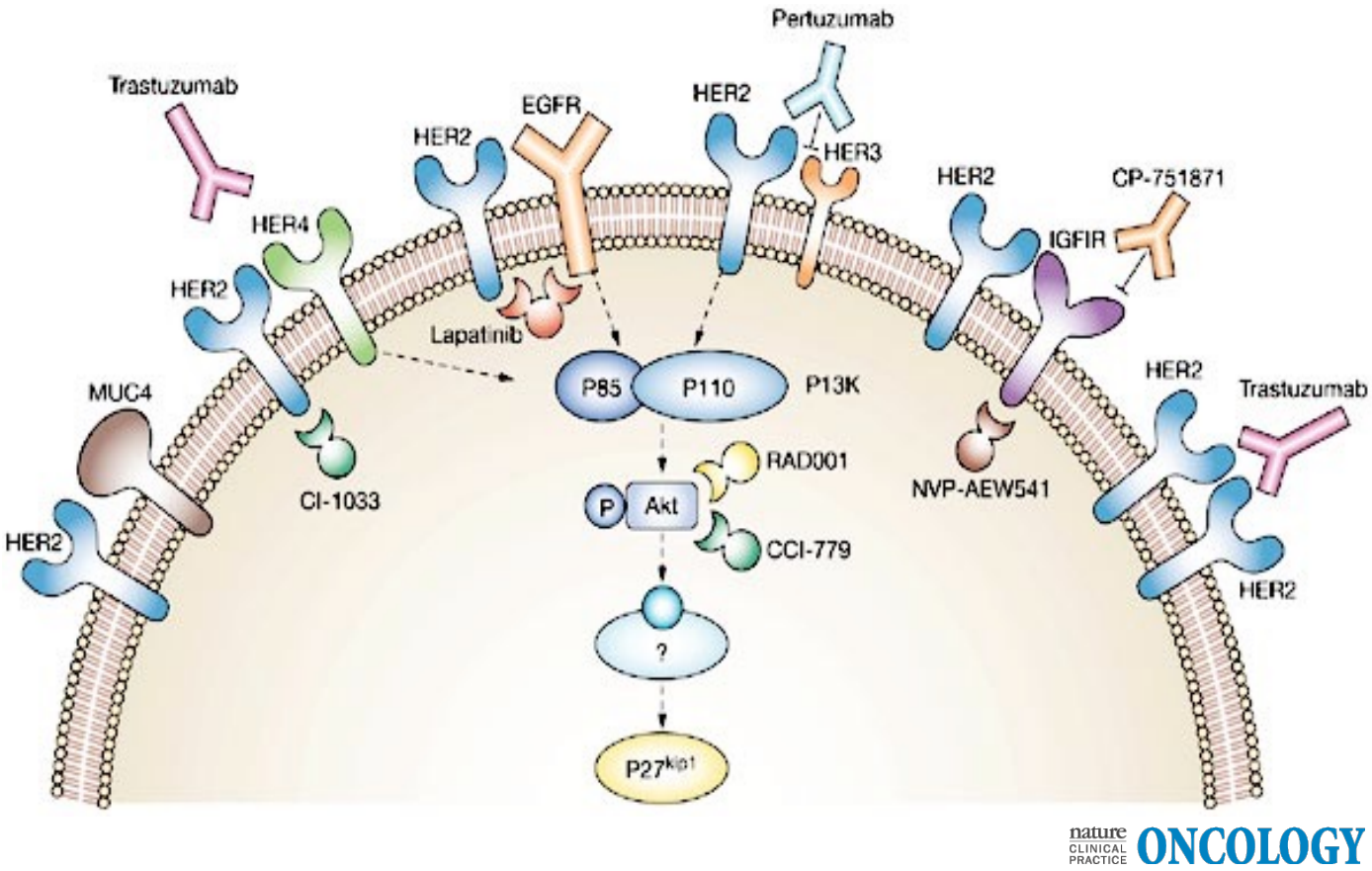
- In **HER2+ breast cancer**, the cancer cells have an abnormally high number of HER2 genes per cell thus a **higher number of HER2 protein on the surface of these cancer cells**. This is called HER2 protein over-expression (HER2+).

- Approximately **20% of breast cancer patients have tumors that are HER2+** . This abnormality in HER2 production can occur in many other types of cancer.

Approved Targeted-Therapies for Her2+ Breast Cancer



✦ These targeted therapies have shown significant clinical benefit.

✦ However, a large percentage of patients with advanced HER2+ BC eventually relapse after treatment, suggesting that **tumors acquire or intrinsically possess mechanisms for escape from HER2 inhibition**.

Example: Combinations of Targeted Therapies in Breast Cancer

The pipeline of network analysis consists of 4 main steps:

4. Construction of **combinations of interventions** with OCSANA and identification of optimal therapeutic interventions.

3. **Identification of a Core Signal Transduction Network of Dysregulated Pathways in HER2+ BC**. Assembling of a **comprehensive network** for the set of functionally enriched genes, their transcription factor and master regulators.

2. Identification of **transcription factors** and **master regulators** responsible for the expression patterns observed in the functionally enriched gene set identified on step 1.

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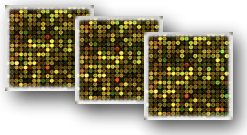
Stage I
Functionally enriched set of genes



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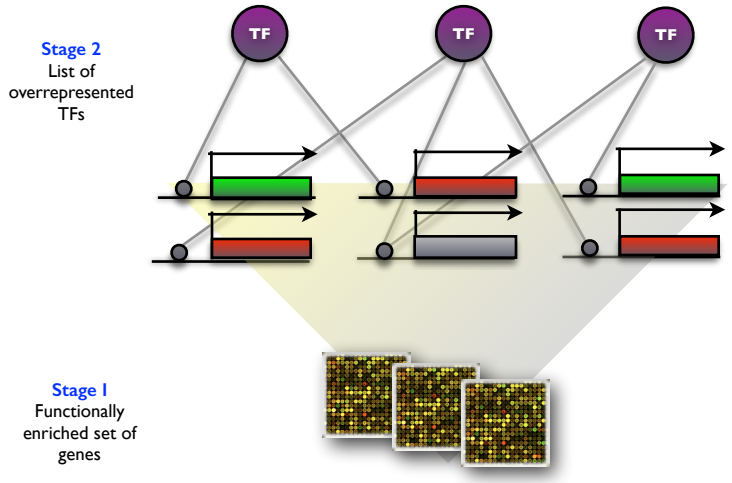

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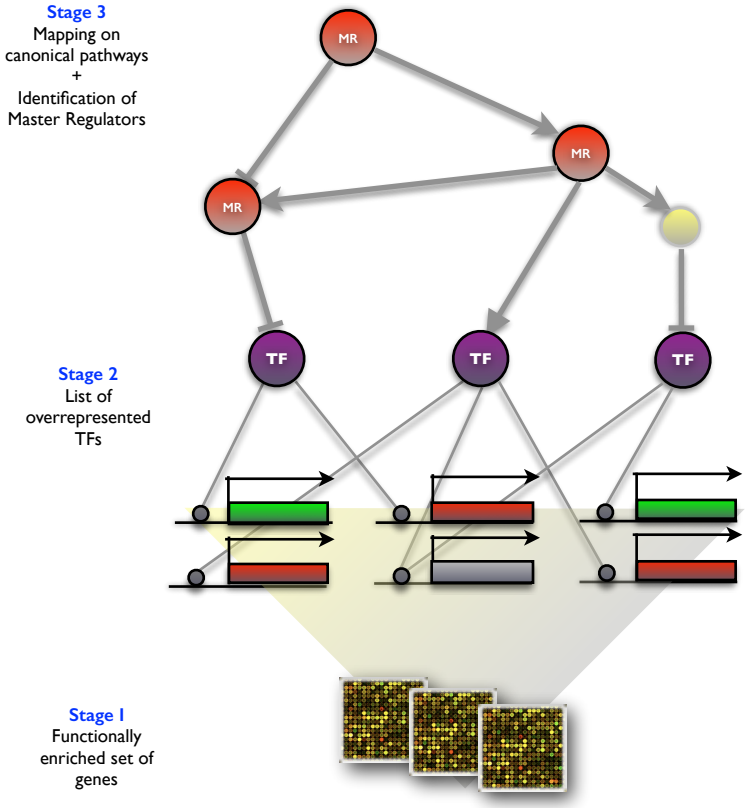

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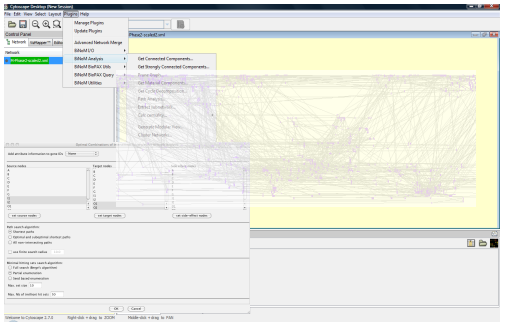
Stage 4
Identification of Optimal Combinations of Interventions from Network Analysis

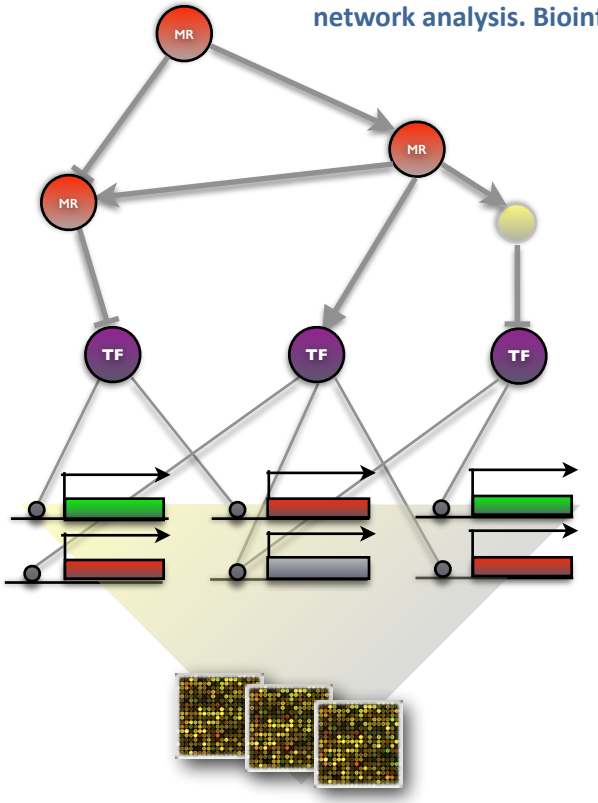


OCSANA

Vera-Licona *et al.* OCSANA: optimal combinations of interventions from network analysis. Bioinformatics, 2013.

Stage 3
Mapping on canonical pathways
+
Identification of Master Regulators

Stage 2
List of overrepresented TFs



Stage I
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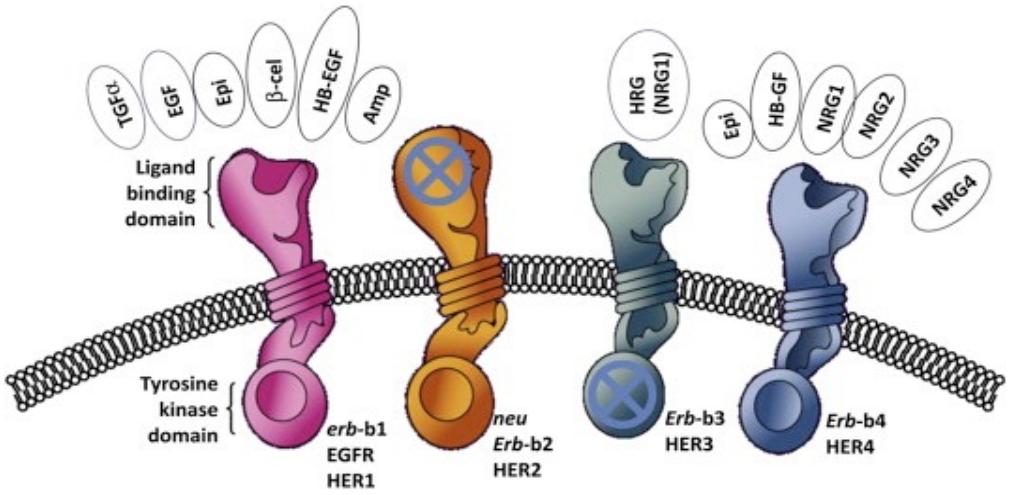
Family of HER receptors and associated activating ligands.



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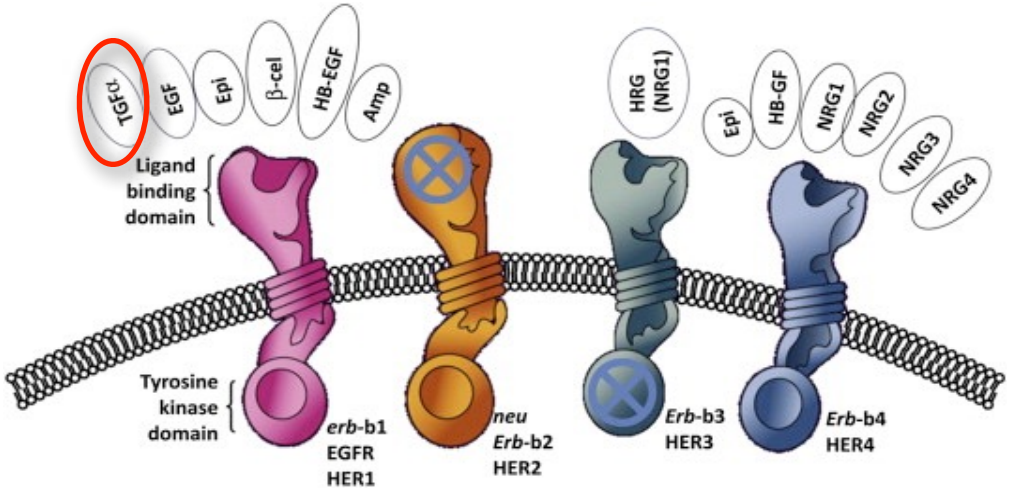

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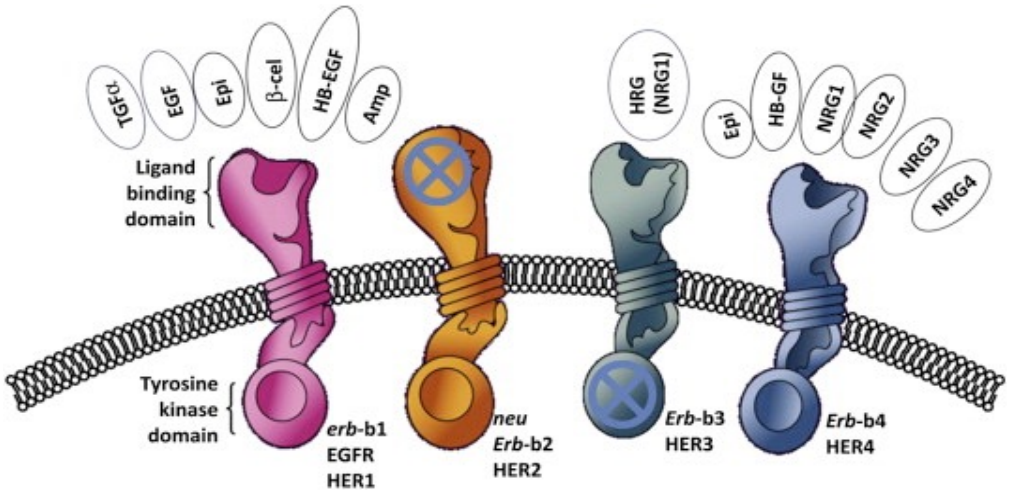

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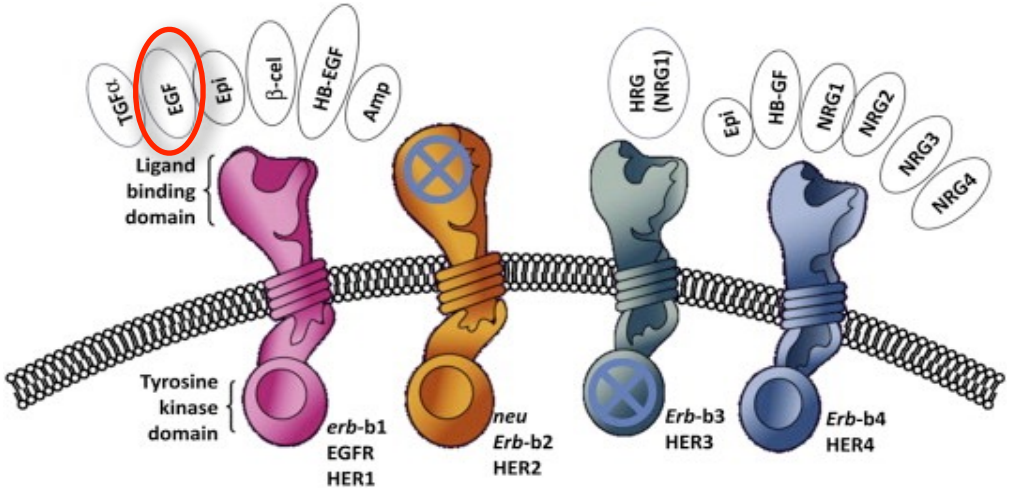

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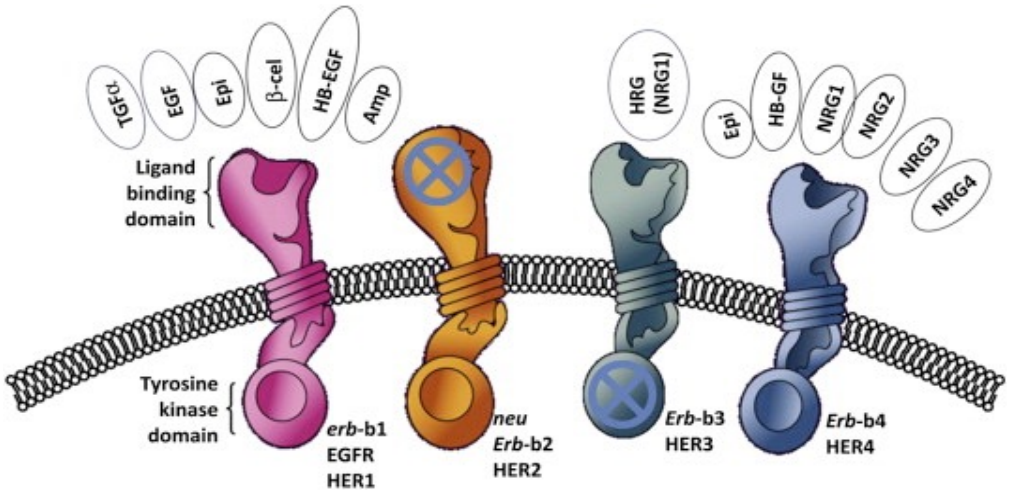

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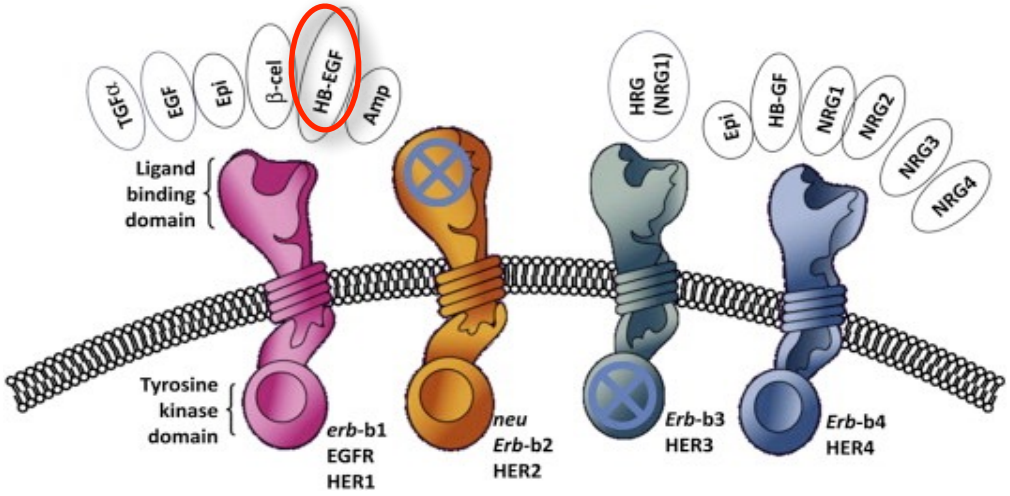

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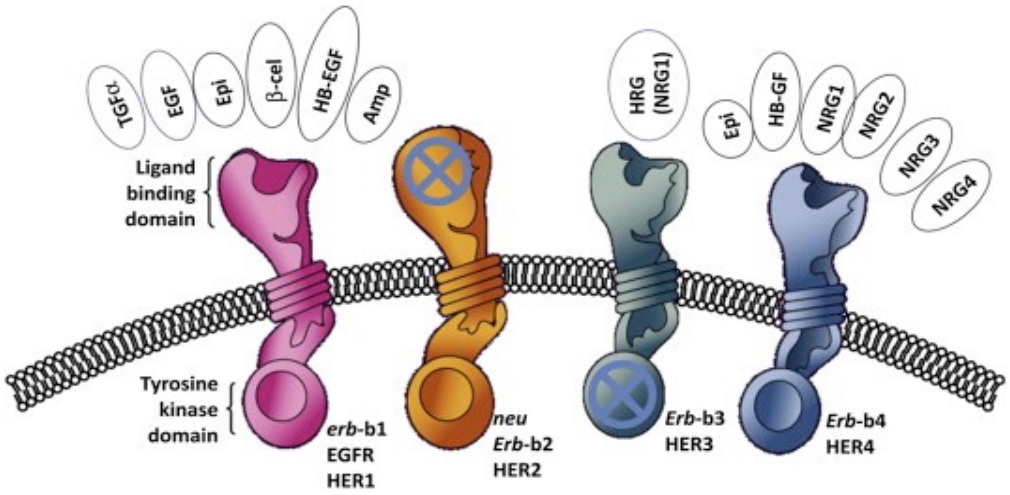

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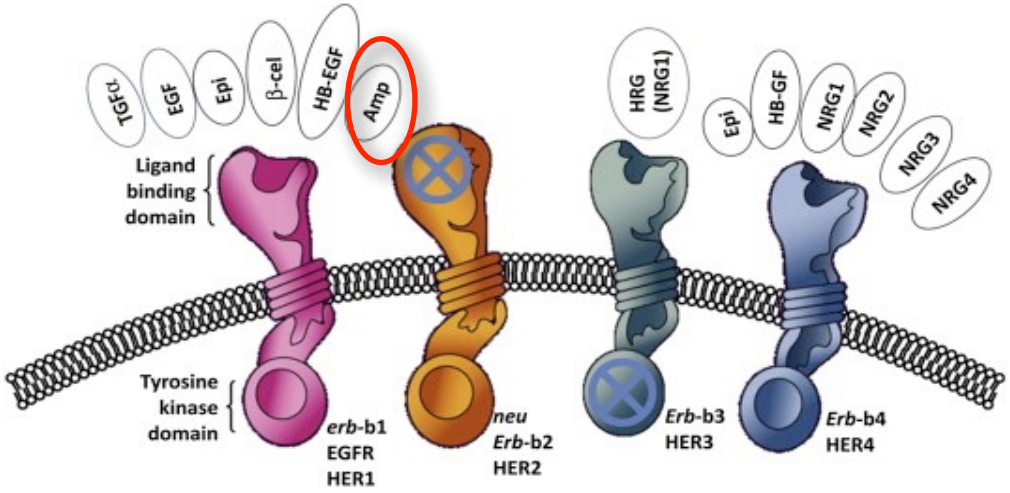

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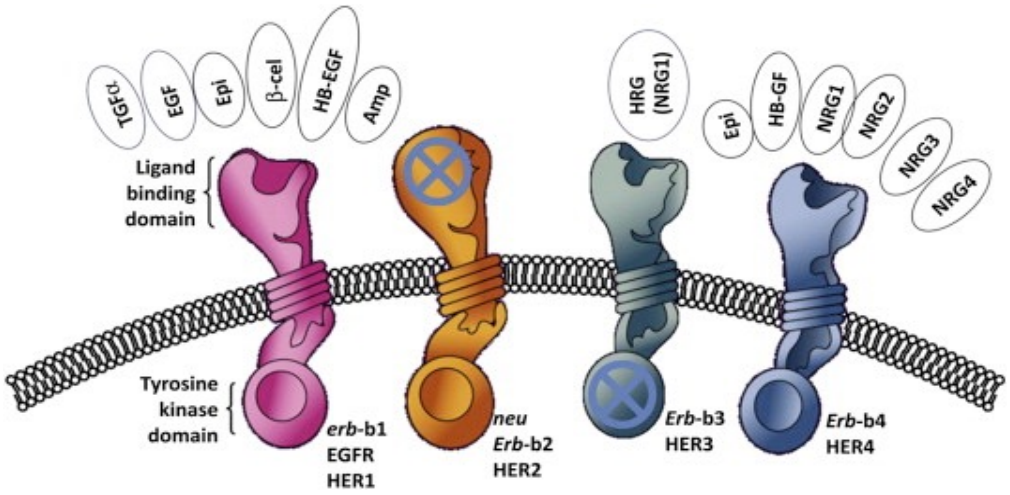

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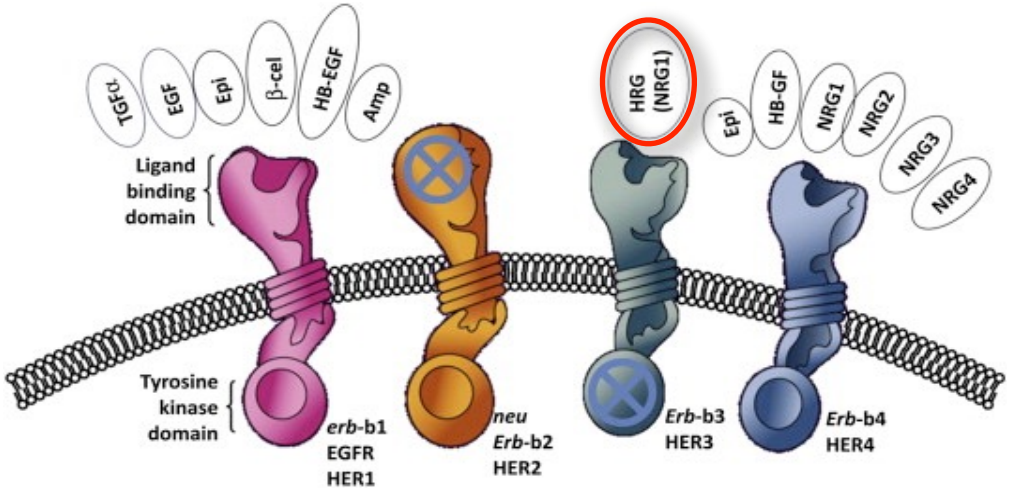

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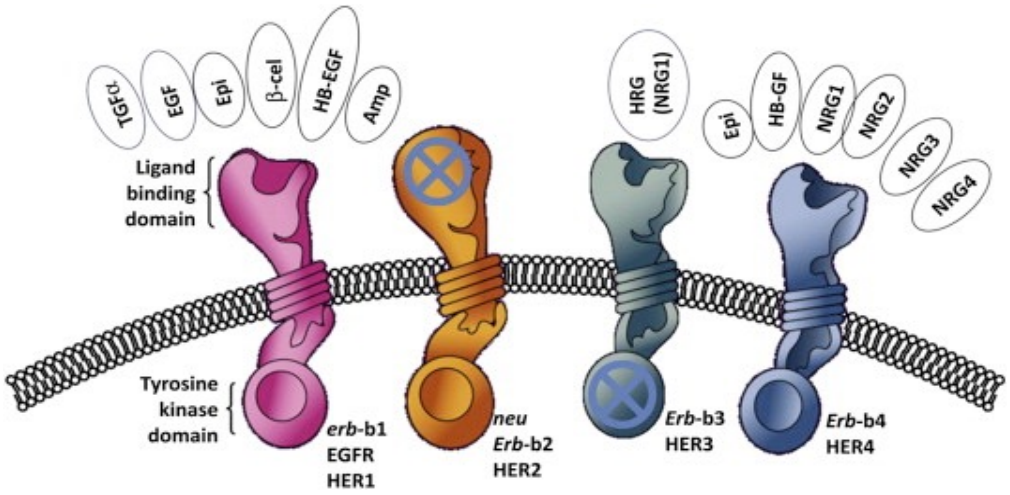

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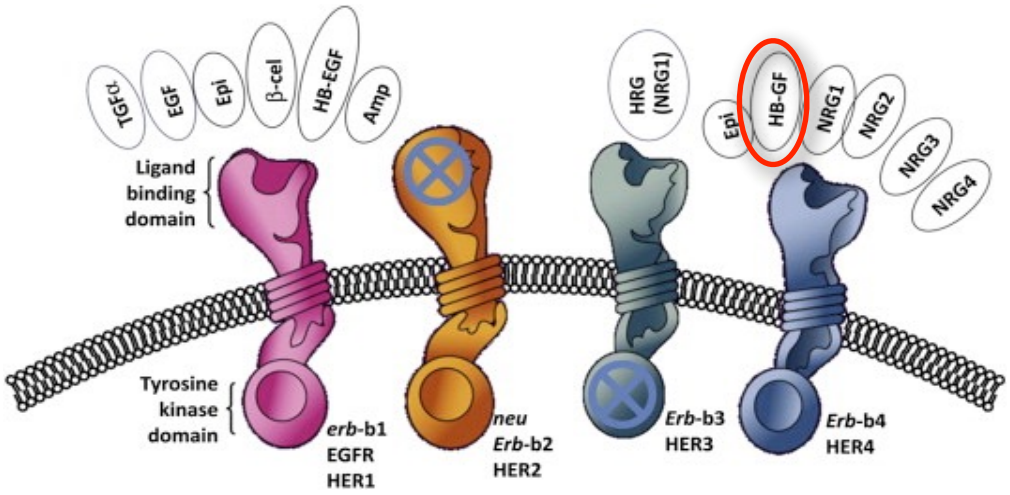

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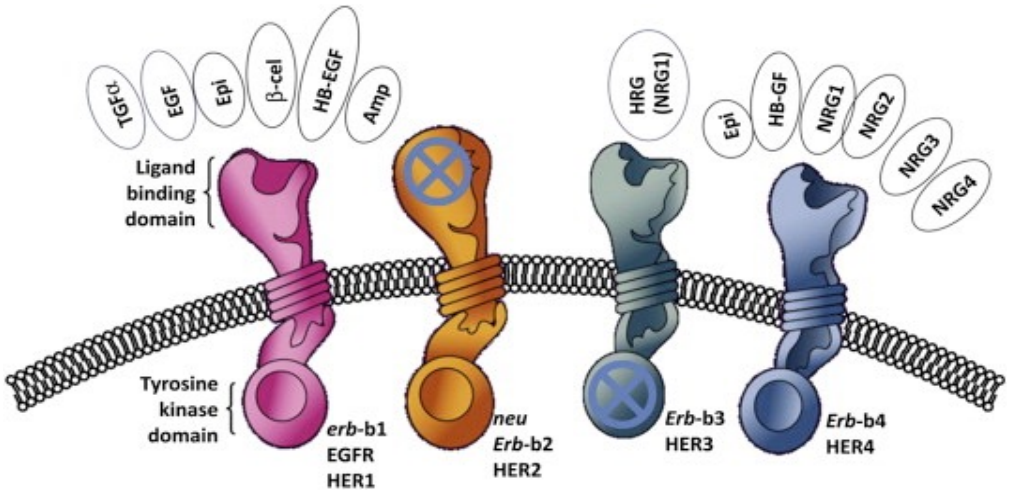

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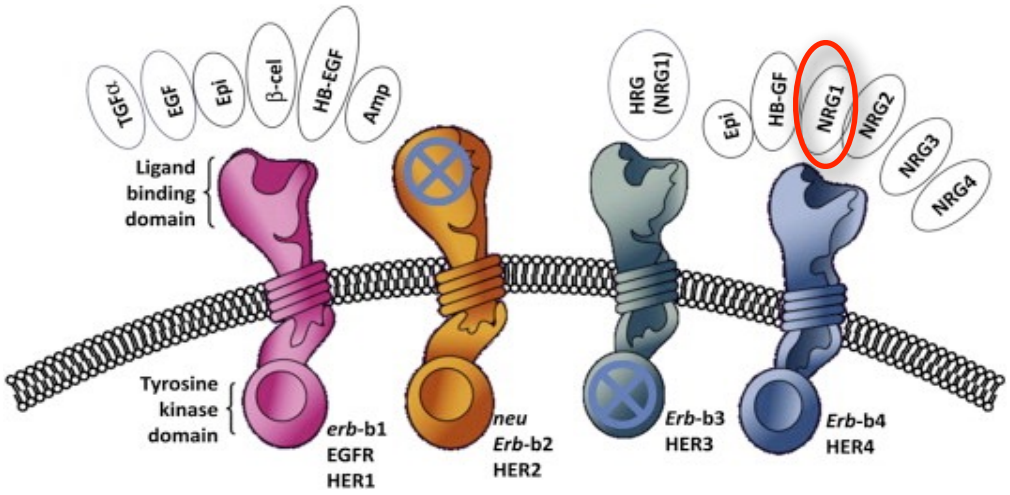

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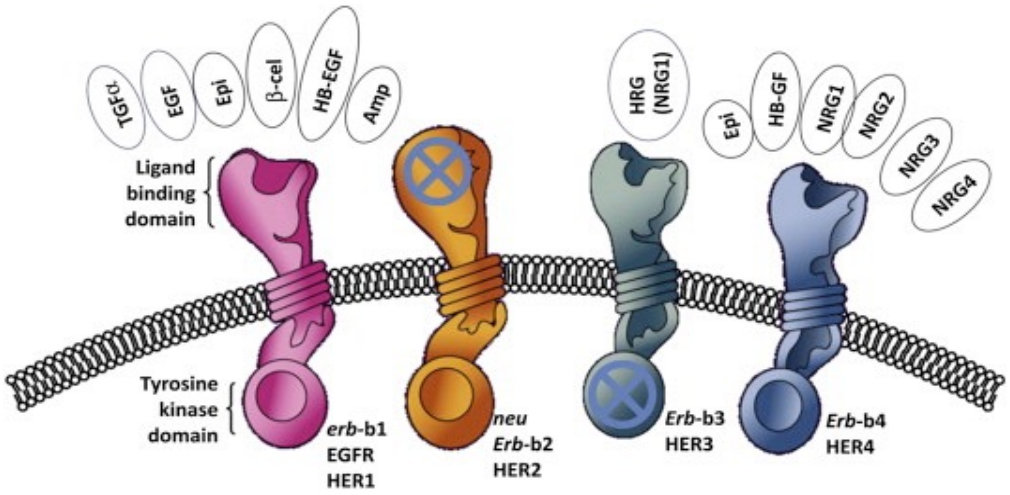

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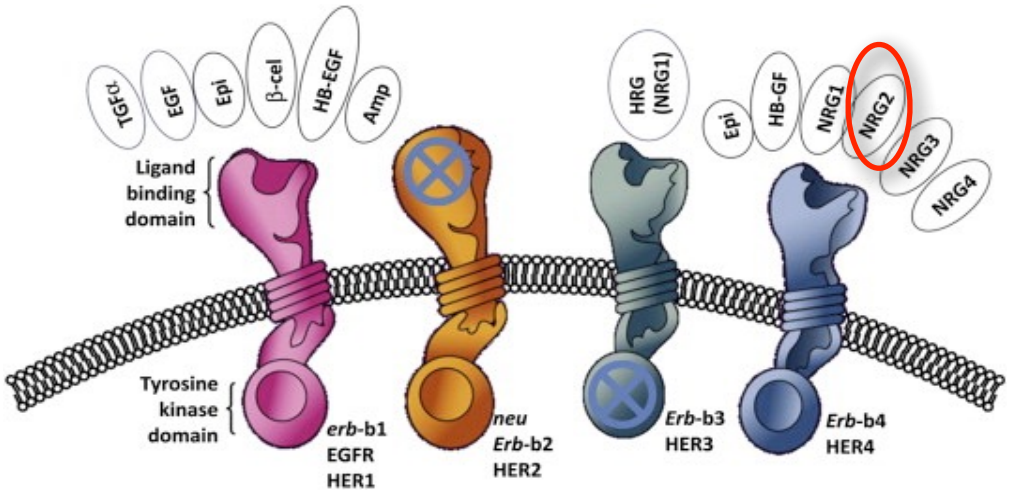

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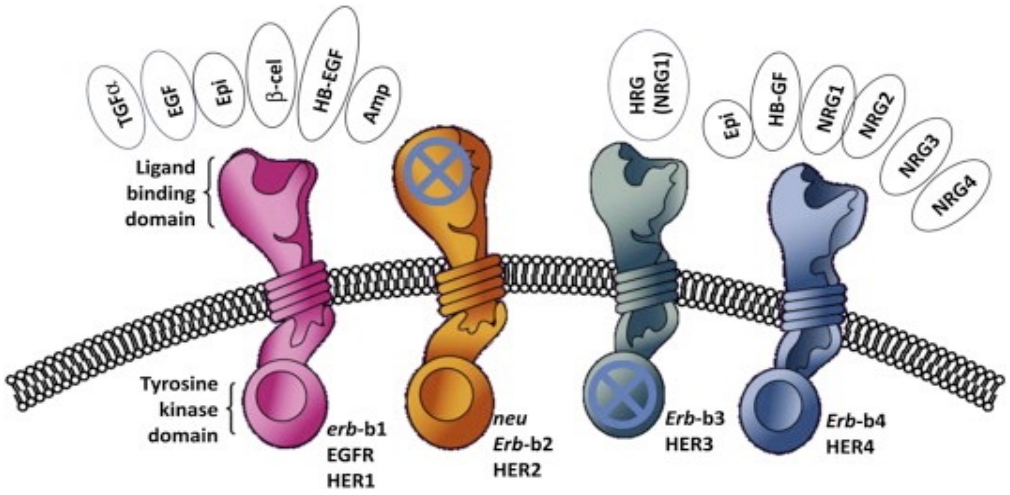

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1) Does ErbB2 has access to all the OFTEN genes that are highly dysregulated in HER2?
YES. Thus it is natural to consider it as THE guilty gene causing the disease.
Found 3657 elementary paths and 208 elementary nodes if we consider ANSIP of length at most 10.

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Found 17 optimal CIs. The only CI of size 1 is ErbB2 itself and the other CIs require to be of size at least 3.

However we know that this view of the problem might be reduced as resistance to treatment targeting ErbB2 alone, might occur.

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4) We simulated an scenario where both drugs, **Trastuzumab** and **Lapatinib** are combined. We aim to **reveal complementary intervention strategies** to ensure all the pathways are intervened.

We applied OCSANA algorithm to our network top 3 master regulators.
Found 36 CIs of size at least three. Here is and example with one of the most prevalent interventions suggested:

Intervention Set	Size	Score
[SRC, PIP3, ERK2]	3	6654.37

Literature Validation (PIP3)

PNAS

Feedback upregulation of HER3 (ErbB3) expression and activity attenuates antitumor effect of PI3K inhibitors

Anindita Chakrabarty[a], Violeta Sánchez[a], María G. Kuba[b], Cammie Rinehart[a], and Carlos L. Arteaga[a,c,d,1]

Departments of [a]Medicine, [b]Pathology, and [c]Cancer Biology and [d]Breast Cancer Research Program, Vanderbilt–Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN 37232

Edited by Peter K. Vogt, The Scripps Research Institute, La Jolla, CA, and approved February 4, 2011 (received for review December 2, 2010)

We examined the effects of an inhibitor of PI3K, XL147, against human breast cancer cell lines with constitutive PI3K activation. clinical development; it exhibits an IC_{50} against WT and mutant p110α of approximately 40 nM (12).

Upon inhibition of PI3K, the cell can maintain some level of PIP3 through partial restoration of HER3 phosphorylation which may limit the net inhibitory effect of the PI3K inhibitor thus suggesting that additional blockage of PIP3 is indeed necessary (for example via the antagonist PTEN).

Additionally in [Abramson et al. CCR 2011:17(5)] is suggested, as with one of our predicted combinations that, to inhibit the HER2 network and its output PI3K/Akt another rational therapeutic combination is trastuzumab or lapatinib plus a HER3 or an AKT inhibitor.

Literature Validation (SRC)

Nat Med. 2011 Apr;17(4):461-9. doi: 10.1038/nm.2309. Epub 2011 Mar 13.

Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways.

Zhang S, Huang WC, Li P, Guo H, Poh SB, Brady SW, Xiong Y, Tseng LM, Li SH, Ding Z, Sahin AA, Esteva FJ, Hortobagyi GN, Yu D.

Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Abstract

Trastuzumab is a successful rationally designed ERBB2-targeted therapy. However, about half of individuals with ERBB2-overexpressing breast cancer do not respond to trastuzumab-based therapies, owing to various resistance mechanisms. Clinically applicable regimens for overcoming trastuzumab resistance of different mechanisms are not yet available. We show that the nonreceptor tyrosine kinase c-SRC (SRC) is a key modulator of trastuzumab response and a common node downstream of multiple trastuzumab resistance pathways. We find that SRC is activated in both acquired and de novo trastuzumab-resistant cells and uncover a novel mechanism of SRC regulation involving dephosphorylation by PTEN. Increased SRC activation conferred considerable trastuzumab resistance in breast cancer cells and correlated with trastuzumab resistance in patients. Targeting SRC in combination with trastuzumab sensitized multiple lines of trastuzumab-resistant cells to trastuzumab and eliminated trastuzumab-resistant tumors in vivo, suggesting the potential clinical application of this strategy to overcome trastuzumab resistance.

In this work the authors showed how SRC, a non-membrane tyrosine kinase, is a common signaling node in trastuzumab resistance caused by different mechanisms in HER2-positive breast cancers. A SRC inhibitor restored trastuzumab sensitivity in vitro and in mouse tumor models, suggesting a new way to tackle drug resistance in breast tumors.

Literature Validation (ERK)

Cancer Therapy: Preclinical

Clinical Cancer Research

Dual mTORC1/2 and HER2 Blockade Results in Antitumor Activity in Preclinical Models of Breast Cancer Resistant to Anti-HER2 Therapy

Celina García-García[1], Yasir H. Ibrahim[1], Violeta Serra[1], Maria Teresa Calvo[1], Marta Guzmán[1], Judit Grueso[1], Claudia Aura[2], José Pérez[1], Katti Jessen[3], Yi Liu[3], Christian Rommel[3], Josep Tabernero[1], José Baselga[4,5], and Maurizio Scaltriti[4,5]

Abstract

Purpose: The PI3K/Akt/mTOR pathway is an attractive target in HER2-positive breast cancer that is refractory to anti-HER2 therapy. The hypothesis is that the suppression of this pathway results in sensitization to anti-HER2 agents. However, this combinatorial strategy has not been comprehensively tested in models of trastuzumab and lapatinib resistance.

Experimental Design: We analyzed *in vitro* cell viability and induction of apoptosis in five different cell lines resistant to trastuzumab and lapatinib. Inhibition of HER2/HER3 phosphorylation, PI3K/Akt/mTOR, and extracellular signal-regulated kinase (ERK) signaling pathways was evaluated by Western blotting. Tumor growth inhibition after treatment with lapatinib, INK-128, or the combination of both agents was evaluated in three different animal models: two cell-based xenograft models refractory to both trastuzumab and lapatinib and a xenograft derived from a patient who relapsed on trastuzumab-based therapy.

Results: The addition of lapatinib to INK-128 prevented both HER2 and HER3 phosphorylation induced by INK-128, resulting in inhibition of both PI3K/Akt/mTOR and ERK pathways. This dual blockade produced synergistic induction of cell death in five different HER2-positive cell lines resistant to trastuzumab and lapatinib. *In vivo*, both cell line–based and patient-derived xenografts showed exquisite sensitivity to the antitumor activity of the combination of lapatinib and INK-128, which resulted in durable tumor shrinkage and exhibited no signs of toxicity in these models.

Conclusions: The simultaneous blockade of both PI3K/Akt/mTOR and ERK pathways obtained by combining lapatinib with INK-128 acts synergistically in inducing cell death and tumor regression in breast cancer models refractory to anti-HER2 therapy. *Clin Cancer Res; 1–10. ©2012 AACR.*

Current & Future Work

UCONN HEALTH
CENTER FOR QUANTITATIVE MEDICINE

- **Data Integration into Cellular Signaling Networks for Combinations of Targeted Therapies in Disease Networks**
  - Integration of high through-put data to better **prioritize** combinations of interventions
  - Integration of data from **drugome** and **drug-target interactions**

- **Dynamical Modeling**

- Implement signal propagation functions into network's edges to better quantify **information transduction in signaling networks** (signal propagation).

Acknowledgements

Institut Curie

Emmanuel Barillot

Eric Bonnet

Andrei Zinovyev