Completing signaling networks by abductive reasoning with perturbation experiments

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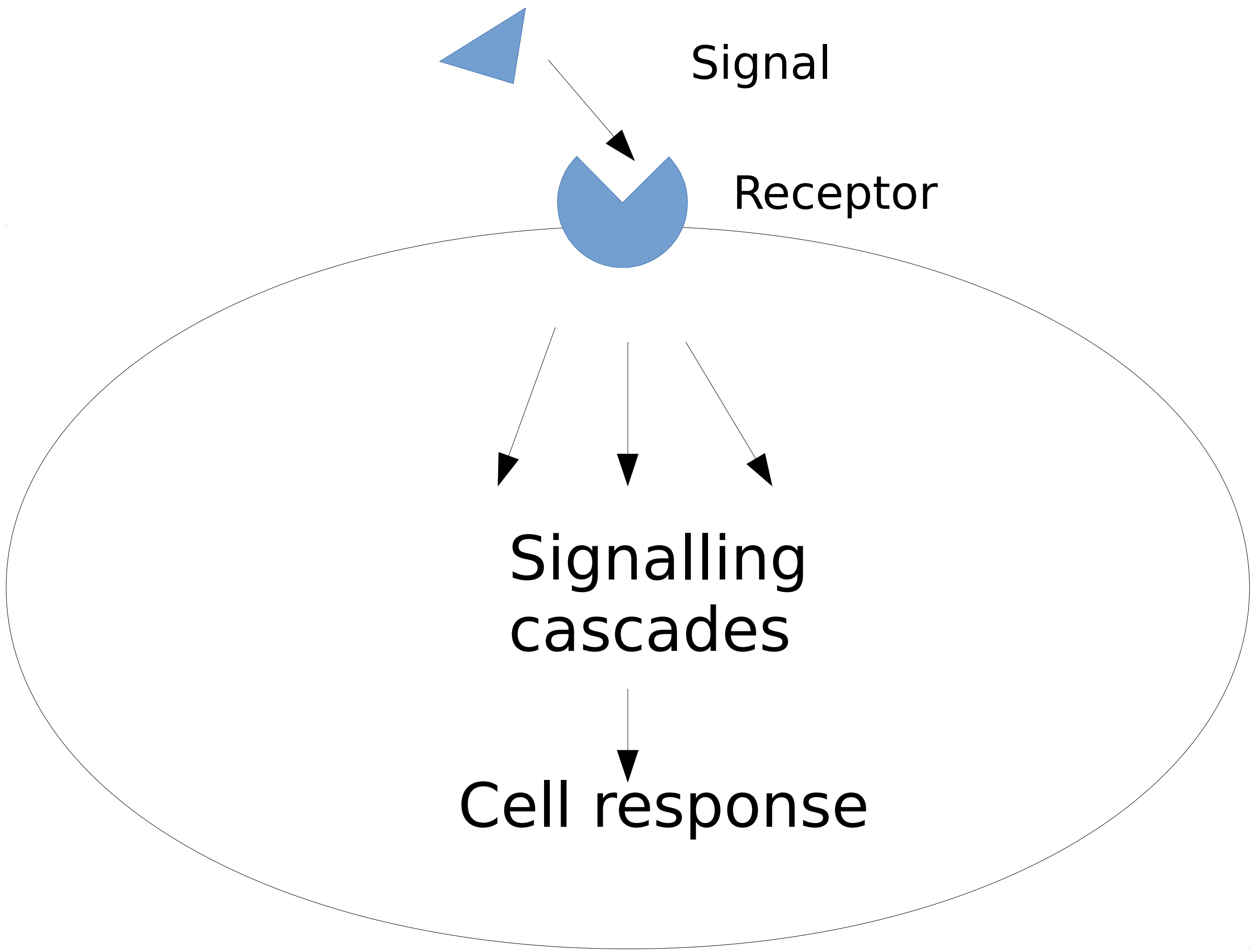
Context

➔ Signaling networks model the **flow of information** in cells



Context

➔ Signaling networks model the **flow of information** in cells

➔ With the rise of available **high-throughput data,** networks always **larger** and more **complex**

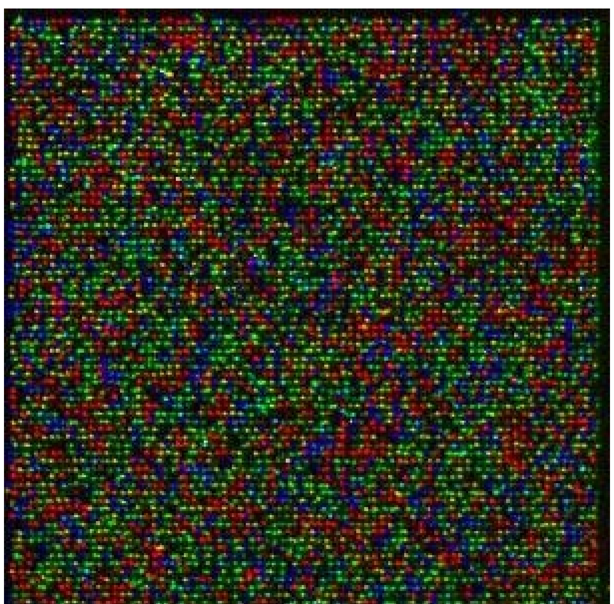


Image from *http://www.bio-itworld.com*

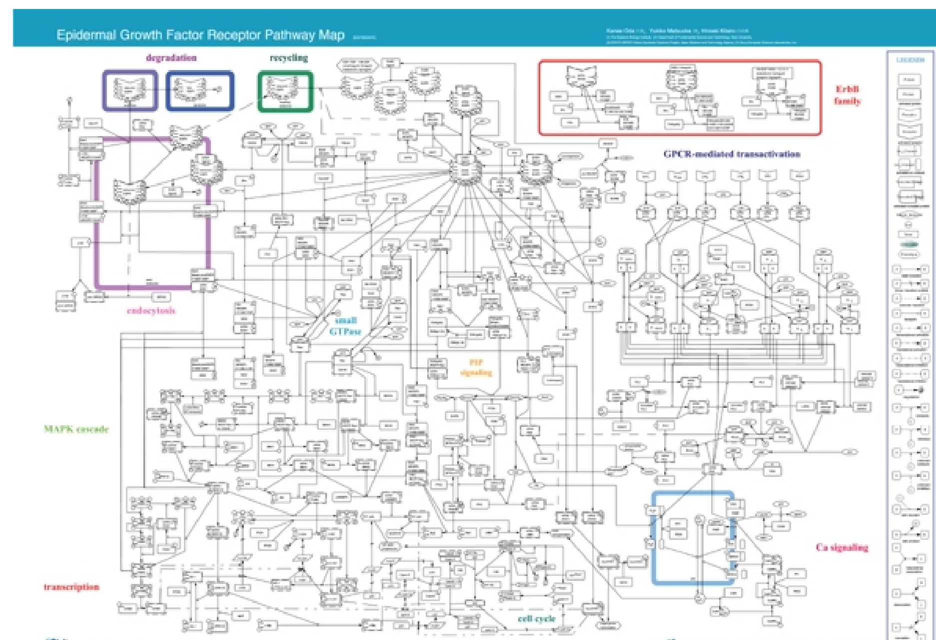


Image from Oda *et al. A comprehensive pathway map of epidermal growth factor receptor signaling,* MSB, 2005

Context

- ➔ Signaling networks model the **flow of information** in cells
- ➔ With the rise of available **high-throuput data,** networks always **larger** and more **complex**
- ➔ **Automatic methods** based on Systems Biology **standards** are necessary for their **analysis**

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- ➔ **Automatic methods** based on Systems Biology **standards** are necessary for their **analysis**

In particular, methods that allow to **complete** signaling networks using **experimental results**

The completion problem

➔ Take as input an **interaction graph** and steady-state shift or perturbation **experiment results**

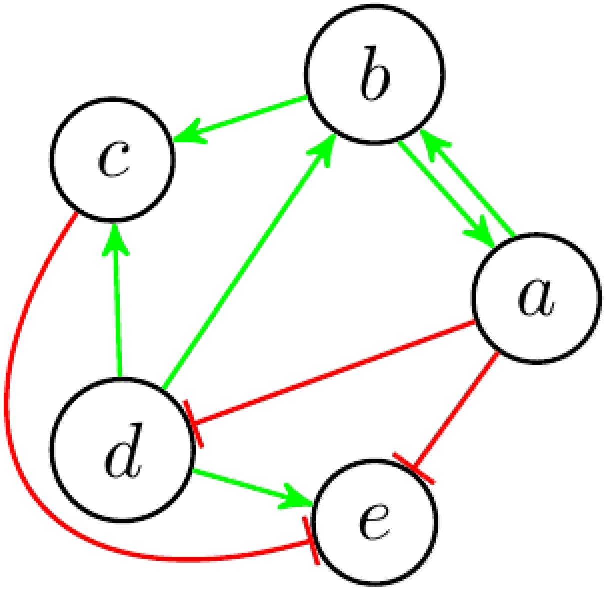

Image from Gebser *et al. Repair and Prediction (under Inconsistency) in Large Biological Networks with Answer Set Programming,* KR, 2010

The completion problem

- ➔ Take as input an **interaction graph** and steady-state shift or perturbation **experiment results**

- ➔ For every experimental result, **check** if the result can be **explained** by the graph

- ➔ If not, **find hypotheses** that **complete** the network so that the result can be explained

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➔ Different **semantics/frameworks** : signaling paths (Klamt et al. 2006), Sign Consistency Model (Siegel et al. 2006), Causality networks (Inoue et al. 2013, Yamamoto et al. 2014)

➔ Different **formalisms** : graph theory (Samaga et al. 2009), integer linear programming (Melas et al. 2013), answer set programming (Gebser et al. 2010), first-order logic (Inoue et al. 2013, Yamamoto et al. 2014)

Our contribution

A method that:

➔ Takes as input a **SBGN-AF** network and **perturbation experiments**

➔ Uses a **path definition** that extends signaling paths

➔ Realizes both explanation and completion task in the same **first-order logic abductive framework**

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Applied on the **FSHR-induced signaling network**

A standard: the SBGN-AF language

- ➔ The **Systems Biology Graphical Notation Activity Flow** langage is a **standard** to represent biological networks
- ➔ **Widely used** in a number of softwares (e.g. CellDesigner) and databases (e.g. BioModels)
- ➔ It **extends** classical **interaction graphs** with logical operators

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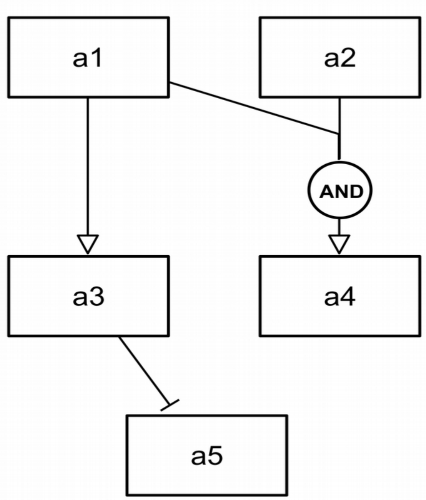
$\mathcal{S}$



$tran(\mathcal{S})$

$activity(a1)$	
$activity(a2)$	
$activity(a3)$	$stimulates(a1, a3)$
$activity(a4)$	$stimulates(o1, a4)$
$activity(a5)$	$inhibits(a3, a5)$
$and(o1)$	
$input(a1, a2, o1)$	

Translation proposed in: Rougny *et al. Analizing SBGN-AF Networks using Normal Logic Programs,* In Handbook Logical Modeling of Biological Systems, 2014

Paths in SBGN-AF maps

➔ We introduce two predicates :

stimulates•(A,B) : there is a positive path between *A* and *B*

inhibits•(A,B) : there is a negative path between *A* and *B*

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➔ Two predicates defined by 12 **transitivity rules** formalized in FOL

➔ **No constraints**: *stimulates•(A,B)*∧*inhibits•(A,B)* is consistent

➔ Takes into account **logical operators**

Paths in SBGN-AF maps

General axioms

$$stimulates(A, B) \rightarrow stimulates^{\bullet}(A, B) \tag{1}$$

$$inhibits(A, B) \rightarrow inhibits^{\bullet}(A, B) \tag{2}$$

$$stimulates^{\bullet}(A, B) \wedge stimulates(B, C) \rightarrow stimulates^{\bullet}(A, C) \tag{3}$$

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Axioms for the AND operator

$$and(O) \wedge input(A, B, O) \wedge stimulates^{\bullet}(C, A) \wedge stimulates^{\bullet}(C, B) \rightarrow stimulates^{\bullet}(C, O) \tag{7}$$

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Axioms for the OR operator

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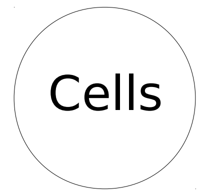
Formalization of experiments



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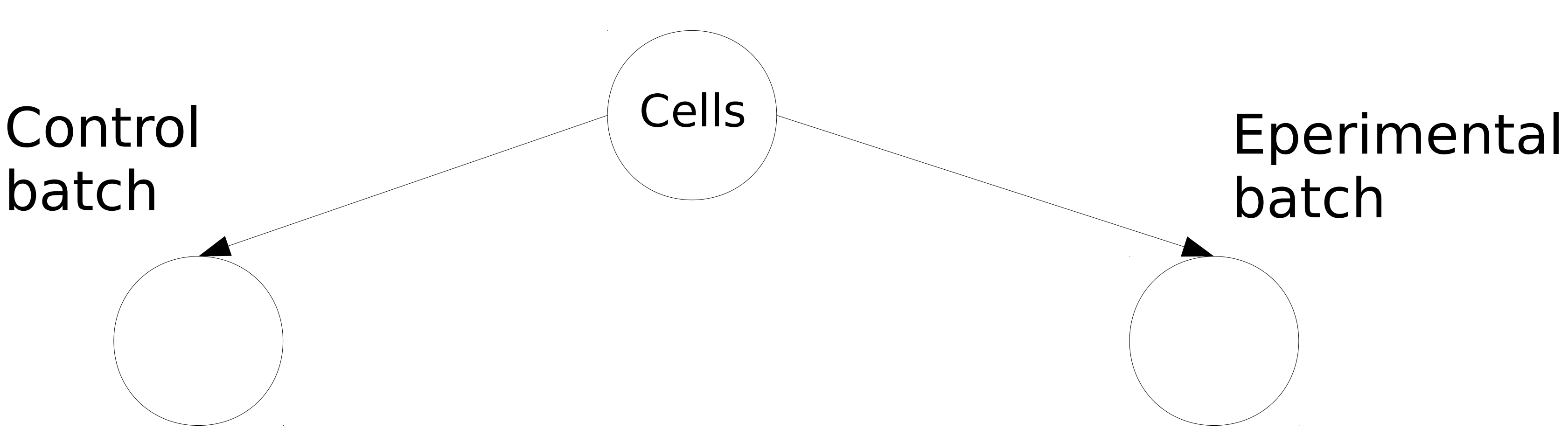

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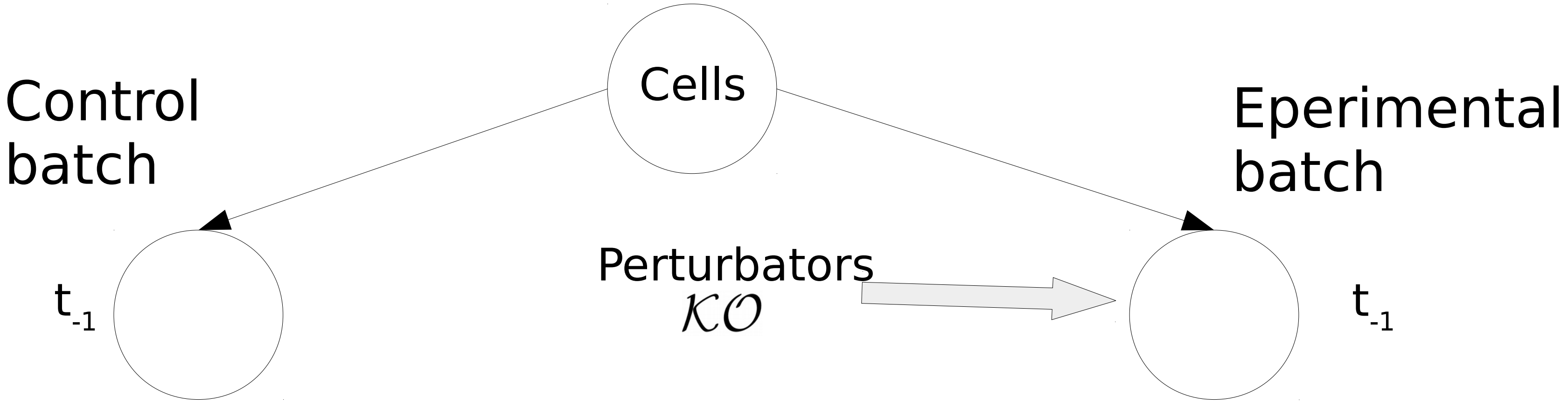

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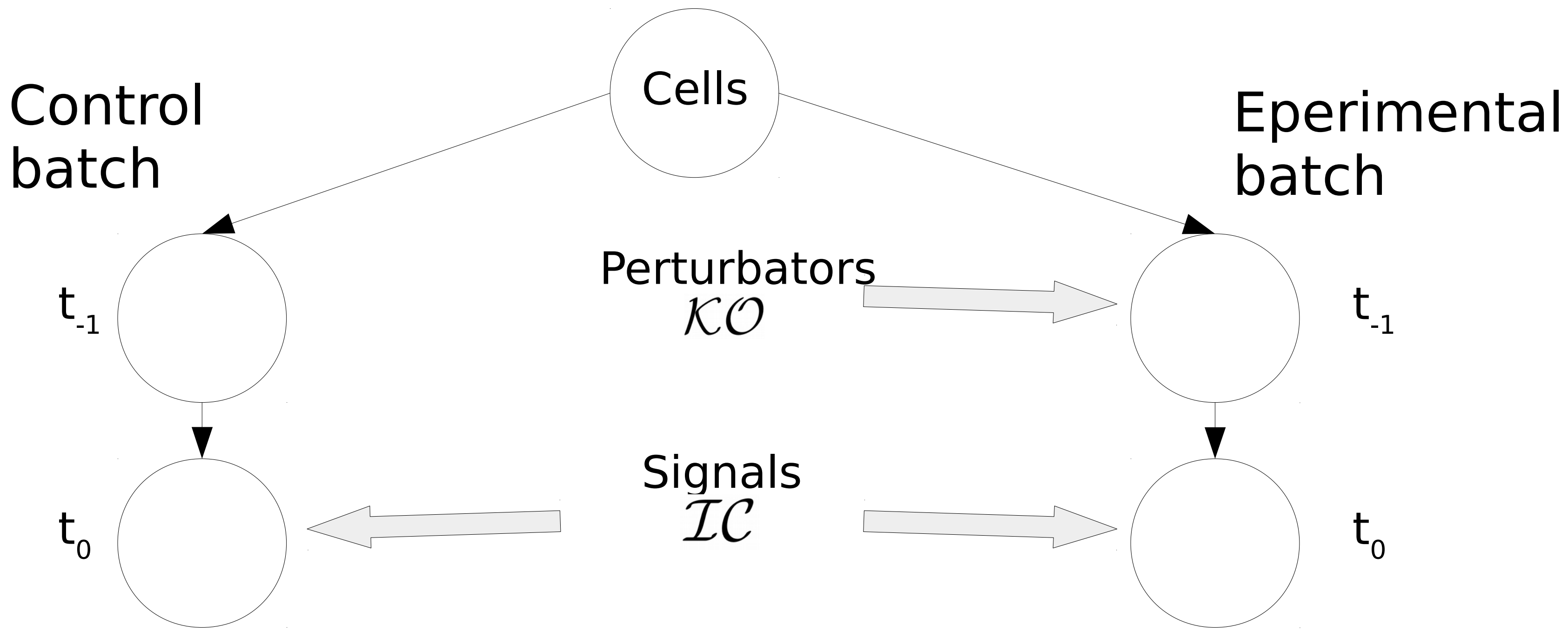

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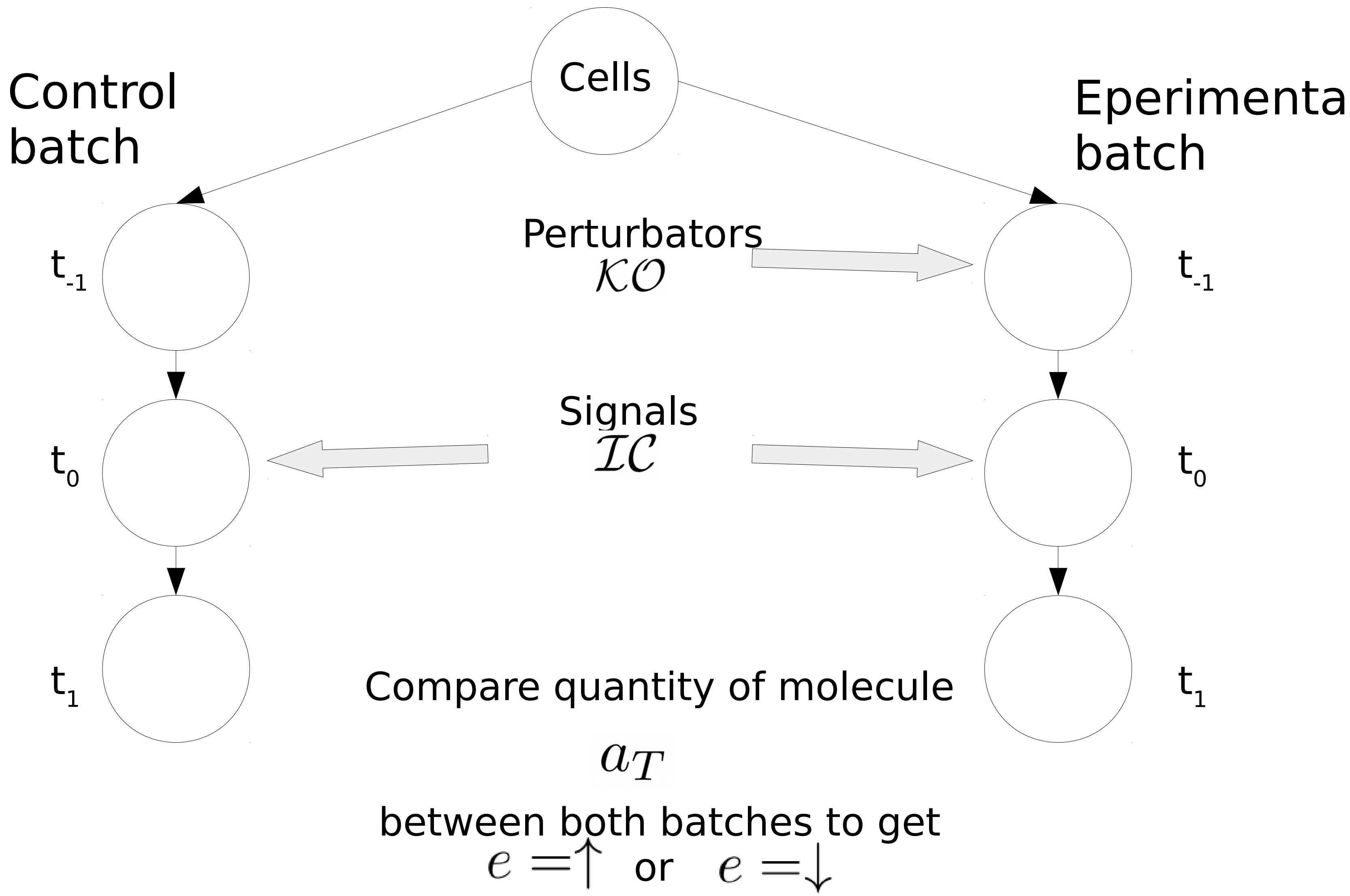

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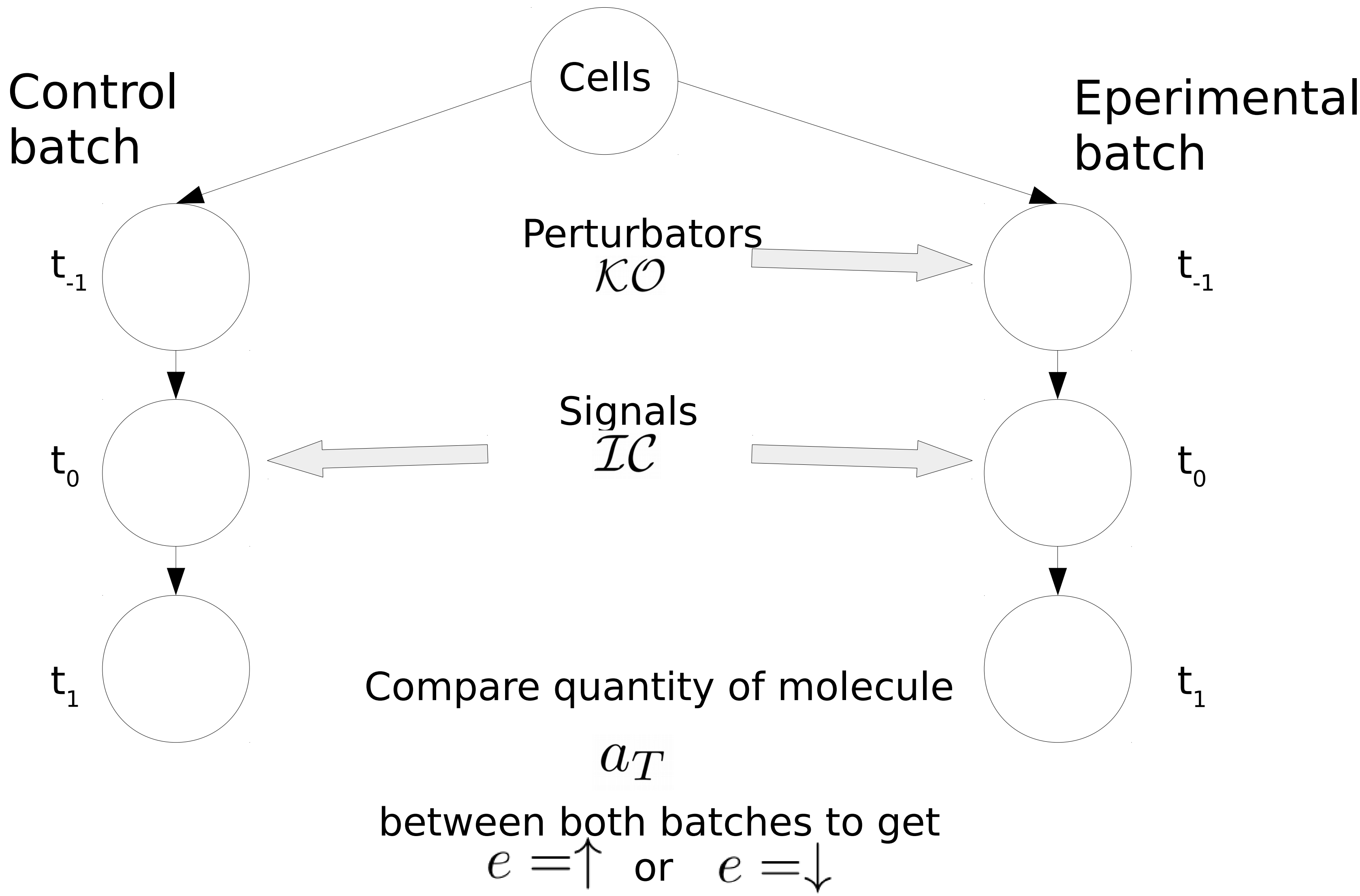

$$\mathcal{E} = (\mathcal{IC}, \mathcal{KO}, a_T, e)$$

Formalization of experiments

In terms of paths, $\mathcal{E} = (\mathcal{IC}, \mathcal{KO}, a_T, e)$ can be expressed as :

if $e = \uparrow$

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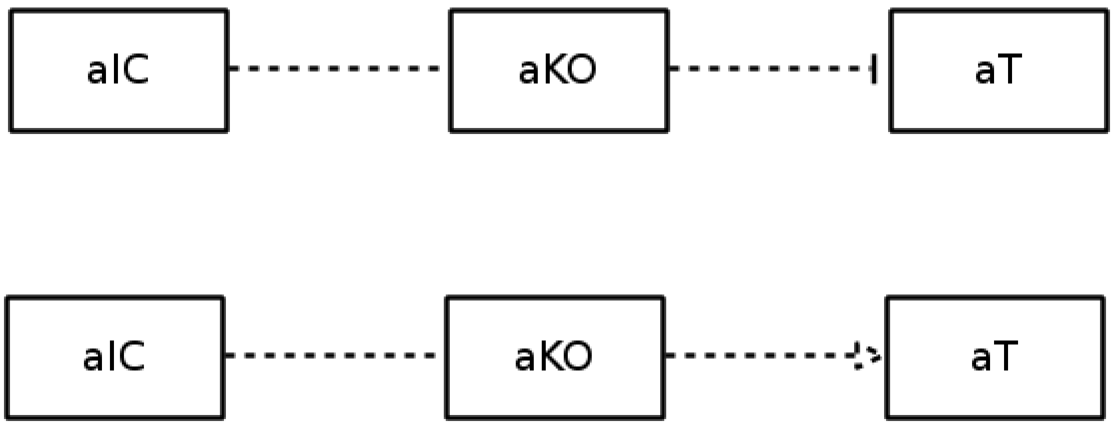

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$$O_{\mathcal{E}} = \bigvee_{a_{KO} \in \mathcal{KO}} \begin{bmatrix} (stimulates^{\bullet}(a_{\mathcal{IC}}, a_{KO}) \wedge inhibits^{\bullet}(a_{KO}, a_T)) \vee \\ (inhibits^{\bullet}(a_{\mathcal{IC}}, a_{KO}) \wedge stimulates^{\bullet}(a_{KO}, a_T)) \end{bmatrix} \text{ if } e = \uparrow;$$

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Abductive Setting

- $\mathcal{S}$ an SBGN-AF map
- $\mathcal{E} = (\mathcal{IC}, \mathcal{KO}, a_T, e)$ an experimental observation
- B the background theory formed of the translation of $\mathcal{S}$ into predicates and axioms (1-12)
- $O_{\mathcal{E}}$ the observation formalized from $\mathcal{E}$

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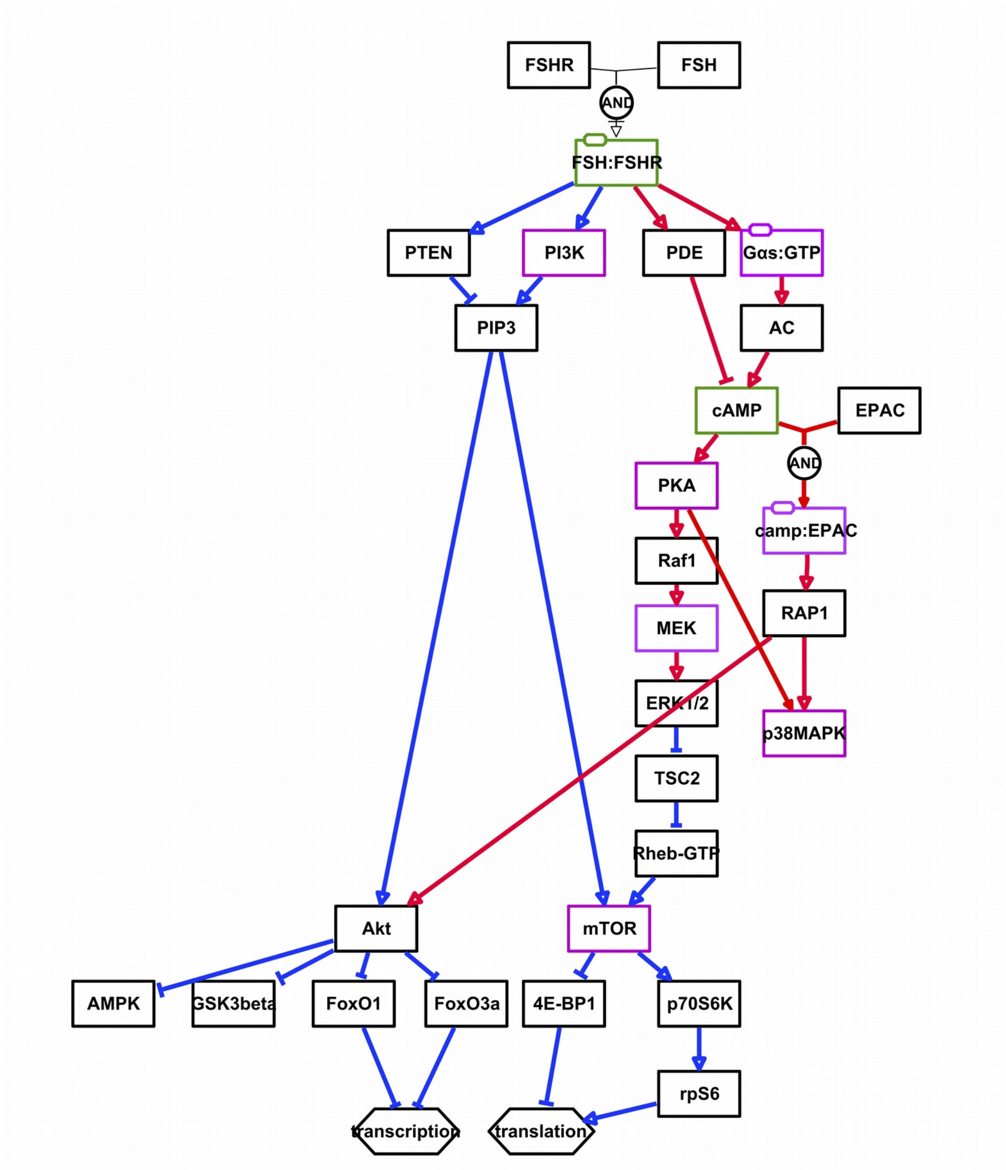
Then, solving both the explanation and the completion task consists in searching for **all minimal sets of arcs** H such that

$$B \cup H \models O_{\mathcal{E}} \text{ and } B \cup H \not\models \Box.$$

Application to the FSHR-induced network



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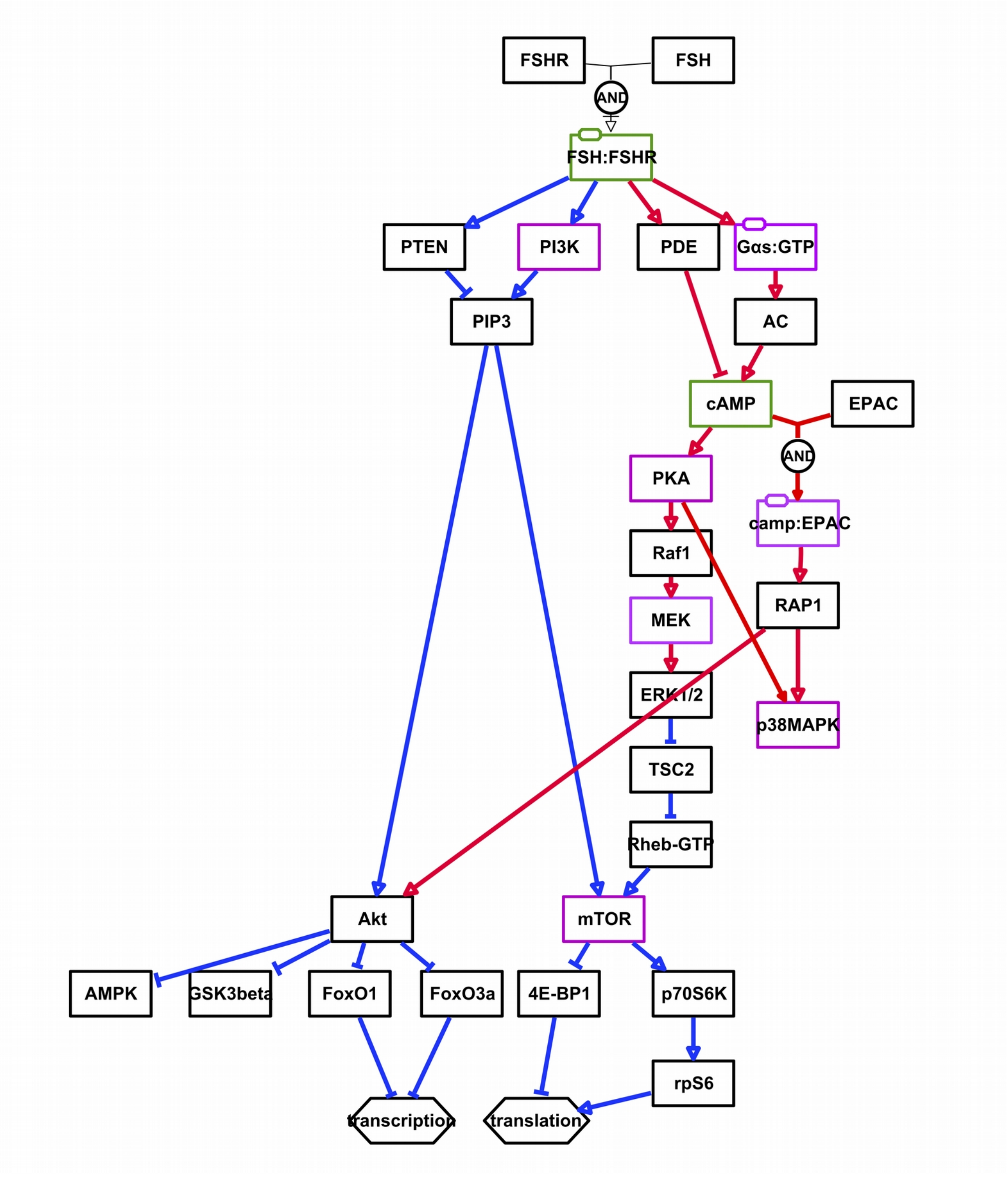

- ➔ Models the response of male and female sexual cells to FSH
- ➔ Two pathways: the PI3K and Gαs

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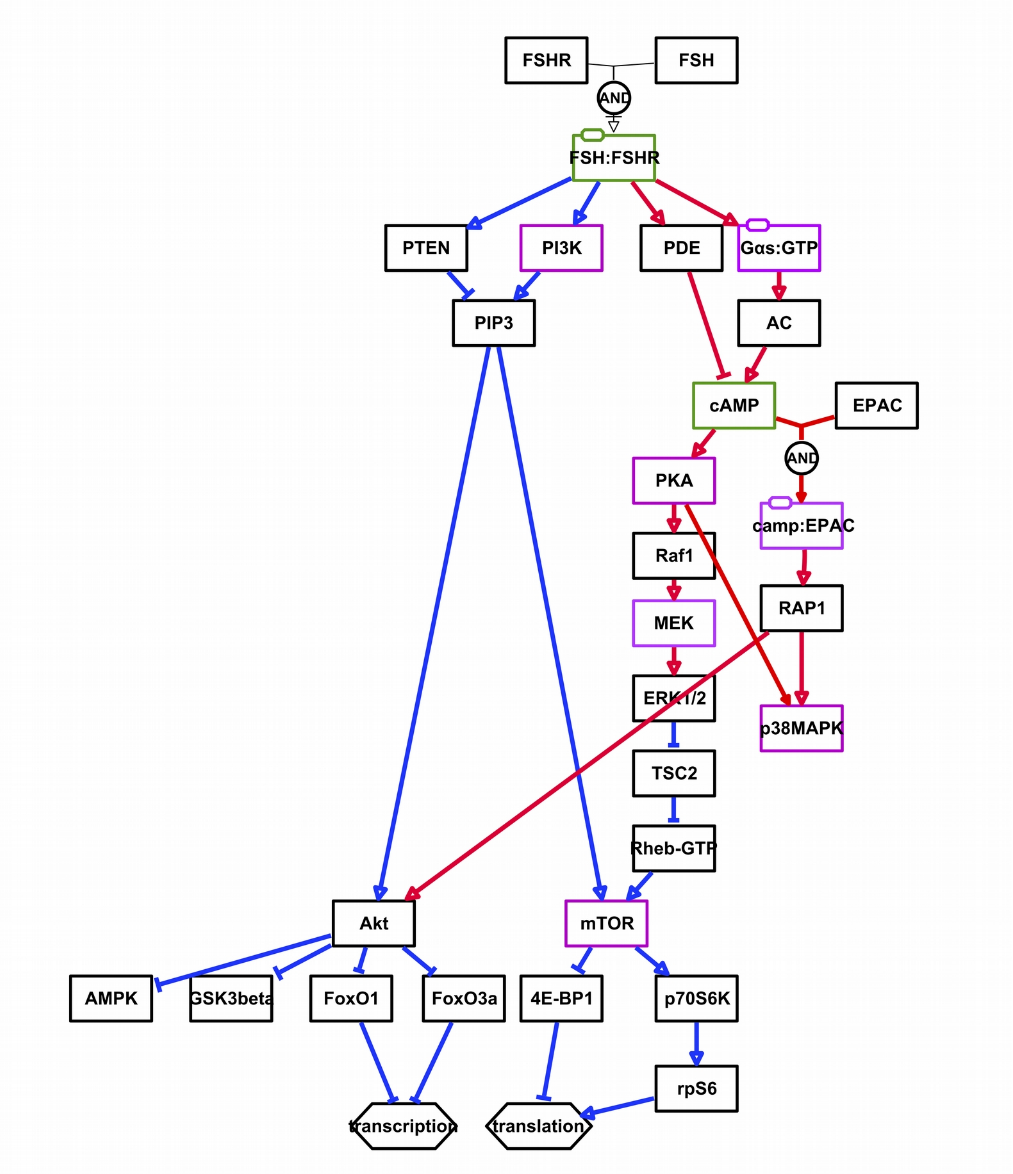

- ➔ Models the response of male and female sexual cells to FSH
- ➔ Two pathways: the PI3K and Gαs

- ➔ Dataset of **29 experimental results**
- ➔ Completion task realized with the consequence finding software **SOLAR**
- ➔ Among 29 experimental results,
  - ➔ **17 could be eplaine**d by the network
  - ➔ 12 remaining ones used to **complete the network**

Application to the FSHR-induced network

- ➔ Each of the 12 remaining observations could be explained by adding **hypotheses containing a unique arc**

- ➔ More than **250 hypotheses** were generated

- ➔ Greedy search algorithm to rank hypotheses based on the **decreasing number** of experimental results they allowed to **explain**

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		1	2	3	4	5	6	7
		stimulates(p38mapk,pi3k)	inhibits(p38mapk,raf1)	inhibits(p38mapk,mek)	inhibits(p38mapk,erk12)	inhibits(rps6,rap1)	inhibits(mtor,camp_epac)	inhibits(rps6,camp_epac)
1	$(\{camp, epac\}, pi3k, akt, \downarrow)$							
2	$(\{camp, epac\}, pi3k, rps6, \downarrow)$							
3	$(\{camp, epac\}, p38mapk, akt, \downarrow)$							
4	$(\{camp, epac\}, pi3k, p70s6k, \downarrow)$							
5	$(\{camp, epac\}, pi3k, rps6, \downarrow)$							
6	$(\{fsh\_fshr, epac\}, pka, akt, \uparrow)$							
7	$(\{fsh\_fshr, epac\}, p38mapk, akt, \downarrow)$							
8	$(\{camp, epac\}, pka, p70s6k, \uparrow)$							
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11	$(\{fsh\_fshr, epac\}, mek, p38mapk, \downarrow)$							
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The four first hypotheses

1. stimulates(p38mapk,pi3k)

2. inhibits(p38mapk,raf1)
3. inhibits(p38mapk,mek)
4. inhibits(p38mapk,erk12)

have evidence in the literature

Conclusion and prospects

- ➔ Method to complete SBGN-AF maps with perturbation experiments

- ➔ Logical operators are taken into account

- ➔ Results on the FSHR-mediated network look promising

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- ➔ Better hypotheses selection
- ➔ Deal with cycles (in particular negative cycles)

Thank You !

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