Boolean models of human preimplantation embryo development inferred using SCIBORG

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Séminaire Santé Numérique

Thursday, November 7th 2024

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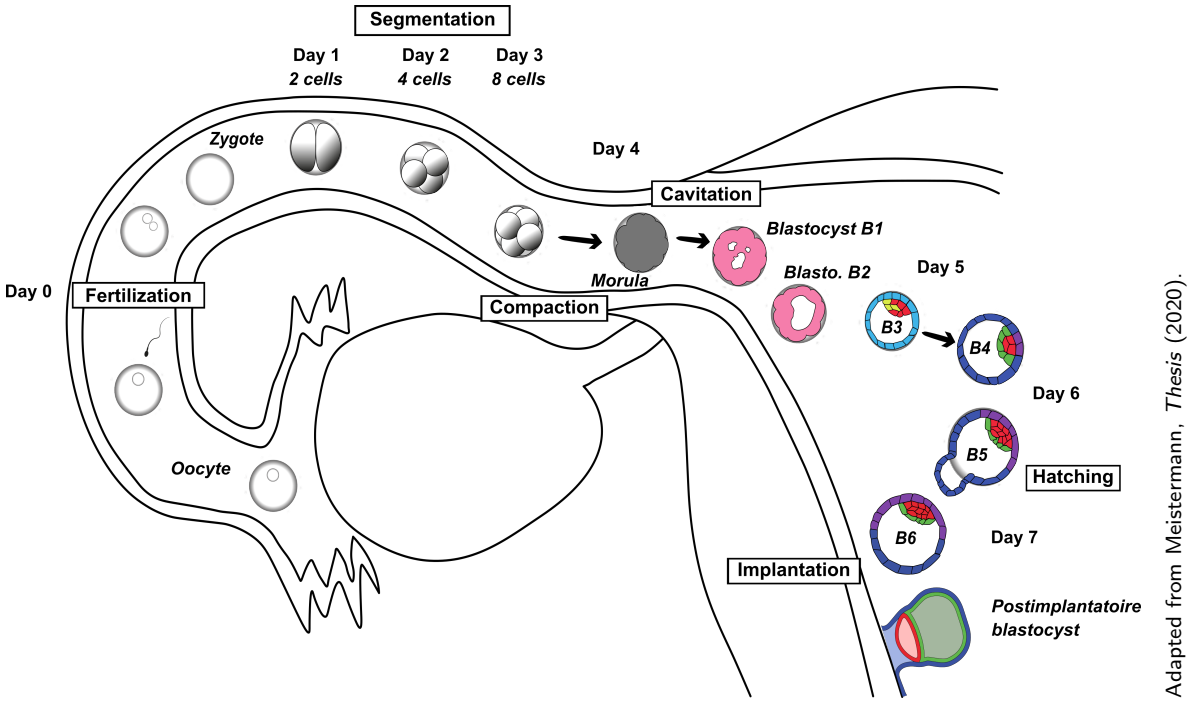
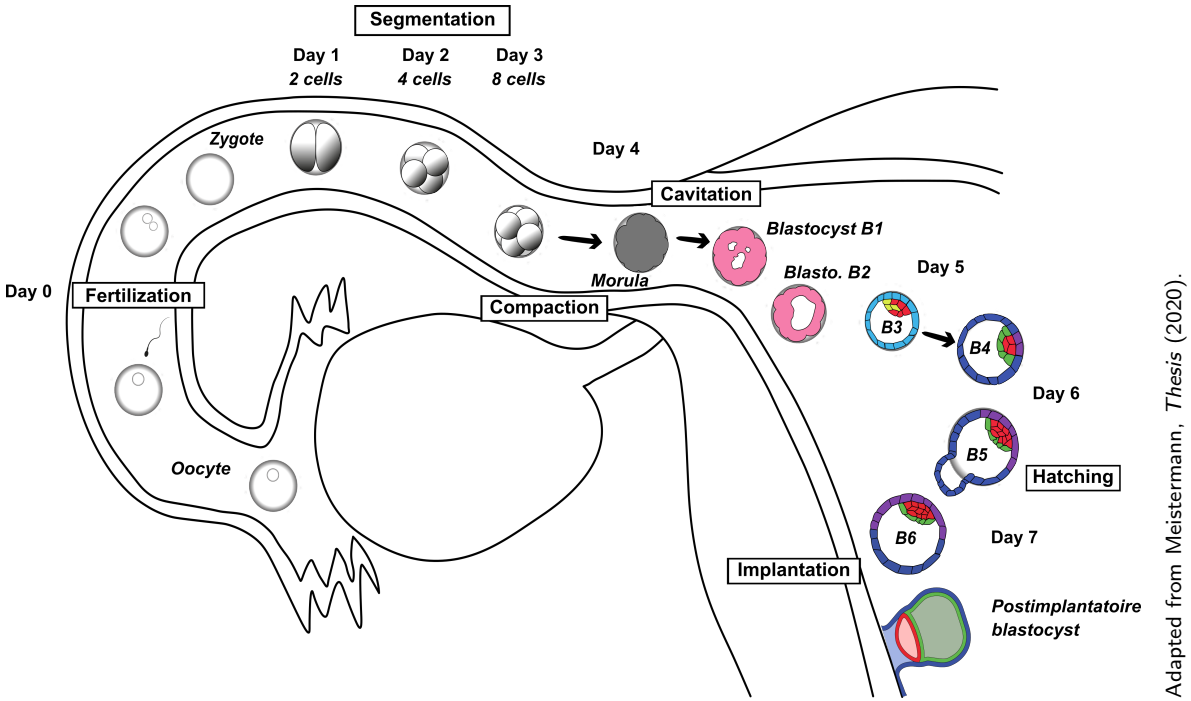
CENTRALE NANTES

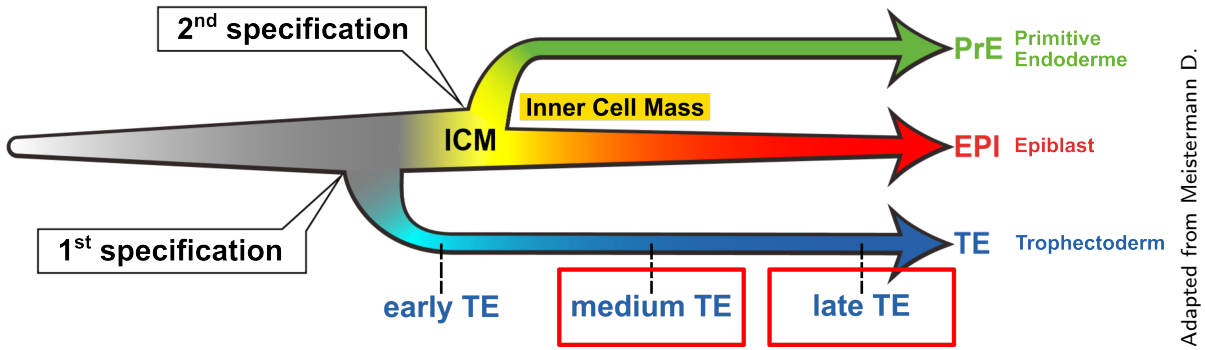
Human preimplantation embryonic development



Adapted from Meistermann, *Thesis* (2020).

Human preimplantation embryonic development





[Meistermann et al., *Cell Stem Cell* (2021)]

Context

Study human embryo is complex

- Biological mechanisms
- Legal constraints
- Experimental concerns

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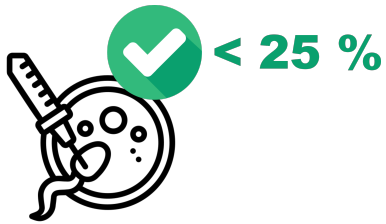

Poor success of IVF

[De Geyter et al., *Human Reproduction* (2024)]

IVF = in vitro fertilization

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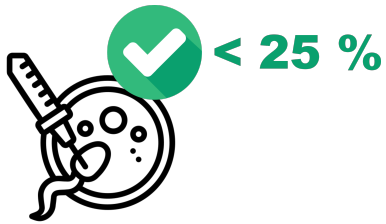

Poor success of IVF

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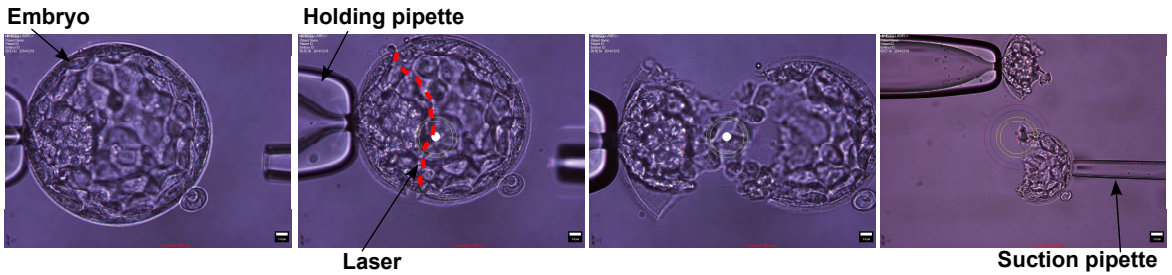
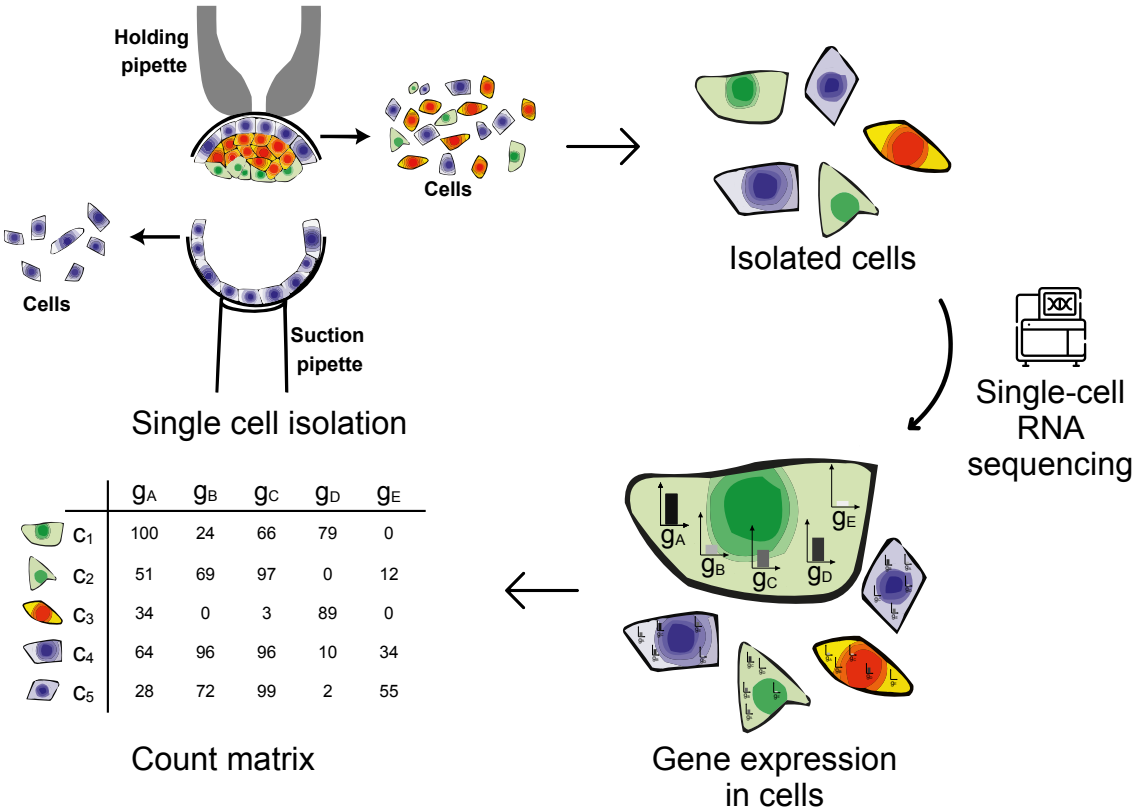
→ **In silico model of human embryonic development**

IVF = in vitro fertilization

Data generation



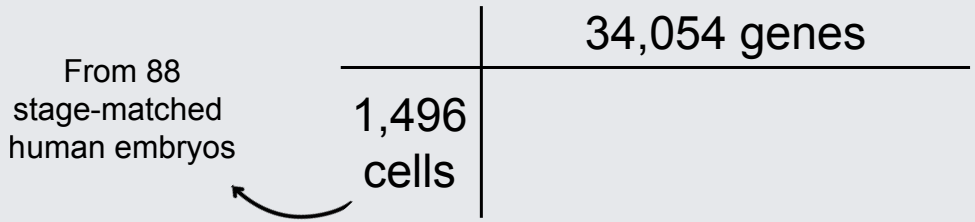


	g_A	g_B	g_C	g_D	g_E
C_1	100	24	66	79	0
C_2	51	69	97	0	12
C_3	34	0	3	89	0
C_4	64	96	96	10	34
C_5	28	72	99	2	55

Data and preliminary study

[Meistermann et al., *Cell Stem Cell* (2021)]

Count Matrix



Data and preliminary study

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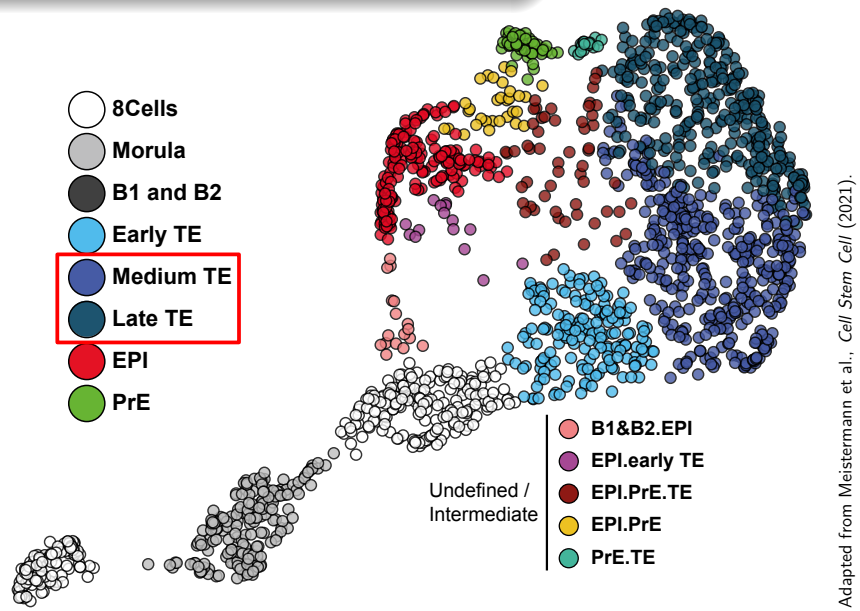
Count Matrix

	34,054 genes
1,496 cells	

From 88 stage-matched human embryos

- **Clustering** of cells (8 stages)



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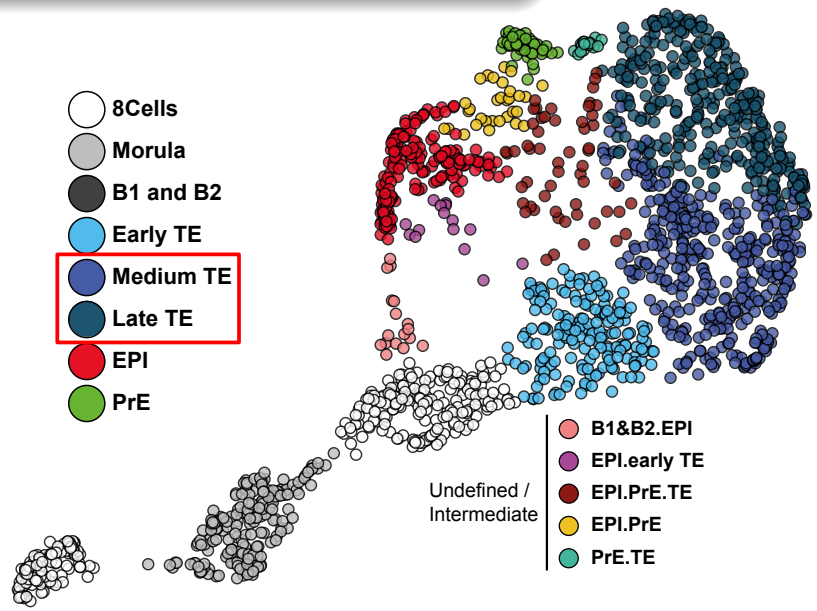

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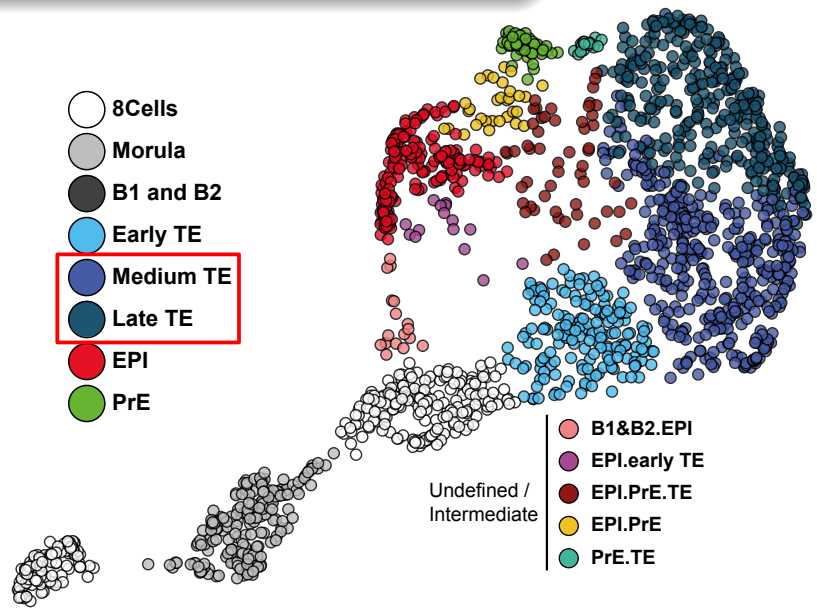
From 88 stage-matched human embryos

- **Clustering** of cells (8 stages)
- Identification of **gene modules** $\rightarrow$ 438 transcription factors
- **Pseudotime** evolution of cells at different developmental stages



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Modeling single-cell data: existing tools

SCNS		[Moignard et al., *Nature biotech.* (2015)]
Gene expression state changes	Cell ordering	State transition graph: high combinatory (require small number of studied genes)

BoNesis		[Chevalier et al., *ICTAI* (2019)]
Prior gene interactions (Dorothea database)	Cell ordering and dynamical constraints	Mean of cells and gene expression

RE:IN		[Dunn et al., *EMBO journal* (2019)]
Prior gene interactions (gene expression correlation)	Perturbations experiments	Biological system allowing perturbations / Limited number of perturbations

State-of-the-art tool review

Method	System size	Cell heterogeneity	Cellular dynamic evolution	Exhaustive enumeration	Validation
SCNS	• $\approx$ 40 genes • $\approx 4,000$ cells	✓	✓	✓	✓ *
BoNesis	• $\approx 1,000$ genes • $\approx$ 600 cells	✗	✓	✗	✗
RE:IN	• $\approx$ 20 genes • $\approx$ 30 perturbations	✗	✗	✗	✓

* Thanks to experimental perturbations

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RE:IN	• $\approx$ 20 genes • $\approx$ 30 perturbations	✗	✗	✗	✓
Our goal	• $\approx$ **150 genes** • $\approx$ **700 cells**	✓	✓	✓	✓

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Objective

Develop a new method to model regulatory mechanisms occurring in developmental stages

- Cell heterogeneity
- Cellular dynamic evolution
- Exhaustive enumeration
- Validation

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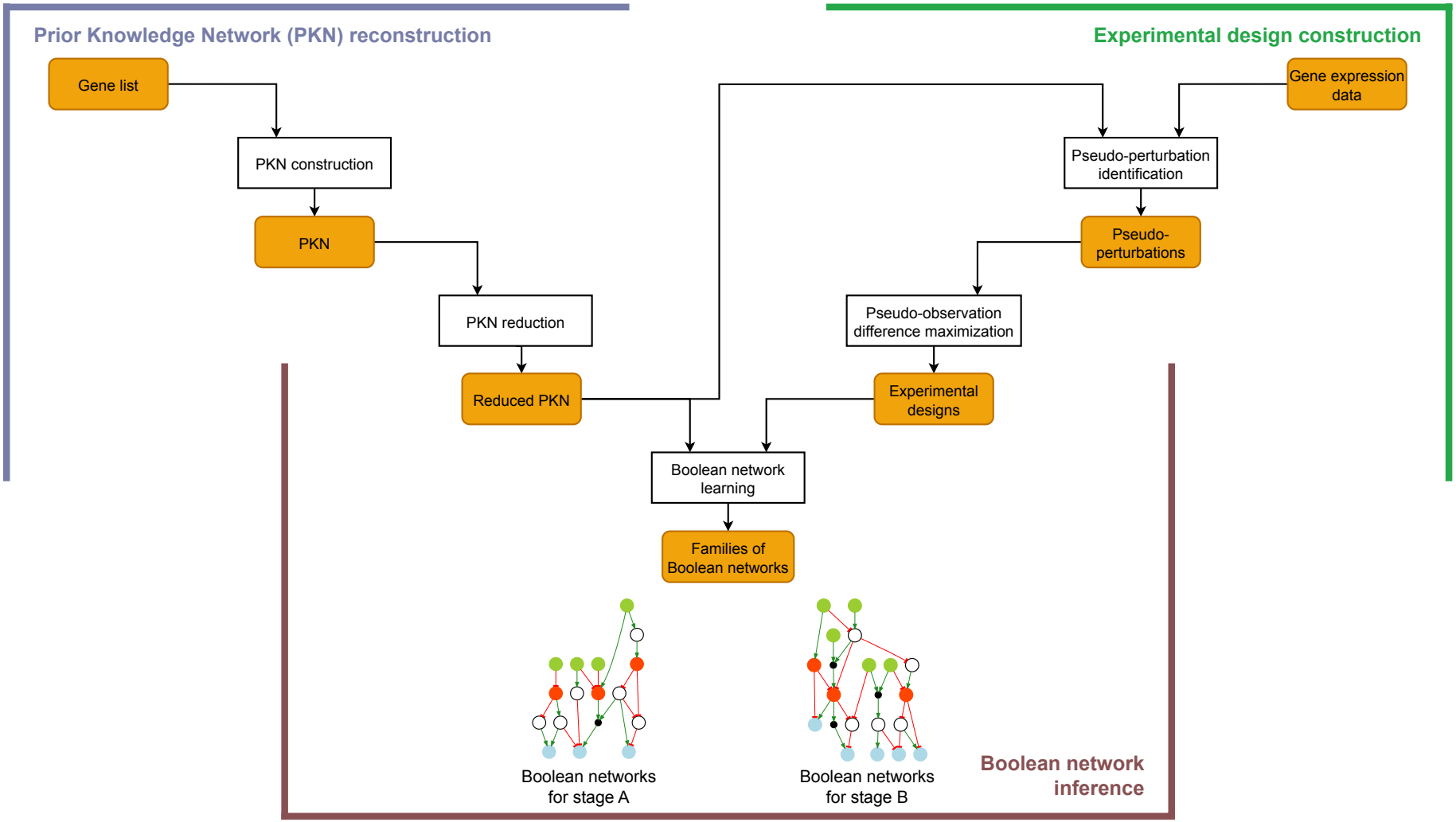
SCIBORG

Using single-cell data to infer Boolean networks modeling regulation of genes

Overview of SCIBORG



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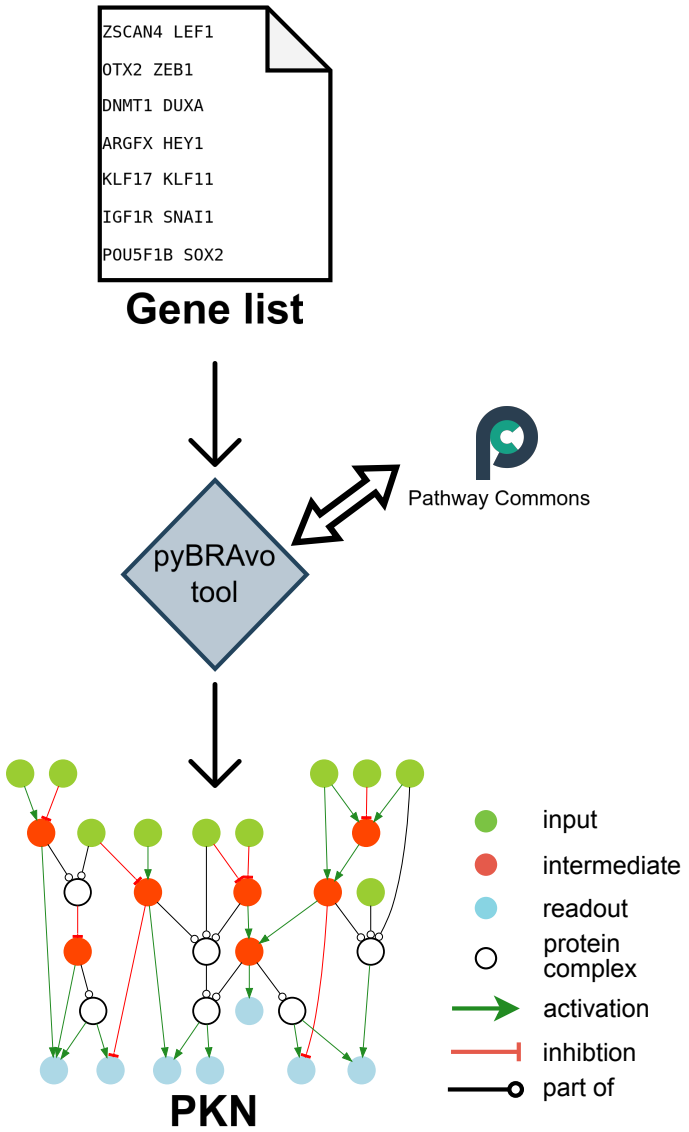
Step 1. PKN reconstruction

Recursive queries on Pathway Commons database, via pyBRAvo [Lefebvre et al., *Database* (2021)]

Input	Output	Parameter
Gene list	PKN	Depth



PKN = prior knowledge network

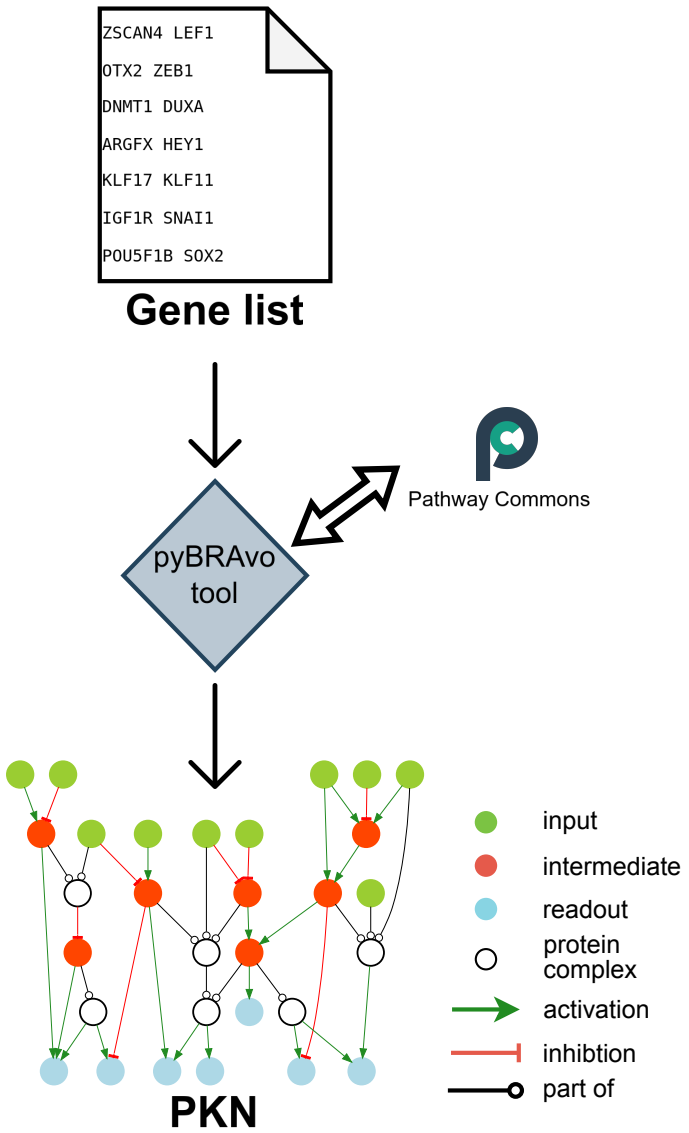
Step 1. PKN reconstruction

Recursive queries on Pathway Commons database, via pyBRAvo [Lefebvre et al., *Database* (2021)]

Input	Output	Parameter
Gene list	PKN	Depth

input & intermediate genes → **possible pseudo-perturbations**

readout genes → **pseudo-observations**



PKN = prior knowledge network

Step 2. Experimental design construction

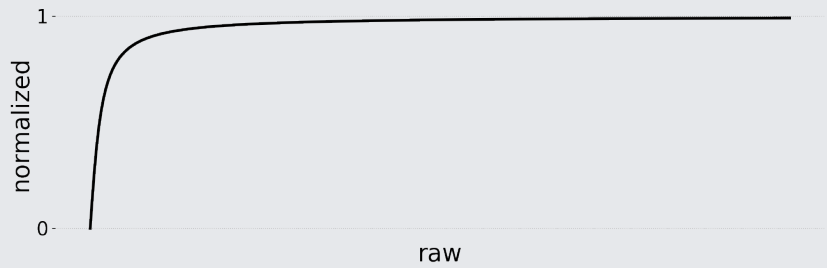
Data preprocessing

- Binarization of input + intermediate genes

$$binarized = \begin{cases} 0, & \text{if } raw < 2, \\ 1, & \text{otherwise.} \end{cases}$$

- Normalization of readout genes

$$normalized = \frac{2}{\pi} \times \arctan(raw)$$



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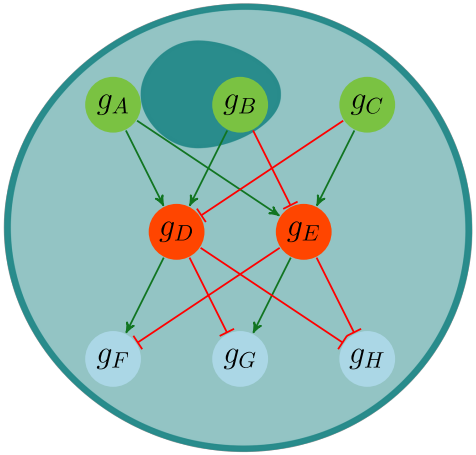
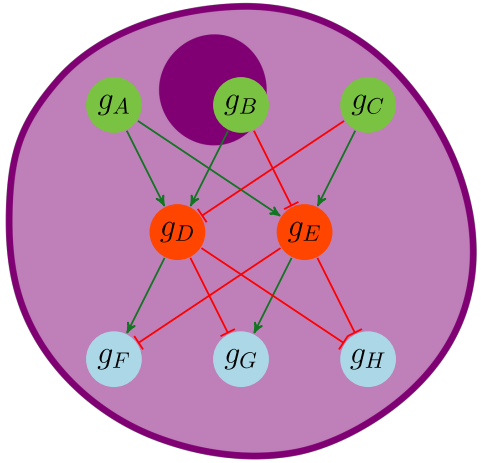
Step 2. Experimental design construction

stage A



stage B



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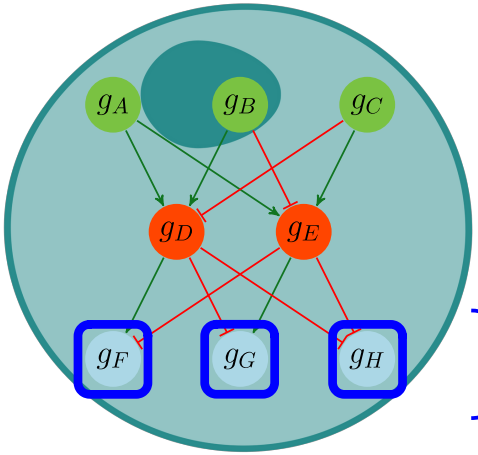
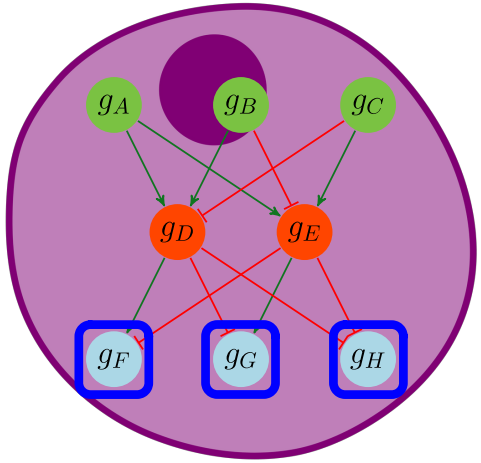


different expressions
=
pseudo-observation

stage B



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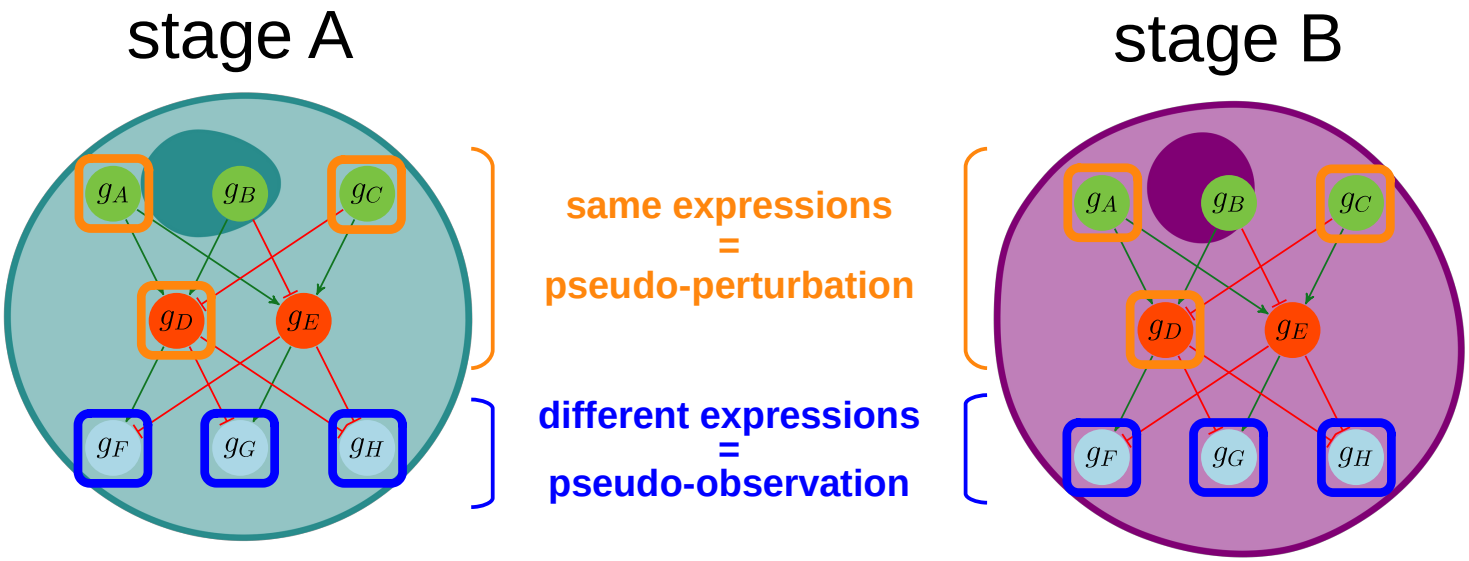

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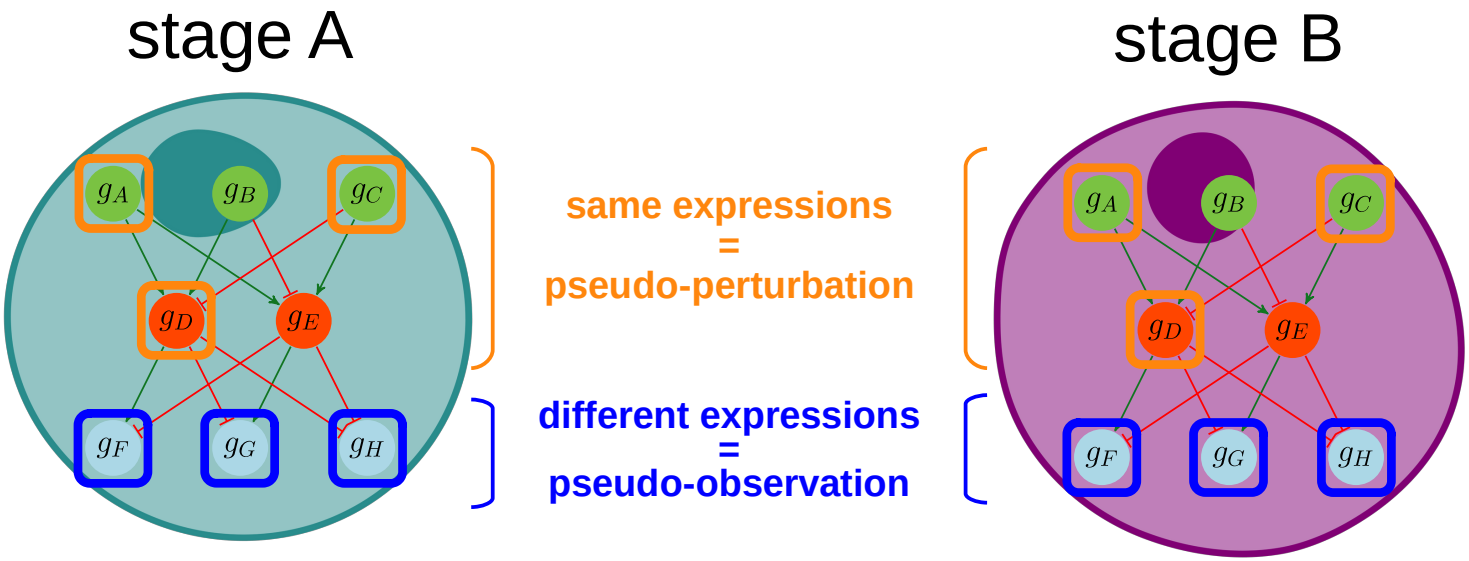

Pseudo-perturbation identification problem statement

Given k,
select k **genes** from gene population,
that maximize the number of **pairs of cells** from stages A and B,
having the **same expression for the k-genes**.

pseudo-perturbations

Step 2. Pseudo-perturbation identification using ASP

	possible pseudo-perturbations					pseudo-observations			
cell	A	B	C	D	E	F	G	H	stage
c_1	1	1	0	1	0	0.8	0.4	0.6	A
c_2	1	0	1	0	0	0.2	0.5	0.3	A
c_3	1	1	0	1	1	0.8	0.3	0.9	A
c_4	1	1	1	0	1	0.6	0.1	0.2	B
c_5	1	0	0	1	1	0.7	0.8	0.5	B
c_6	0	0	1	0	1	0.7	0.2	0.3	B

parameter *k*

ASP = answer set programming

Step 2. Pseudo-perturbation identification using ASP

pseudo-perturbations | pseudo-observations

cell	A	B	C	D	E	F	G	H	stage
c_1	1	1	0	1	0	0.8	0.4	0.6	A
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c_6	0	0	1	0	1	0.7	0.2	0.3	B

parameter *k*

k=3

selected genes: A, C & D

experimental design A

cell	A	C	D	F	G	H	stage
c_1	1	0	1	0.8	0.4	0.6	A
c_2	1	1	0	0.2	0.5	0.3	A

match

match

experimental design B

cell	A	C	D	F	G	H	stage
c_5	1	0	1	0.7	0.8	0.5	B
c_4	1	1	0	0.6	0.1	0.2	B

ASP = answer set programming

Step 2. Pseudo-perturbation identification using ASP

pseudo-perturbations | pseudo-observations

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match

match

experimental design B

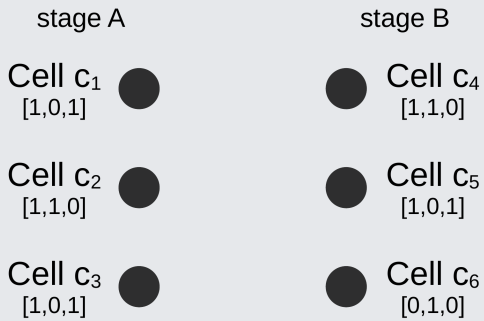
cell	A	C	D	F	G	H	stage
c_5	1	0	1	0.7	0.8	0.5	B
c_4	1	1	0	0.6	0.1	0.2	B

- Optimal number of pseudo-perturbations: 2
- 2 pairs of matching cells: (c_1, c_5), (c_2, c_4)

ASP = answer set programming

Step 2. Maximizing the pseudo-observation difference

Redundancy



2 solutions:

[Bolteau et al., *ISBRA* (2023)] [Bolteau et al., *J. of Computational Biology* (2024)]

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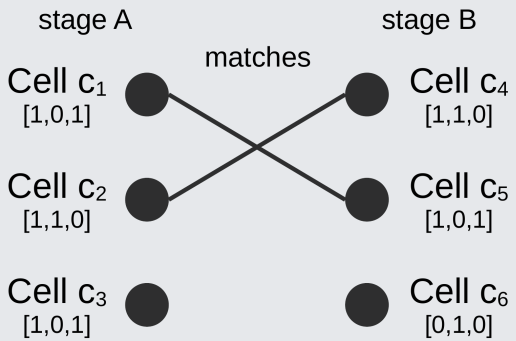

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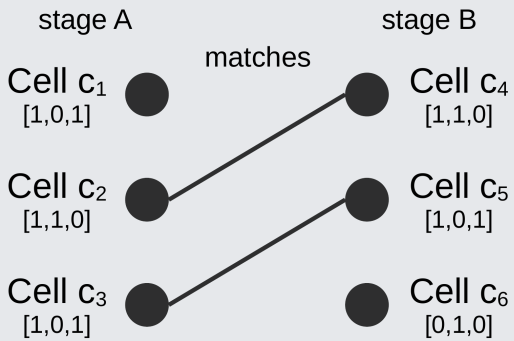

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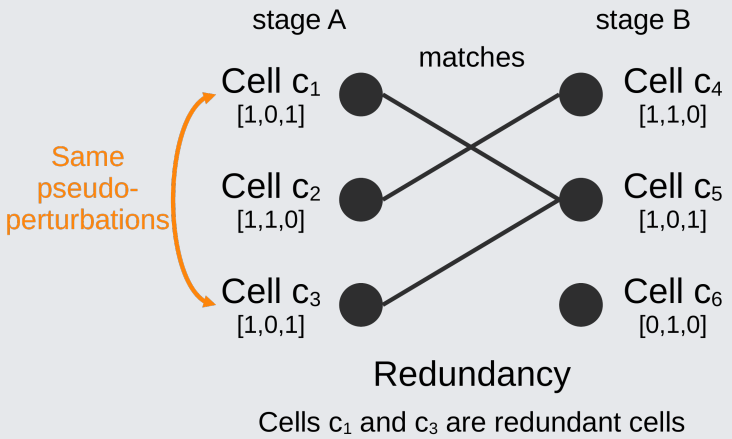

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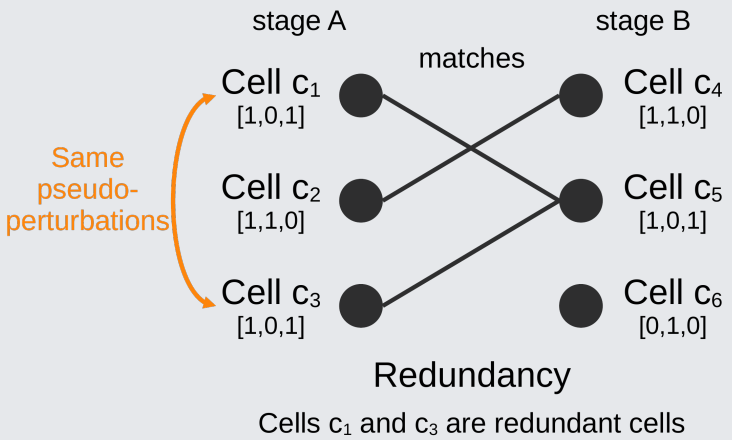

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1. (c_1, c_5), (c_2, c_4)
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Representativity score of pseudo-perturbations:

- Stage A: 100% (3/3)
- Stage B: 66% (2/3)

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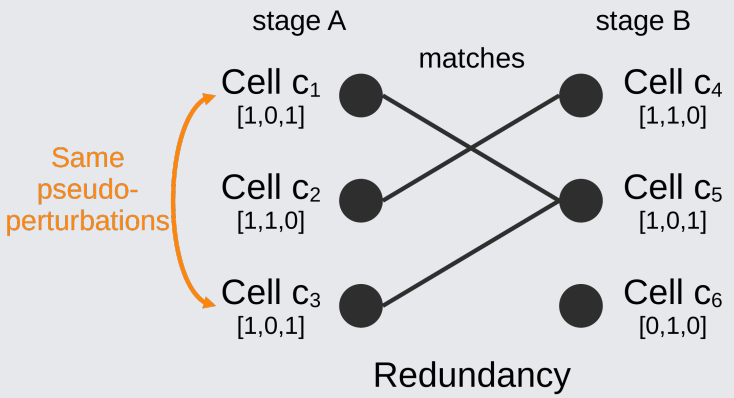

Cells c_1 and c_3 are redundant cells

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Pseudo-observation difference maximization

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c_2	1	1	0	0.2	0.5	0.3	A

match

match

cell	A	C	D	F	G	H	stage
c_5	1	0	1	0.7	0.8	0.5	B
c_4	1	1	0	0.6	0.1	0.2	B

Solution 1

vs.

cell	A	C	D	F	G	H	stage
c_3	1	0	1	0.8	0.3	0.9	A
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match

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Solution 2

experimental design for stage A

experimental design for stage B

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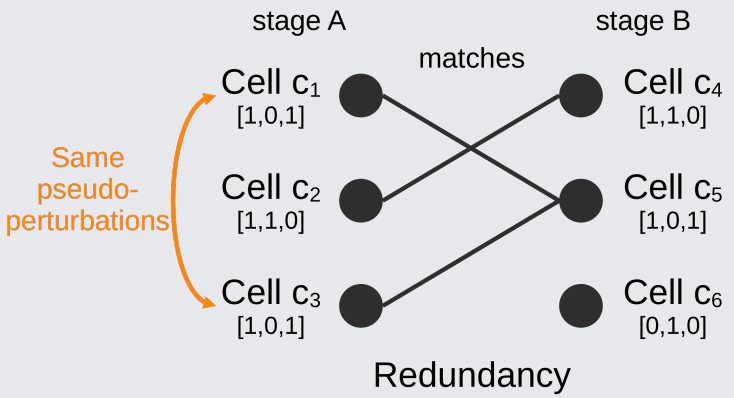
Step 2. Maximizing the pseudo-observation difference

Redundancy



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match, match

cell	A	C	D	F	G	H	stage
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c_4	1	1	0	0.6	0.1	0.2	B

Solution 1

$\text{diff}(c_1, c_5) = |0.8-0.7| + |0.4-0.8| + |0.6-0.5| = 0.6$

vs.

cell	A	C	D	F	G	H	stage
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match, match

cell	A	C	D	F	G	H	stage
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Solution 2

experimental design for stage A — experimental design for stage B

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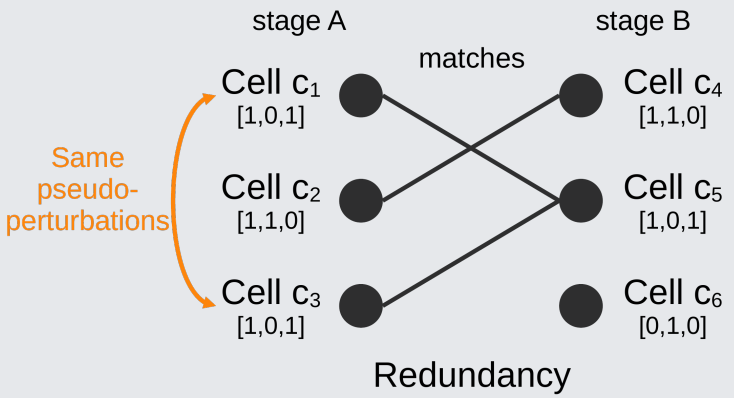
Step 2. Maximizing the pseudo-observation difference

Redundancy



2 solutions:

1. (c_1, c_5), (c_2, c_4)
2. (c_3, c_5), (c_2, c_4)

Representativity score of pseudo-perturbations:

- Stage A: 100% (3/3)
- Stage B: 66% (2/3)

Pseudo-observation difference maximization

cell	A	C	D	F	G	H	stage
c_1	1	0	1	0.8	0.4	0.6	A
c_2	1	1	0	0.2	0.5	0.3	A

match, match

cell	A	C	D	F	G	H	stage
c_5	1	0	1	0.7	0.8	0.5	B
c_4	1	1	0	0.6	0.1	0.2	B

Solution 1

$\text{diff}(c_1, c_5) = |0.8-0.7| + |0.4-0.8| + |0.6-0.5| = 0.6$

vs.

$\text{diff}(c_3, c_5) = |0.8-0.7| + |0.3-0.8| + |0.9-0.5| = 0.9$

cell	A	C	D	F	G	H	stage
c_3	1	0	1	0.8	0.3	0.9	A
c_2	1	1	0	0.2	0.5	0.3	A

match, match

cell	A	C	D	F	G	H	stage
c_5	1	0	1	0.7	0.8	0.5	B
c_4	1	1	0	0.6	0.1	0.2	B

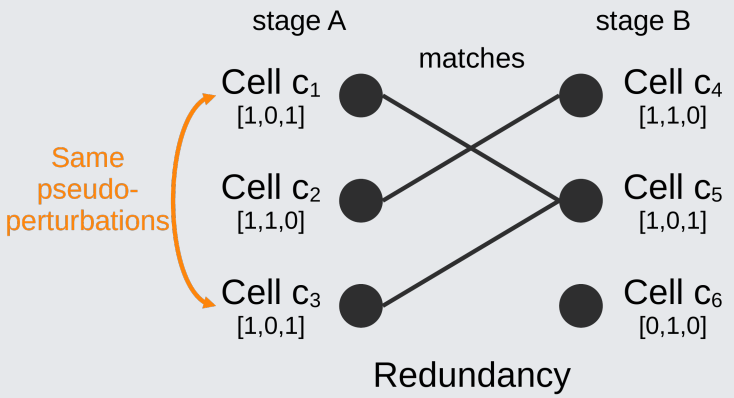
Solution 2

experimental design for stage A — experimental design for stage B

[Bolteau et al., *ISBRA* (2023)] [Bolteau et al., *J. of Computational Biology* (2024)]

Step 2. Maximizing the pseudo-observation difference

Redundancy



Cells c_1 and c_3 are redundant cells

2 solutions:

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match

match

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Solution 2

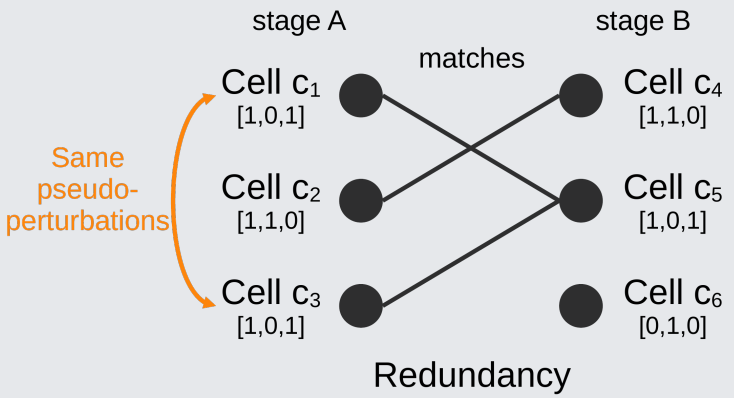
experimental design for stage A

experimental design for stage B

[Bolteau et al., *ISBRA* (2023)] [Bolteau et al., *J. of Computational Biology* (2024)]

Step 2. Maximizing the pseudo-observation difference

Redundancy



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Solution 2

experimental design for stage A — experimental design for stage B

[Bolteau et al., *ISBRA* (2023)] [Bolteau et al., *J. of Computational Biology* (2024)]

Step 3. BN learning using Caspo

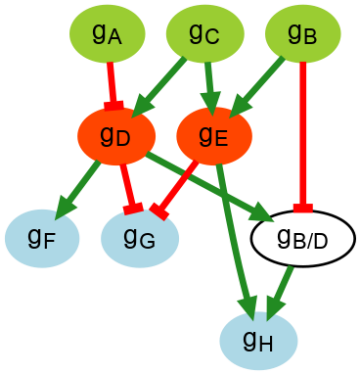
[Guziolowski et al., *Bioinformatics* (2013)]

cell	A	C	D	F	G	H	stage
c_3	1	0	1	0.8	0.3	0.9	A
c_2	1	1	0	0.2	0.5	0.3	A

experimental design of stage A

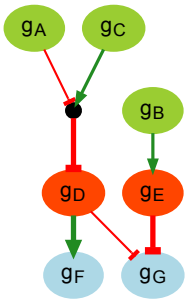
cell	A	C	D	F	G	H	stage
c_5	1	0	1	0.7	0.8	0.5	B
c_4	1	1	0	0.6	0.1	0.2	B

experimental design of stage B

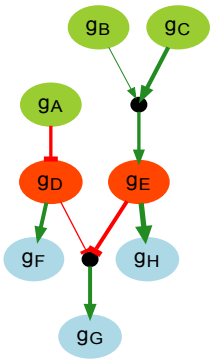


PKN

learning
Boolean networks
(Caspo)



family of Boolean networks of stage A

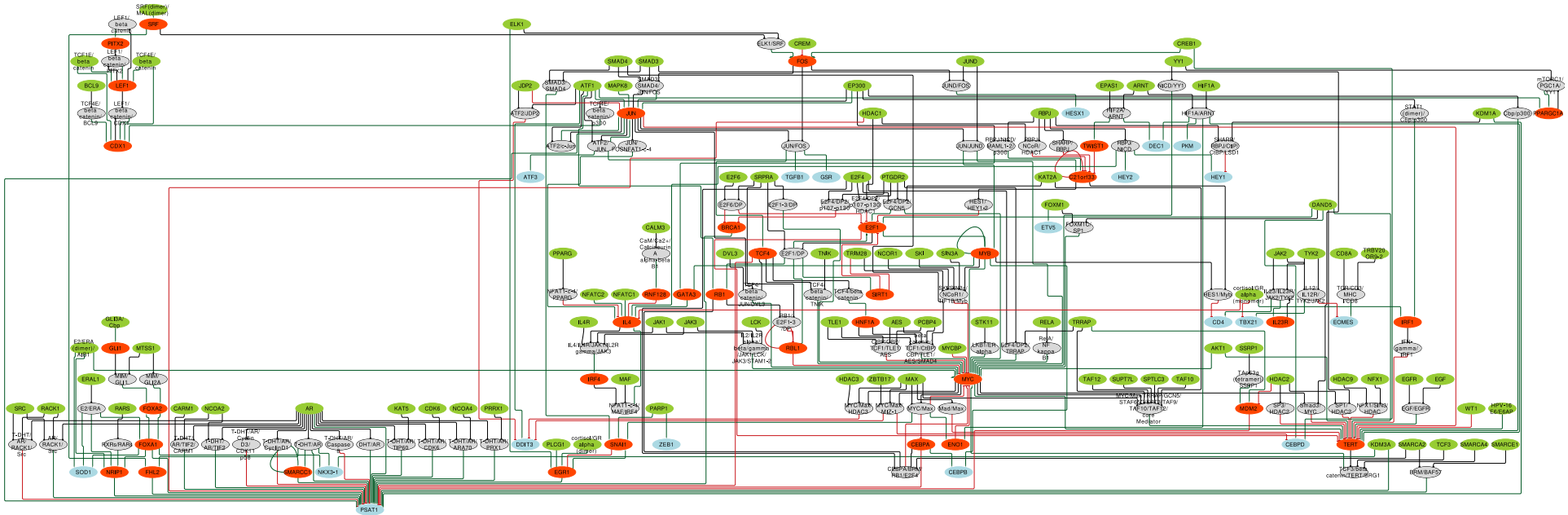


family of Boolean networks of stage B

Reconstructed PKN

Input	Output					Parameter
348 transcription factors from gene module analysis	233 nodes				369 edges	No depth (total reconstruction)
	85 inputs	36 intermediates	19 readouts	85 protein complexes		

[Meistermann et al., *Cell Stem Cell* (2021)]

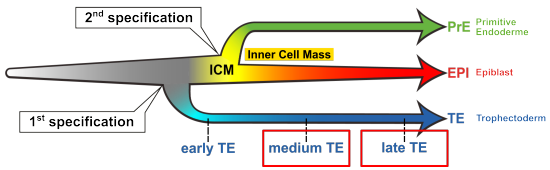


[Bolteau et al., *in prep.*]

Pseudo-perturbation identification

Focus on medium and late TE stages

(TE maturation)

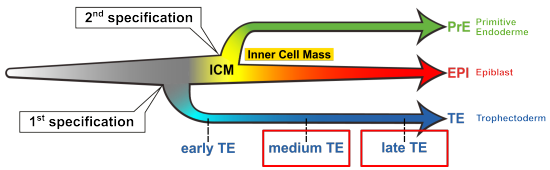


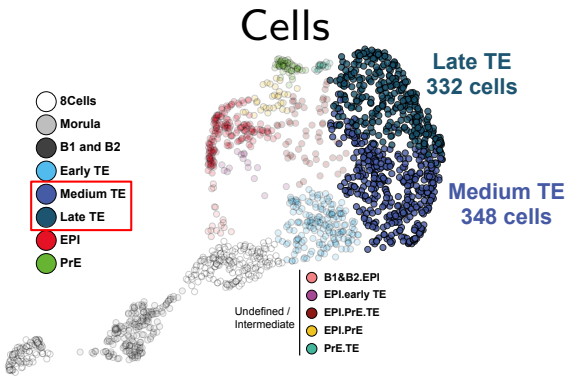
TE = trophectoderm

Pseudo-perturbation identification

Focus on medium and late TE stages

(TE maturation)





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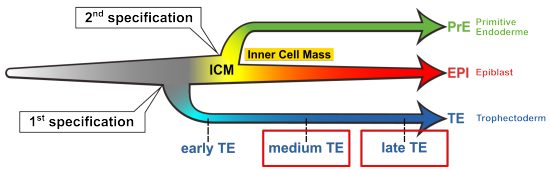
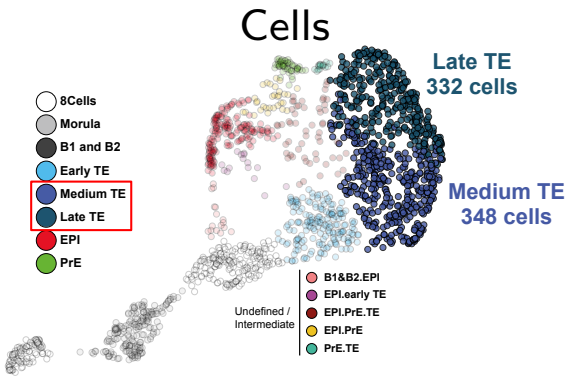




Genes

Choose k genes
from 85 inputs and 36 intermediates
to identify pseudo-perturbations

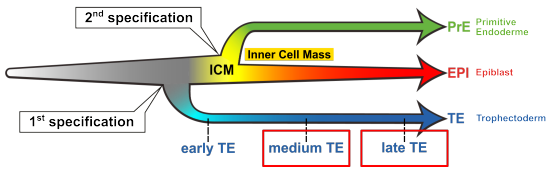
$$\binom{85+36}{k} \iff \binom{121}{k}$$

TE = trophectoderm

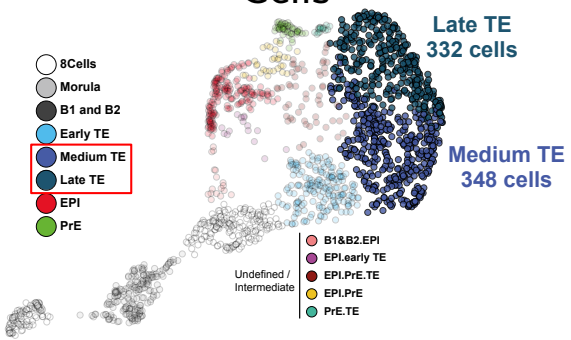
Pseudo-perturbation identification

Focus on medium and late TE stages

(TE maturation)



Cells



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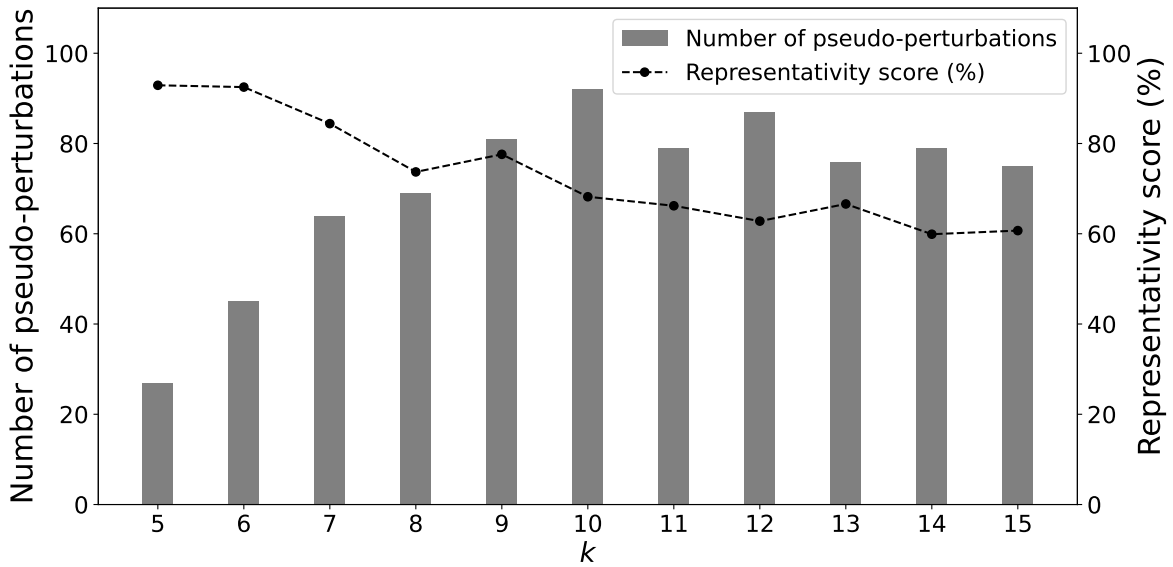


TE = trophectoderm

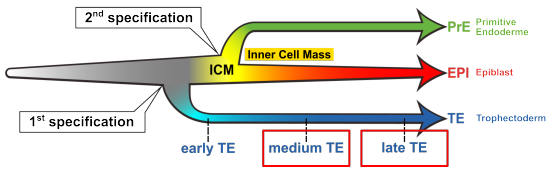
Execution time: 30 hours on a computer cluster (1.5 To RAM)

[Bolteau et al., *in prep.*]

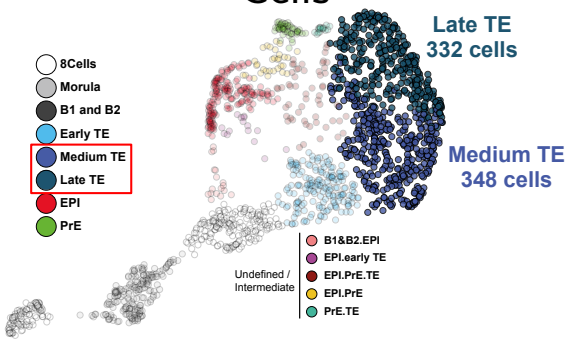
Pseudo-perturbation identification

Focus on medium and late TE stages

(TE maturation)



Cells



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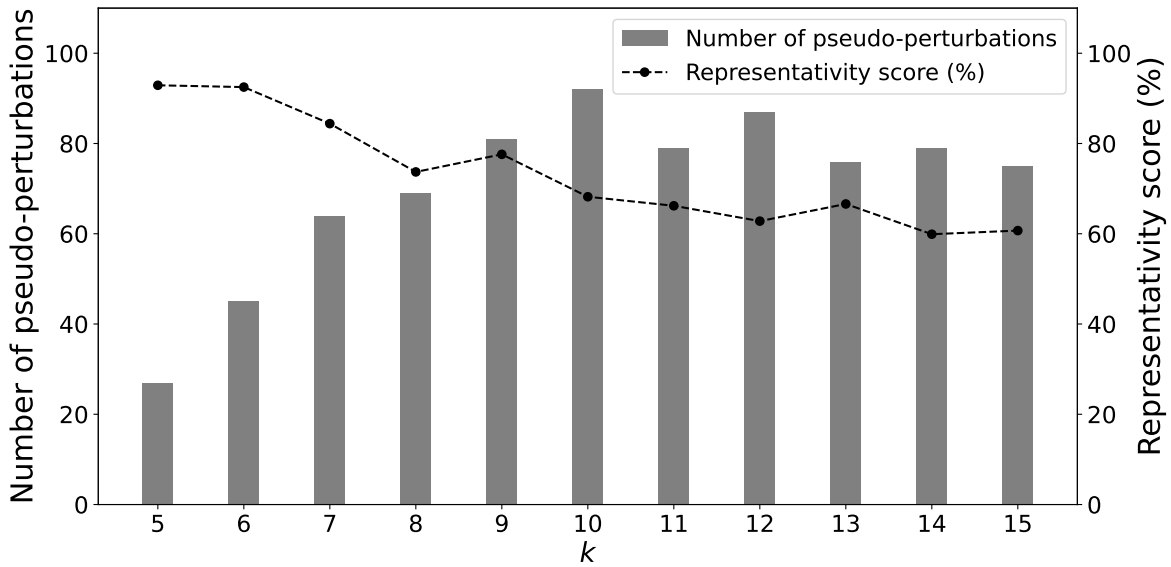


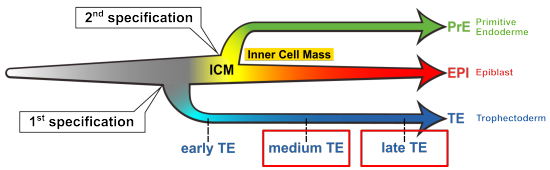
$k = 10$ the best parameter value for pseudo-perturbation identification

TE = trophectoderm Execution time: 30 hours on a computer cluster (1.5 To RAM) [Bolteau et al., *in prep.*]

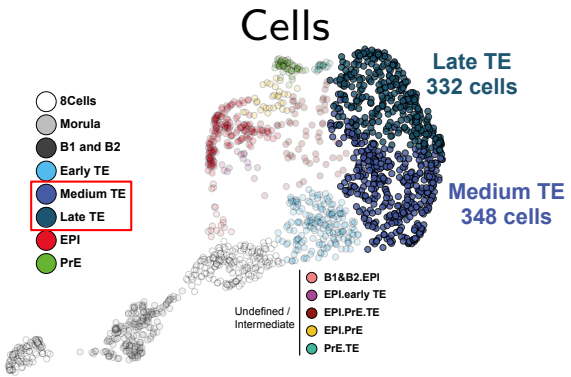
Pseudo-perturbation identification

Focus on medium and late TE stages

(TE maturation)



Cells



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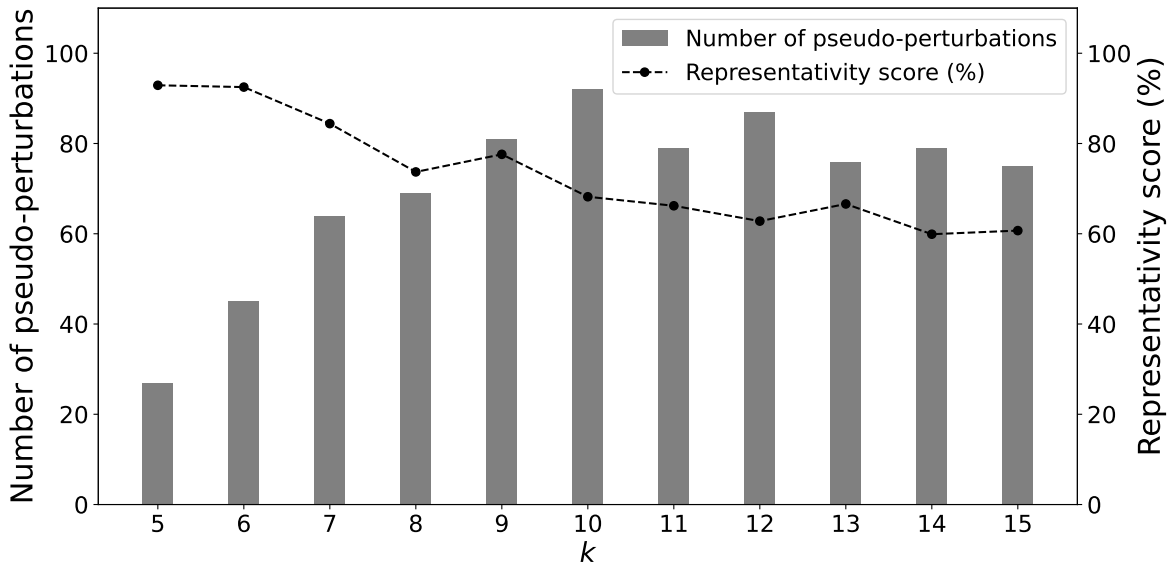


Research space

$$\binom{|genes|}{k} \times 2^{|cells_A| \times |cells_B|}$$

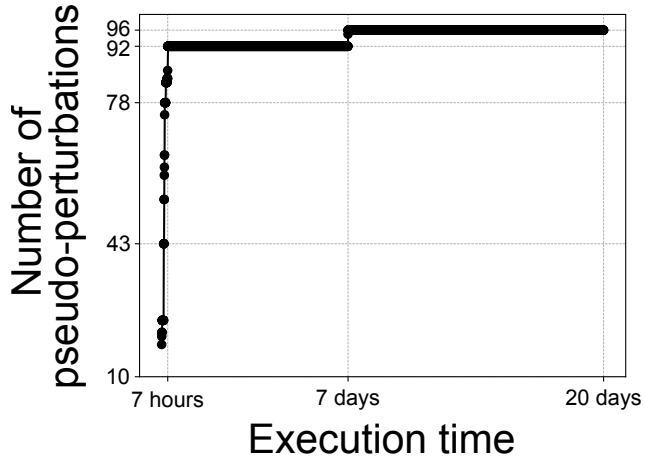
$$= \binom{121}{10} \times 2^{348 \times 332}$$

$$= 3.26 \times 10^{34793}$$

$k = 10$ the best parameter value for pseudo-perturbation identification

TE = trophectoderm Execution time: 30 hours on a computer cluster (1.5 To RAM) [Bolteau et al., *in prep.*]

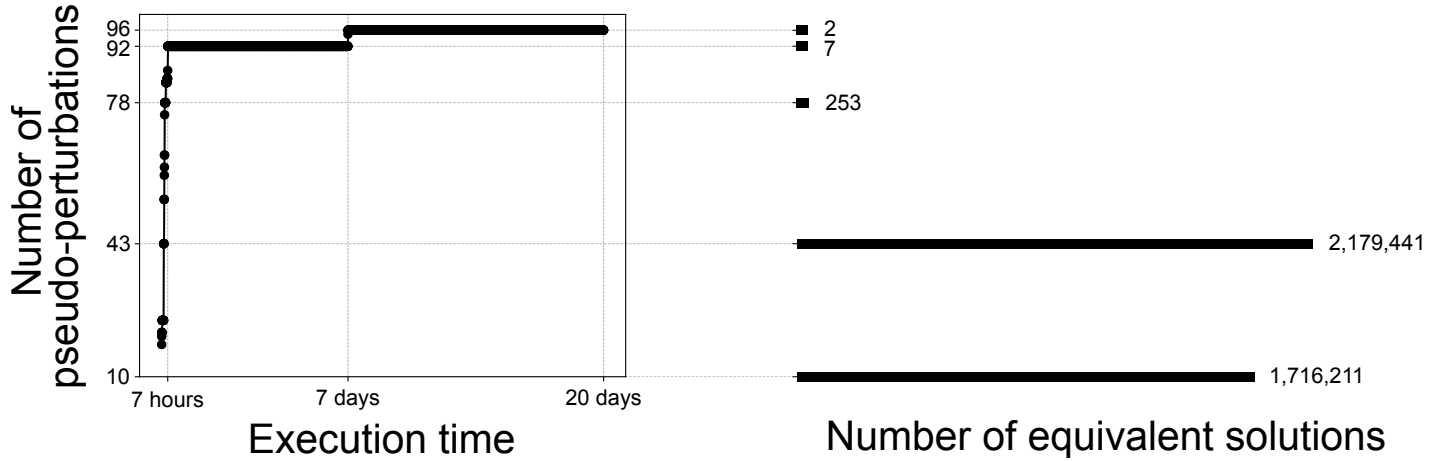
Convergence of the identified pseudo-perturbations



Convergence of the number of pseudo-perturbations

[Bolteau et al., *in prep.*]

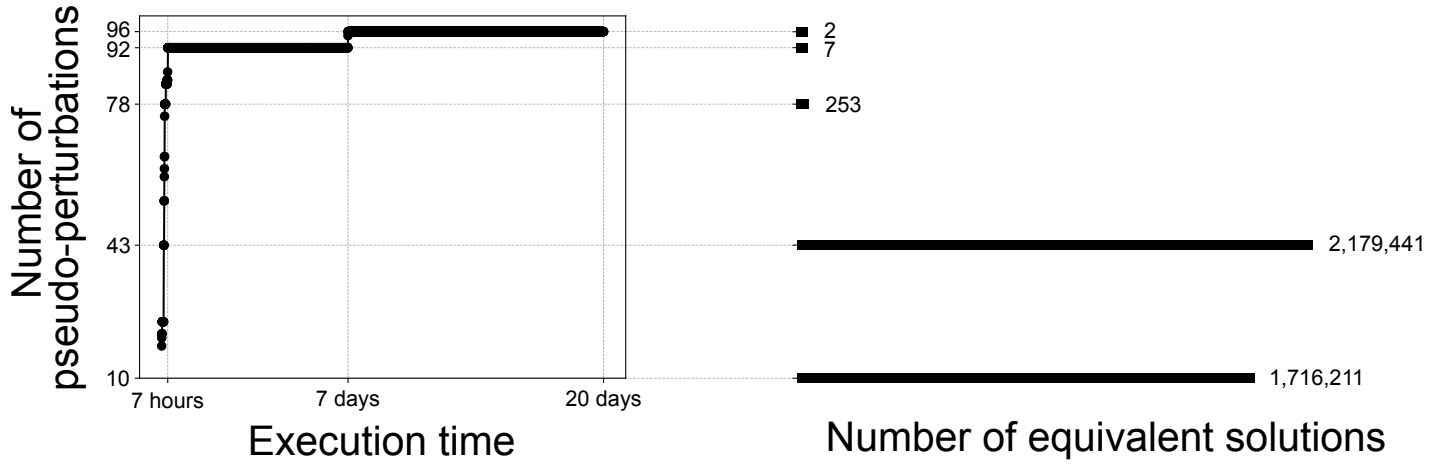
Convergence of the identified pseudo-perturbations



Convergence of the number of pseudo-perturbations and equivalent solutions

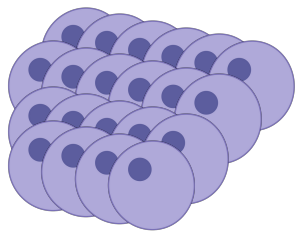
[Bolteau et al., *in prep.*]

Convergence of the identified pseudo-perturbations



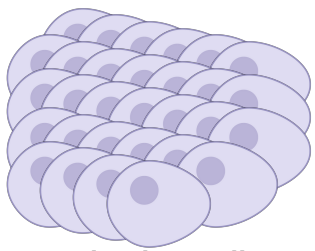
Execution time: 7 days on a computer cluster (1.5 To RAM)

Convergence of the number of pseudo-perturbations and equivalent solutions

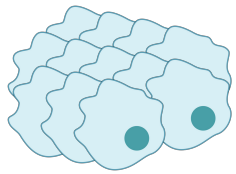


Pseudo-perturbation cells (96)

BN learning



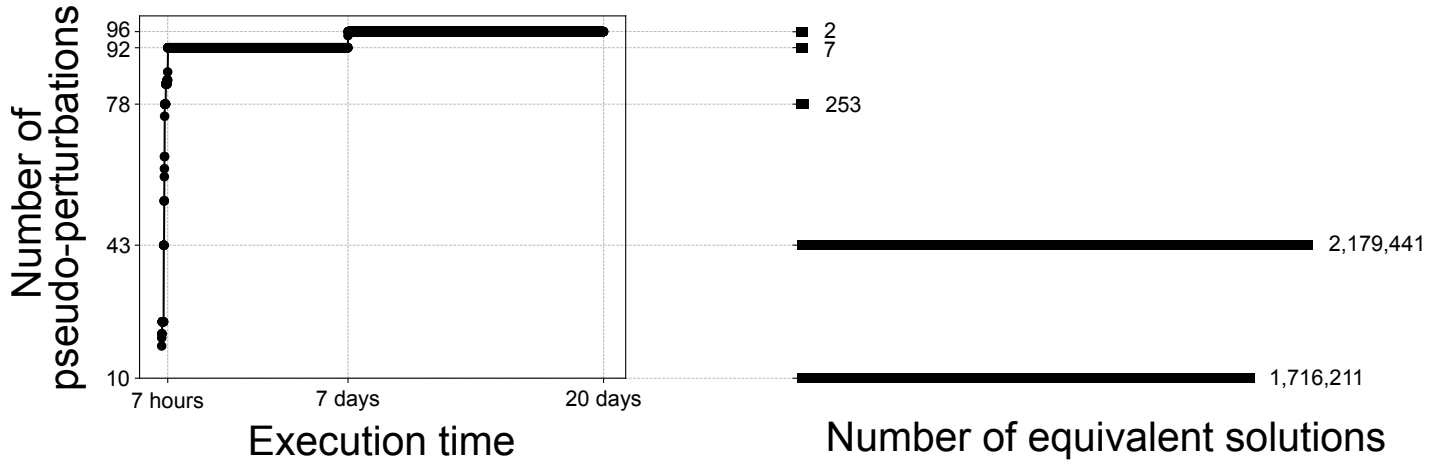
Redundant cells



Others cells

[Bolteau et al., *in prep.*]

Convergence of the identified pseudo-perturbations



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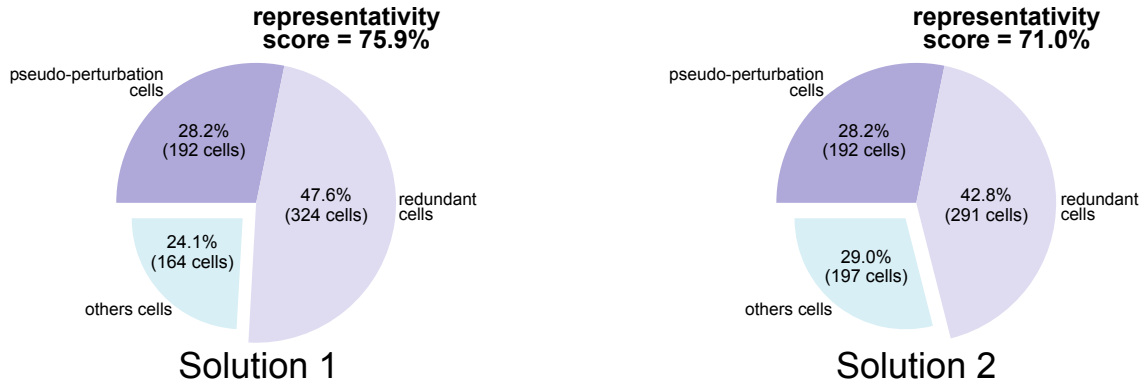
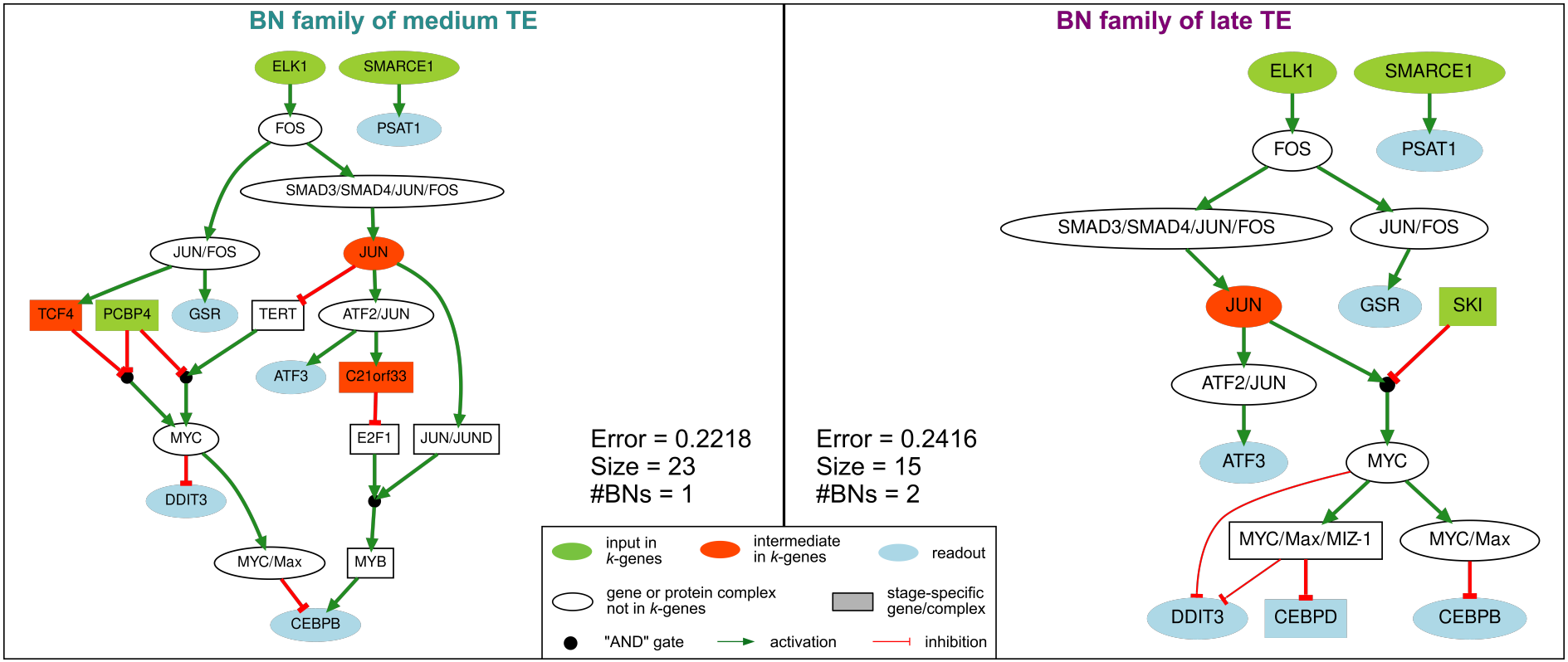
Convergence of the number of pseudo-perturbations and equivalent solutions



The 96 pseudo-perturbations are representative of more than 70% of the cell population

[Bolteau et al., *in prep.*]

Regulatory mechanisms in the learned models



[Bolteau et al., *in prep.*]

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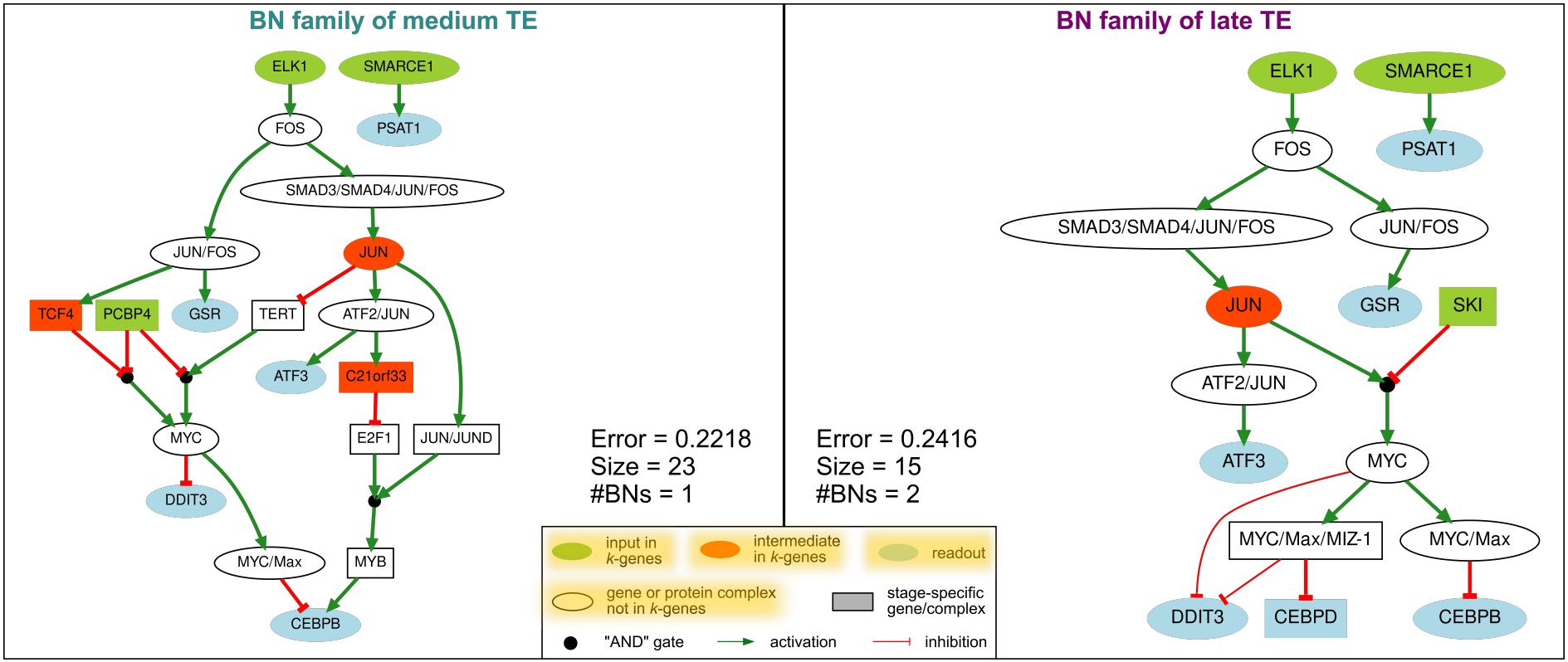

[Bolteau et al., *in prep.*]

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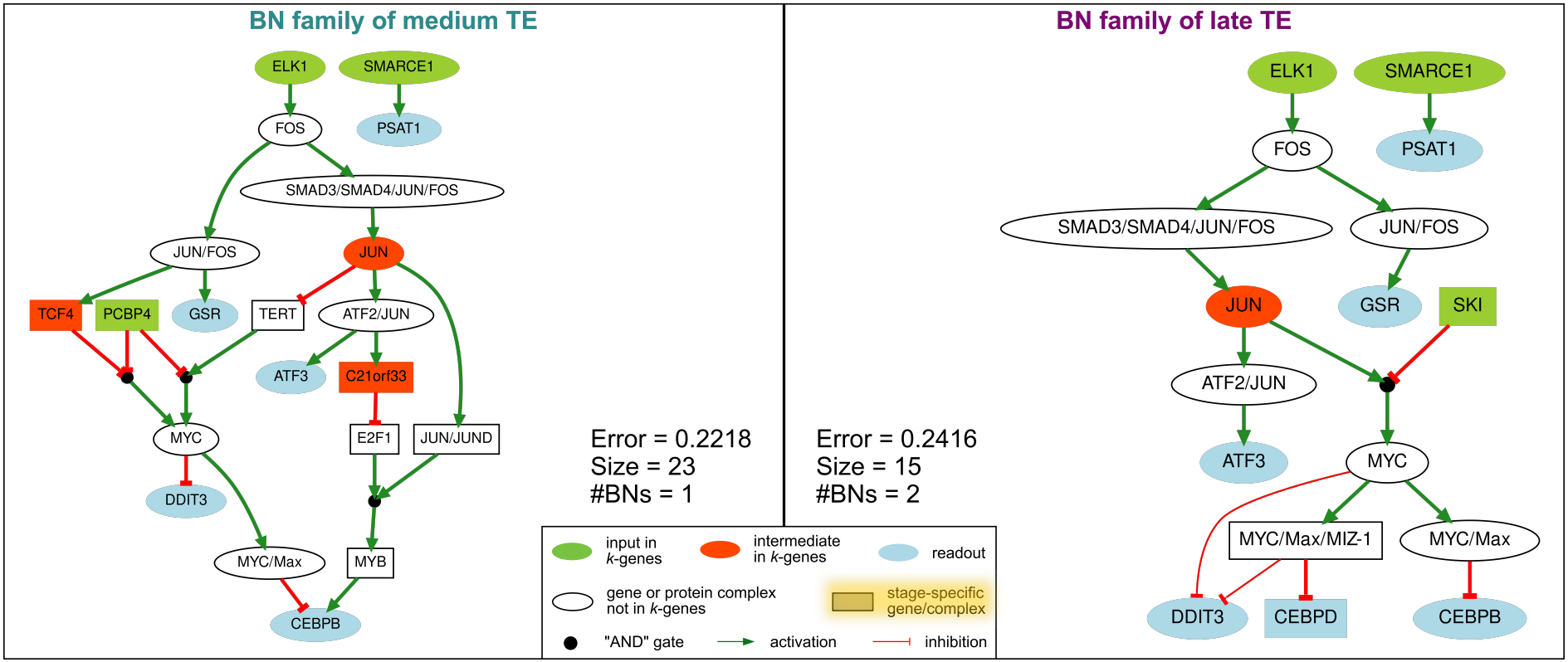
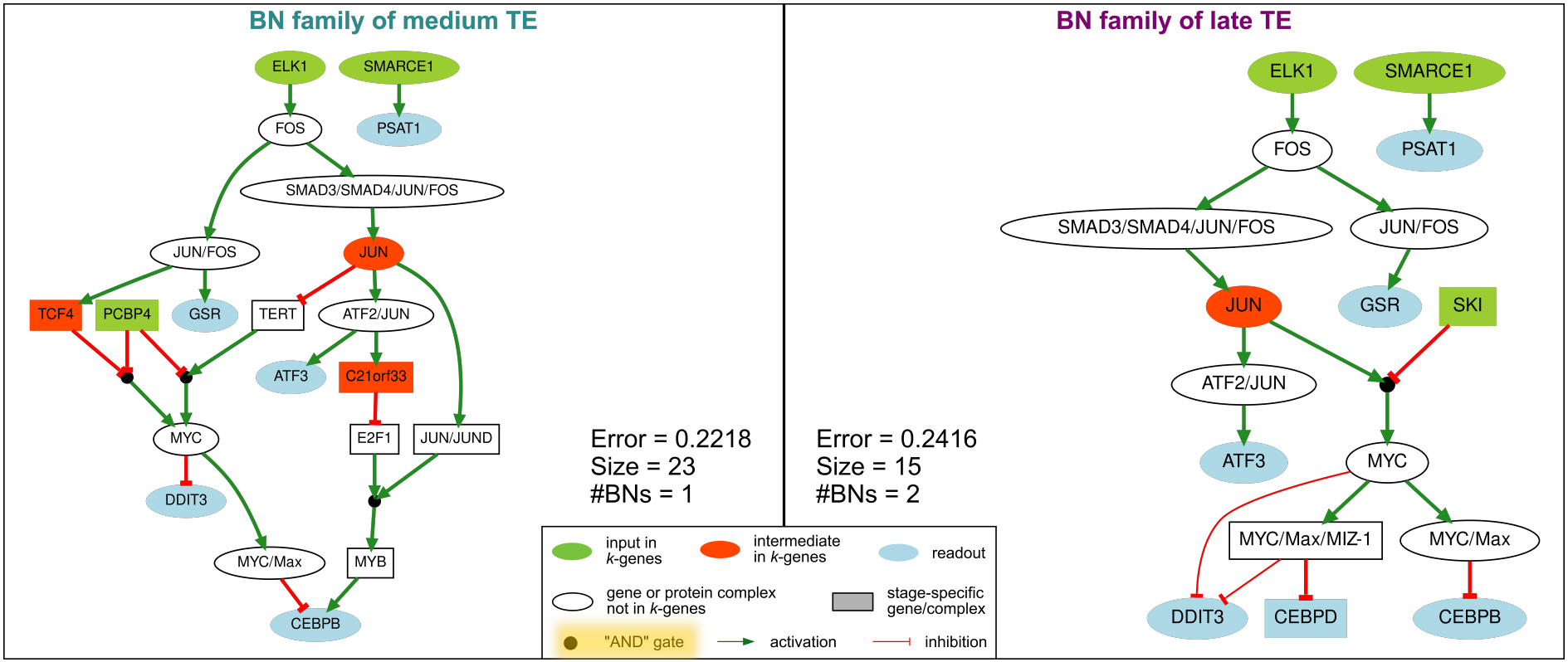


[Bolteau et al., *in prep.*]

Regulatory mechanisms in the learned models



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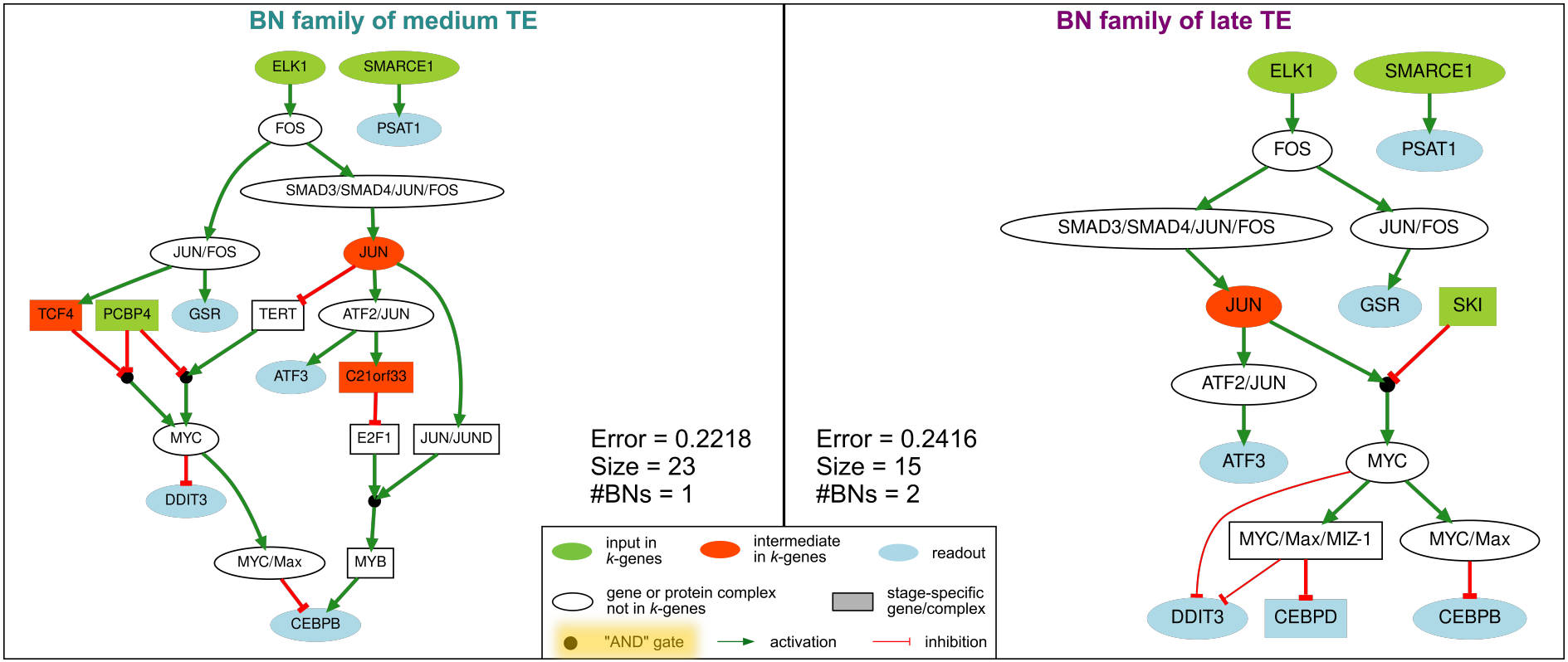
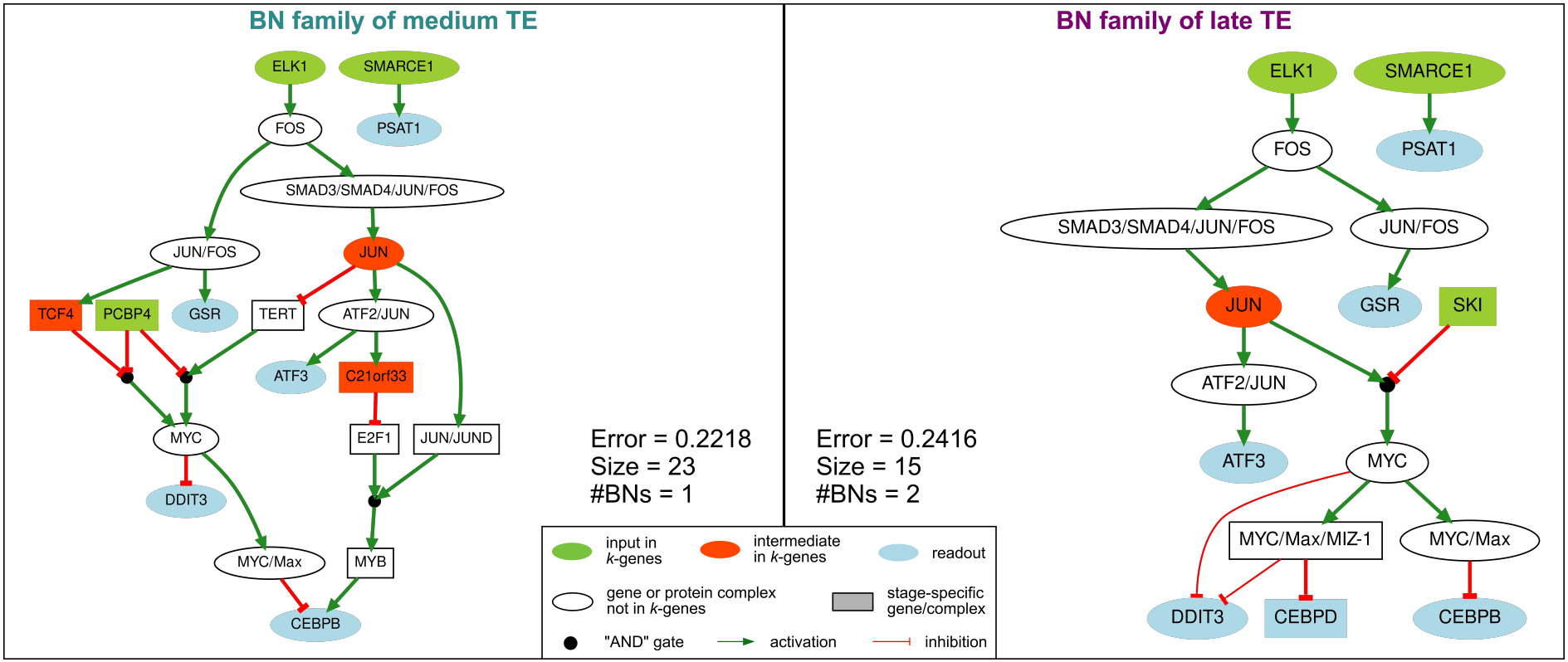
Regulatory mechanisms in the learned models



$$\mathrm{MYC} = (\neg \mathrm{TCF4} \wedge \neg \mathrm{PCBP4}) \vee (\neg \mathrm{PCBP4} \wedge \mathrm{TERT})$$

[Bolteau et al., *in prep.*]

Regulatory mechanisms in the learned models



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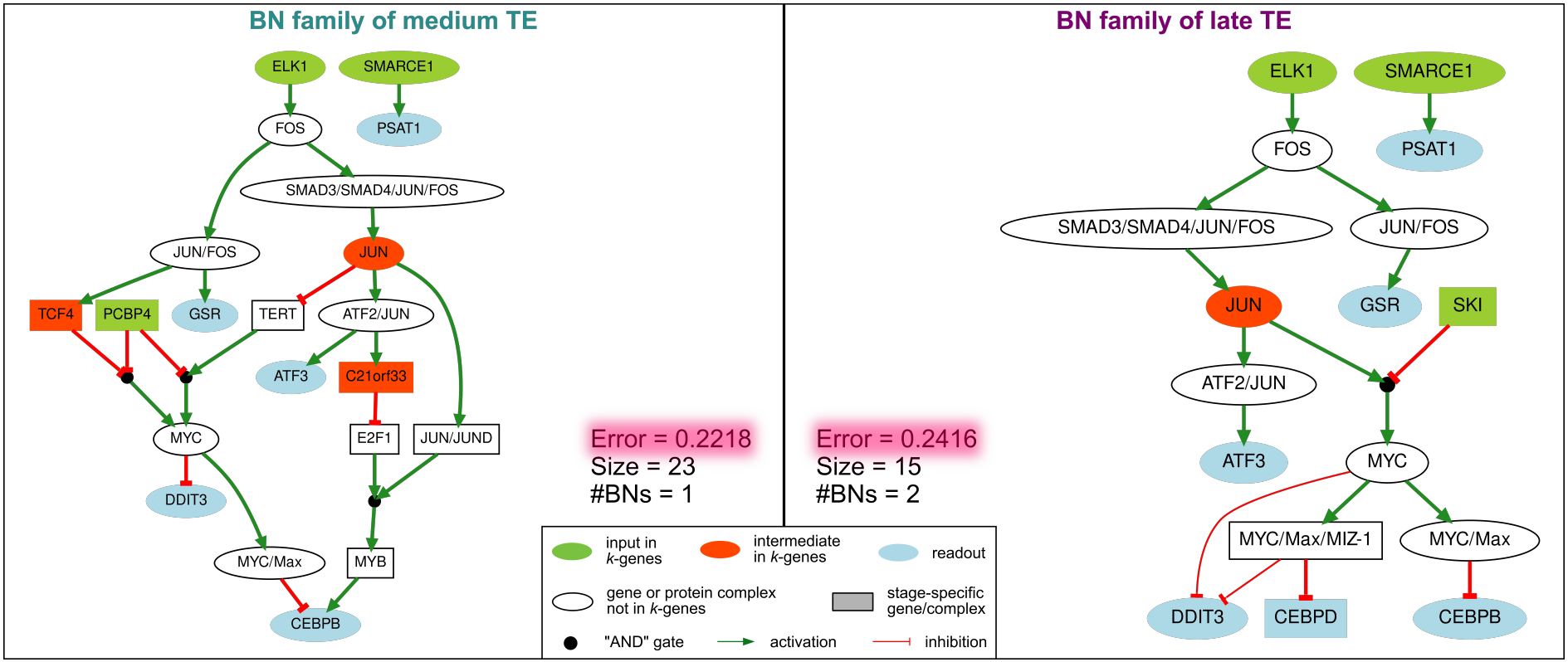

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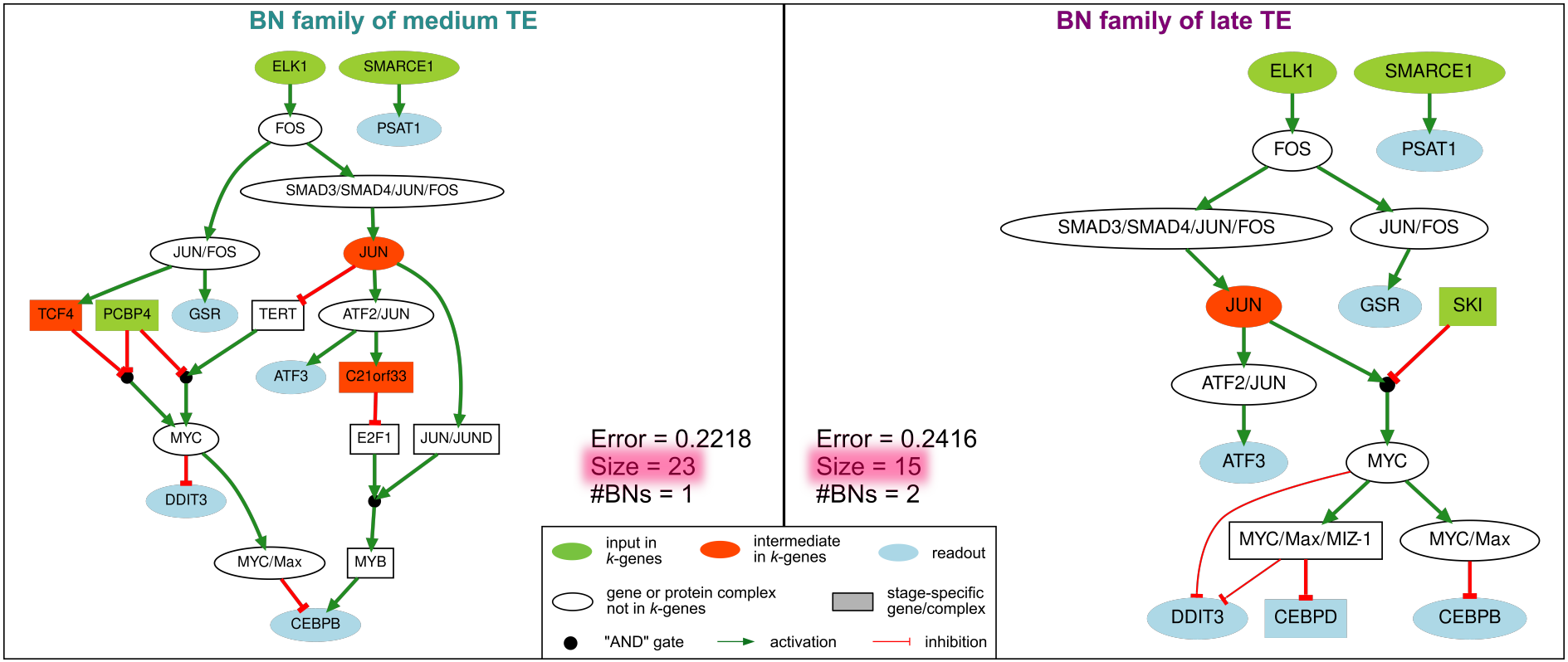

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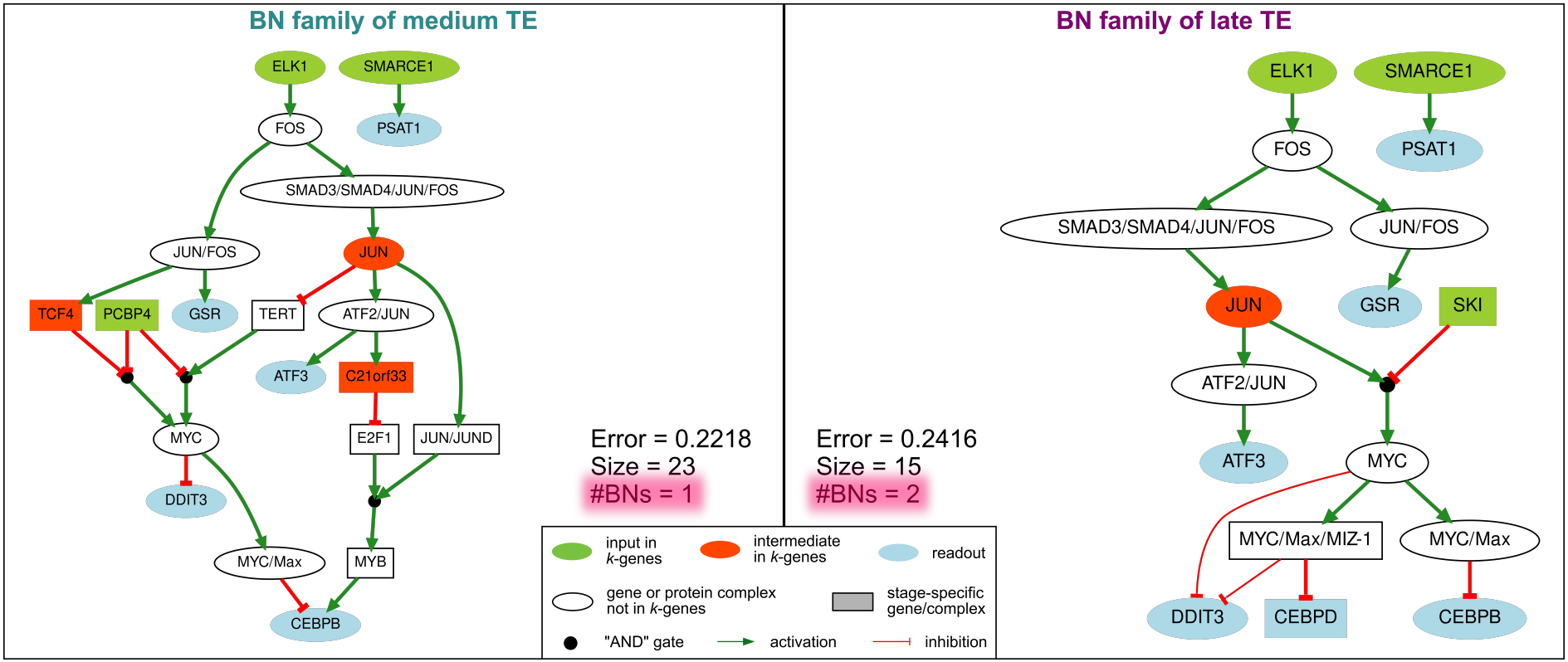
Regulatory mechanisms in the learned models



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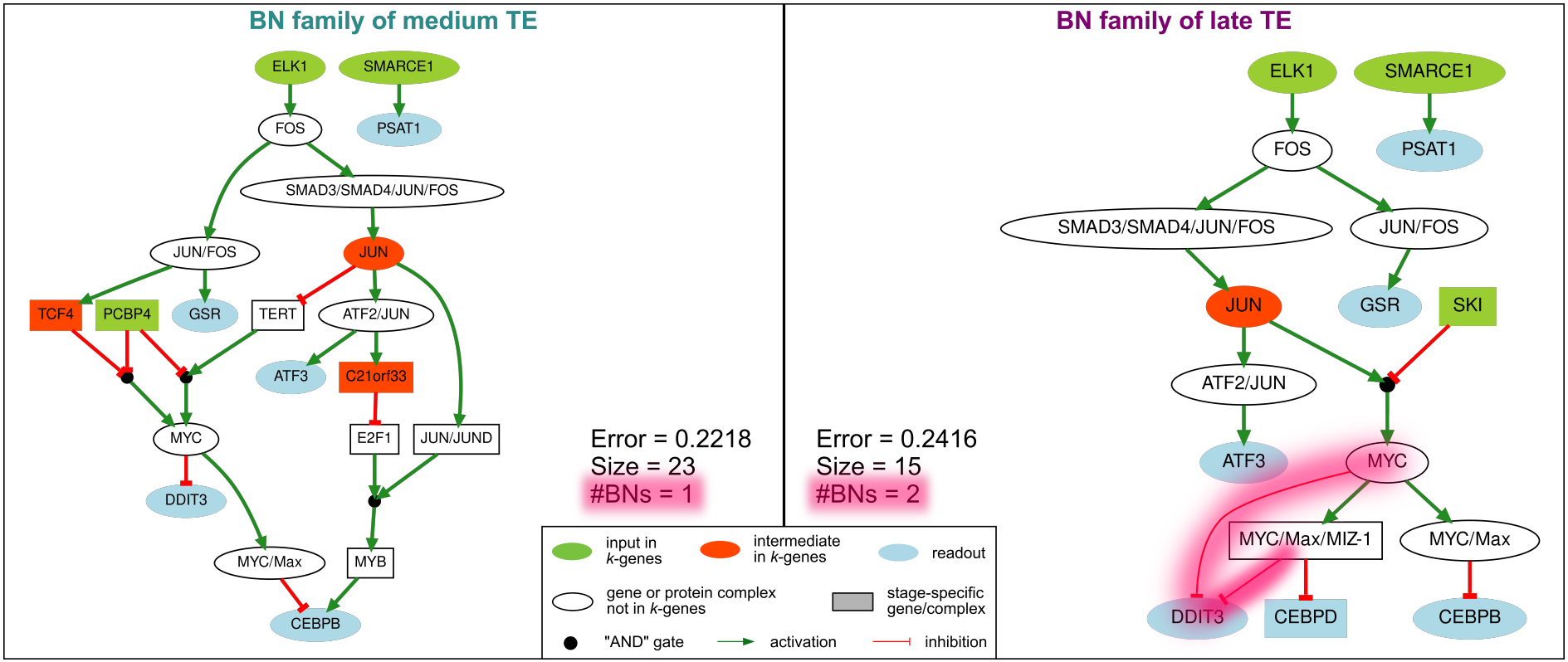

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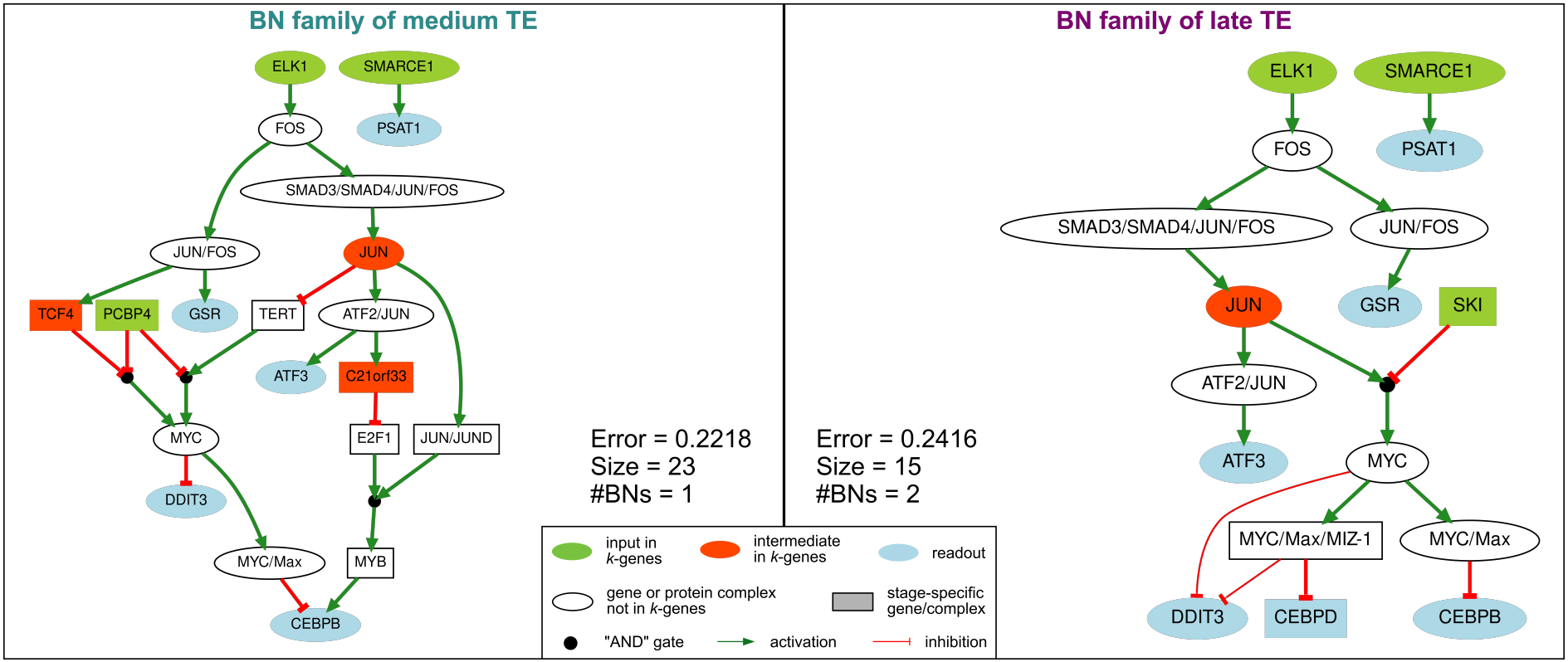
Regulatory mechanisms in the learned models



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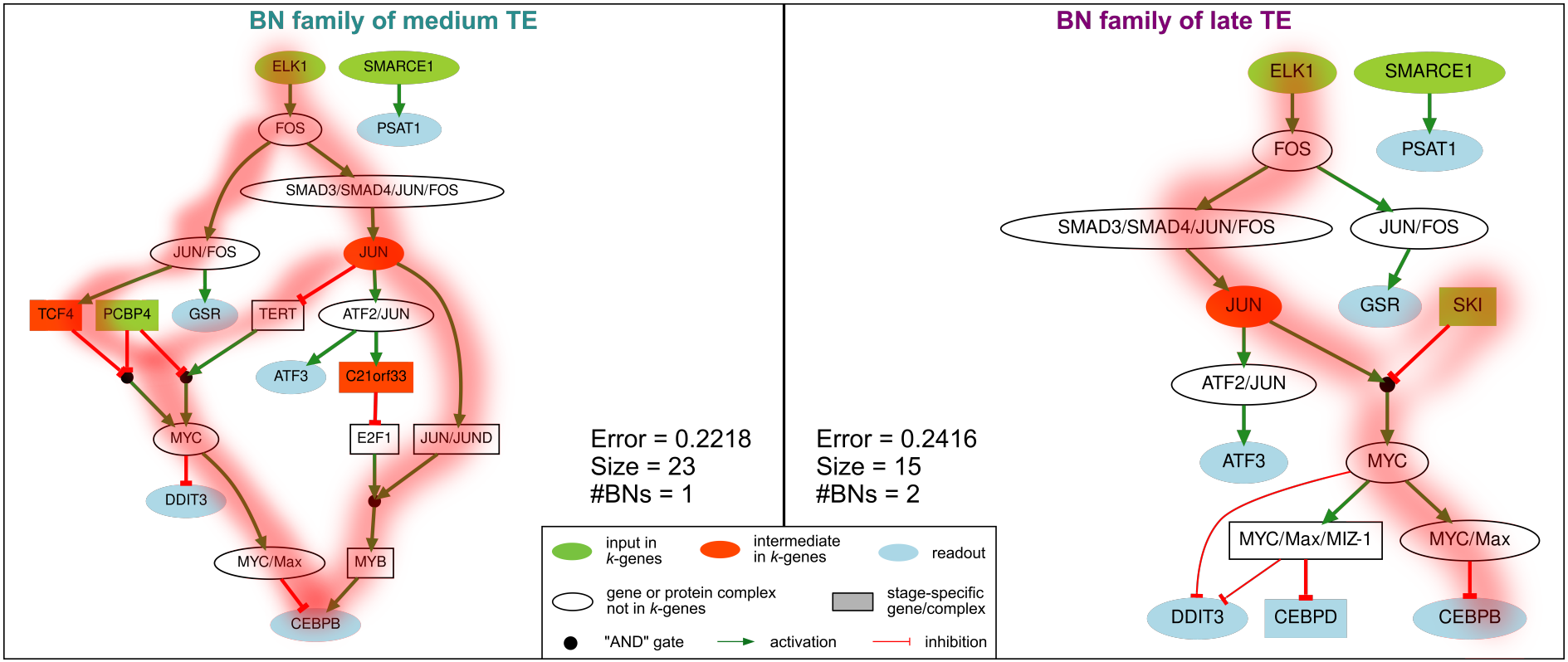

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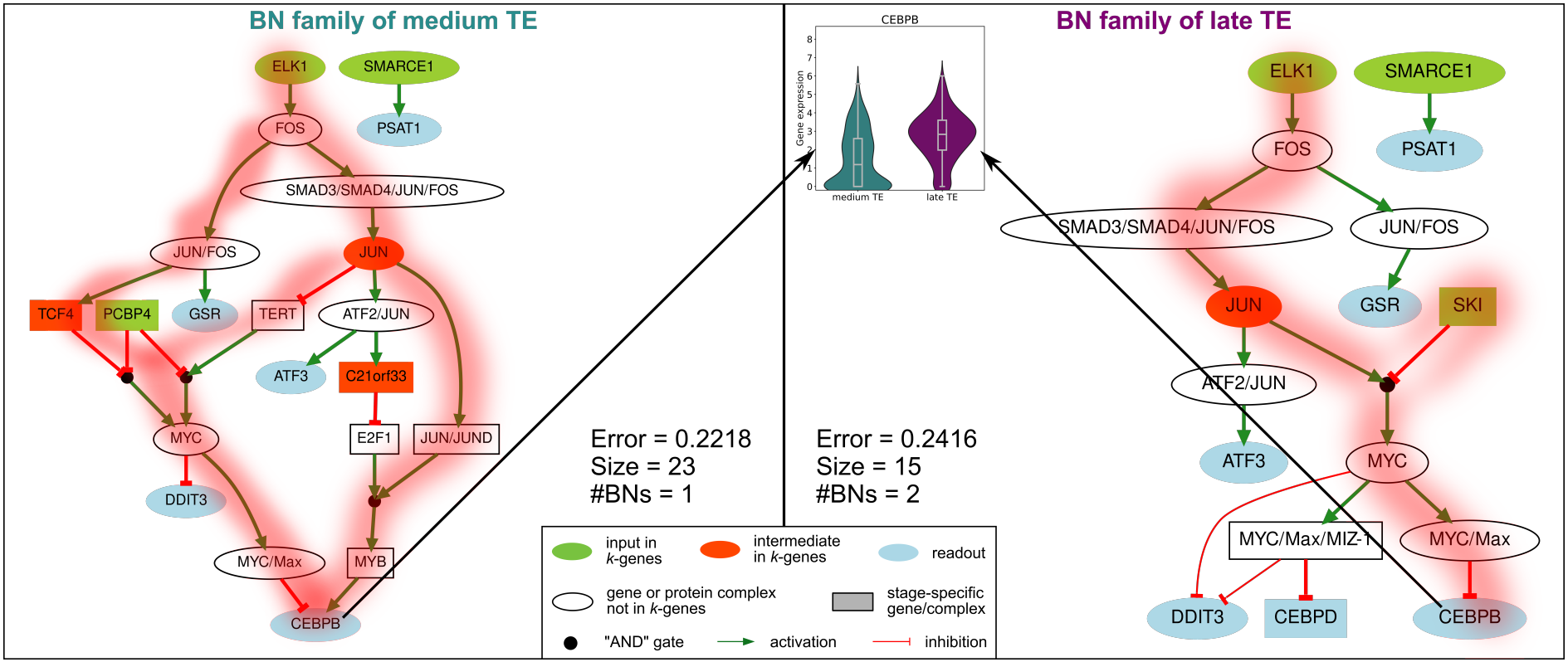

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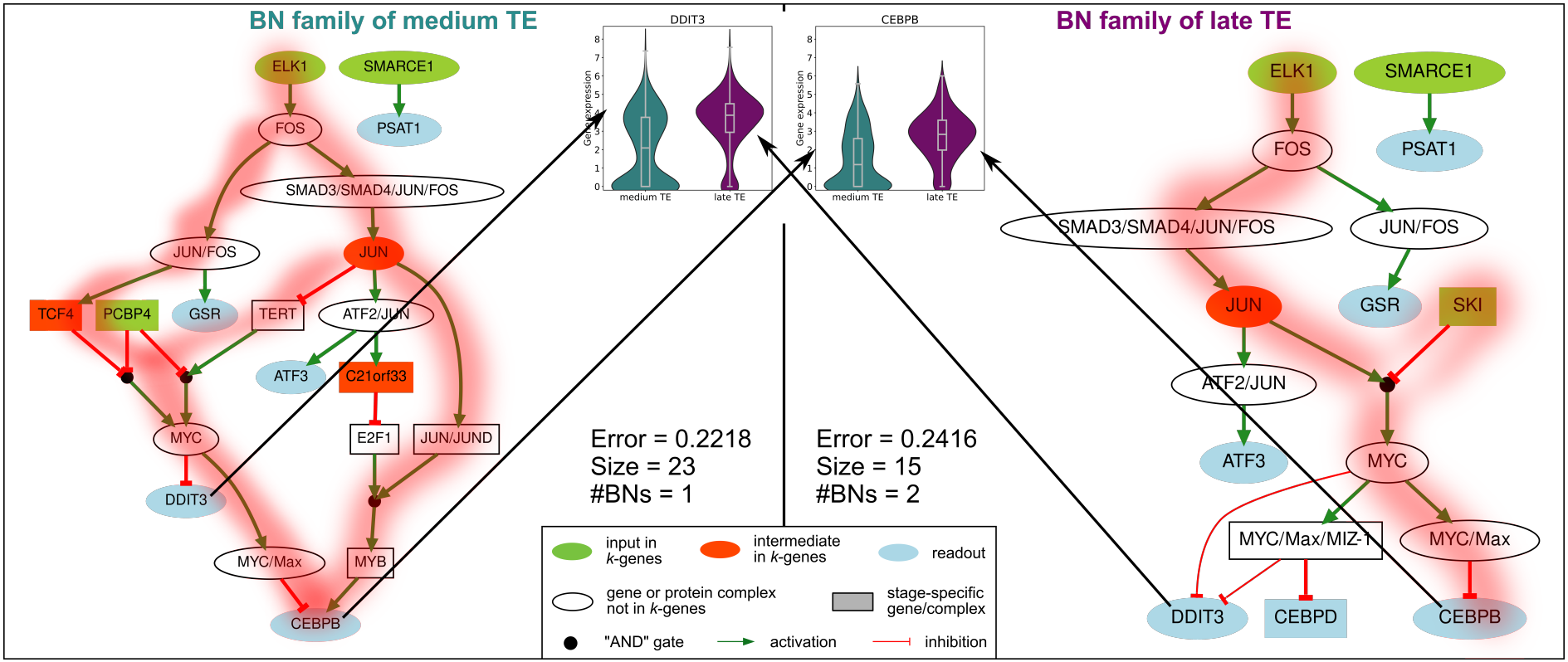

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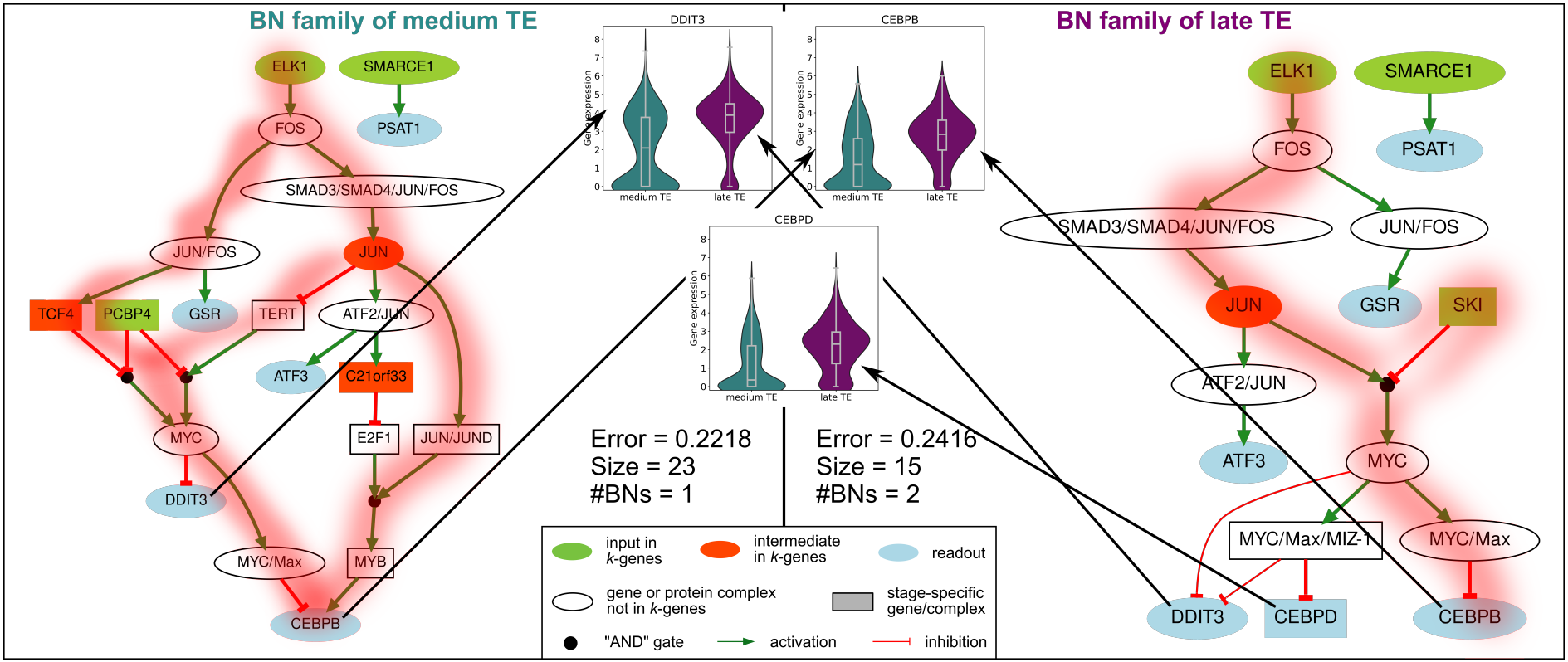

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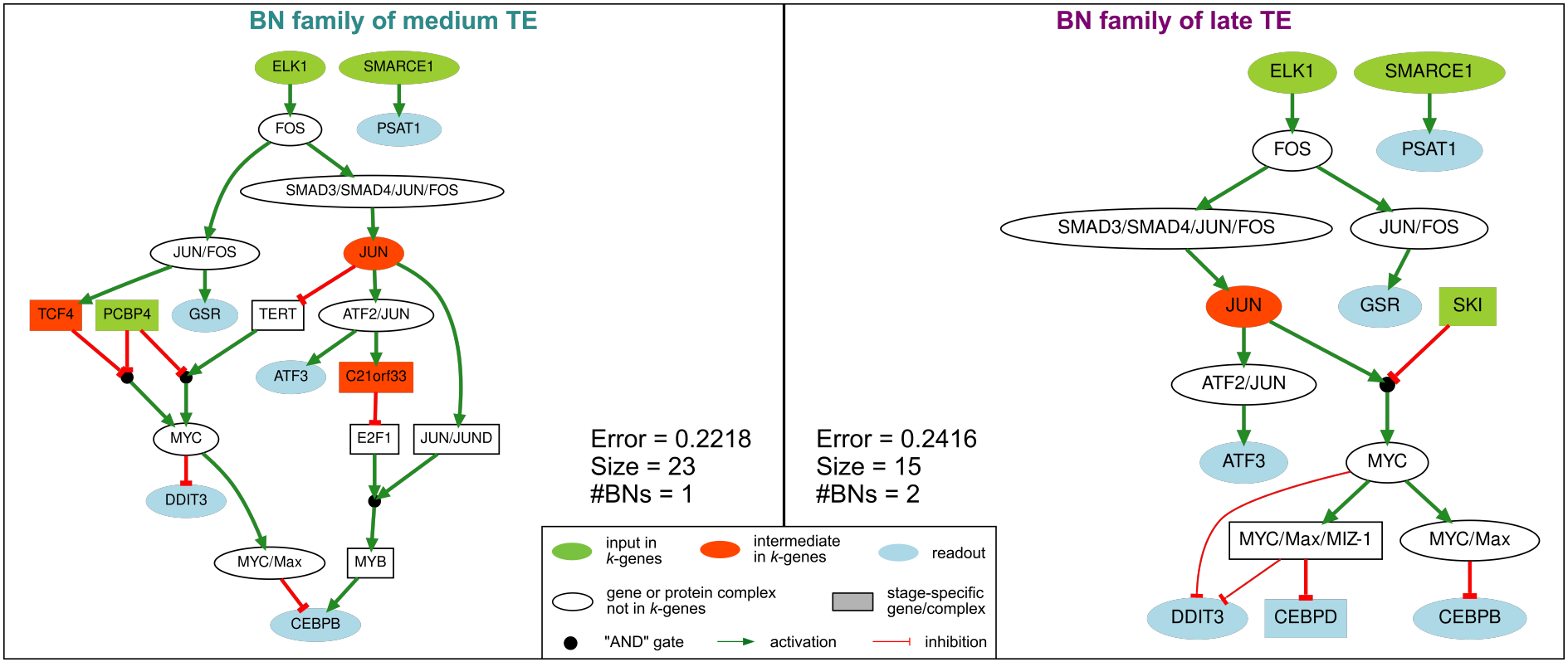

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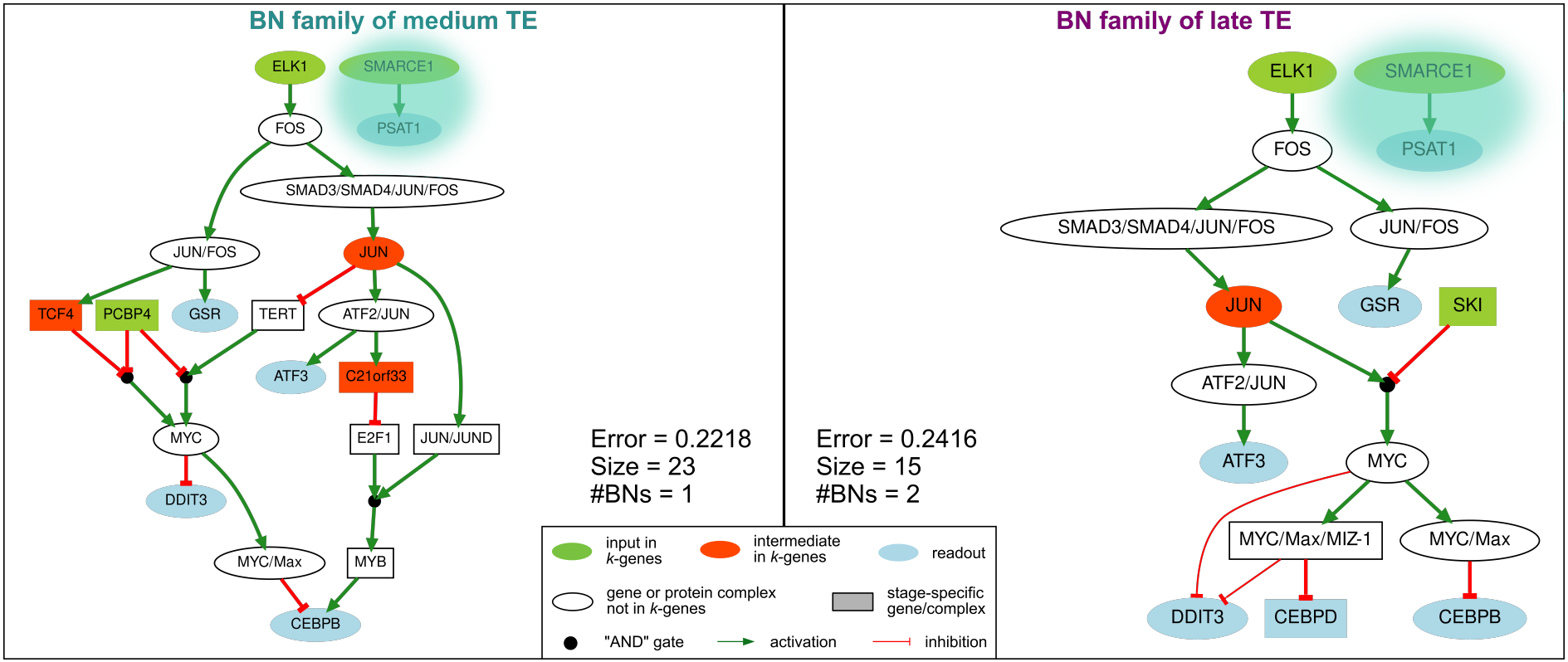

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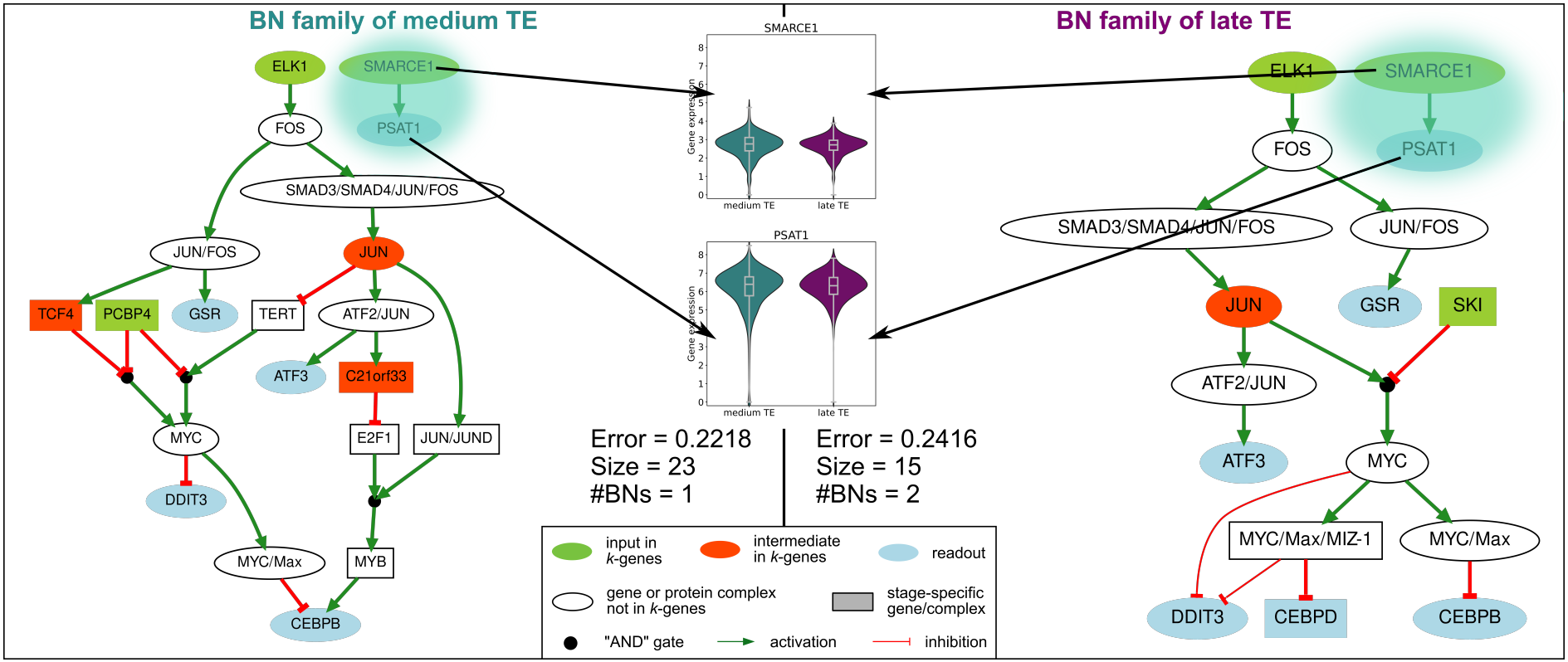

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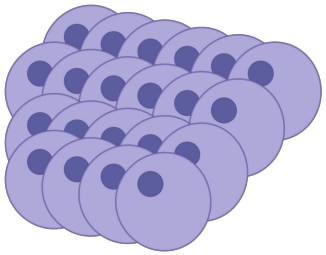
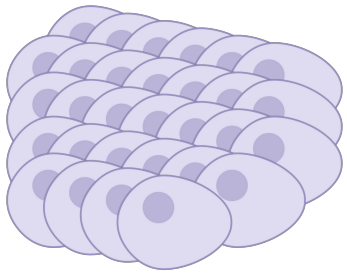
Validation of the learned models: Cell classifier



Pseudo-perturbation cells
(training set)



Redundant cells
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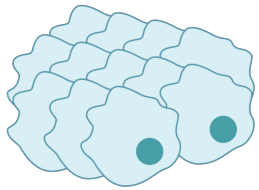

Other cells
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[Bolteau et al., *in prep.*]

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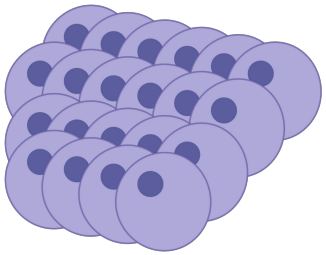

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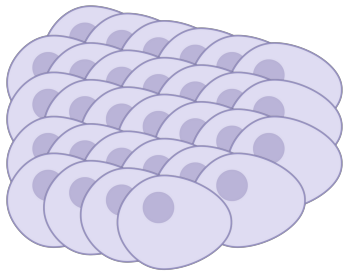
Accuracy	BAC	Medium TE accuracy	Late TE accuracy
72 %	72 %	64 %	81 %



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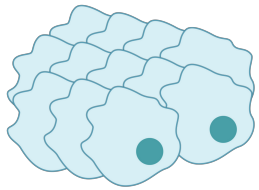

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Accuracy	BAC	Medium TE accuracy	Late TE accuracy
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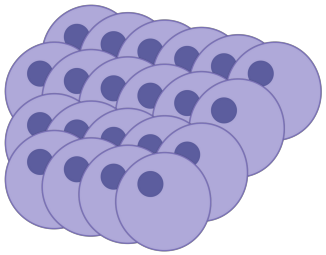

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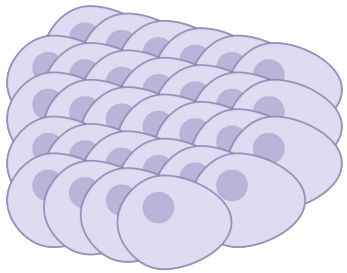

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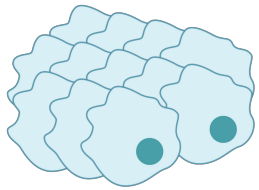

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SCIBORG learns accurate models

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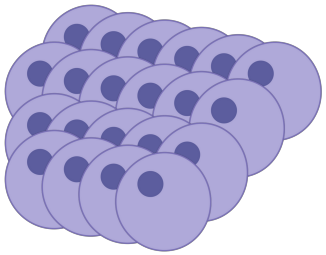

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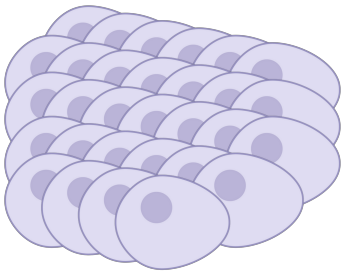

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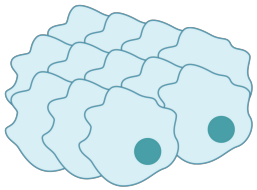

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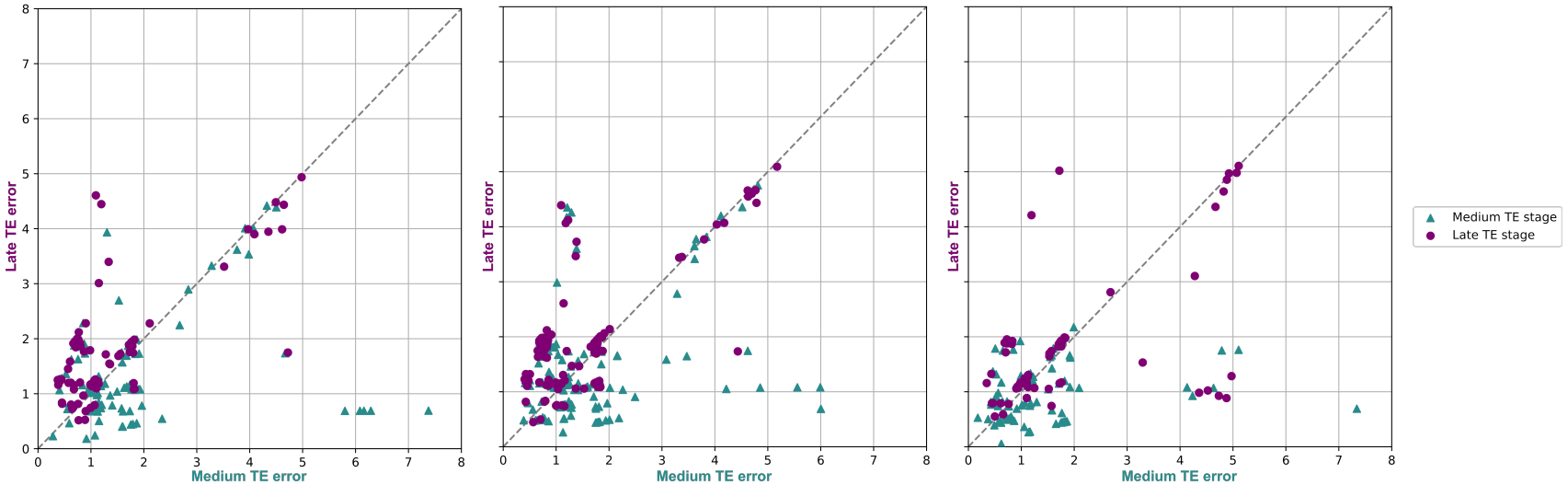

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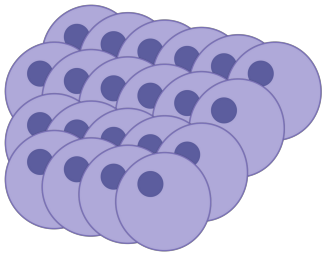

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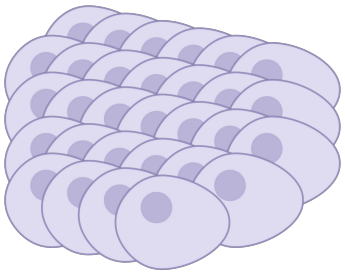

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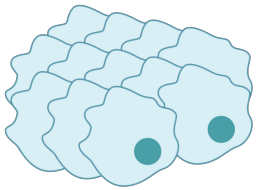

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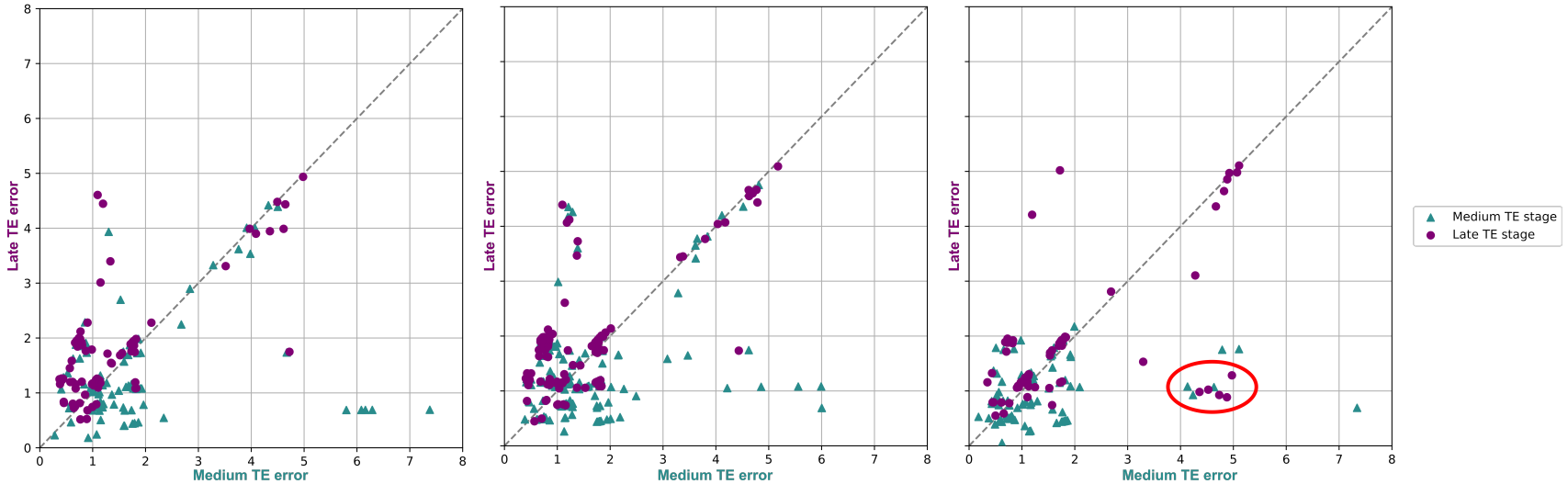

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Conclusion

Convergence of pseudo-perturbation identification

- Efficient program
- Limited number of equivalent solutions
- Pseudo-perturbations representativity

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Robustness in both equivalent solutions

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Gene regulatory mechanisms

- Distinguishing 2 stages
- Potential key genes

Conclusion

Complementarity with the state-of-the-art methods

Method	Cell heterogeneity	Cellular dynamic evolution	Exhaustive enumeration	Validation
SCIBORG		 *		

* Secondary objective

Conclusion

Complementarity with the state-of-the-art methods

Method	Cell heterogeneity	Cellular dynamic evolution	Exhaustive enumeration	Validation
SCIBORG	✓	✗*	✓	✓

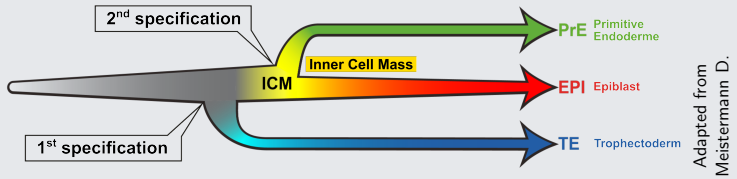
* Secondary objective

Open source python package

https://github.com/mathieubolteau/SCIBORG/

Perspectives

Study other developmental stages via exploration other cell fates (PrE, EPI)



PrE = primitive endorderm ; EPI = epiblast ; TE = trophectoderm

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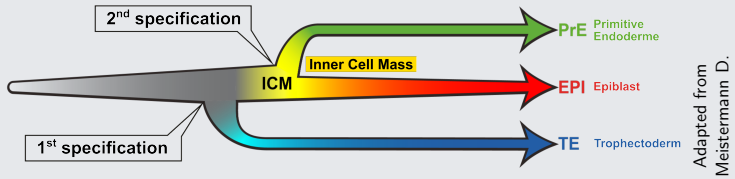
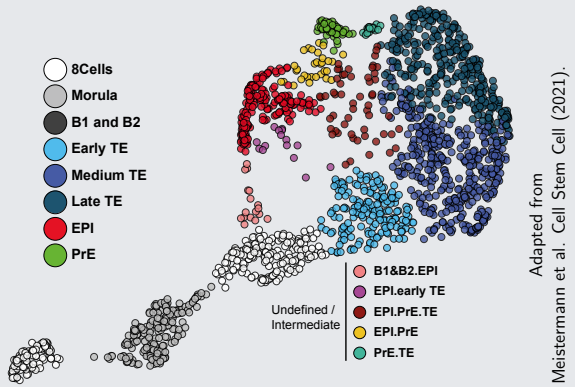


A tool for classifying undefined cells



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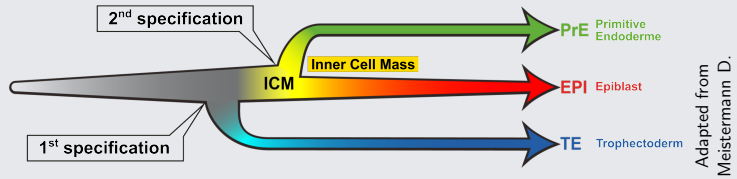

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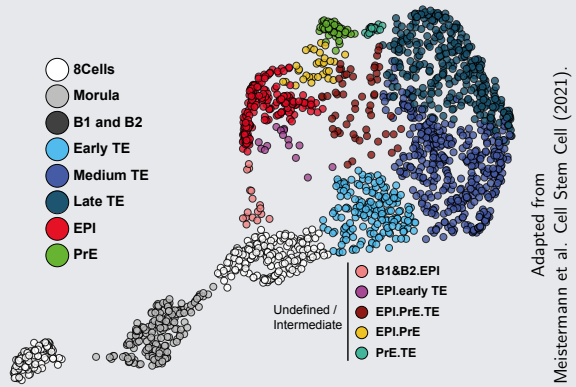

Biological validation using blastoids

PrE = primitive endorderm ; EPI = epiblast ; TE = trophectoderm

Perspectives

Apply SCIBORG on other biological studies	Inner lymphoid cell development (CRCI2NA lab)	Cell differentiation in Duchenne muscular dystrophy (TaRGeT lab)

Perspectives

Apply SCIBORG
on other biological studies

Inner lymphoid cell development (CRCI2NA lab)

Cell differentiation in Duchenne muscular dystrophy (TaRGeT lab)

Modeling dynamic processes
to deal with more than two stages
(caspo-ts)

[Razzaq et al., *PLOS Comp. Bio.* (2018)]

- Preliminary work has been conducted
  (Centrale Nantes students supervision)
- Work to be continued with another Ph.D. thesis

Aknowledgements

- Jérémie Bourdon @LS2N, Nantes University
- Carito Guziolowski @LS2N, Centrale Nantes
- Laurent David @CR2TI, CHU de Nantes, Nantes University
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