Robust control of Boolean networks in systems biology

Sam Pastva,
with Eva Šmijáková, David Šafránek, and Luboš Brim

Modelling gene interactions

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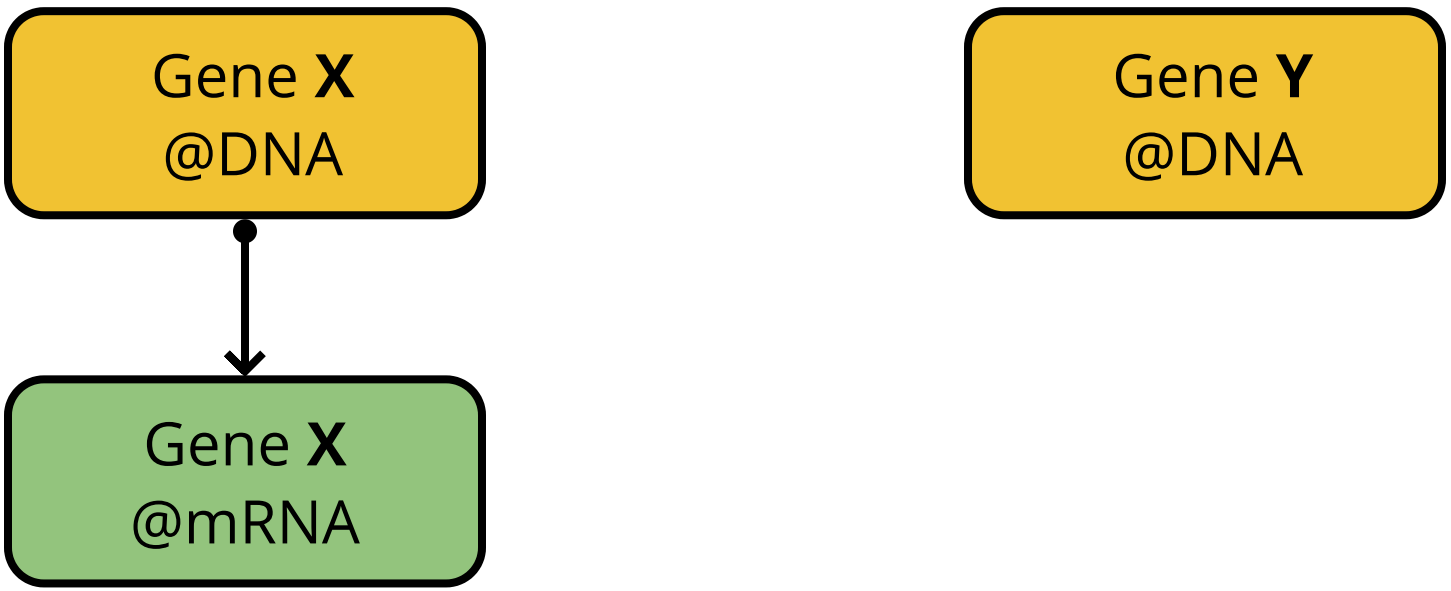

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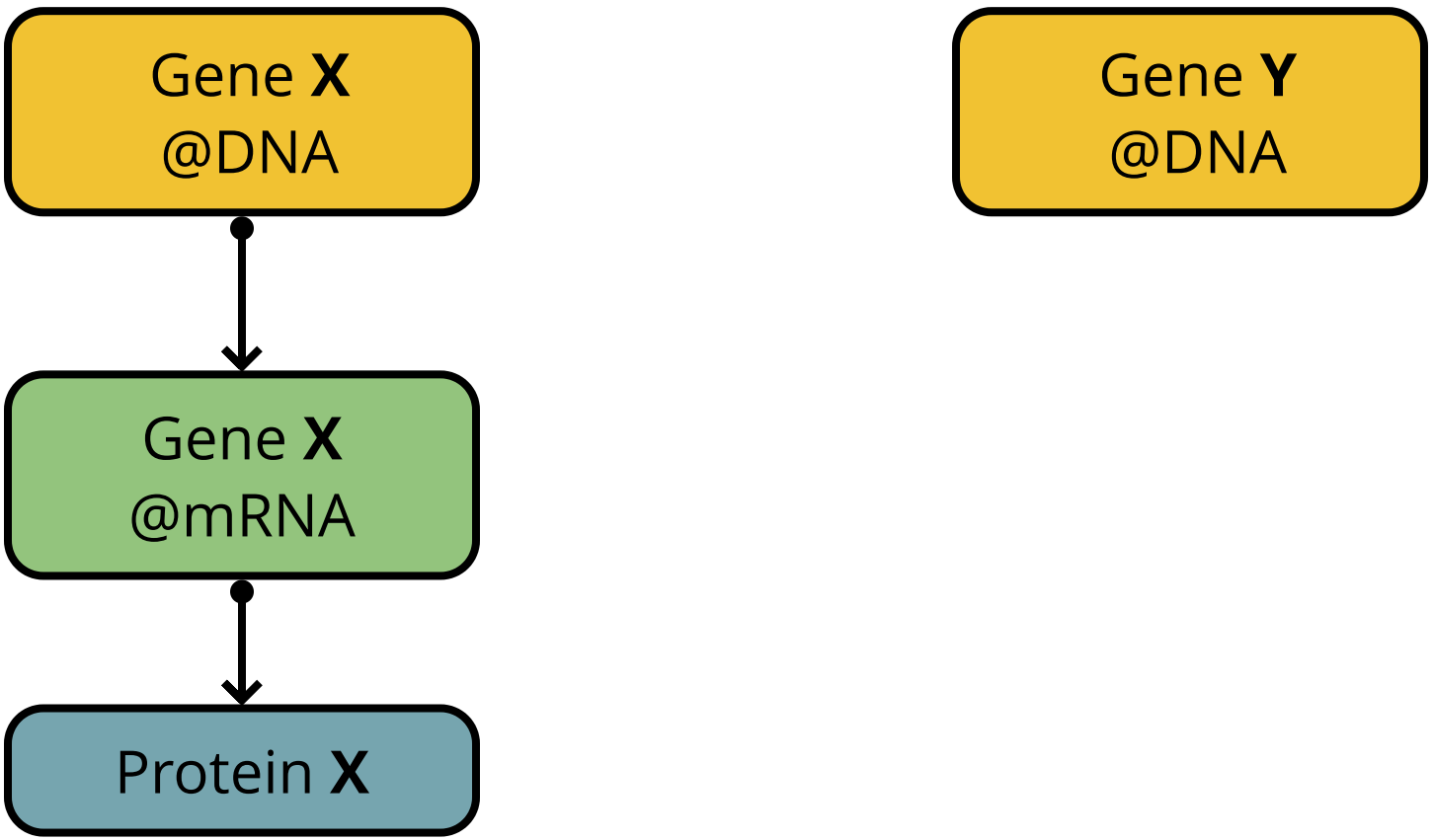

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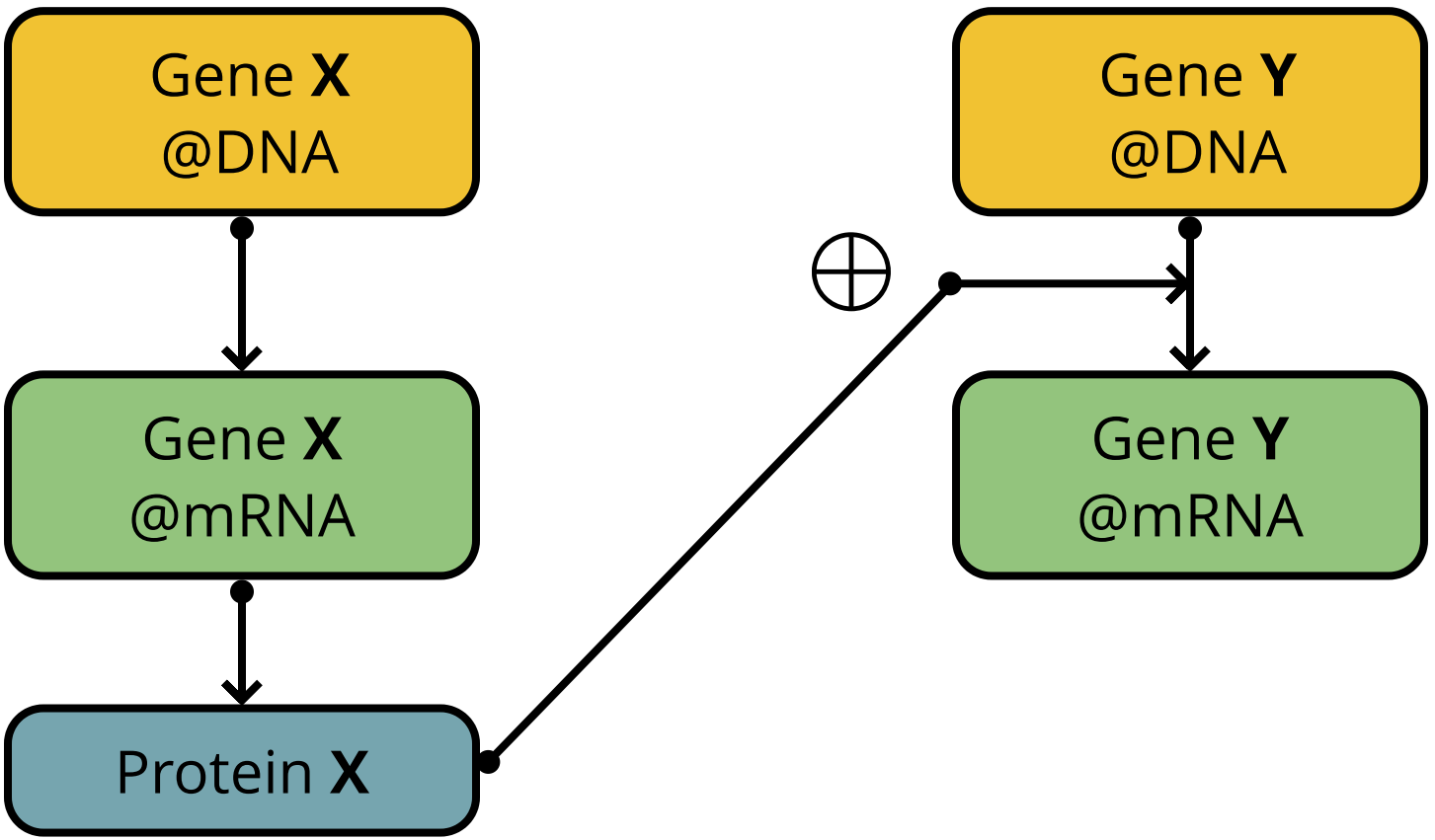

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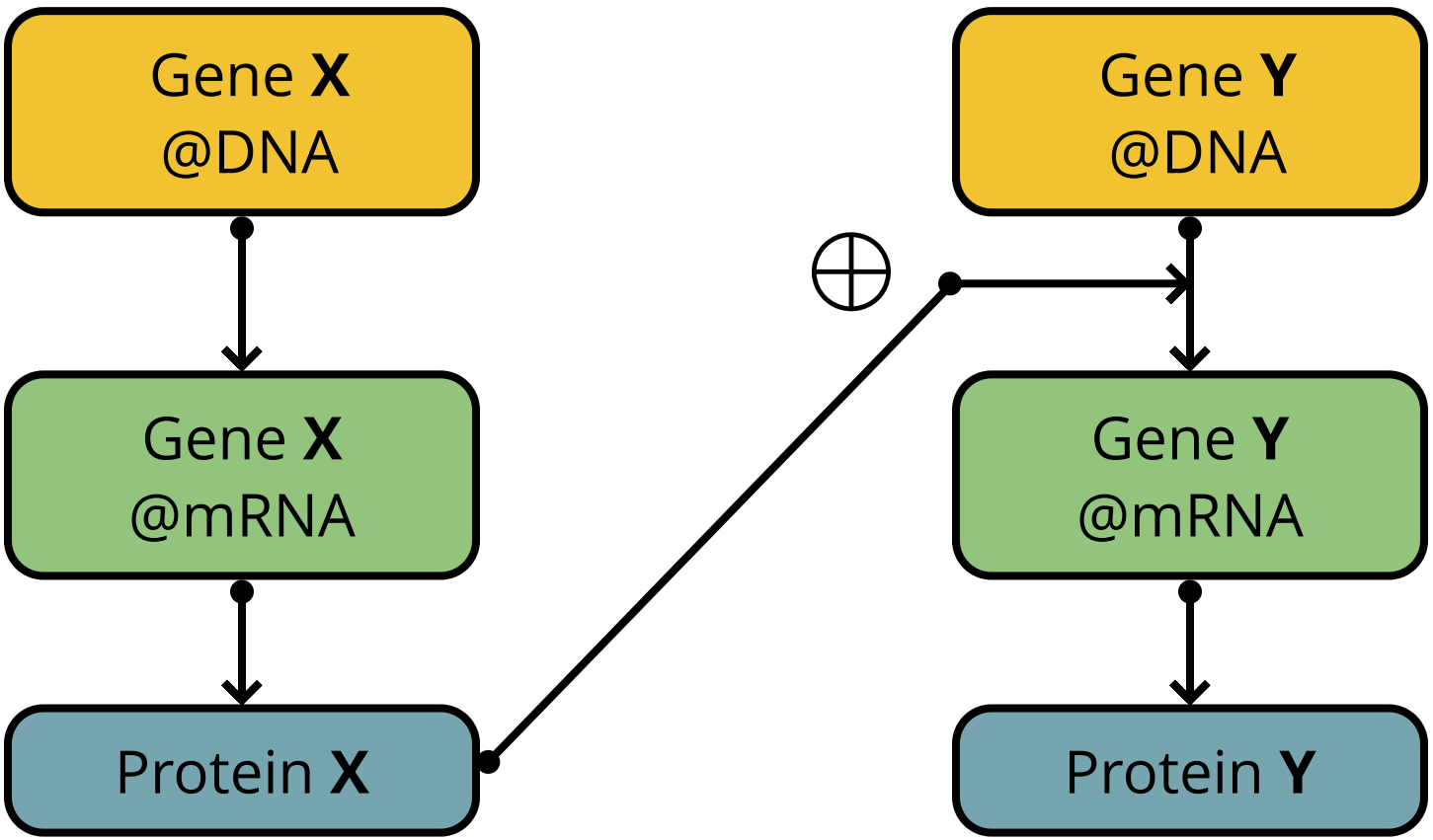

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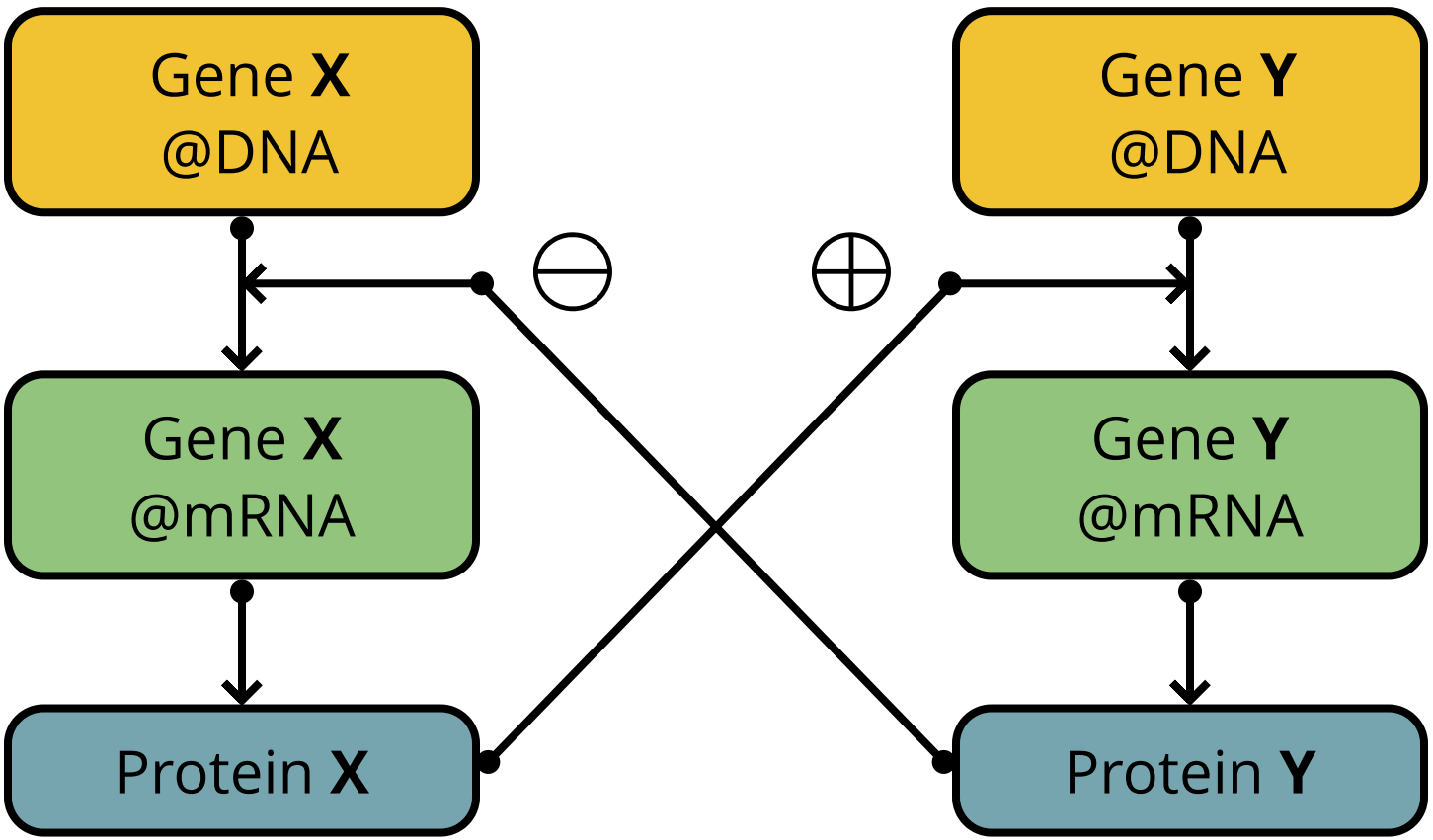


Gene **X**
Gene **Y**


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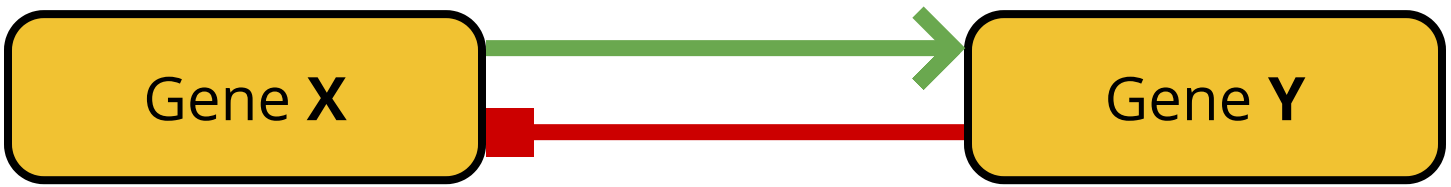
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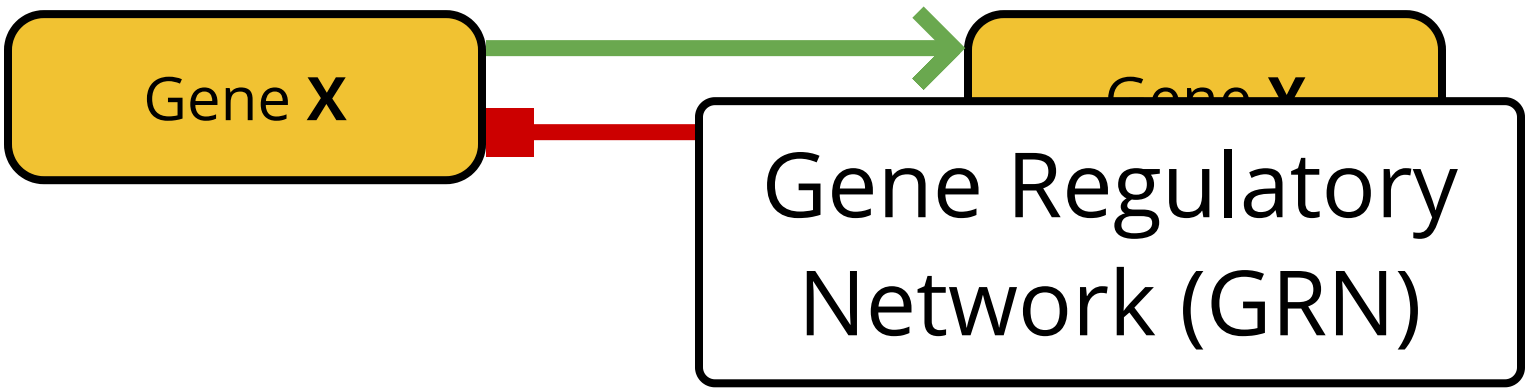
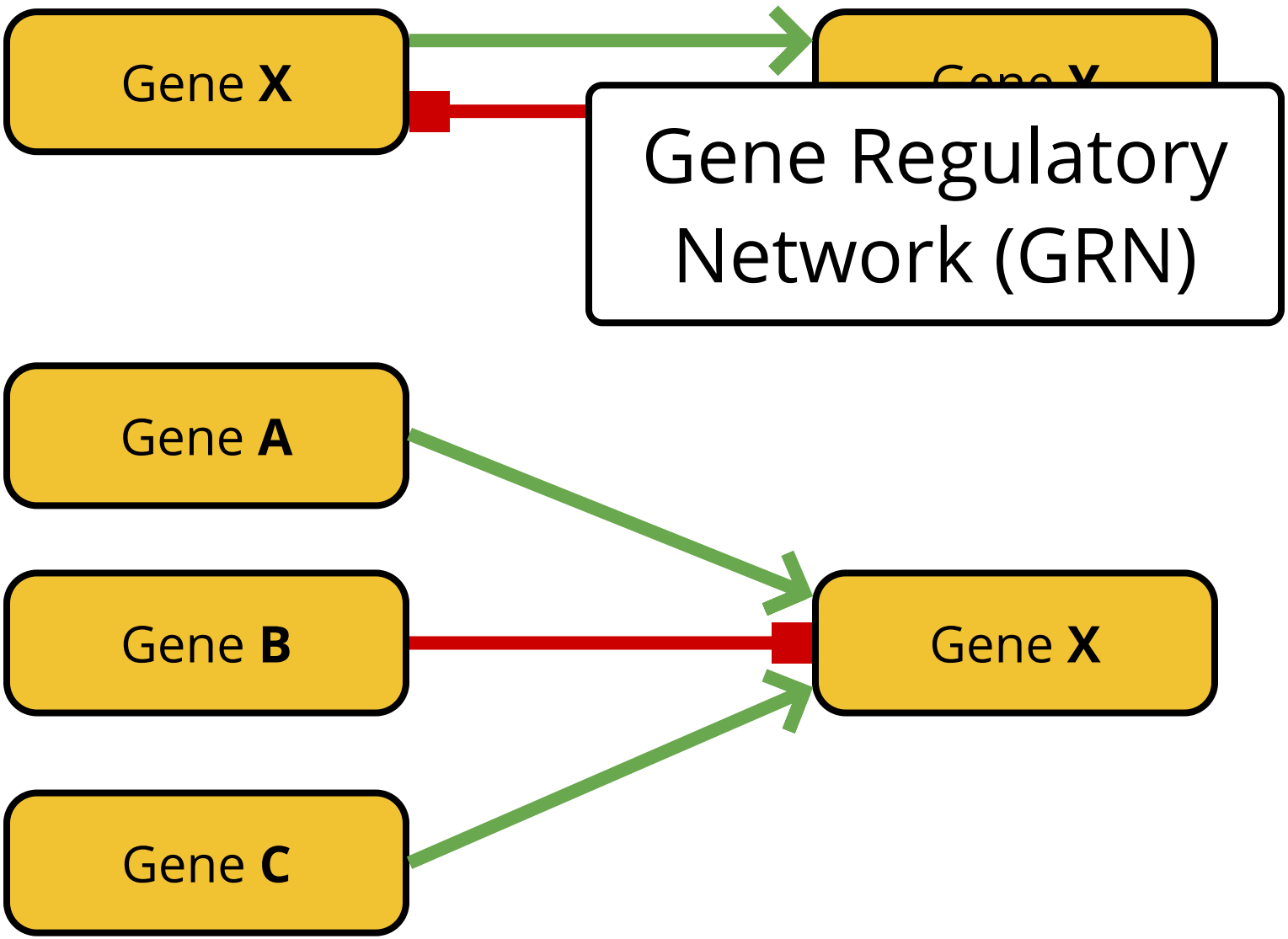

Gene **X**
Gene Regulatory Network (GRN)


Gene X
Gene Regulatory Network (GRN)
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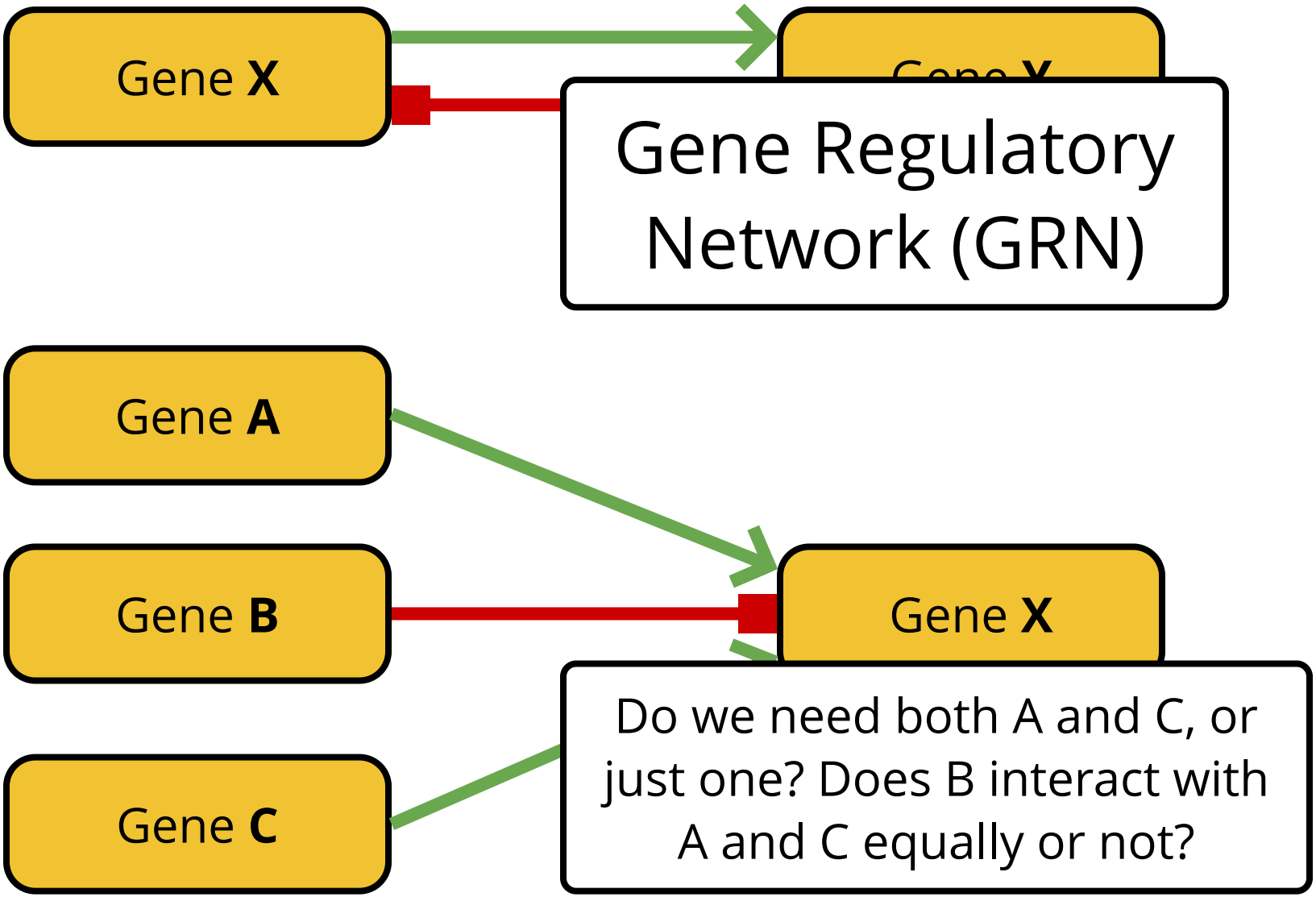
Gene B
Gene C
Gene X


Gene X
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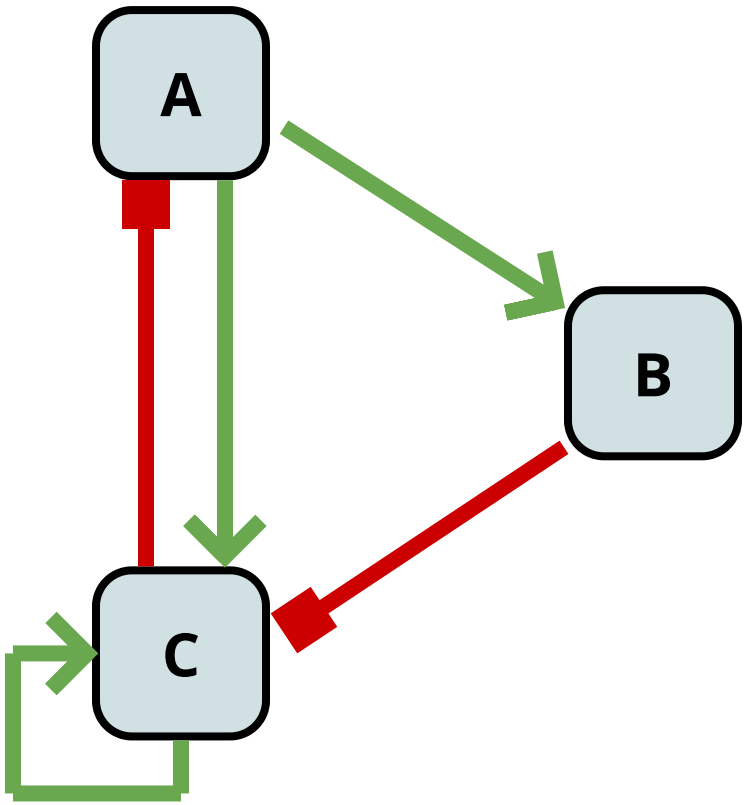
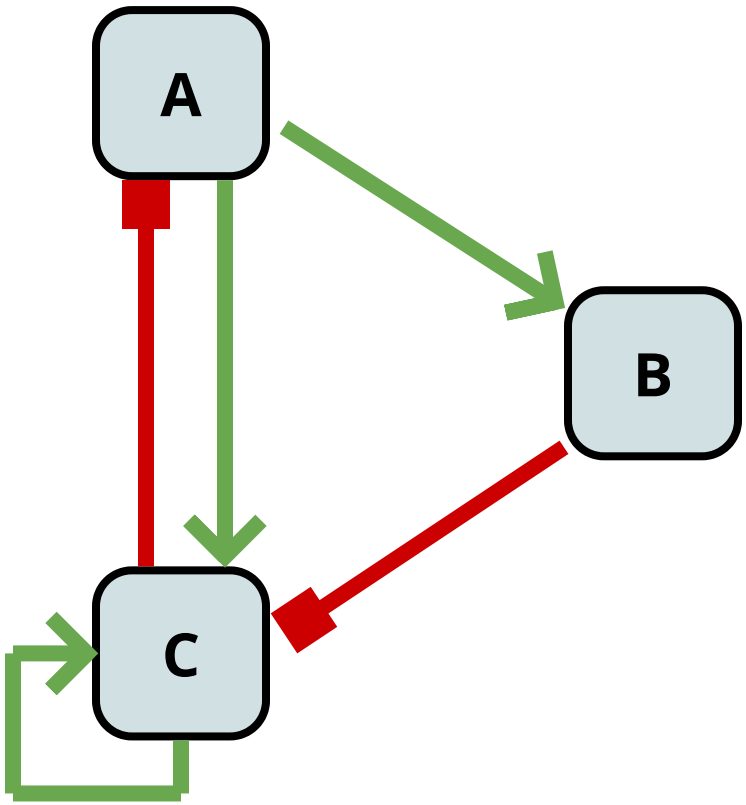
Gene X
Do we need both A and C, or just one? Does B interact with A and C equally or not?


A
B
C



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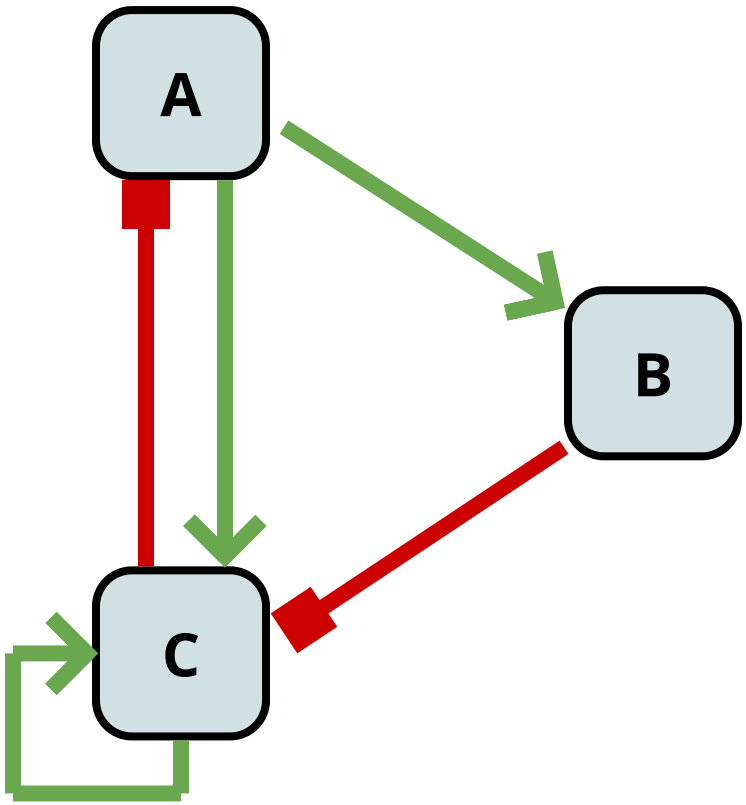

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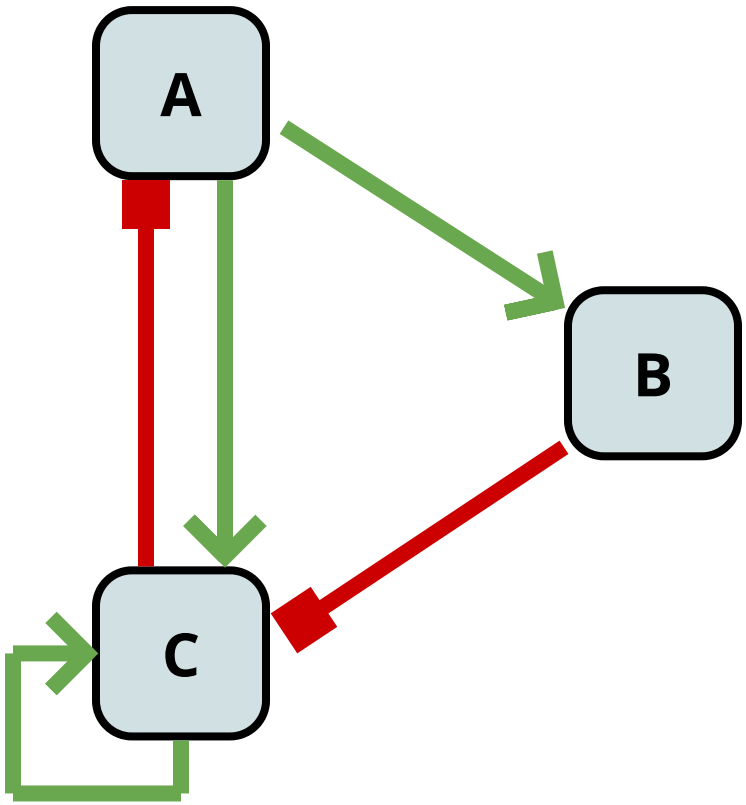

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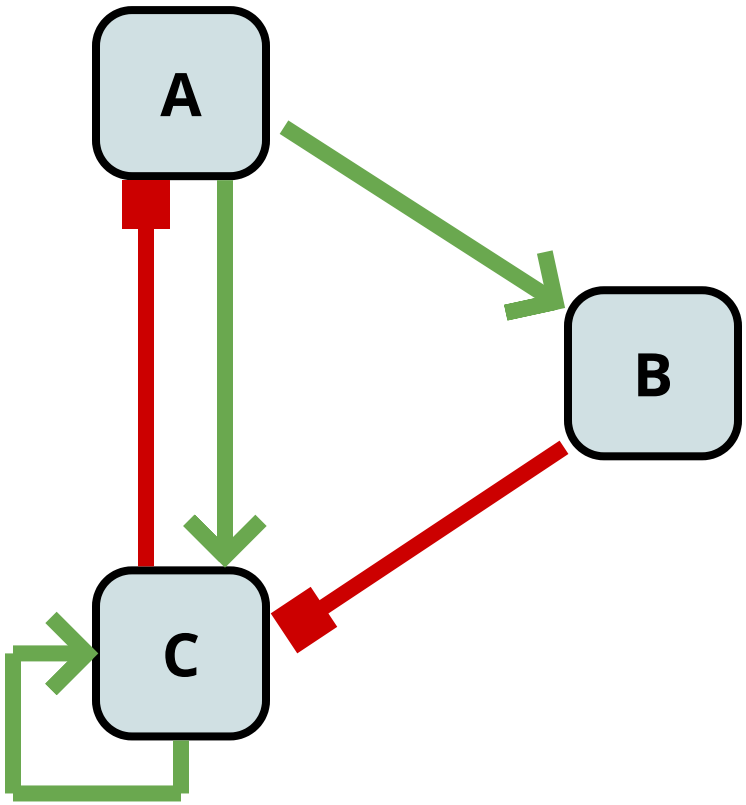

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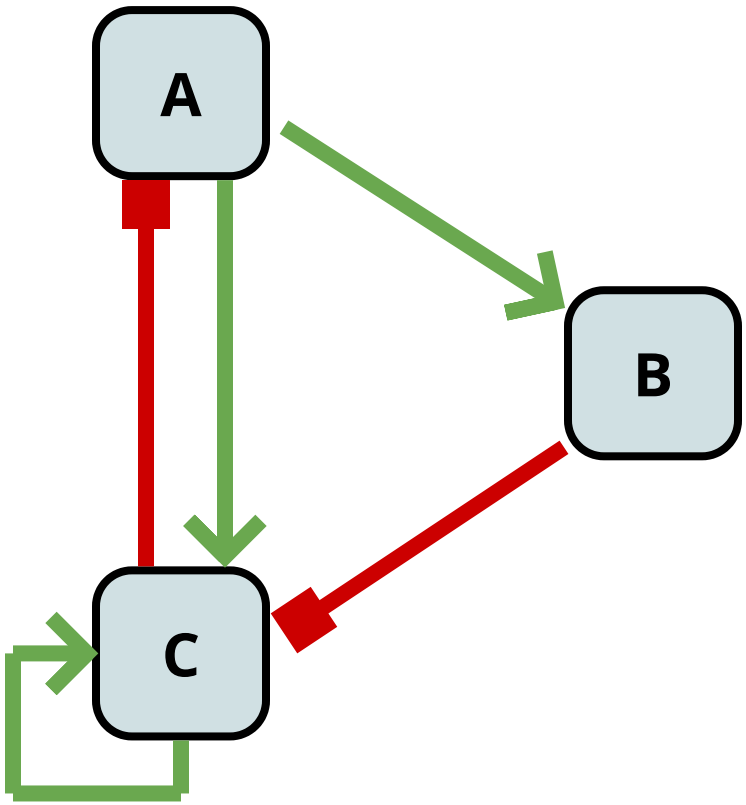

Boolean Network (BN)

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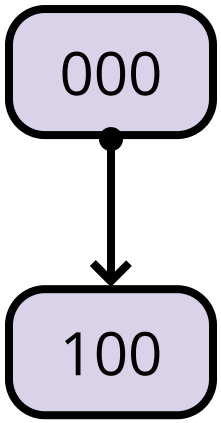

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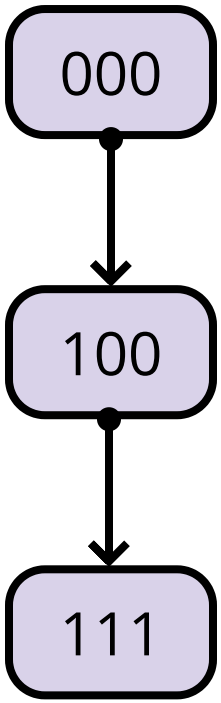

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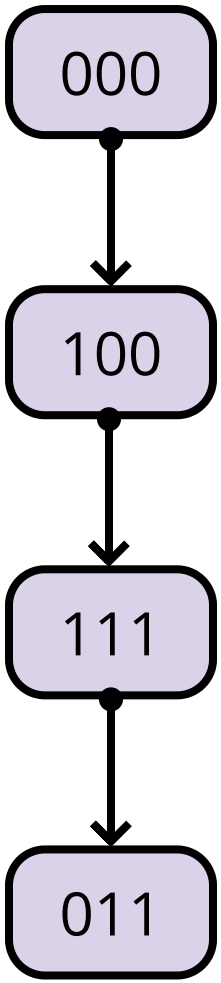

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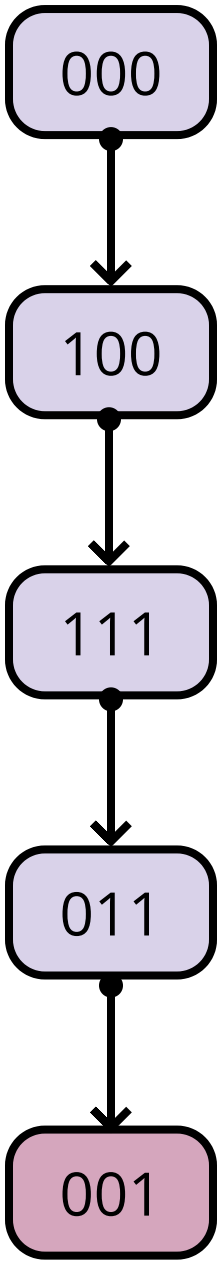

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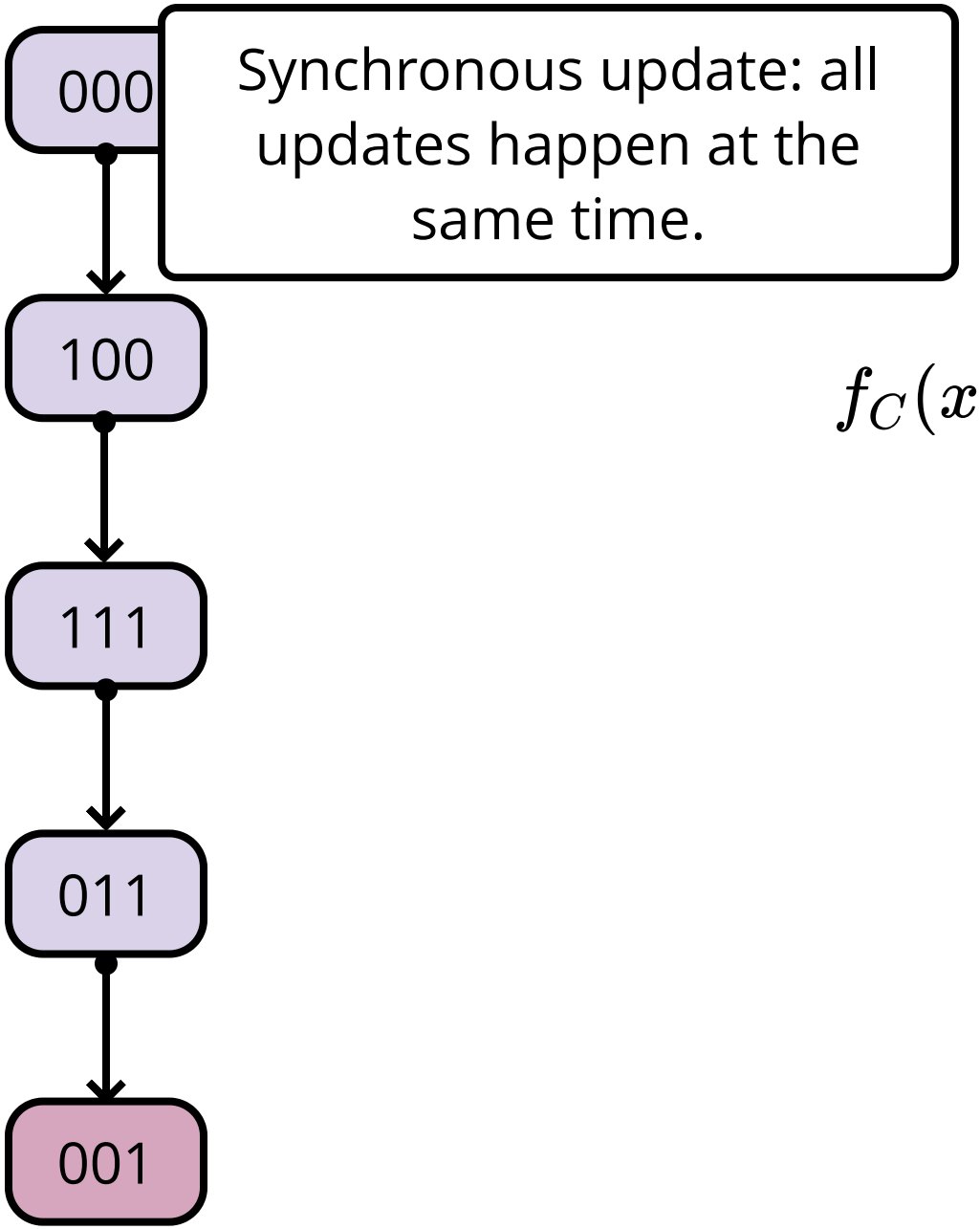

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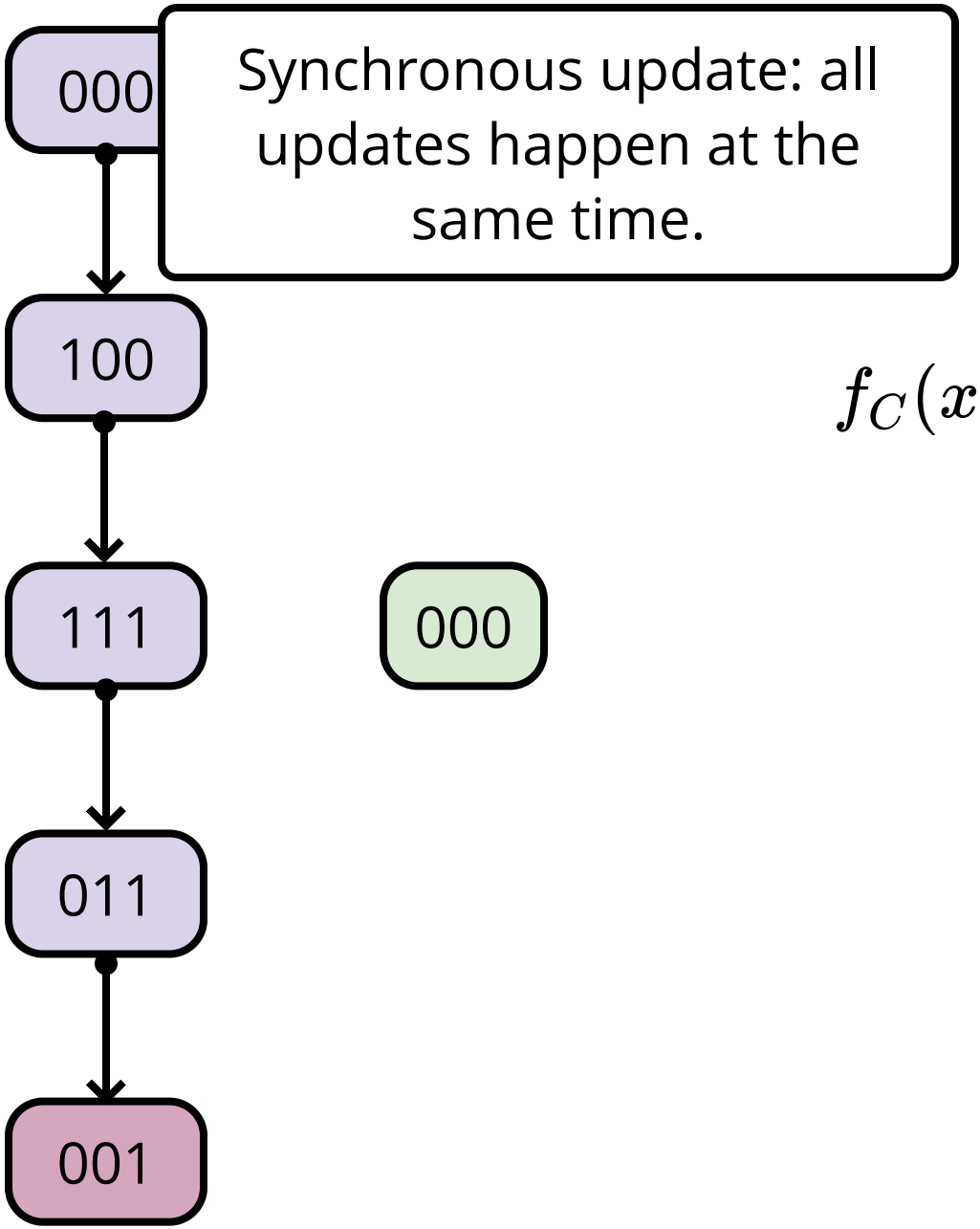

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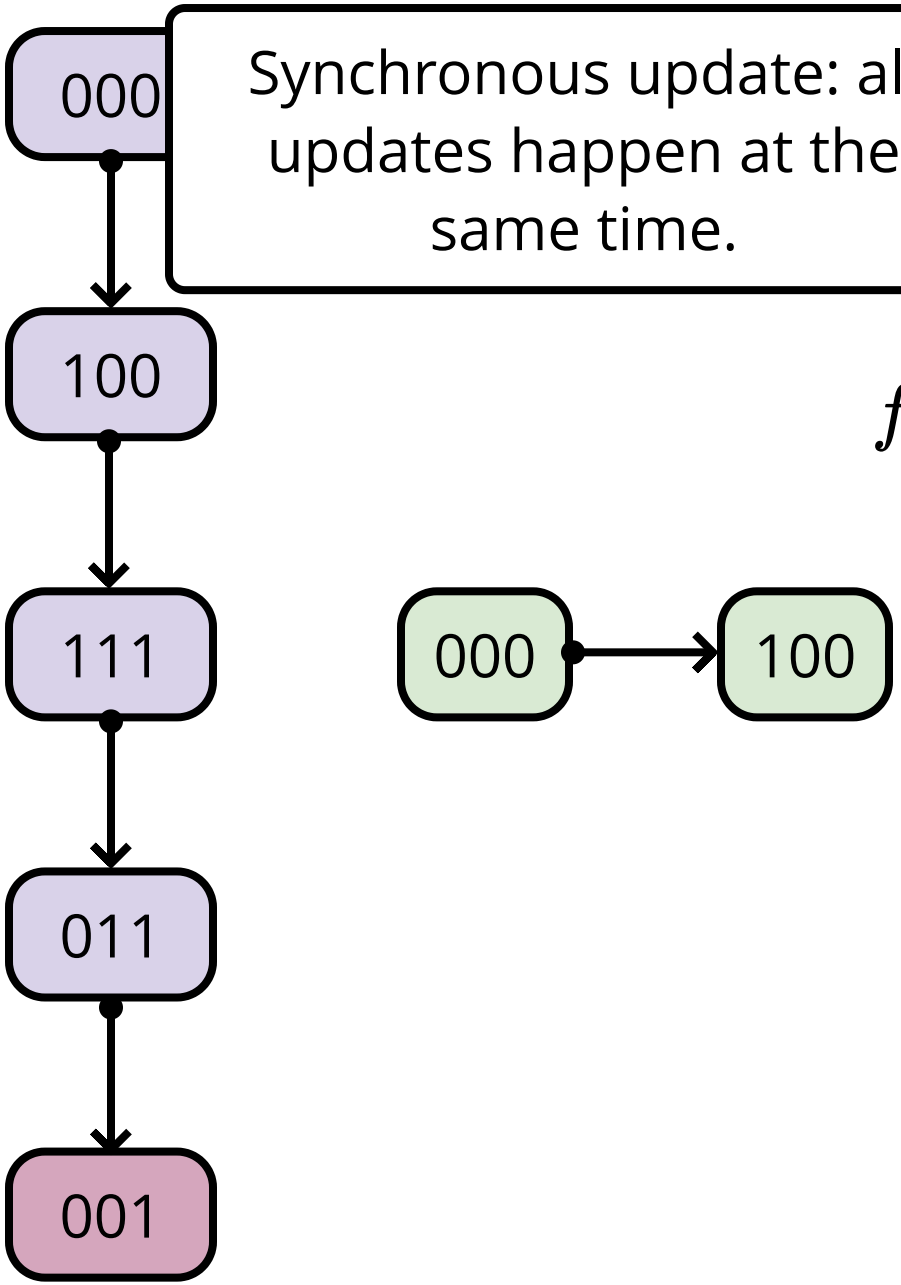

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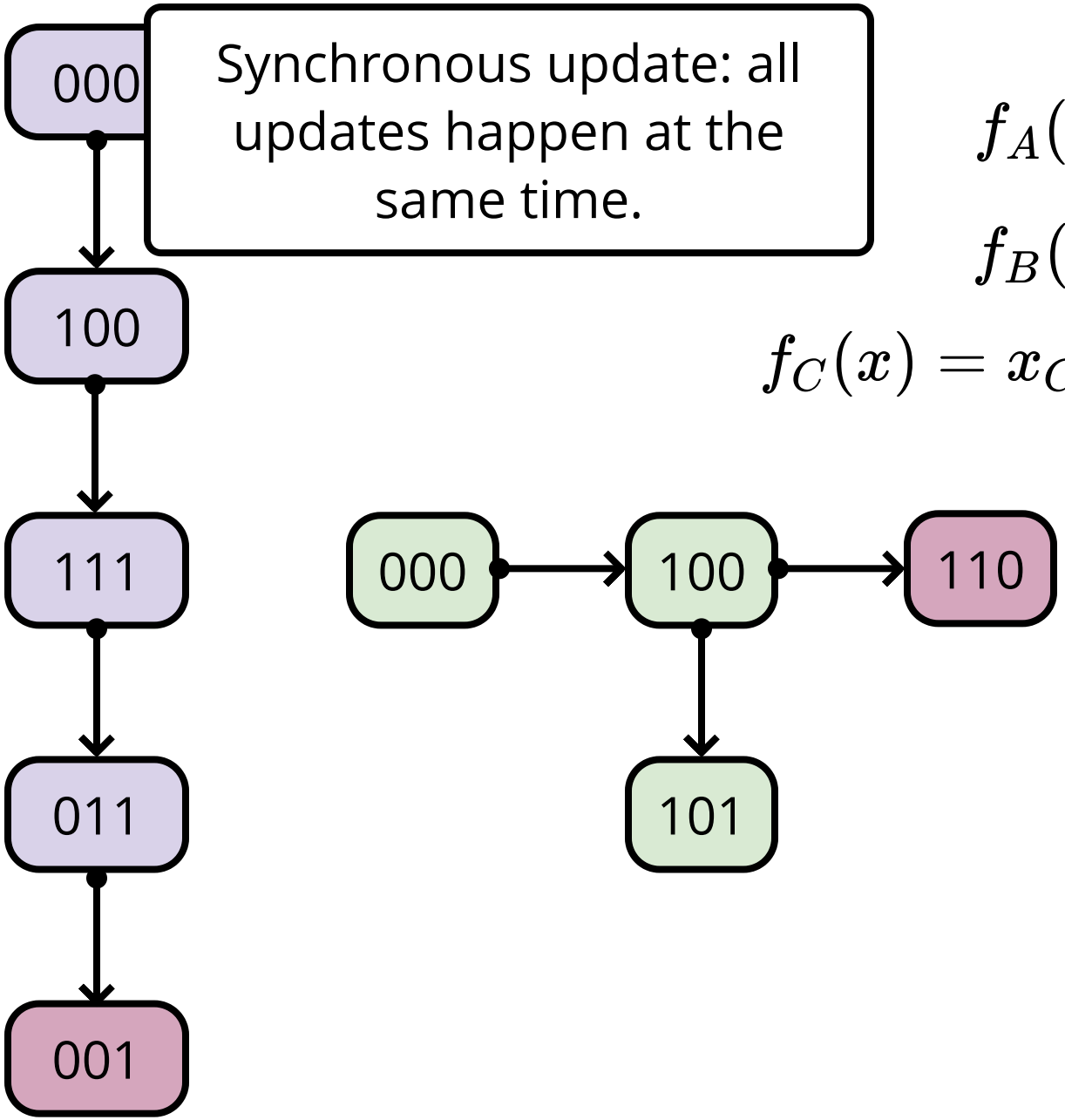

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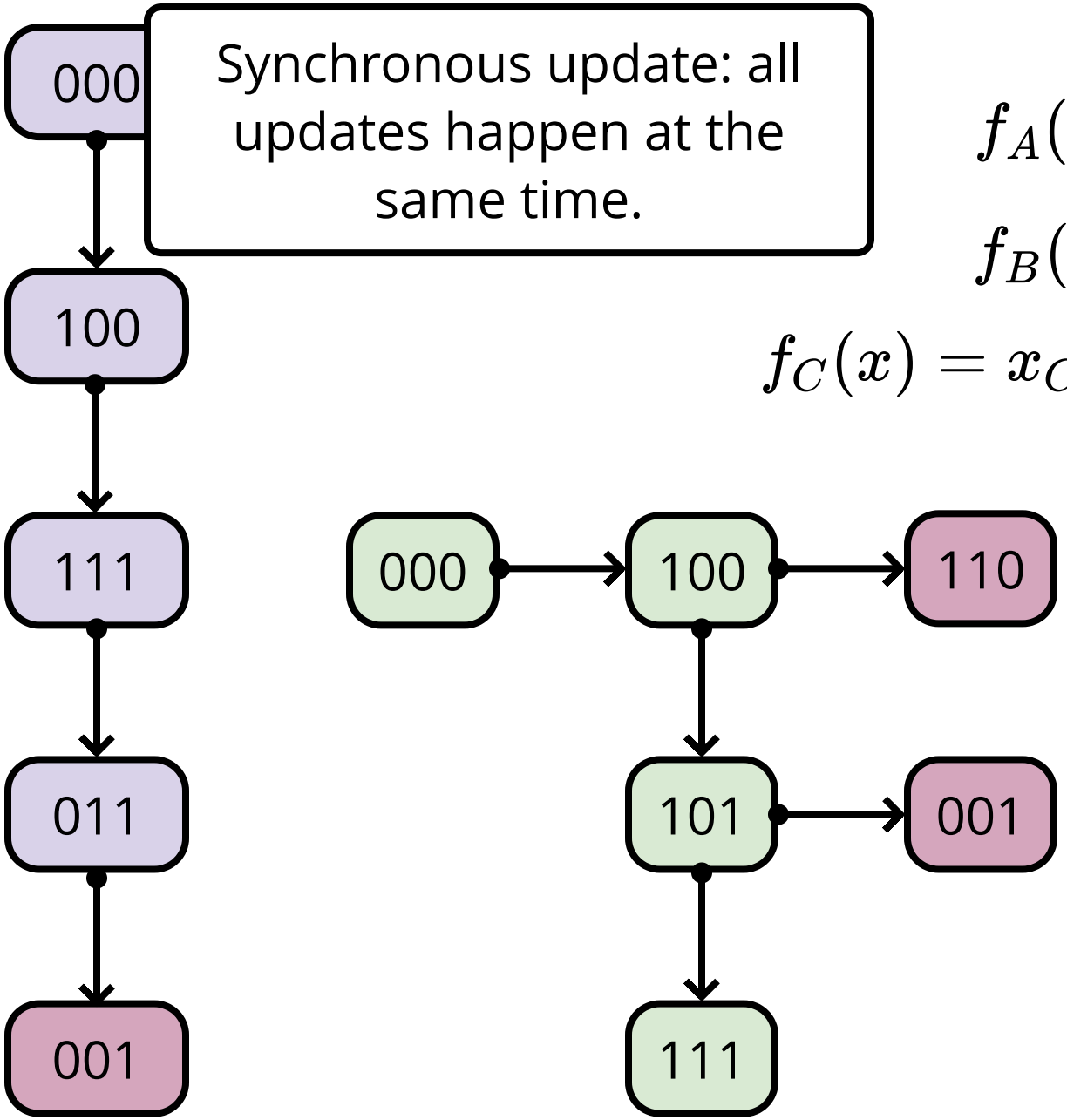

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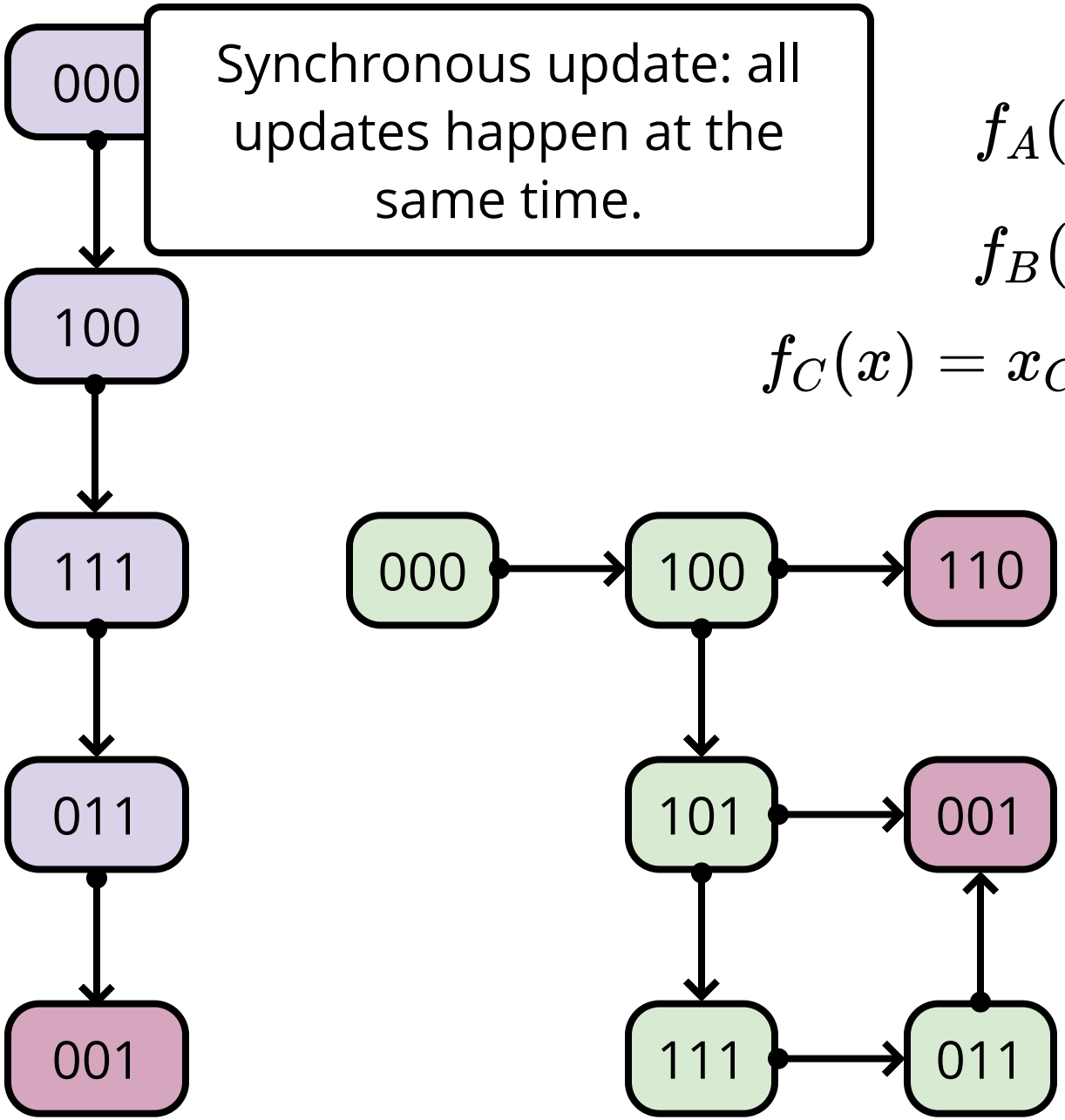

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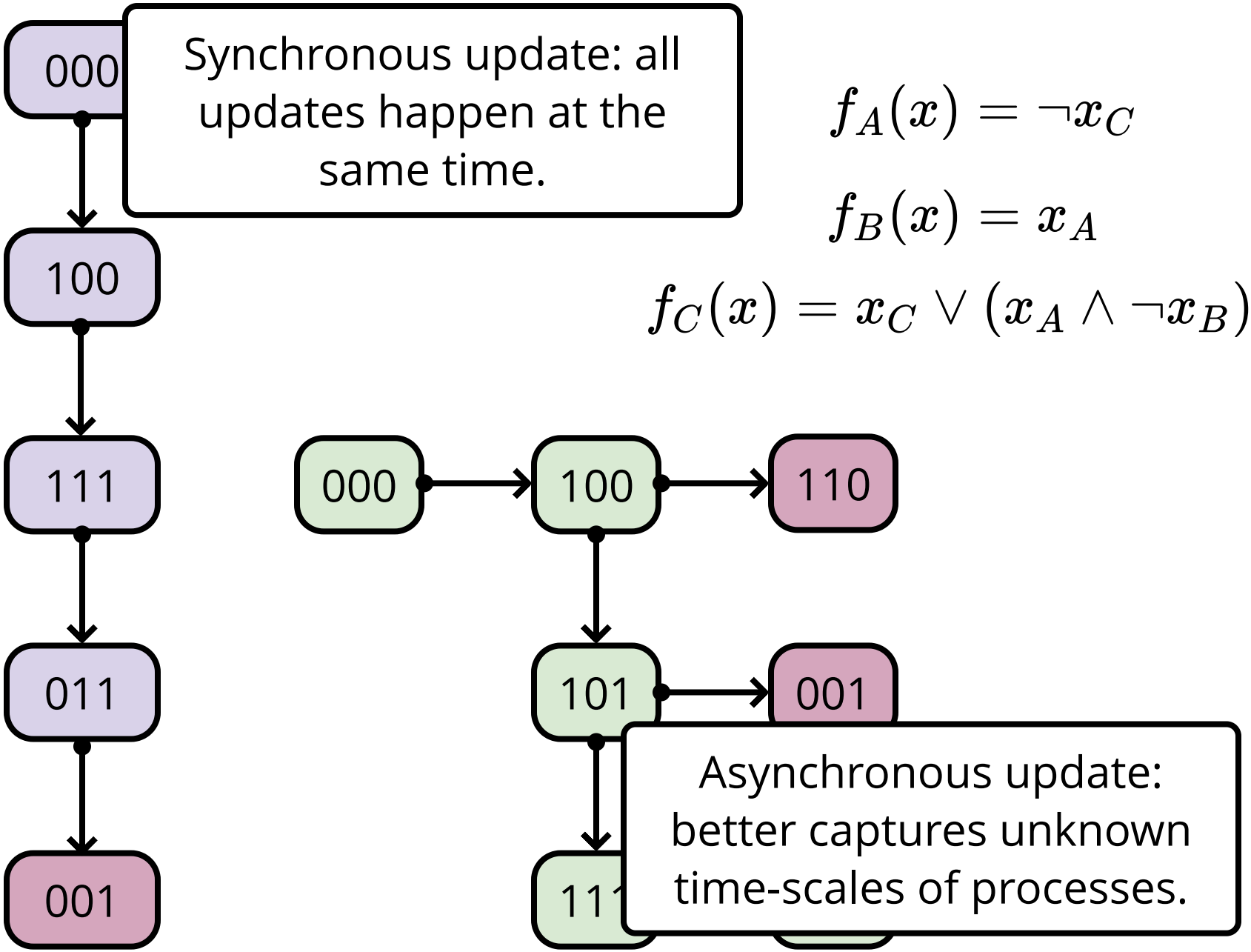
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Synchronous update: all updates happen at the same time.
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Asynchronous update: better captures unknown time-scales of processes.

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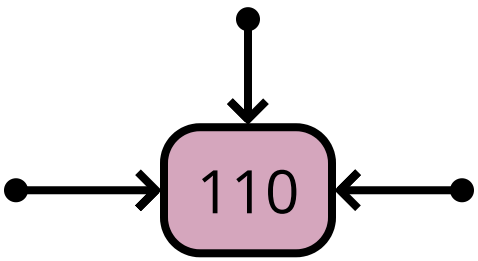

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- Single state (*fixed-point attractor*)
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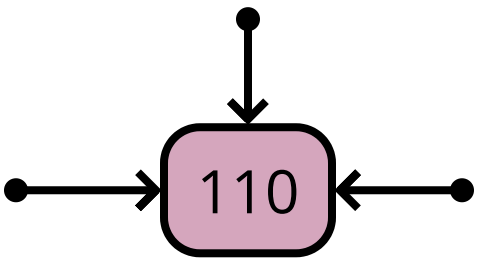

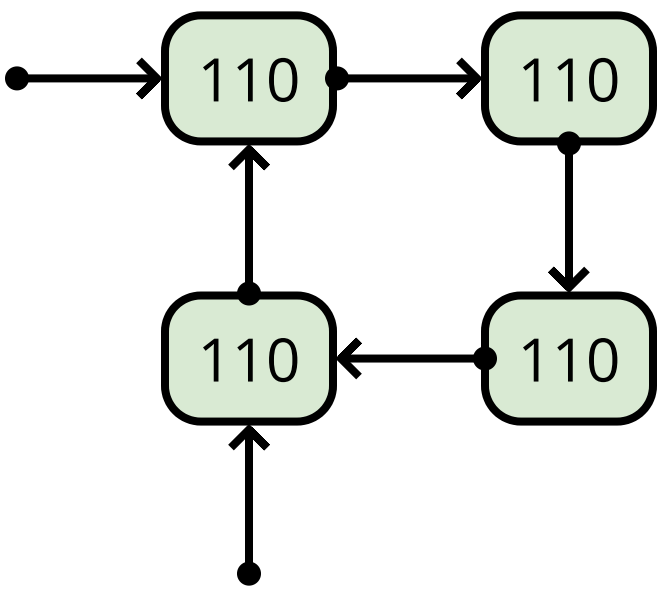

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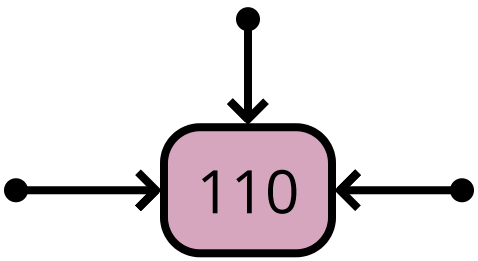

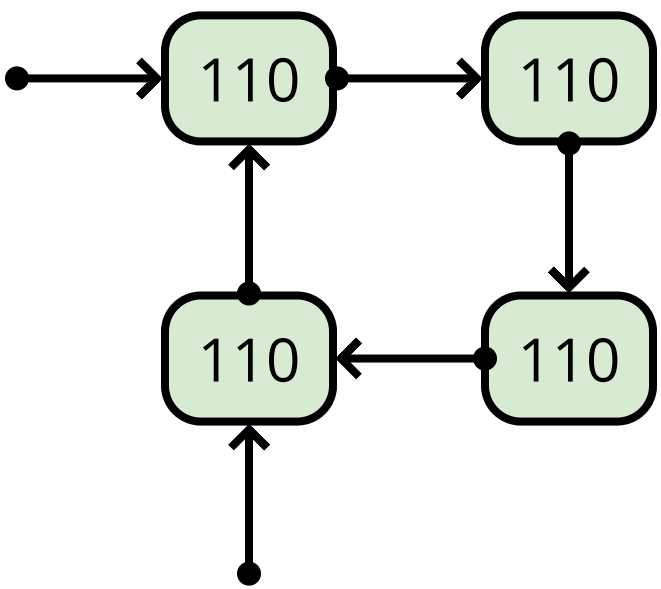

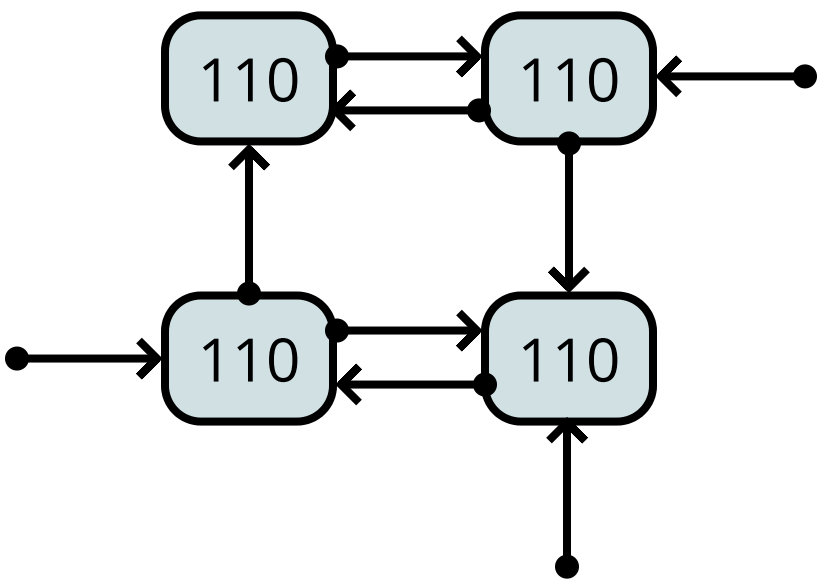

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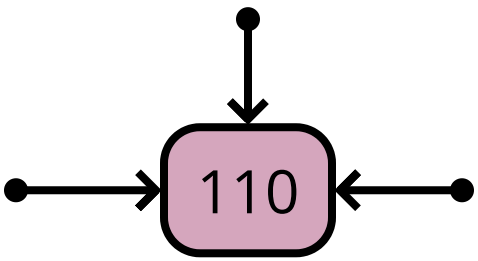

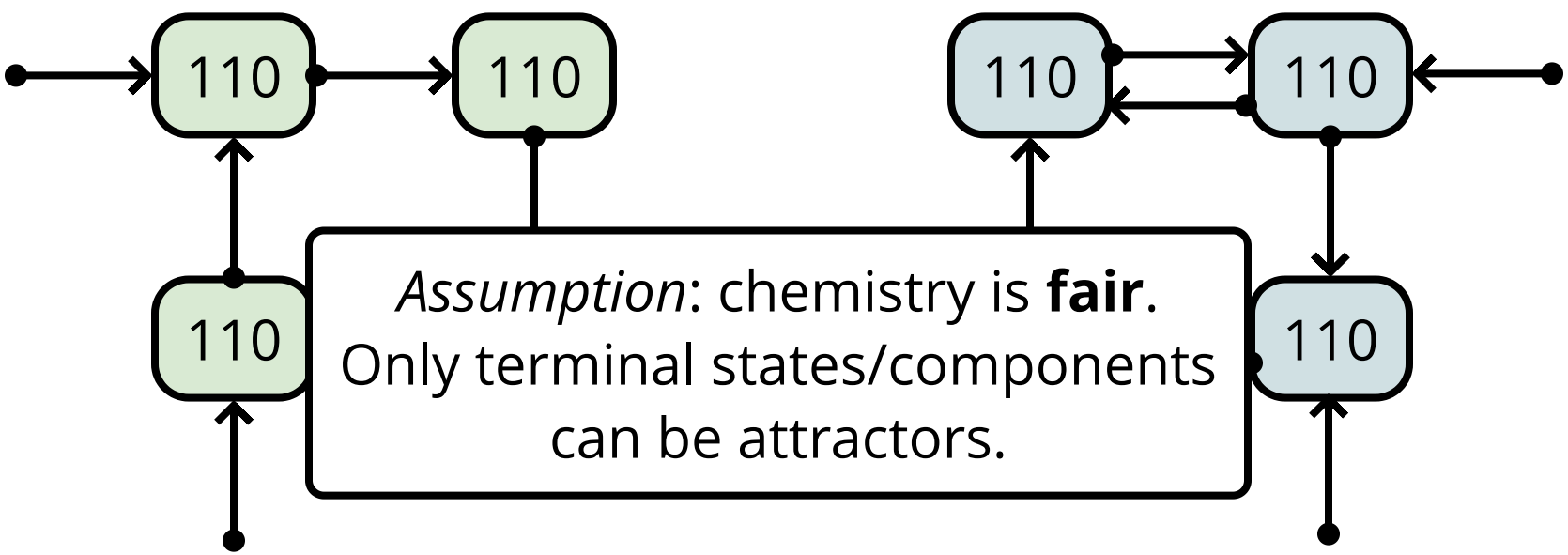

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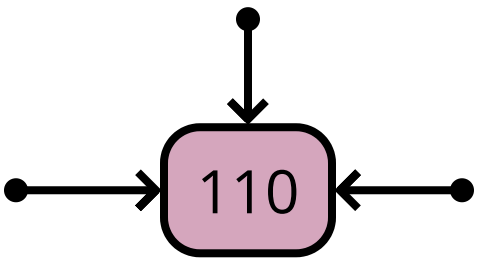

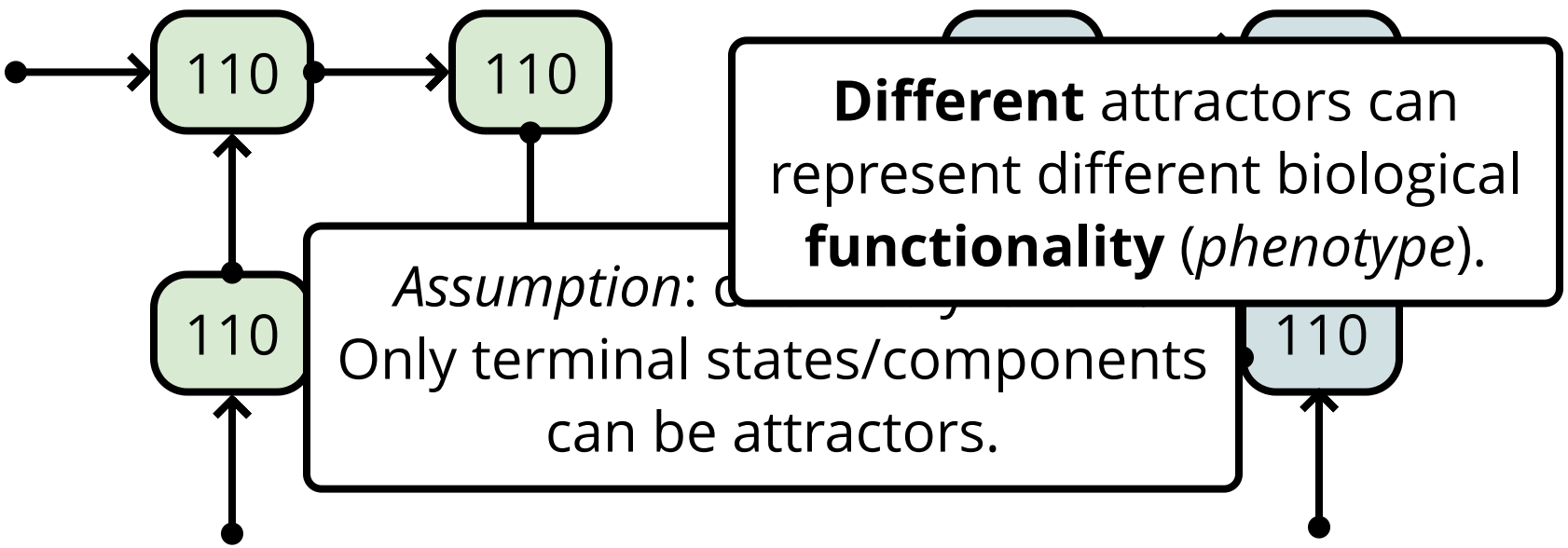

Addressing model uncertainty

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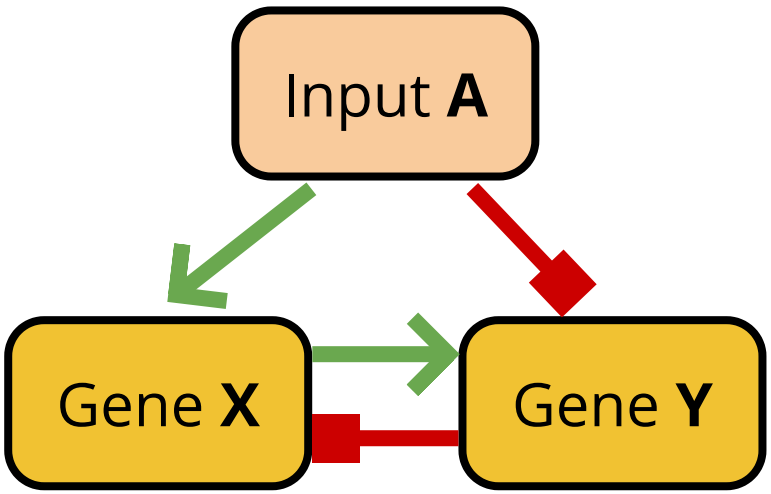

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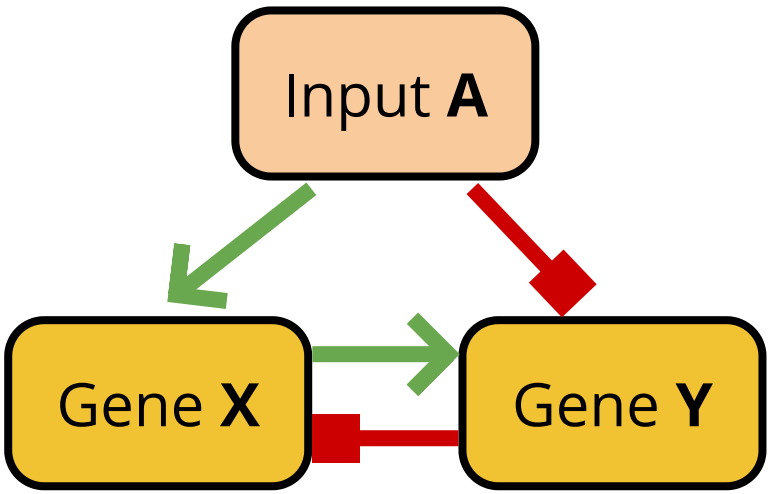

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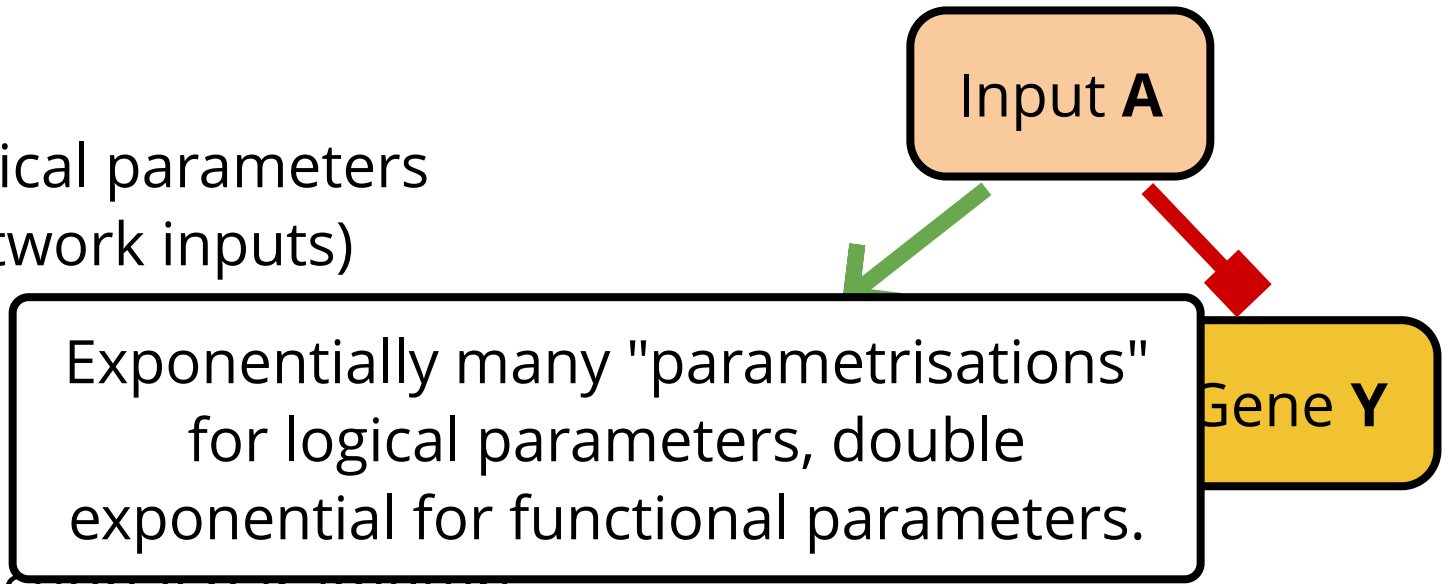

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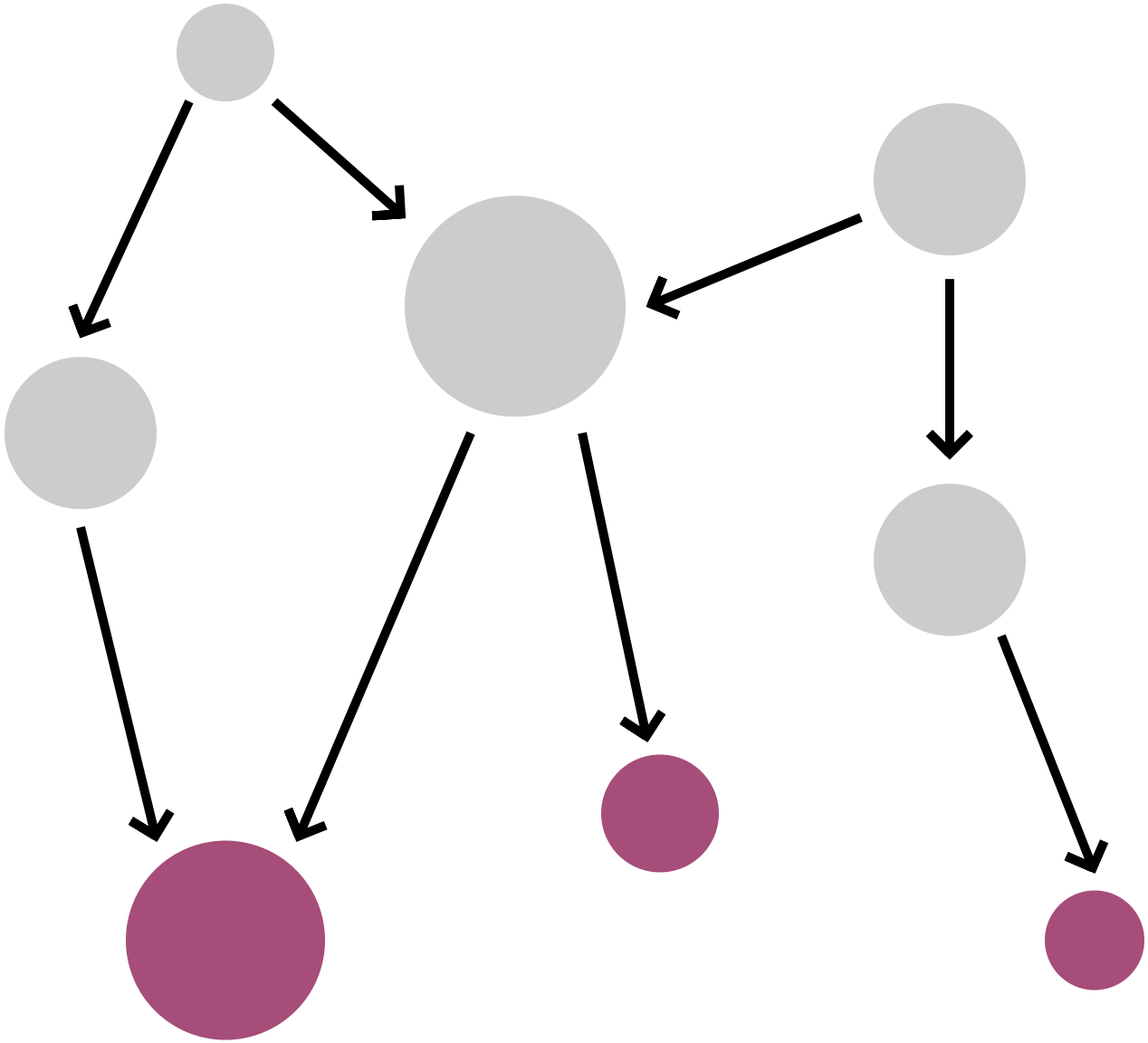

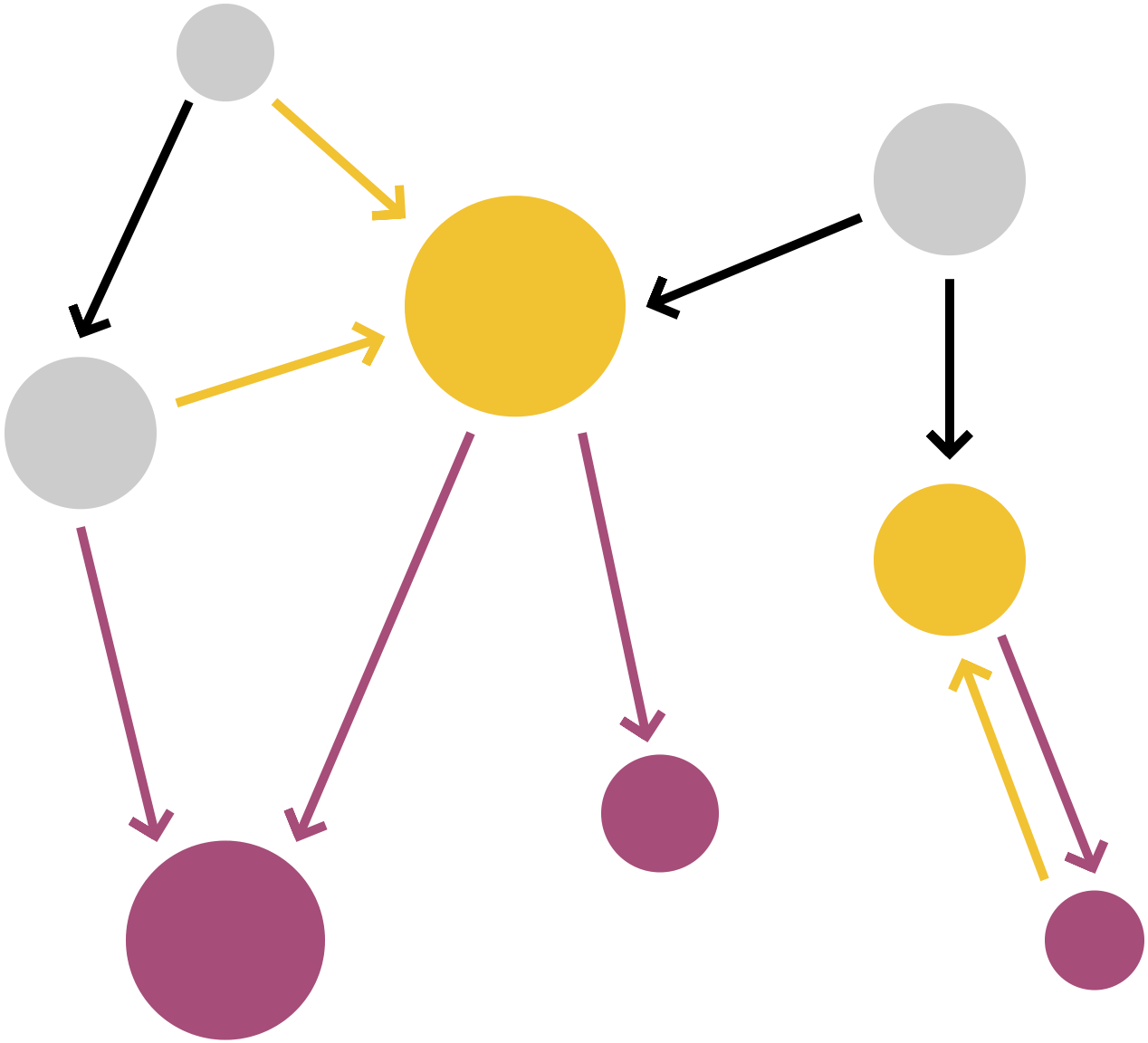

Control of Boolean networks

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Classical control theory for BNs

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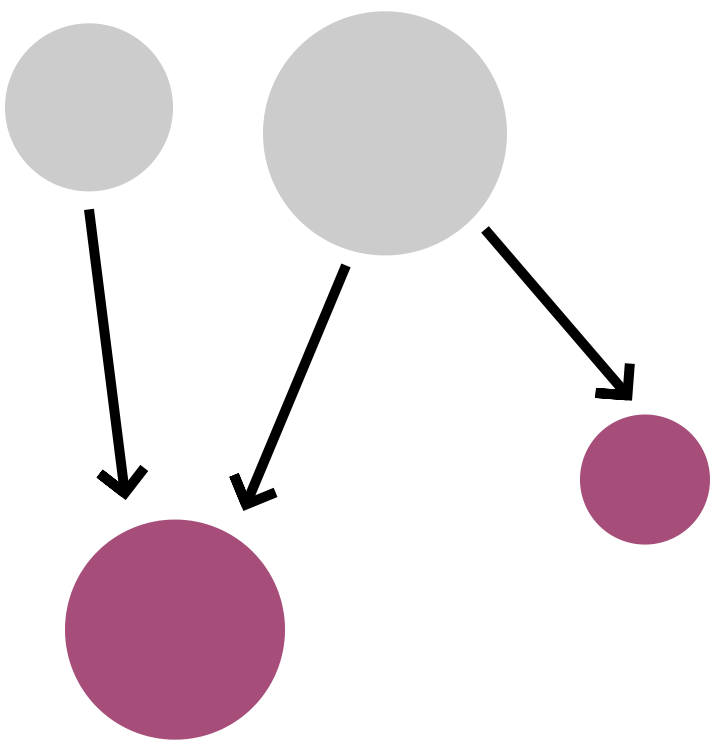
- Every *intervention* is very costly;
- Interventions (mostly) cannot be applied indefinitely.

Boolean network "target" control



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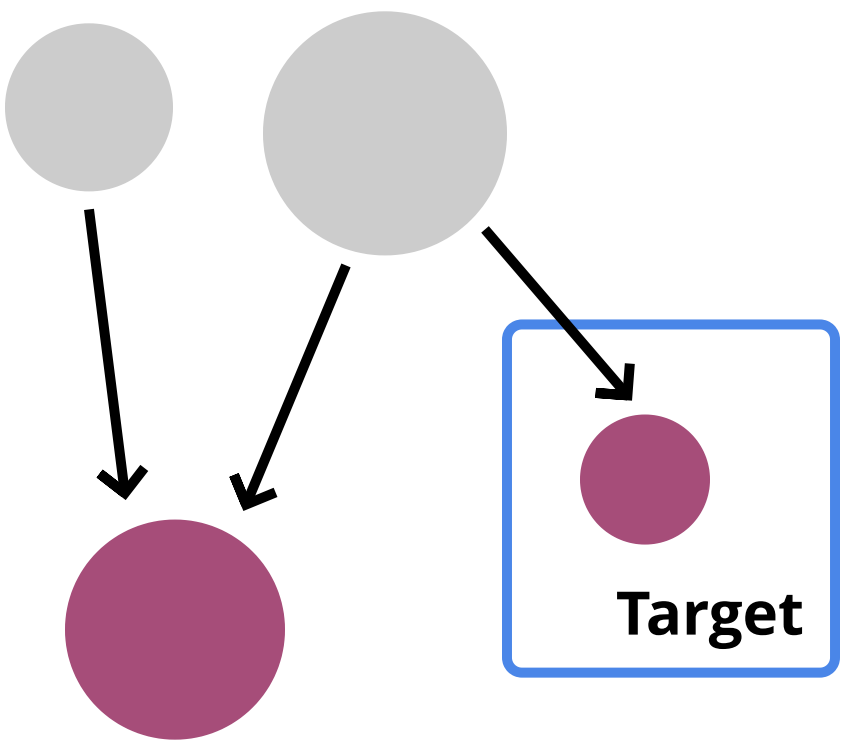
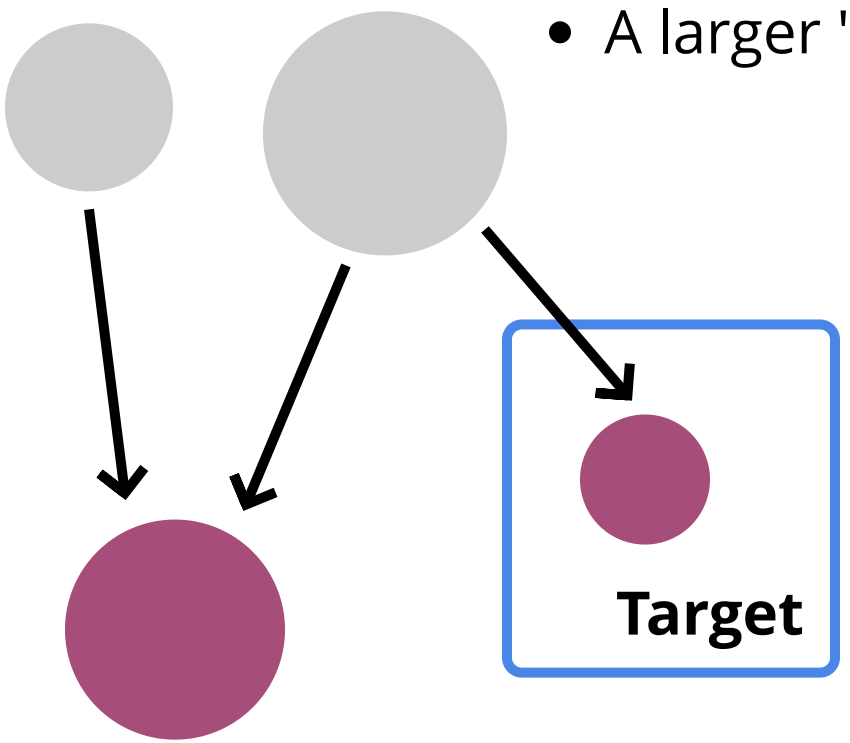


Boolean network "target" control

Target can mean slightly different things, depending on biological context, model, etc...

- A specific attractor(s) (exact set of states)
- Attractor state (must *appear* in the final attr.)
- A larger "subspace" (also called *phenotype*)



Boolean network "target" control

Target can mean slightly different things, depending on biological context, model, etc...

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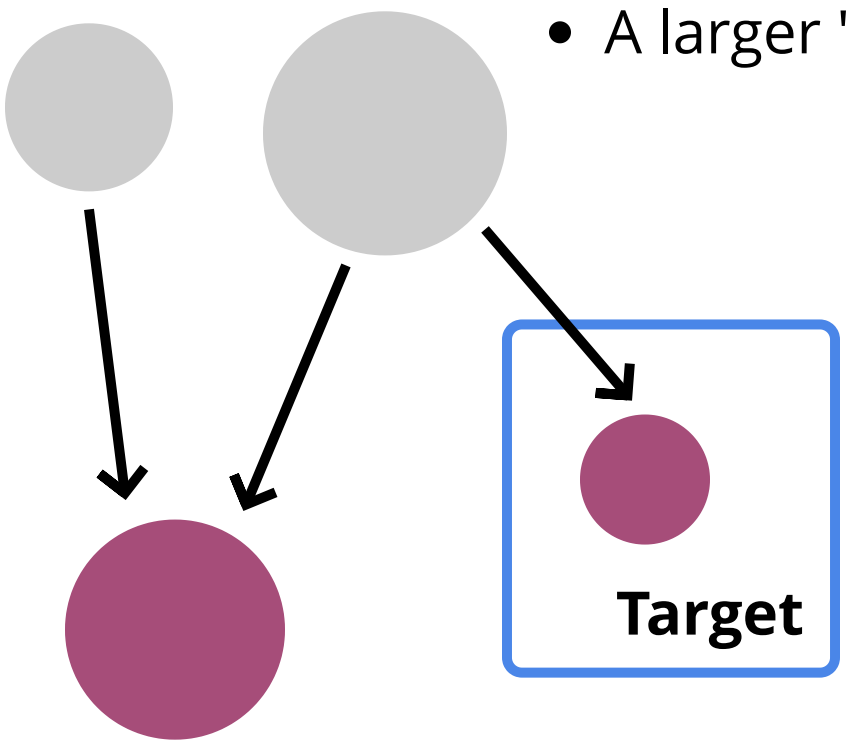

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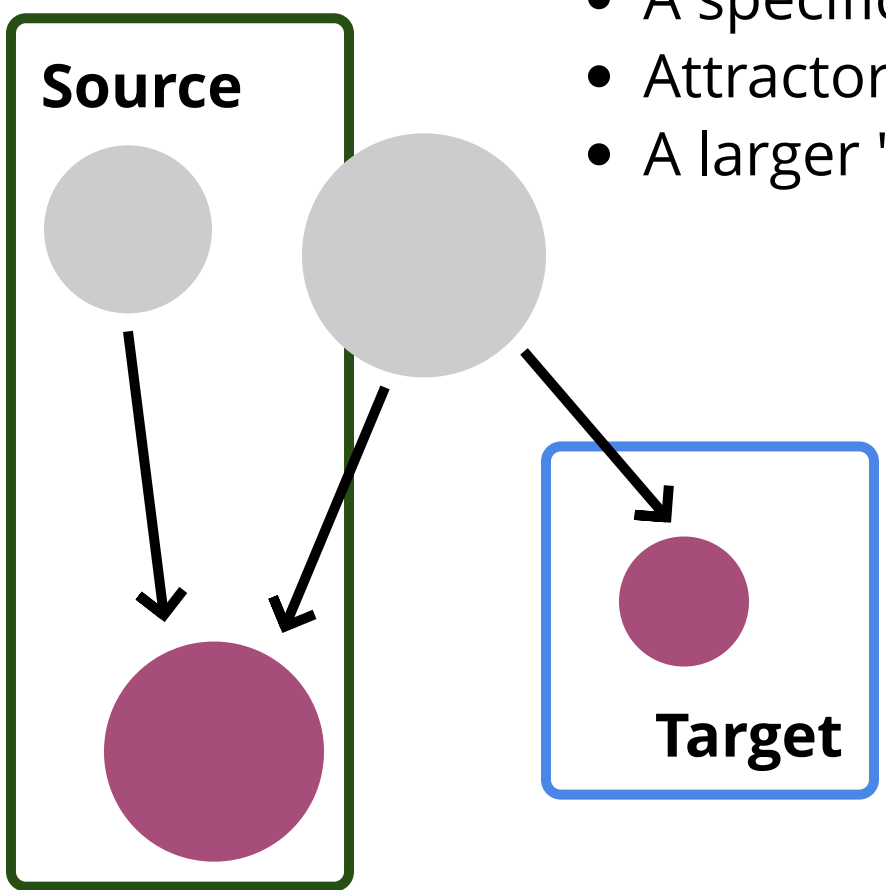

Regardless, *target* must admit some *trap set* in which the model can stay indefinitely.

Optionally, *source* can be specified too: control must work in *all* source states.

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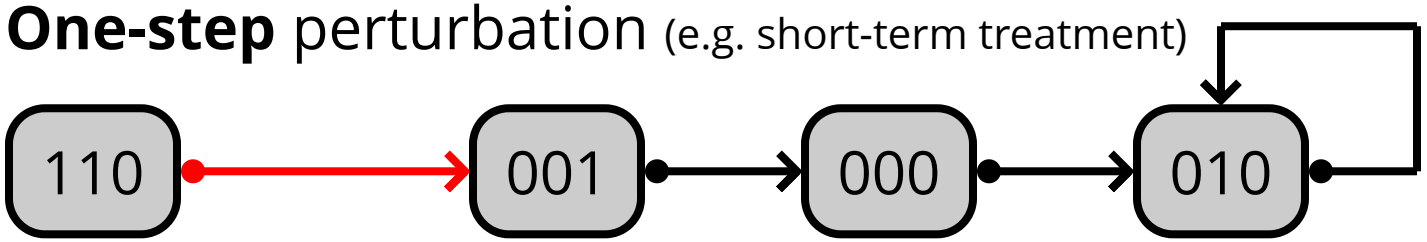

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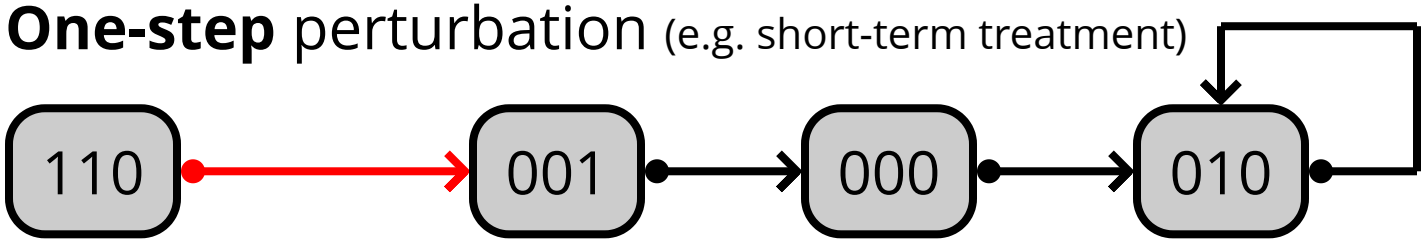

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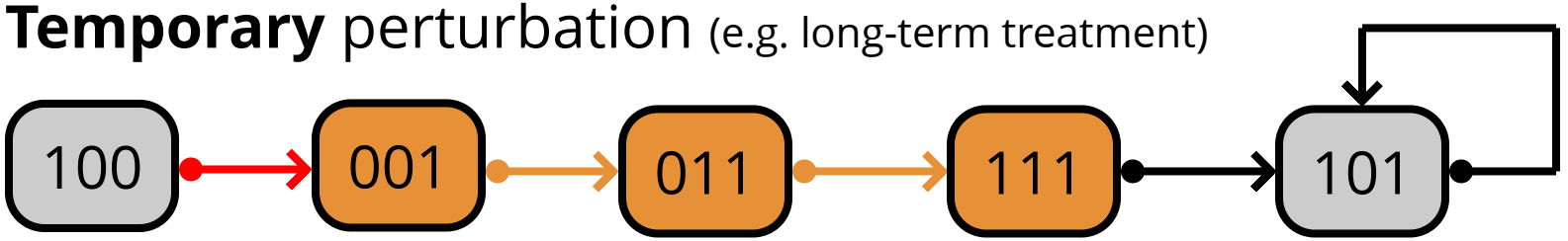

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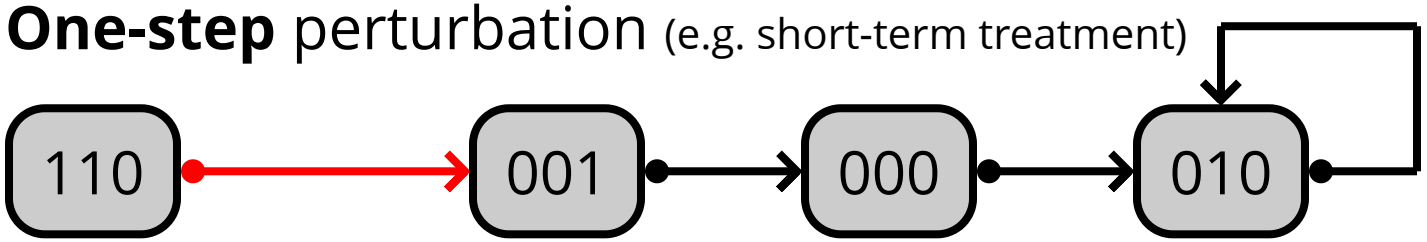

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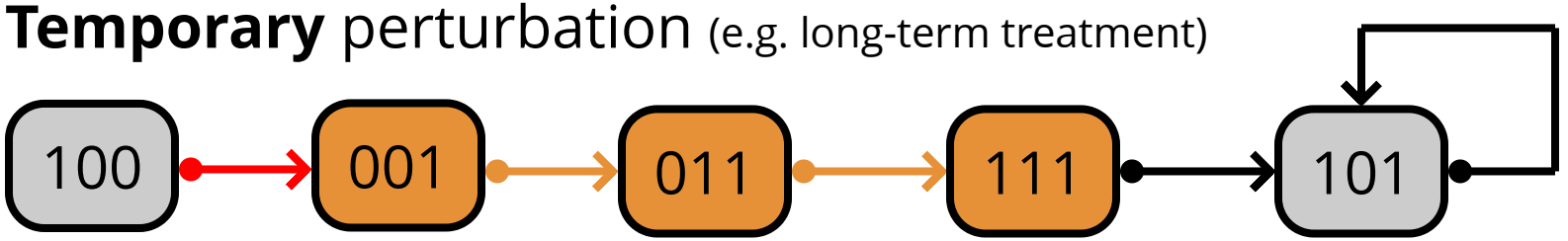
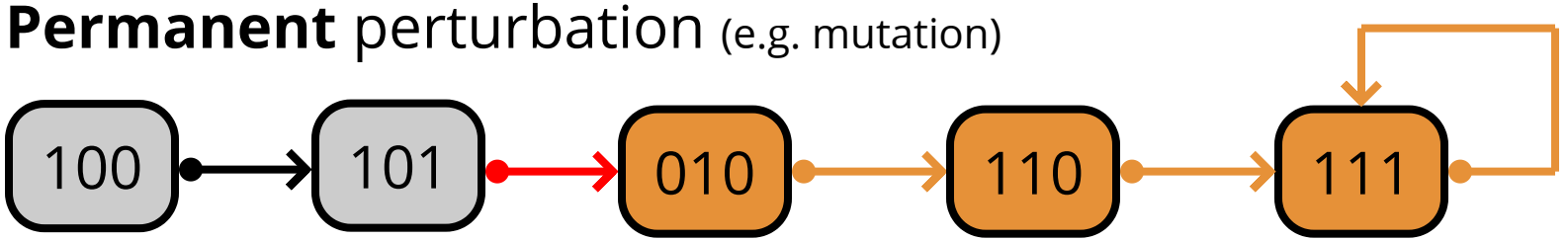
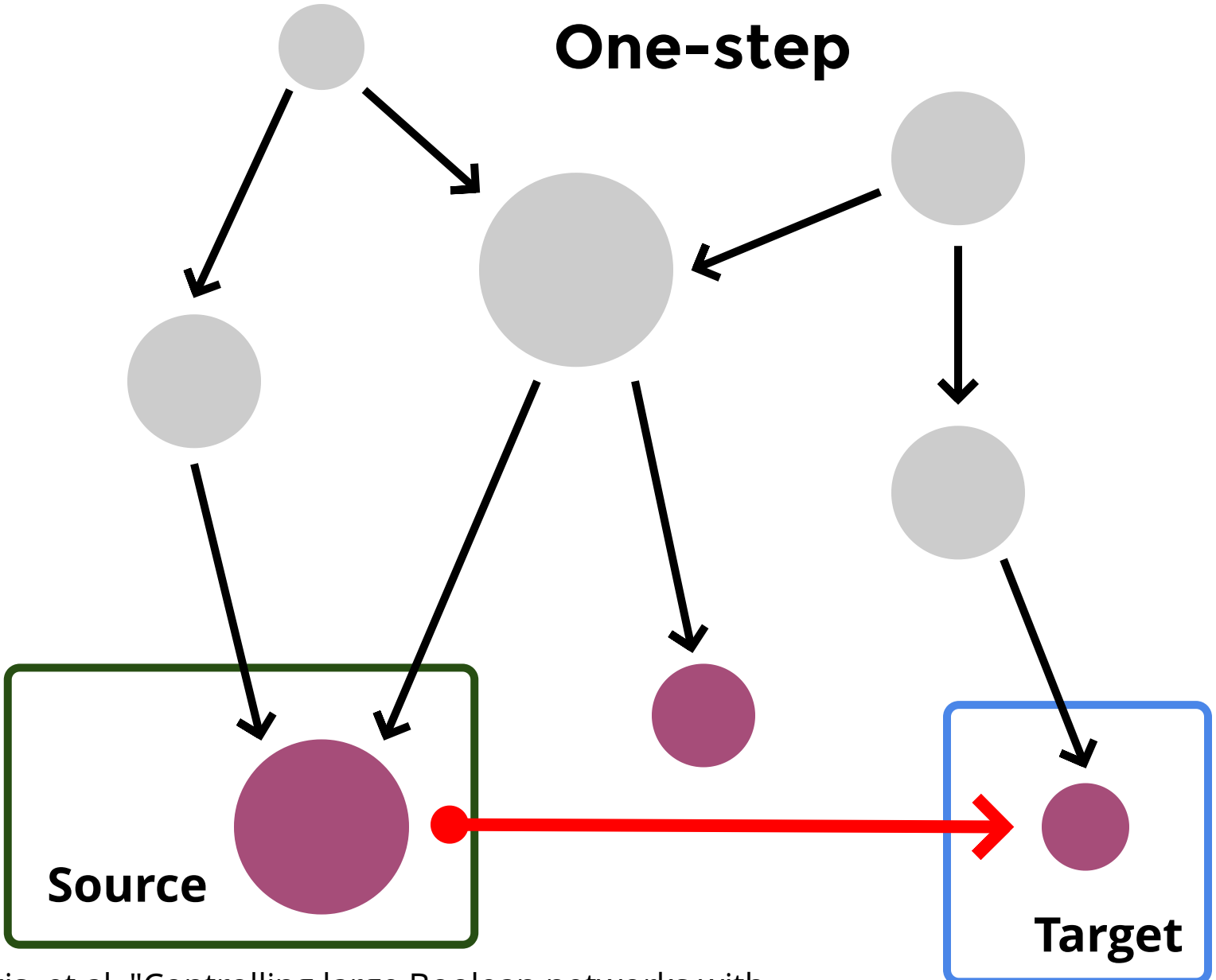
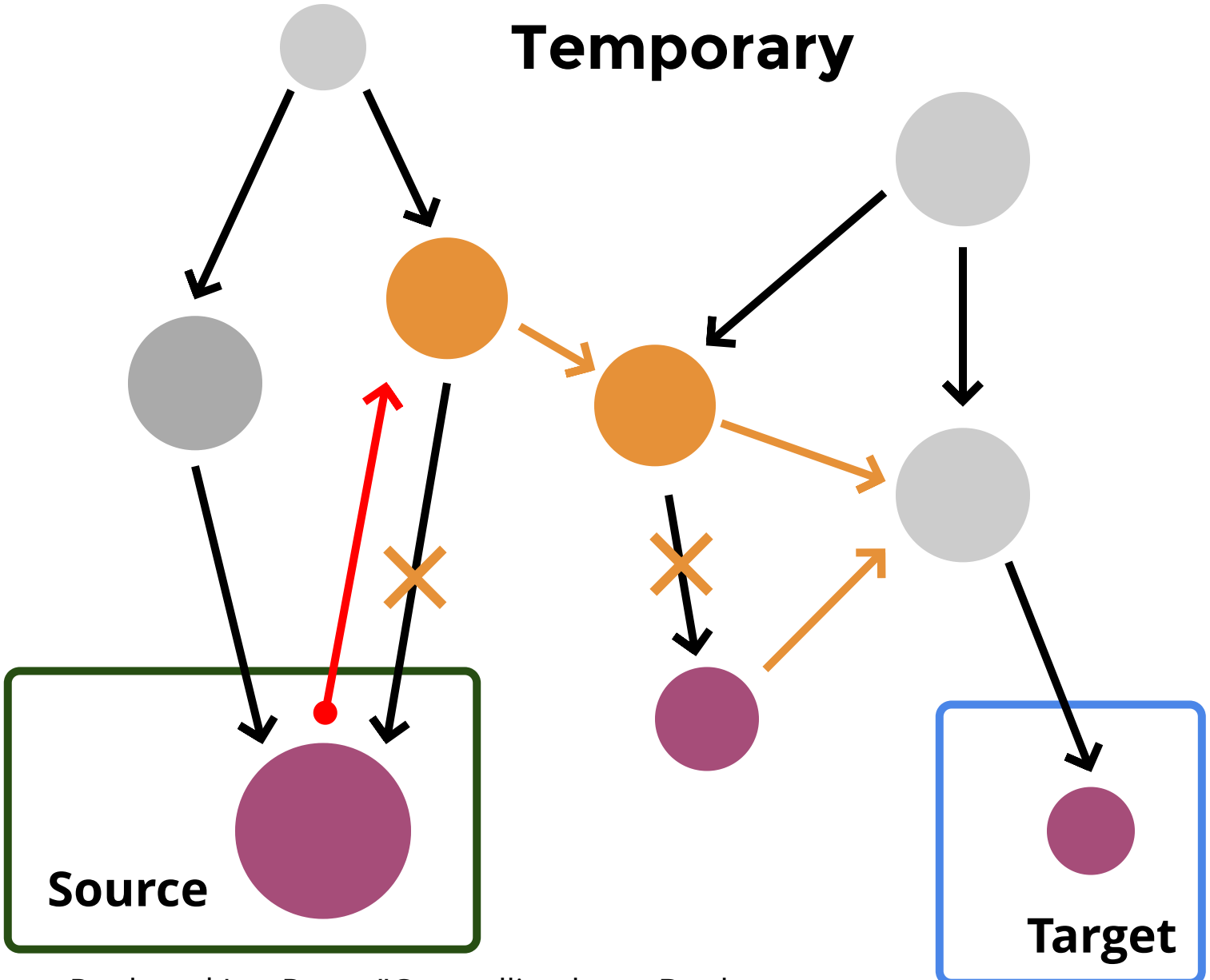


Permanent perturbation (e.g. mutation)





Baudin, Alexis, et al. "Controlling large Boolean networks with single-step perturbations." *Bioinformatics* 35.14 (2019): i558-i567.



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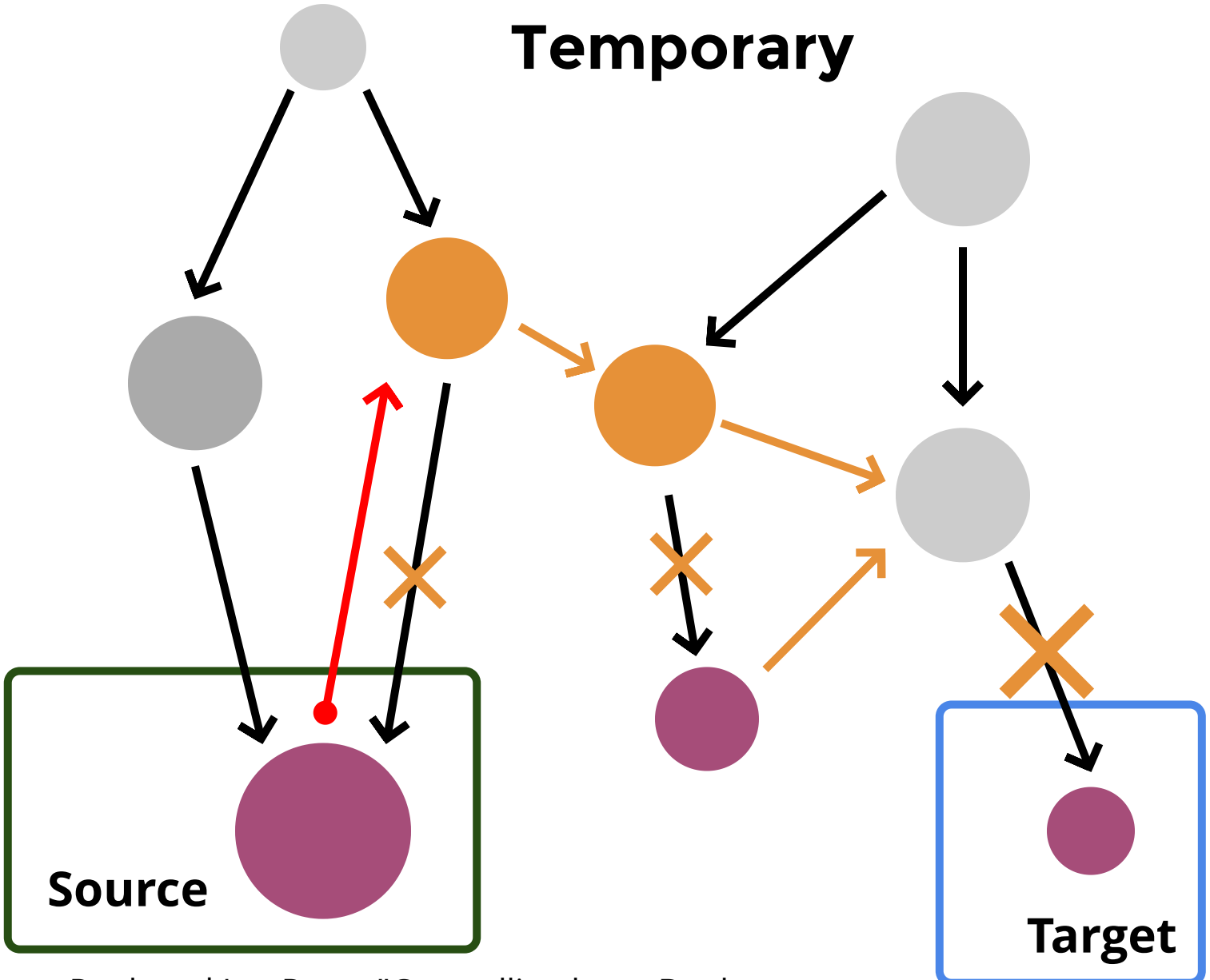

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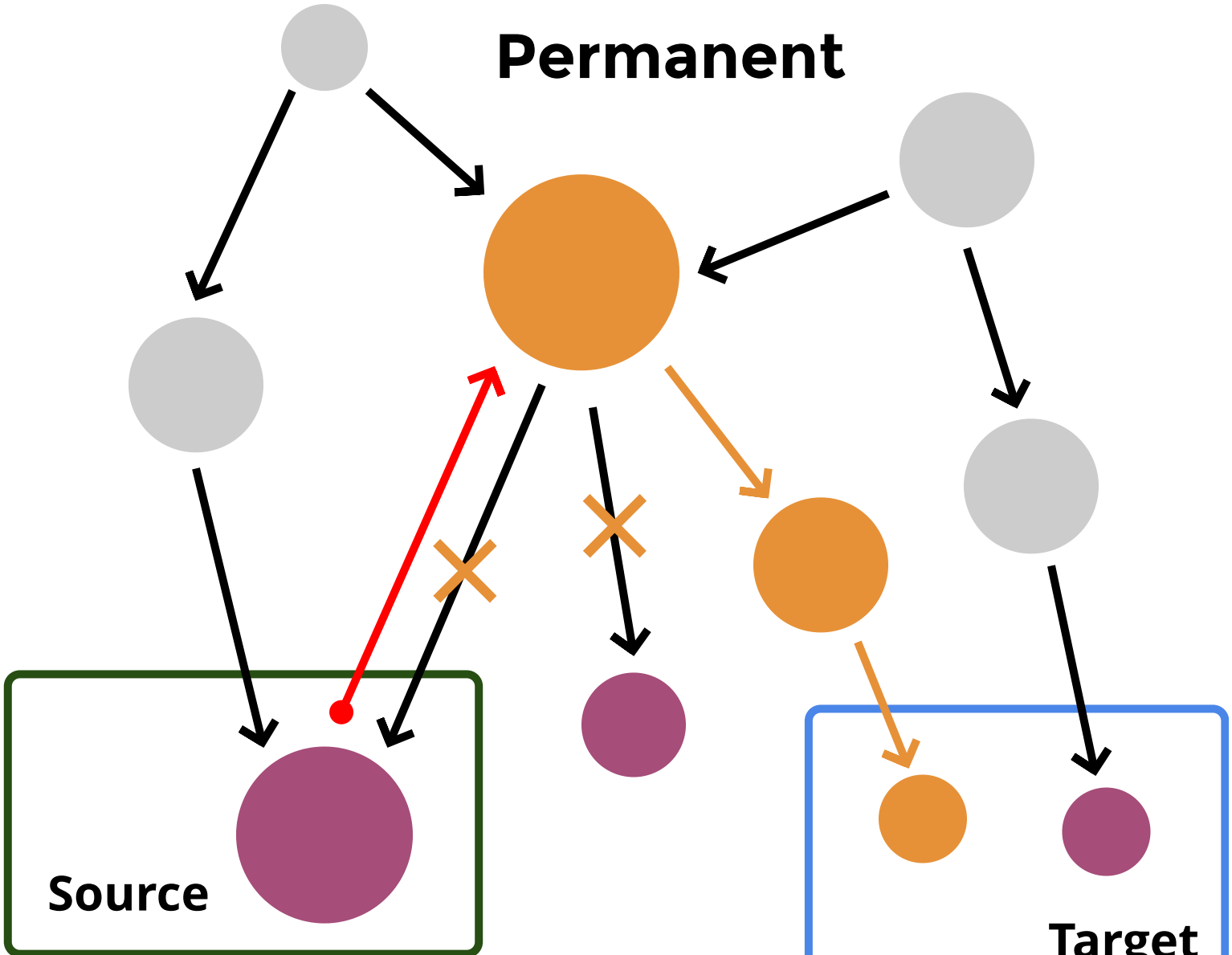

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What perturbations do we actually want?

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Erythrocyte	{EKLF} {Fli1}	–	{C/EBPα, PU1, Gfi1} {C/EBPα, Gfi1, GATA1}	{EgrNab, C/EBPα, GATA1} {EgrNab, C/EBPα, PU1}
Granulocyte	{GATA2, Fli1} {GATA1, Fli1} {Fli1, PU1}	{GATA2, EKLF} {GATA1, EKLF}	–	{EgrNab} {Gfi1}
Monocyte	{GATA2, Fli1} {GATA1, Fli1} {Fli1, PU1}	{GATA2, EKLF} {GATA1, EKLF}	{PU1} {Gfi1},{cJun},{EgrNab}	–

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Additional steps are needed to asses biological viability of perturbations!

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Perturbation robustness

$$\text{robustness}(p) = \frac{\text{\# parameter valuations where perturbation } p \text{ achieves control}}{\text{\# parameter valuations that admit the desired target}}$$

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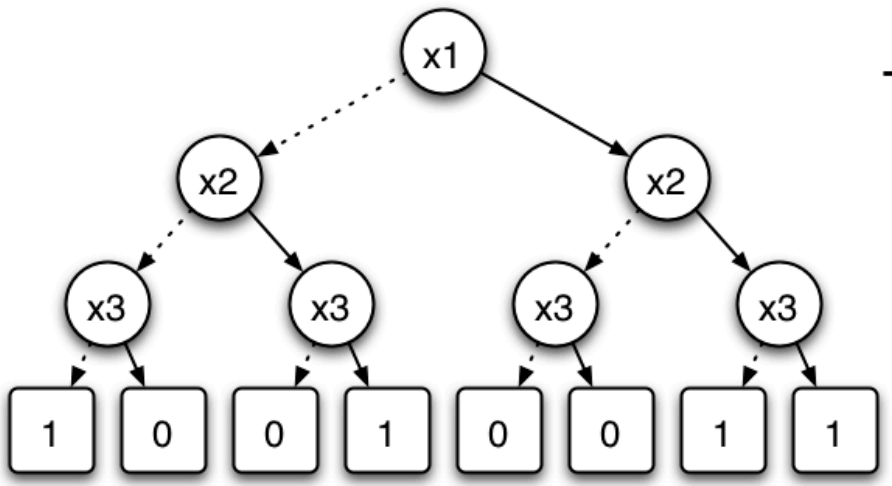
How to compute robust perturbations?

Binary Decision Diagrams



x1	x2	x3	*f*
0	0	0	1
0	0	1	0
0	1	0	0
0	1	1	1
1	0	0	0
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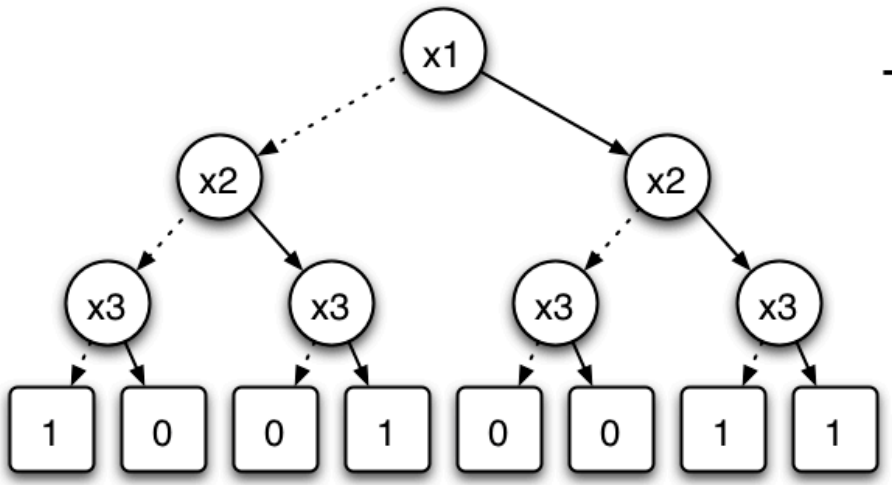

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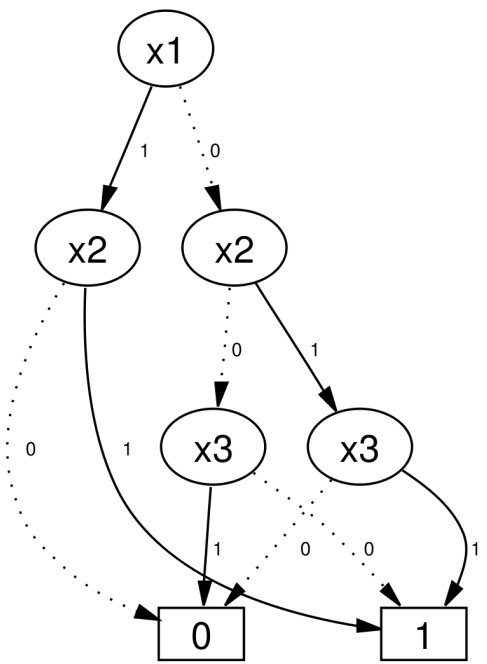

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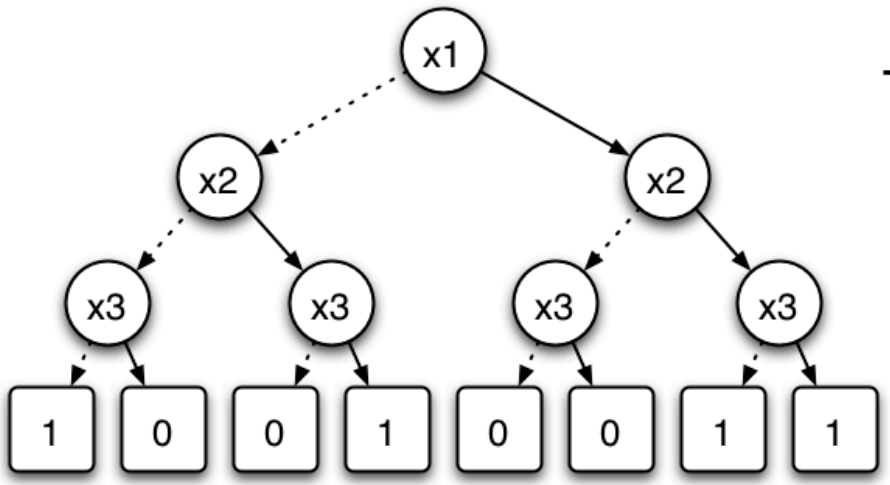

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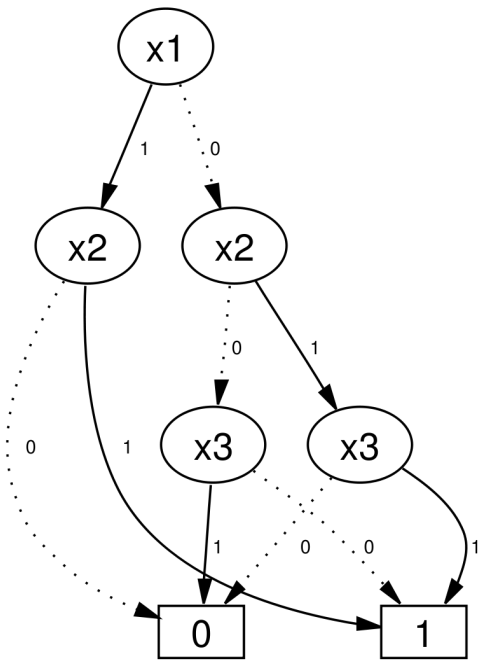

Parametrisation+State of a BN is a bit-vector. Sets/relations of these can be encoded via Boolean functions.

$$s \in X \Leftrightarrow f_{BDD(X)}(s) = 1 \,(\text{with } X \subseteq \{0,1\}^k)$$

$$X \cap Y \equiv f_{BDD(X)} \wedge f_{BDD(Y)}$$

Set operations correspond to logical operations on functions (and graph operations on BDDs)

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Since Boolean network is described by Boolean functions, computing successors/predecessors *(including parameters)* is relatively straightforward.

Benes, N., Brim, L., Pastva, S., Polácek, J., & Šafránek, D. (2019). Formal Analysis of Qualitative Long-Term Behaviour in Parametrised Boolean Networks. *ICFEM*.

Symbolic encoding of perturbations

A perturbation is treated as another type of parameter:

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"Naive" encoding uses two "bits" per variable. Here we show that algorithms also exist for a simpler "one bit" encoding.

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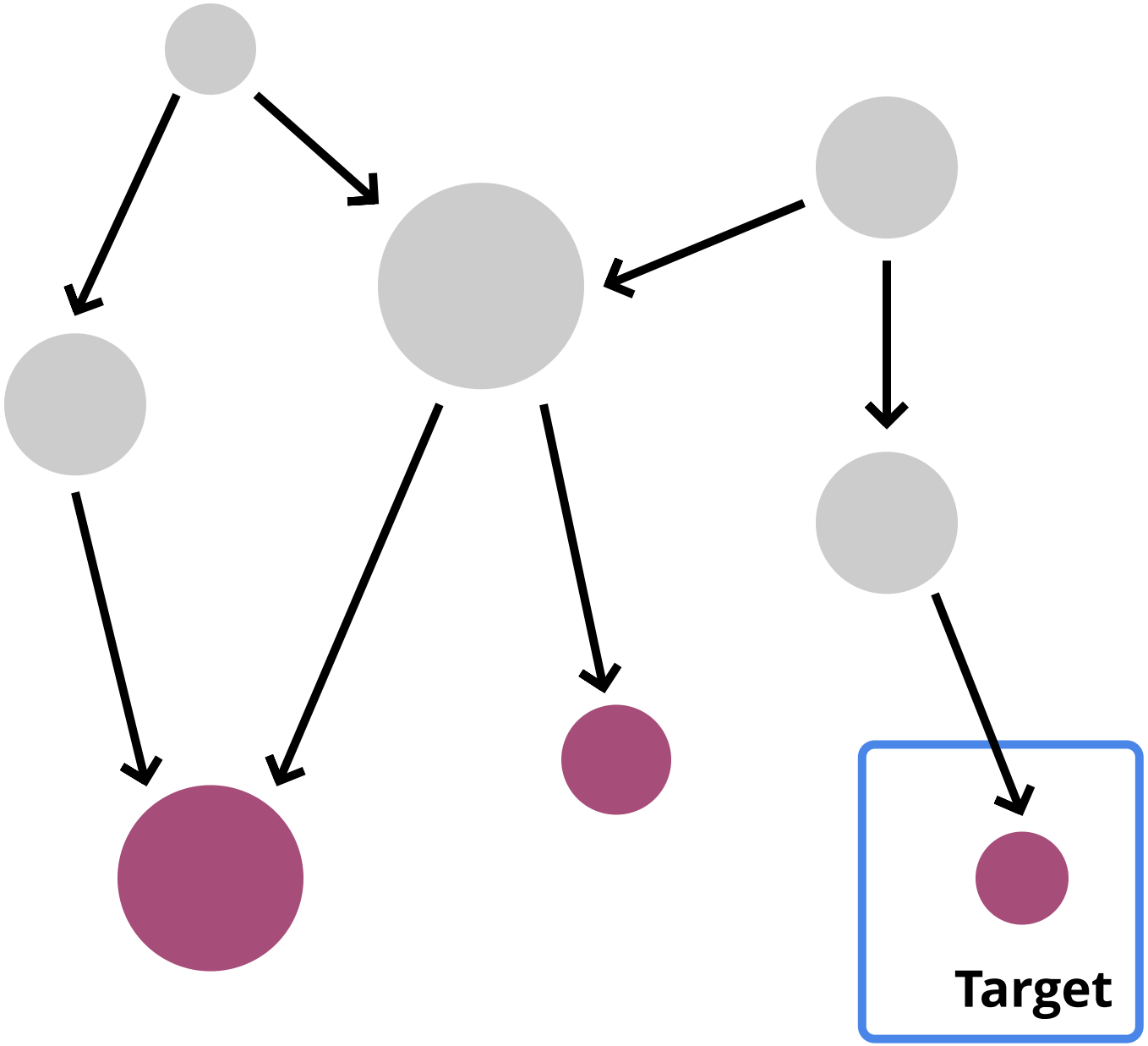
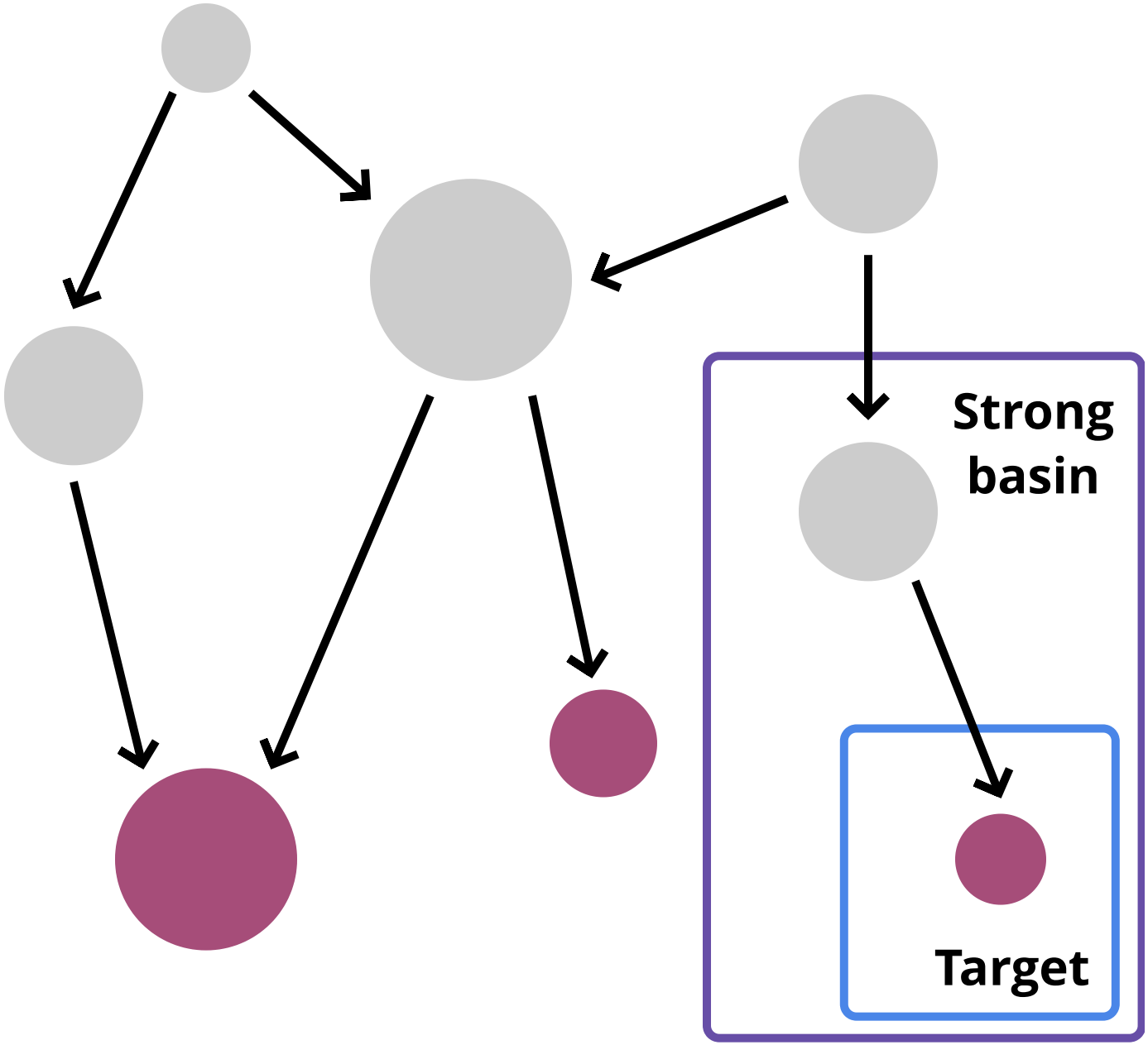
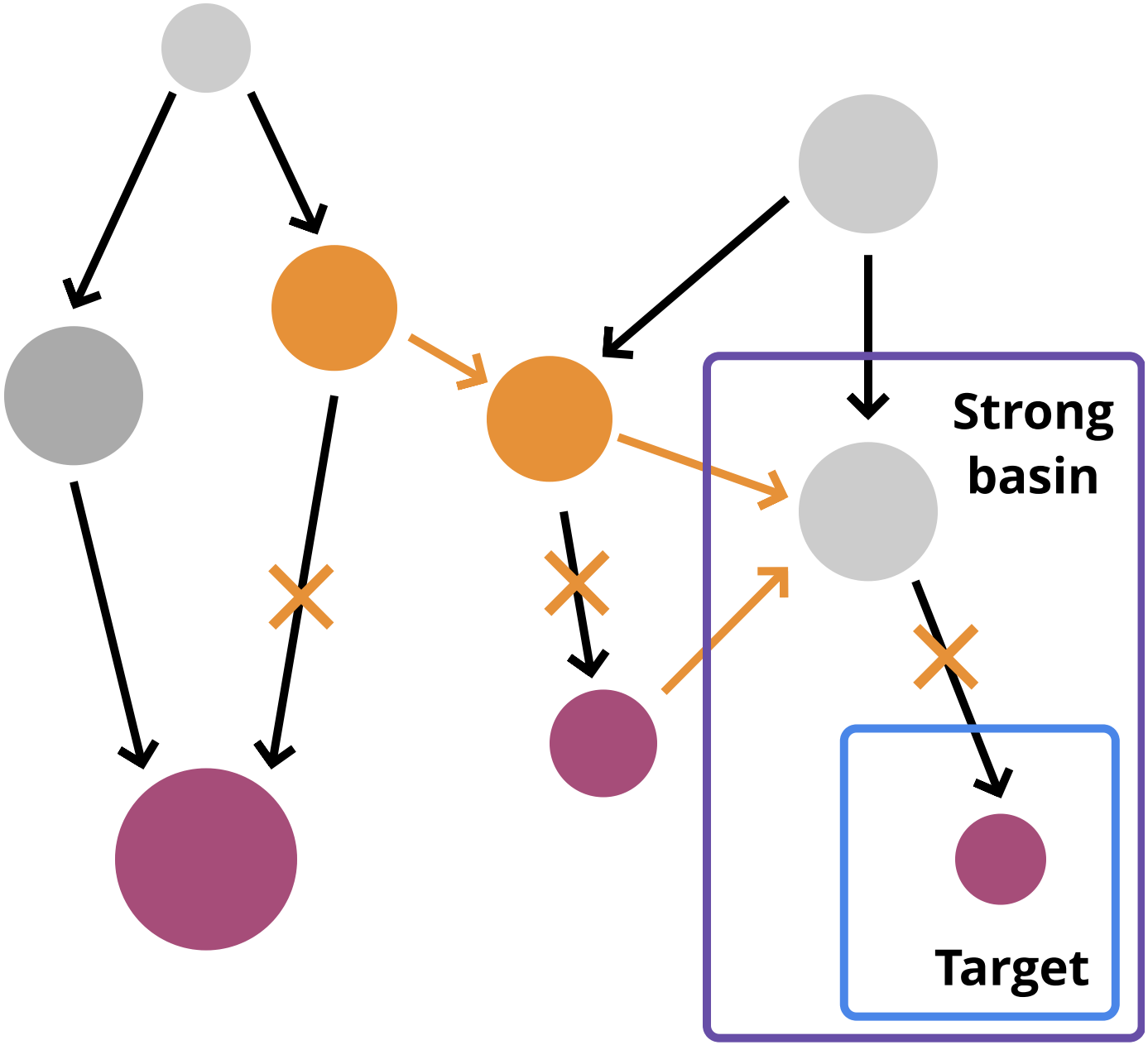

Target


Strong
basin
Target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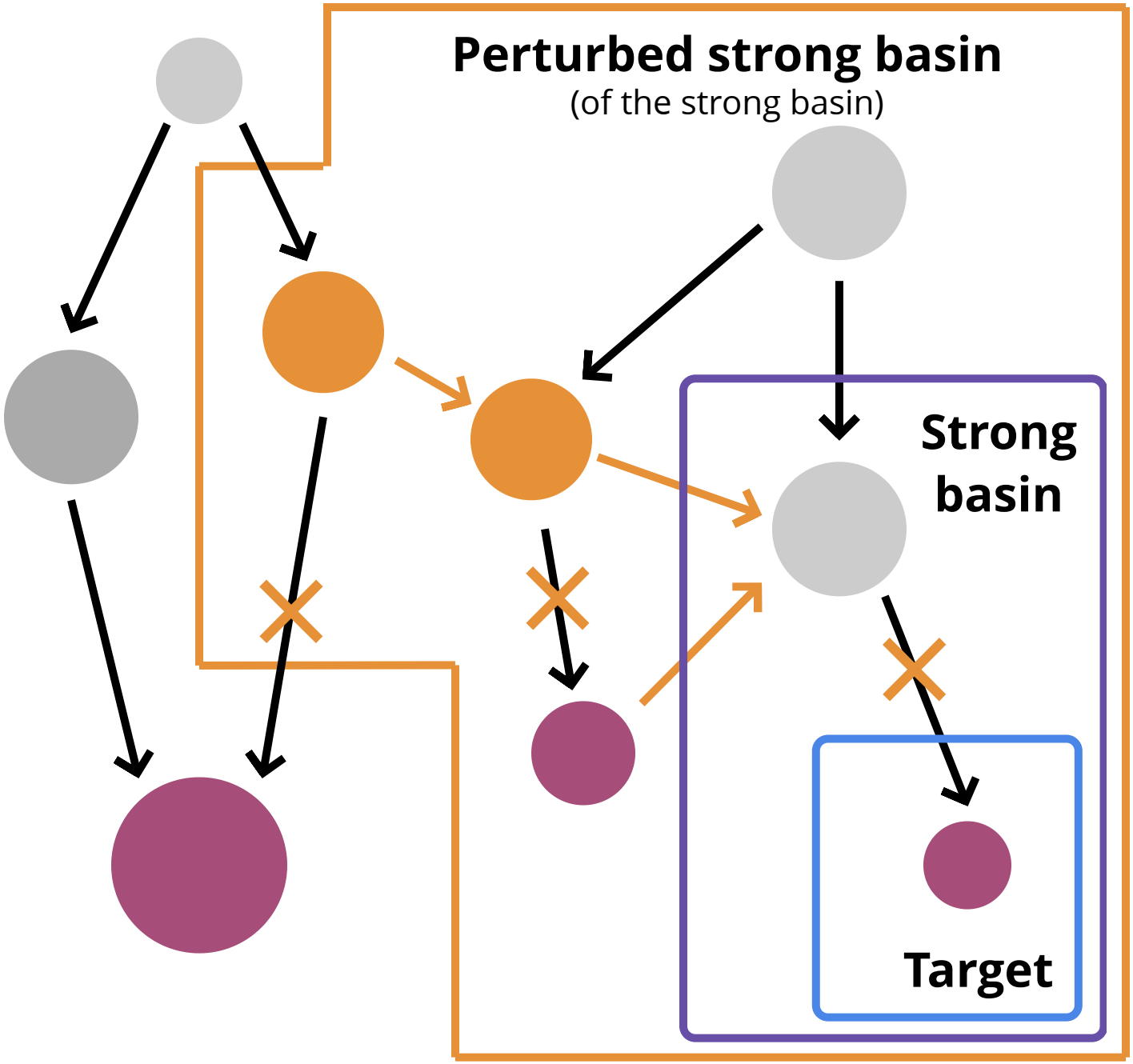
Perturbed strong basin
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Strong basin
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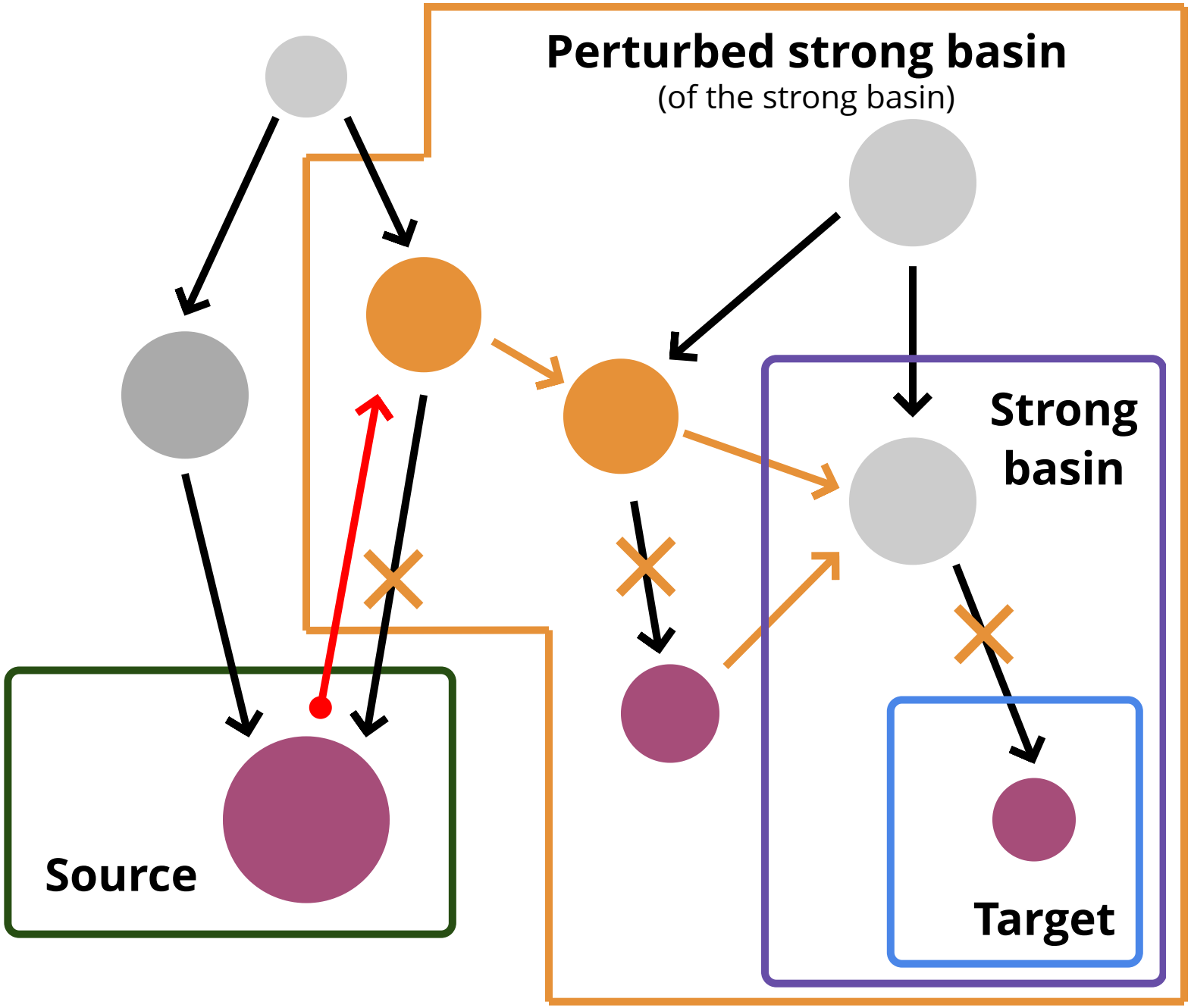
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Algorithm runs symbolically for all perturbations and parametrisations.

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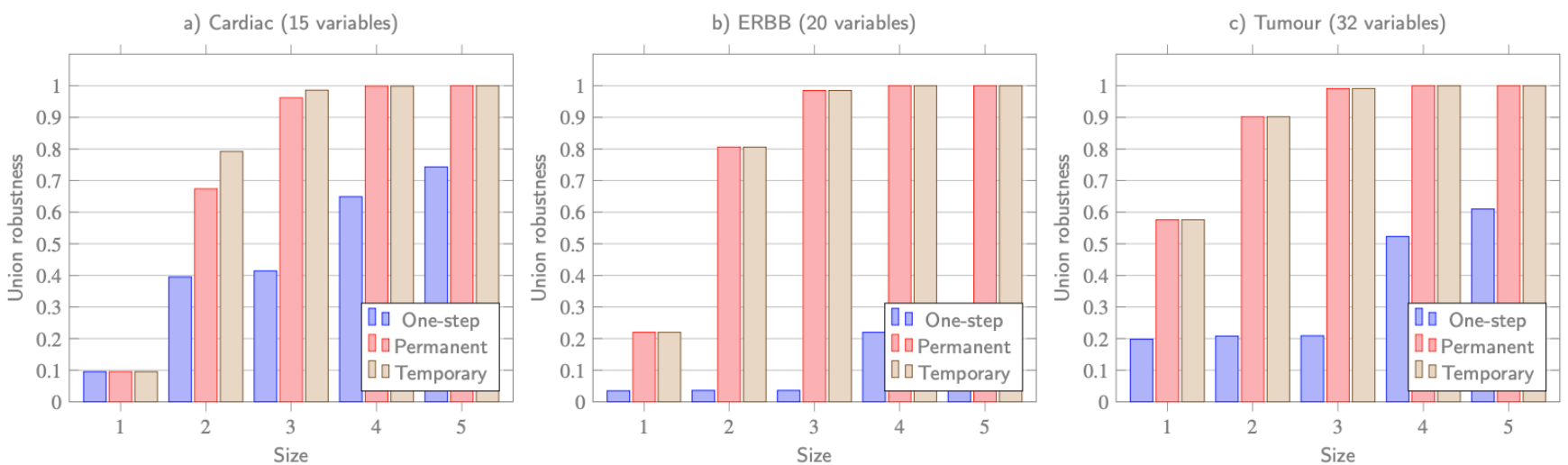

*up to 10^9 parameter valuations/model

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