# Introduction of Priorities in Biological Regulatory Networks

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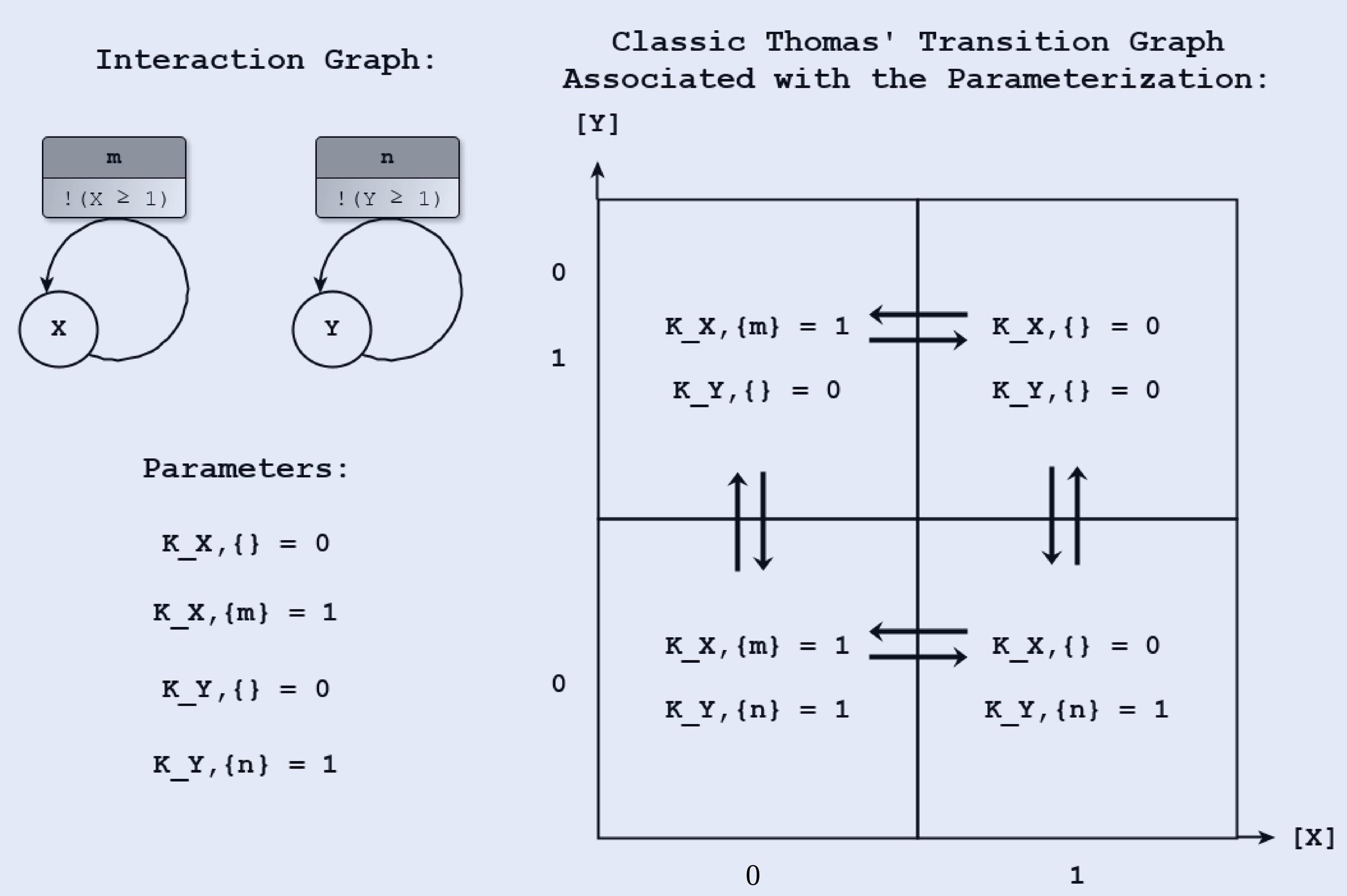
The discrete modeling framework of René Thomas allows to study global **qualitative dynamic,** that is a **non deterministic** succession of events, of biological regulatory network (BRN). Nevertheless among biological regulations, hierarchy may exist. We introduce an extension of the definition of the discrete modeling framework that takes into consideration **priority** regulations and proposes an illustration of the impact of this extension on the **static** and **dynamic** modeling of BRN.

## The Thomas' Modeling Framework [1]




A **biological regulatory network (BRN)** is a graph where :

- A node is a variable that represents biological entities (*e.g.* X, Y) associated with a bound noted $b_v$,
- A labelled edge is an interaction between one or several nodes (*e.g.* ! (X ≥ 1) means a X auto-inhibition).

A <u>local</u> **dynamical parameter** $\mathbf{K_{v\{\omega\}}}$ represents the discrete value toward which <u>a variable</u> is attracted, where :

- **v** is a variable ($v \in V$),
- **ω** is the set of resources which are predecessor multiplexes evaluated to true (*e.g.* $K_{v\{\omega\}}=0$ when Y=0 because ! (Y ≥ 1) is true).
- $0 \leqslant K_{v\{\omega\}} \leqslant b_v$.

## Priority Rules Definition

A BRN is enriched with a set of **priority rules** :

$$\omega_1,\ \neg\omega_2 \rightarrow v$$

with **v** a variable and $\omega_1$, $\omega_2$ two disjunct subsets of the set of predecessors of v.

Each priority rule specify situations where the presence ($\omega_1$) or absence ($\omega_2$) of a set of multiplexes triggers **priority update** of the state one or several target variables.

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$K_{v\{\omega\}}$ is a **priority parameter** if from a given state (noted **η**) :

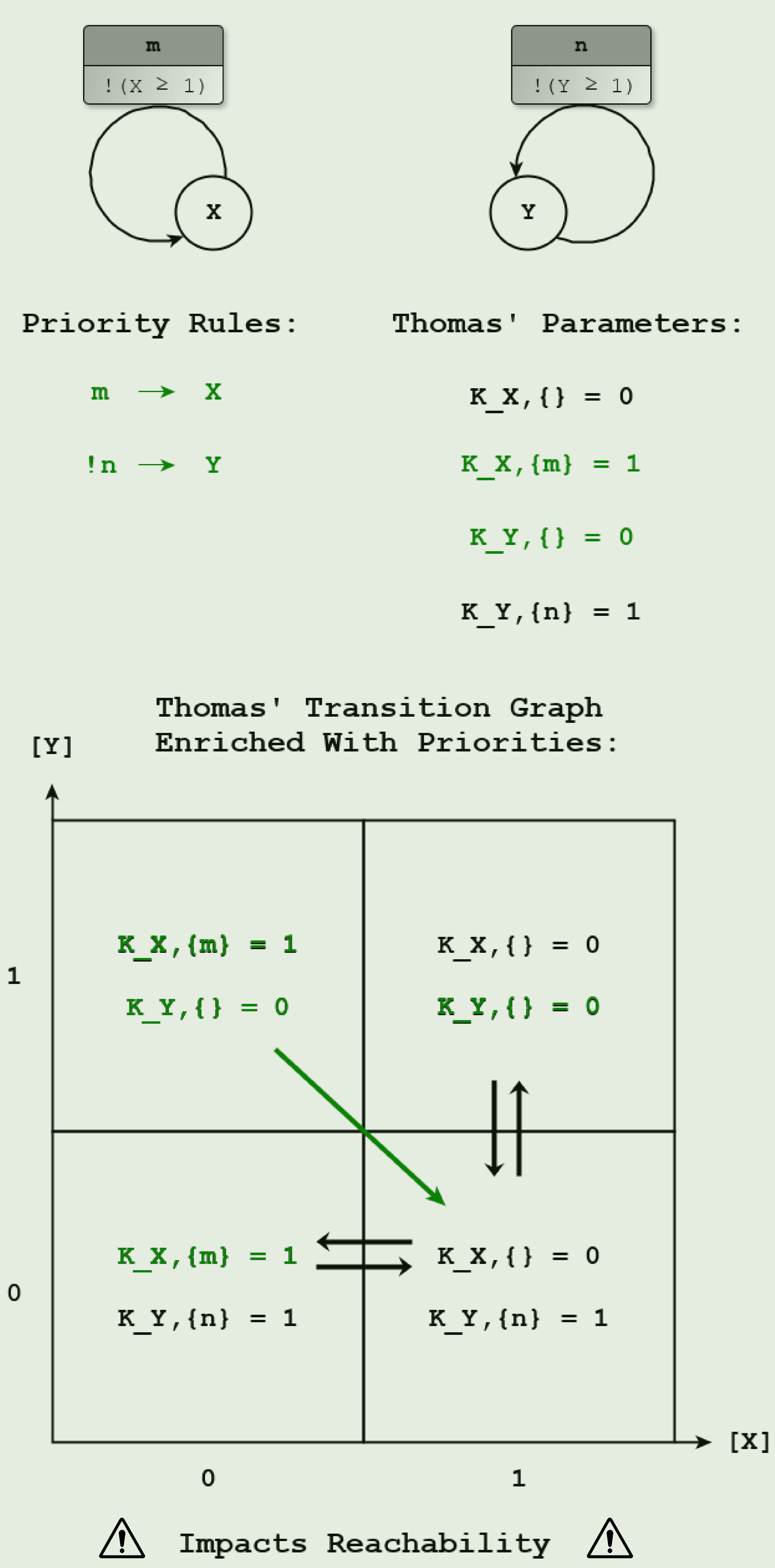
- There is a priority rule $\omega_1, \neg\omega_2 \rightarrow v$ such as :

$$\omega_1 \subseteq \omega,\quad \omega_2 \cap \omega = \emptyset$$

- and :

$$\sigma(K_{v\{\omega\}}) \neq \eta(v)$$

## Priority Rules Example




## Impact of Priority Rules on Global BRN Dynamic

The set of parameters includes classical and priority parameters and allows to build the BRN <u>global</u> dynamic.

**Its transition graph** is defined by:

- a set of nodes that are states of the parameterized BRN,
- a set of transitions $\eta \rightarrow \eta'$.

**In each state η**, where $\mathscr{P}_\eta$ is the set of priority parameters, there exists a transition between states $\eta \rightarrow \eta'$ if :

- <u>Either</u> there exists at least one priority parameter ($\mathscr{P}_\eta \neq \emptyset$) :

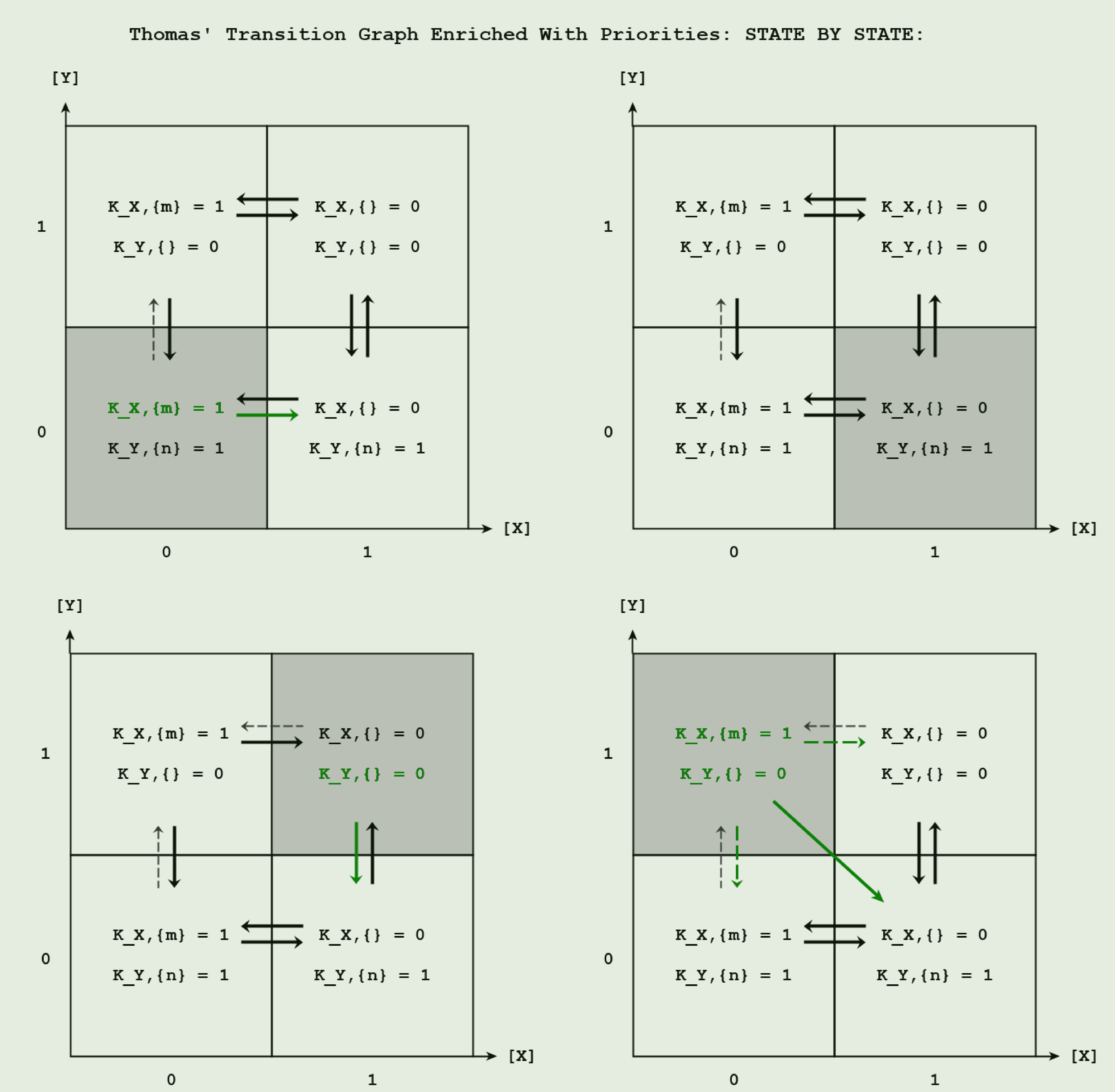
$$\eta'(v) = \sigma(K_{v\{\omega\}}) \quad \text{if } K_{v\{\omega\}} \in \mathscr{P}_\eta$$

$$\eta'(v) = \eta(v) \text{ otherwise.}$$

- <u>Or</u> there is no priority parameter ($\mathscr{P}_\eta = \emptyset$) :

$$\eta'(v) = \eta(v)+1 \quad \text{if } \sigma(K_{v\{\omega\}}) > \eta(v)$$
$$\eta'(v) = \eta(v)-1 \quad \text{if } \sigma(K_{v\{\omega\}}) < \eta(v)$$
$$\forall\ v' \in V,\ v' \neq v \Rightarrow \eta'(v') = \eta(v')$$

## Transition Graph and Partial Asynchrony




[1] Bernot G., Comet JP., Richard A. and Guespin J. Application of formal methods to biological regulatory networks : Extending Thomas's asynchronous logical approach with temporal logic. *J. T.B.. 2004.* 229(3): 339-347.