

Study the preservation of properties of complex systems



Application to gene regulatory networks

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GENetic NETworks: Emergence and Complexity

“Develop scalable computational modeling, inference tools and scalable simulation techniques for complex systems”

From a computer science point of view

“Develop a theoretical framework for modeling complex systems and for analysis of their emergent properties, inspired by the biological processes and based on software engineering methods”

Complex systems ?

A complex system is more than the set of its components.

Systems depend on the way components interact, i.e. on the connectors (glue) used to link subsystems together.

A system is said to be complex when it can inherit from its components some properties which cannot be anticipated from the knowledge issued from the components.

Some Software Engineering elements

System = Components + Connectors

Requirement: system properties must be such as defined by the user

High level formalization:

- Institution theory
 - Signatures = interfaces
 - Formulas = properties
 - Models = systems
 - Satisfaction = verification of properties by systems
- Connectors = how to build systems from subsystems

Complexity in connectors

Let S be a system which results from the connection of several subsystems:

$$S = \text{Conn}(SS_1, \dots, SS_n)$$

The connector Conn is said to be modular if properties of each subsystem SS_i are preserved in the whole system S.

The connector Conn is said to be complex if the behavior of S cannot be deduced from a complete knowledge of all subsystems S_i .

Biological case: the R. Thomas' model of gene regulatory networks

• Network of interactions between genes

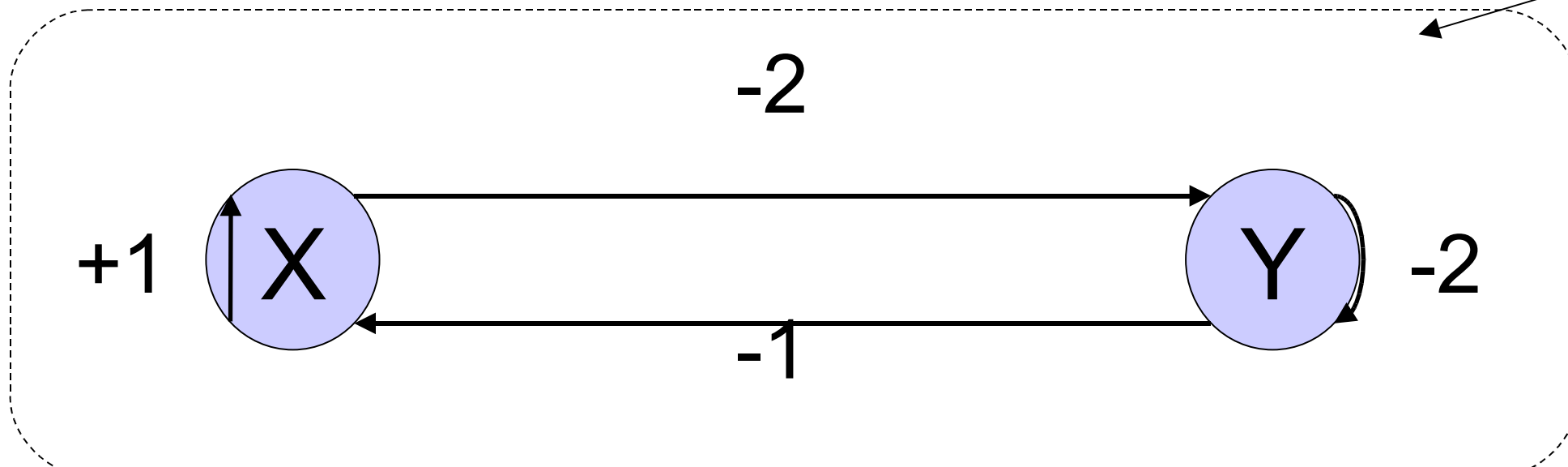
• 2 kinds of interactions

• **Activation:** the source gene *increases* the expression of the target gene

• **Inhibition:** the source gene *decreases* the expression of the target gene

• **Threshold:** interactions are effective only above a certain level of expression of the source gene

Let consider the gene regulatory network GRN:



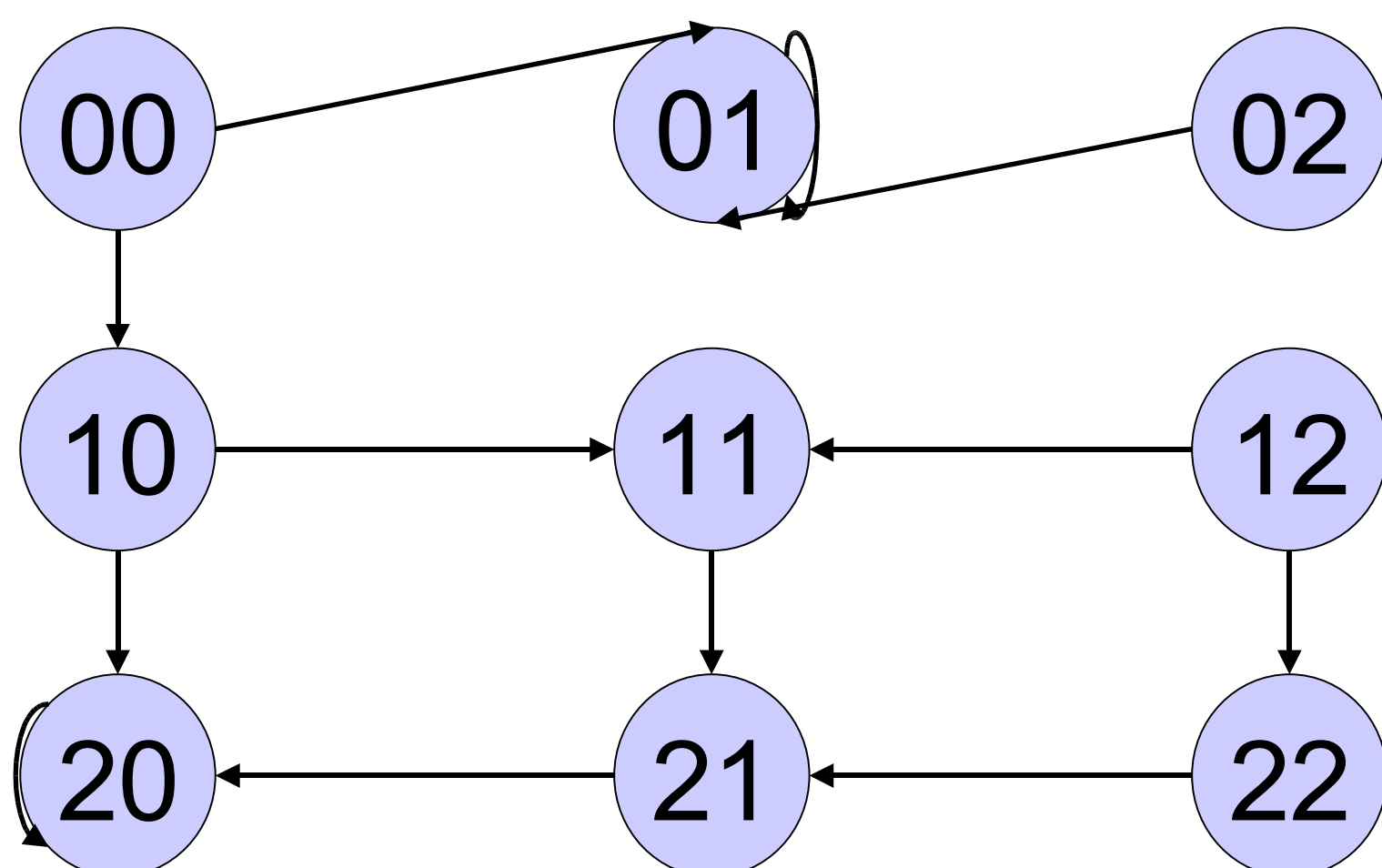
• Each gene has 3 levels of expression

• **Level 0:** X inhibits itself and activates Y; Y activates both X and Y

• **Level 1:** X activates both X and Y; Y inhibits X and activates itself

• **Level 2:** X activates itself and inhibits Y; Y inhibits both X and Y

We study the behavior of the regulatory network, i.e. how the gene expression levels evolve with time.



Properties of the behavior are formally expressed by temporal logic formulas.

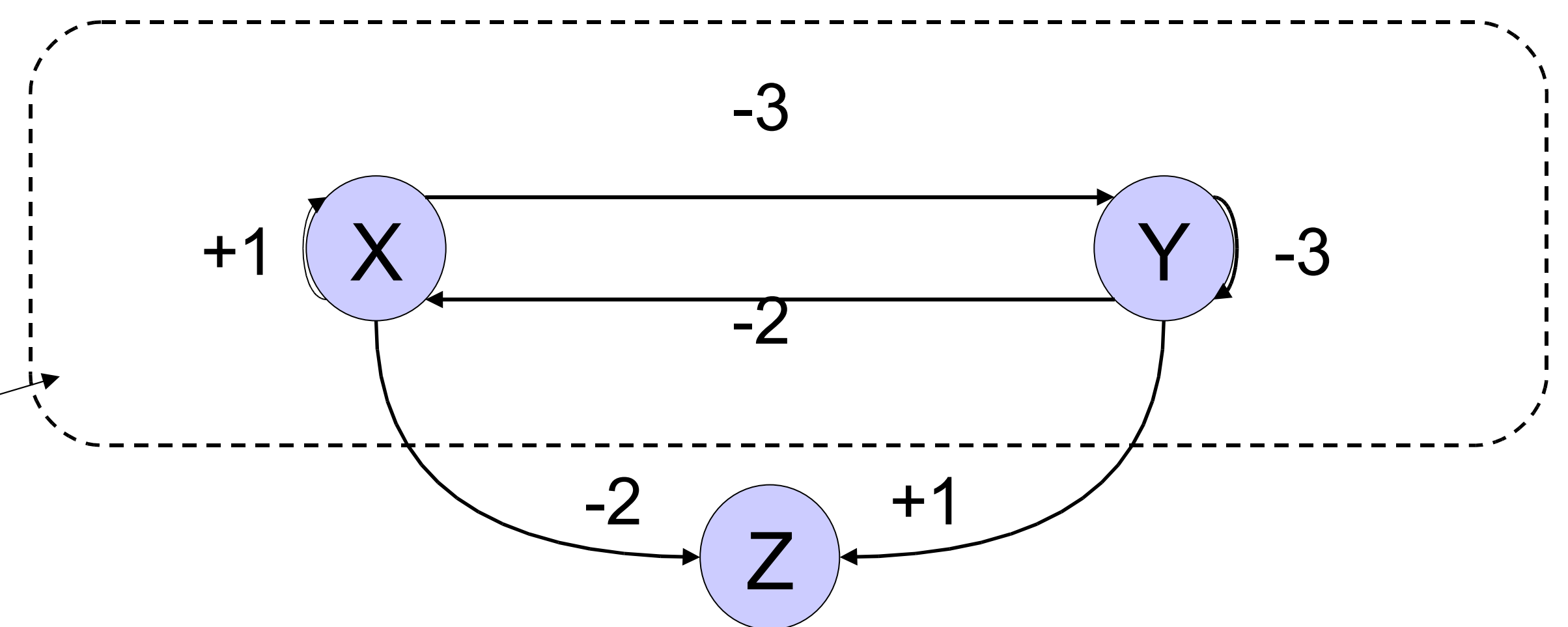
For example, the following temporal formula

$P = \text{AF}(\text{AG}(x=0 \wedge y=1) \vee \text{AG}(x=2 \wedge y=0))$ means that $(x=0$ and $y=1)$ or $(x=2$ and $y=0)$ are steady states of the regulatory network, and that one of them will be necessarily reach.

Example

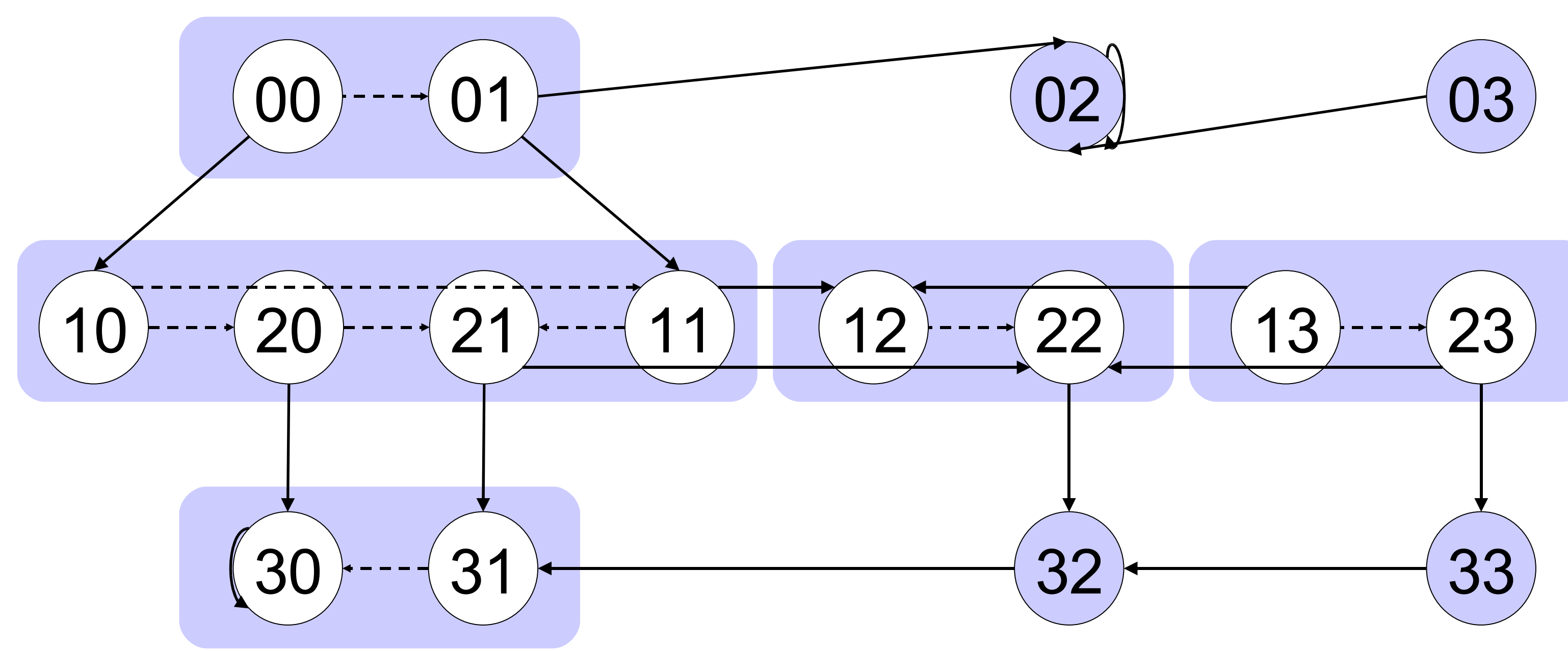
Question: Under which conditions the behavior of a small network is identical when it is alone and when it is included in a larger network?

Same network as GRN except for the thresholds which are shifted with order preservation



Provided that the small network has *no incoming edges*, then we can prove that its behavior is preserved.

Threshold shift	
X	
Small	Large
0	0
1	1,2
2	3
Y	
Small	Large
0	0,1
1	2
2	3



The quotient graph of the behavior of GRN in the larger network (blue partition) is identical to the behavior of RN when it is alone.

Up to the threshold shift, the property P still holds for the larger network:

$$\text{AF}(\text{AG}(x=0 \wedge y=2) \vee \text{AG}(x=3 \wedge y=0))$$

Ongoing research

• Formal research

- Define a connector language
- Divide large networks to identify sub networks and connectors

• Biological research

- Identify adequate connectors to build systems from subsystems corresponding to biological functions
- Aim: to be able to propose to biologists connectors linking sub regulatory networks to design larger regulatory networks, ensuring that a global expected formula is satisfied by the whole system