A Formal Approach to Decipher a Mixture of Genetic and Metabolic Networks

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Workshop *Toward Systems Biology*

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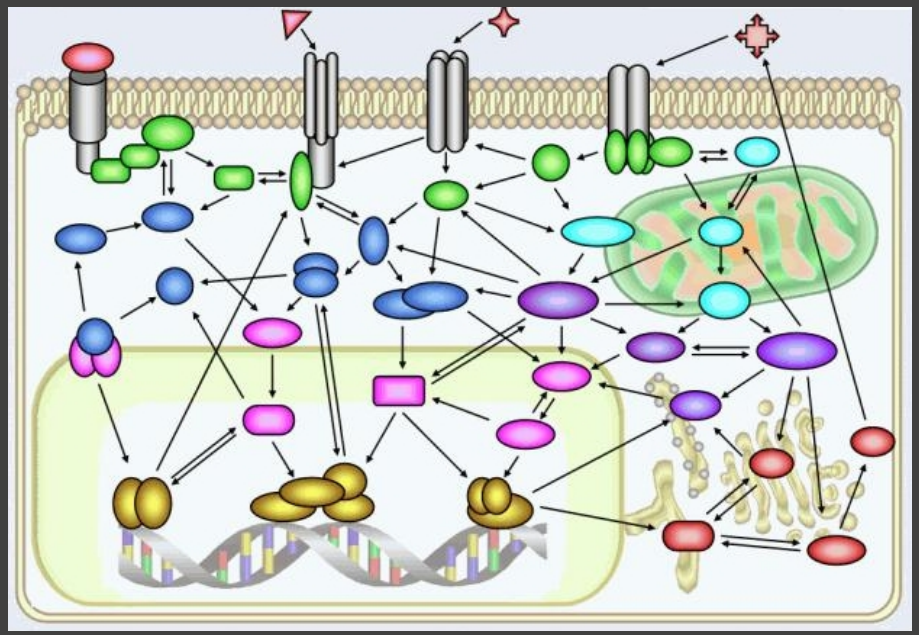
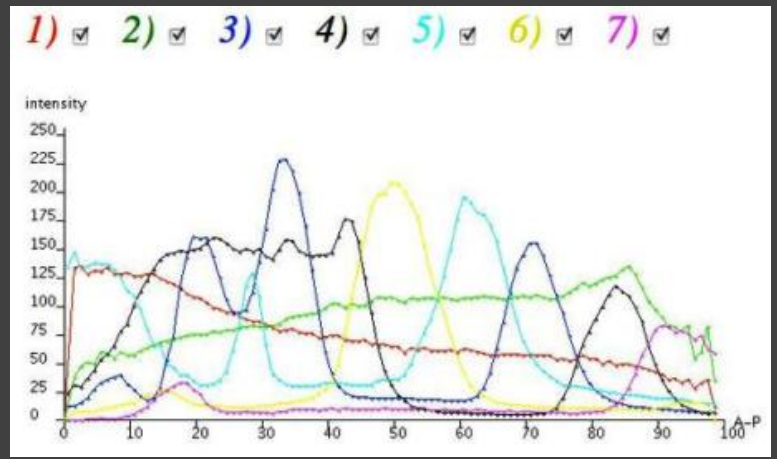
General problems

- exploration of regulatory biological networks
  - qualitative and incomplete data
  - complex relation between structure and global behavior

- modeling of regulatory biological networks
  - which players ?
  - which interactions ? kinetics ? thresholds ?
  - which behaviors ?
  - which possible correction to a deficiency of the model/system ?

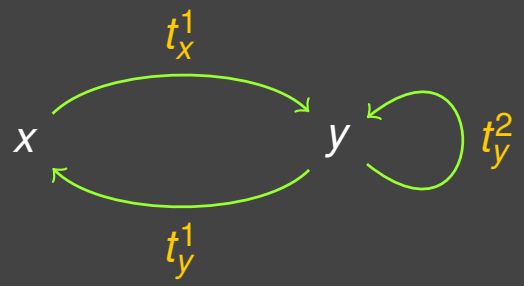




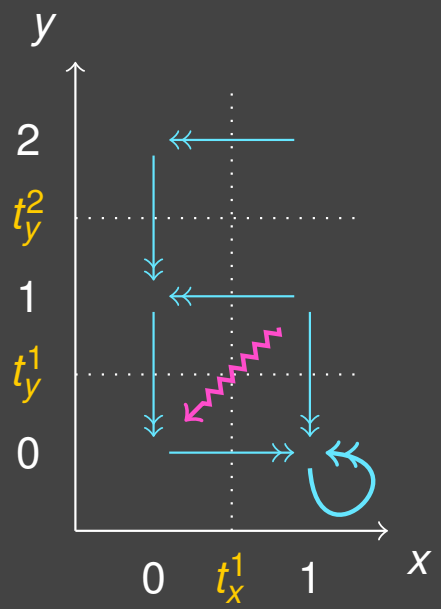
Motivation

Example of discrete modeling (Thomas networks)

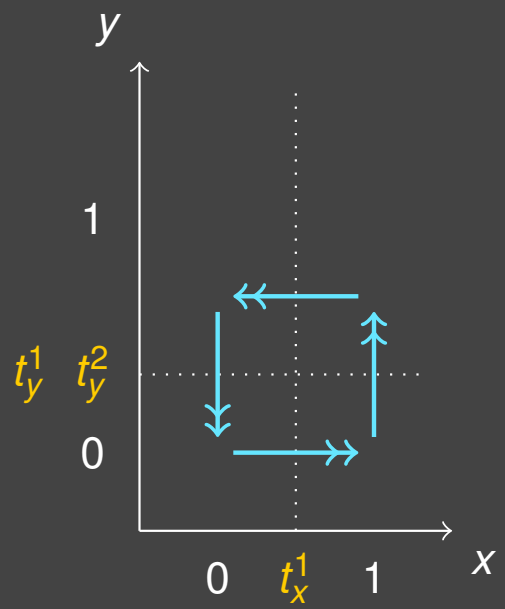
generic structure



possible behavior 1



possible behavior 2



Variables: kinetics, thresholds, existence, composition of interactions, behaviors

Specific problems

Avoid trial-error process – Consider in intension a class of models

Solution

Use of formal approach – Constraint approach

Knowledge declaration

Structure

- nodes of the network (molecular species)
- reactions/interactions (conditions about the current position of the system state + effects on the tendency of the system)
- thresholds of reactions (values are formal entities)

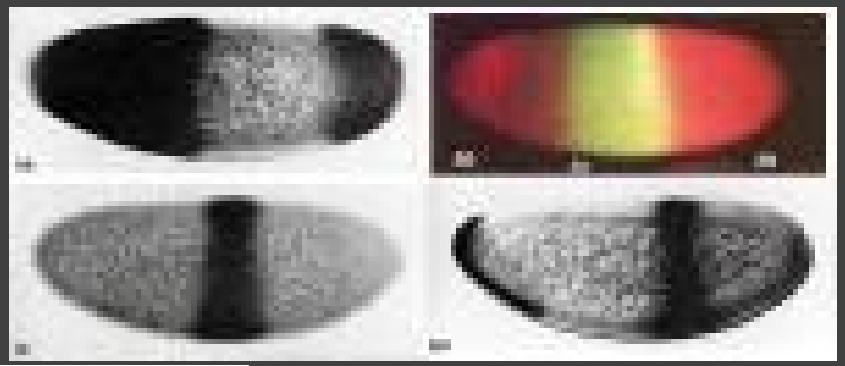
Behaviors

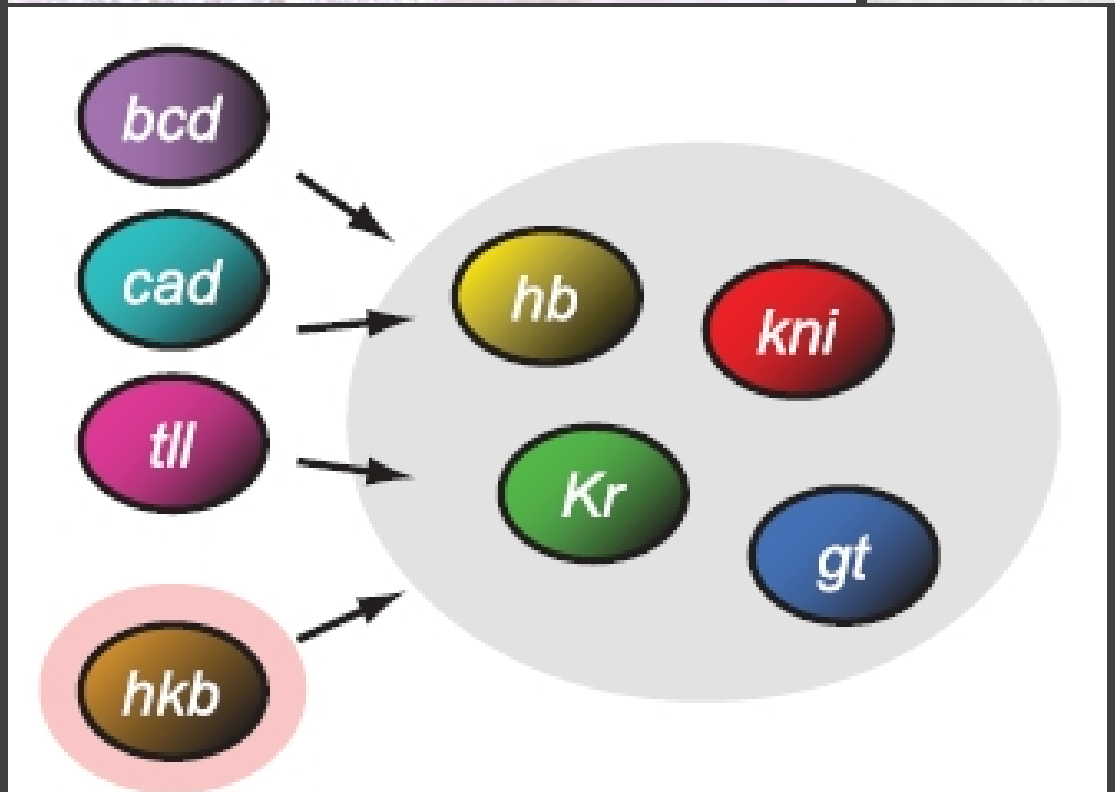
- existence of a path (sequence of transitions)
- possibility to consider several mutant types
- possibility to consider several input contexts

Relation between structure and behaviors

- formalization of Thomas networks (existence of a path constrained to follow the tendencies of the system in each encounter state),
- interaction signs (increasing tendencies $+$ or decreasing $-$ if the threshold of interaction is crossed)

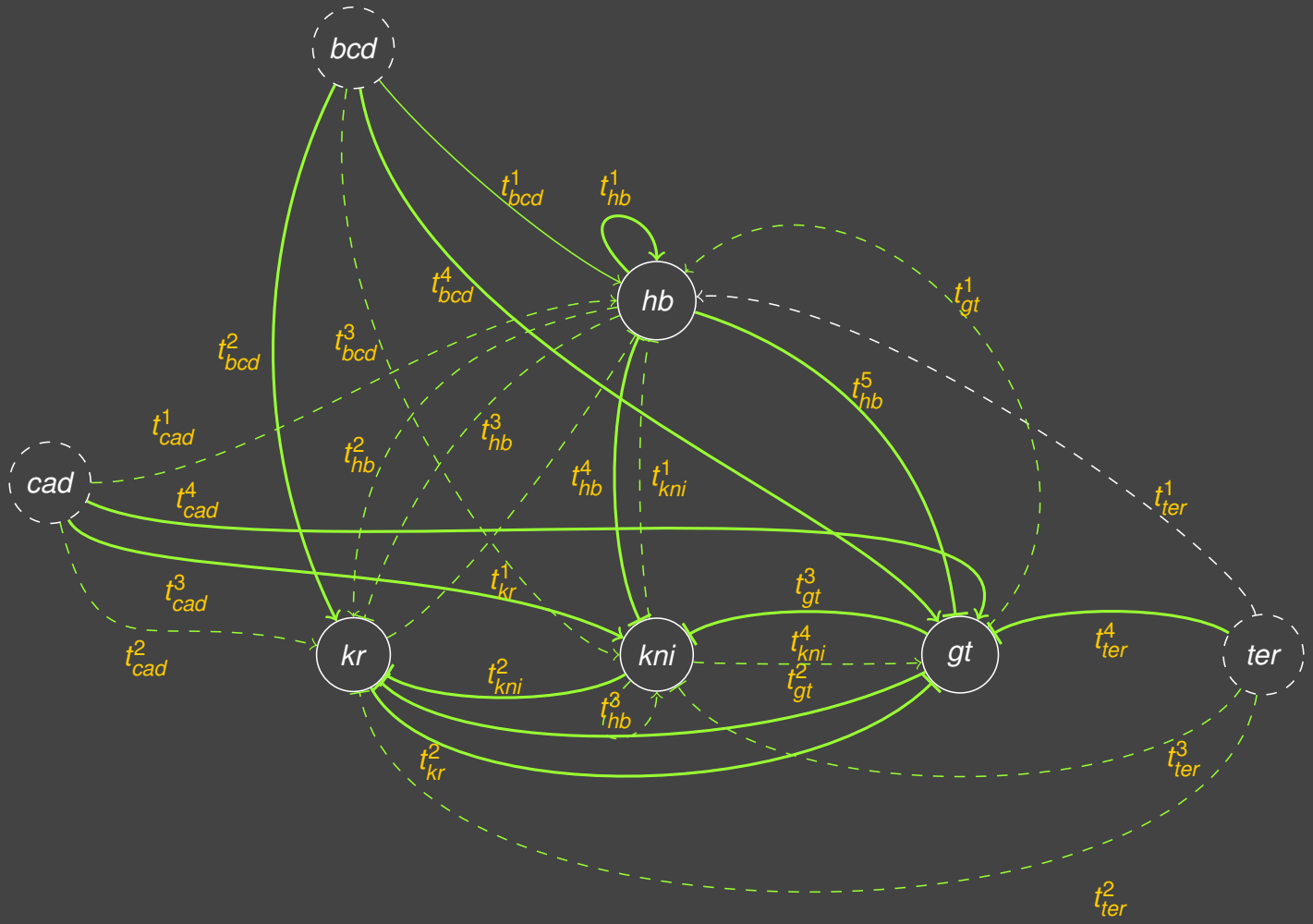
Example on the network controling the drosophila embryo segmentation





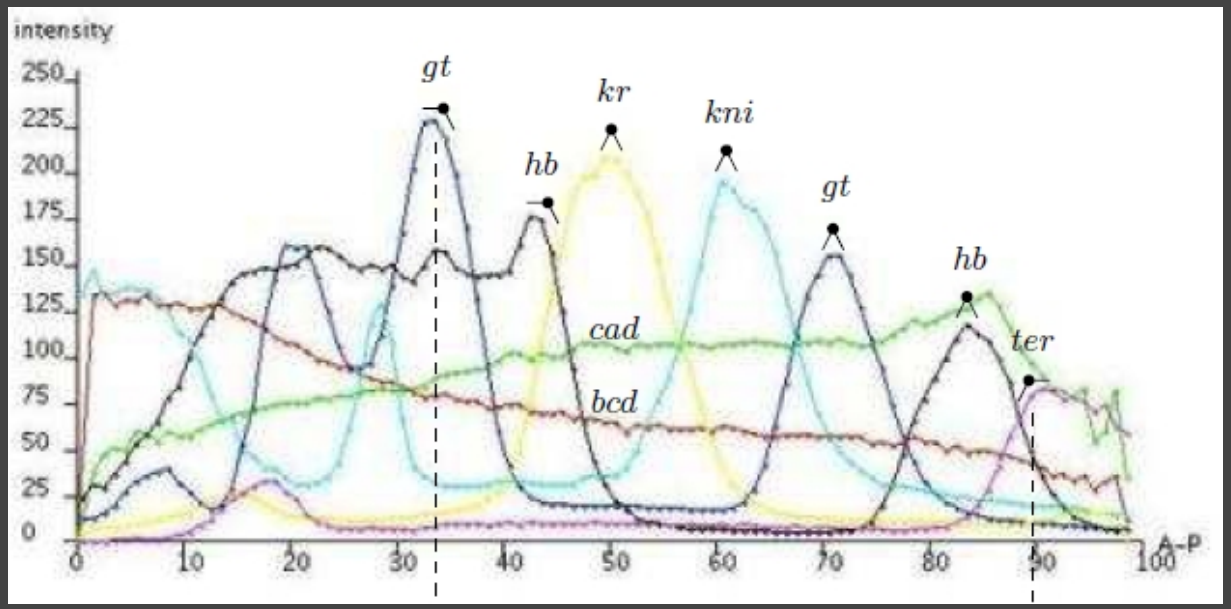
Knowledge declaration – Example on the network controling the drosophila embryo segmentation

Structure and interaction signs



Knowledge declaration – Example on the network controling the drosophila embryo segmentation

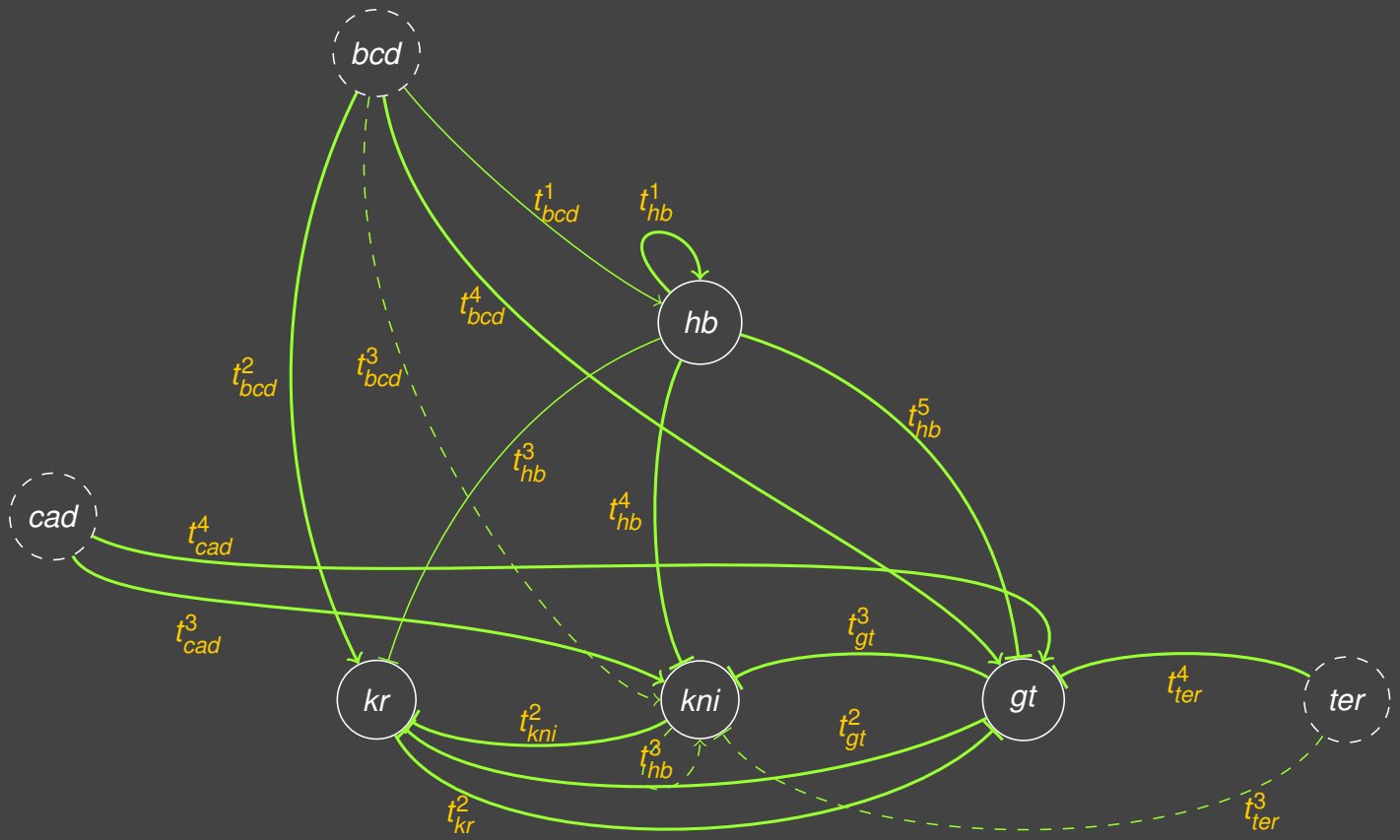
Behaviors



type	*gt*	*hb*	*kr*	*kni*	*gt*	*hb*	*ter*	additional constraints
wt	↘	↘	↓	↓	↓	↓	↓	
*hb*0	↘		↓	↓	↓		↓	
*kr*0		↘				///	///	$S_{gt}^{1,kr0} > 0$
*kni*0	↘	↘	↓		↓	///	///	
*gt*0		↘	↓	↓		///	///	
*ter*0	↘	↘	↓	↓	↓			
*bcd*0				↓	↓	///	///	
*cad*0	↘	↘	↓			///	///	

Search for the minimal network – Example on the network controling the drosophila embryo segmentation

Minimal structure



Multiple automatic functionalities

- consistence
- optimization (minimal number of interactions, of thresholds, etc)
- search for properties (positions of steady states, manner to compose the interactions, etc)
- inconsistency correction (relaxation of constraints)

Semantic of genetic discrete networks

"Genetic" cellular context of node N

- region of concentration space defined by the same positioning compared to the thresholds of interactions onto N
- two states in the same cellular context have the same "genetic" effects

Tendency of N in these cellular contexts

- value toward the direction of evolution of the concentration of N
- modeled by a parameter (not known by default)

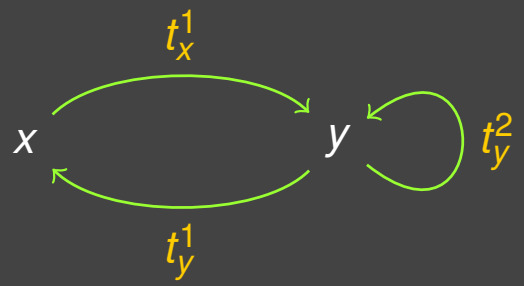
Transitions

- from a state $S1$ to a state $S2$ different: only possible if
  - $S1$ and $S2$ are different by only one component N, and
  - $S2_N$ on the same side compared to $S1_N$ that the tendency of N in $S1$ (the trajectory does not contradict the tendency).
- form a state $S1$ to the same state $S1$: only possible if
  - for all N, the tendency of N in $S1$ is equal to $S1_N$.

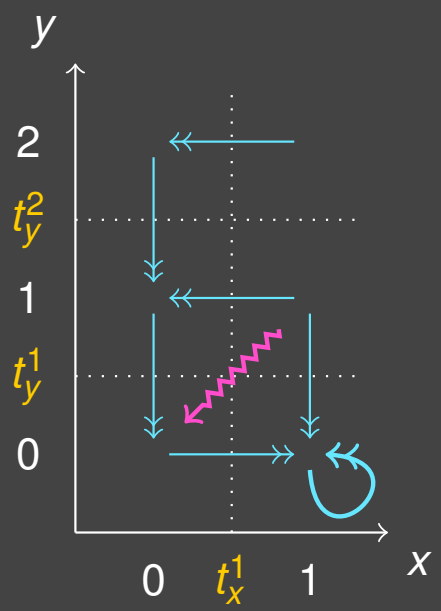
Semantic of genetic discrete networks – Example

Example of discrete modeling (Thomas networks)

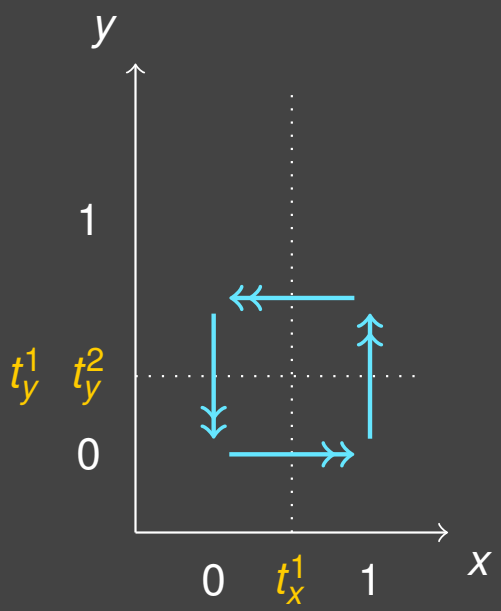
generic structure



possible behavior 1



possible behavior 2



Variables: kinetics, thresholds, existence, composition of intearctions, behaviors

Semantic of metabolic networks

Metabolic reaction

- a set of consummed species
- a set of produced species
- an activation condition (enzymes can interact)

”Production” and ”consumption” cellular contexts of the node N

- region of concentration space defined by the same positioning compared to the thresholds of activation conditions for the production (resp. consumption) of N
- two states in the same ”production” (resp. ”consumption”) cellular context have the same ”production” (resp. ”consumption”) effects

Tendency of N in these cellular contexts

- value $V \in \{min, current\ value, max\}$ toward the direction of evolution of the concentration of N
- $V = min$ if active consumption and no active production
- $V = max$ if active production and no active consumption
- $V = current\ value$ if no active consumption neither active production
- modeled by a parameter if there exist a conflict (both active production and active consumption)

Transition : idem ”genetic” + impossible to contradict the tendency of the arrival state

Semantic of discrete metabolic networks – Example on a complexation-decomplexation reaction $a + b \rightleftharpoons c$

Metabolic reactions

- $\{a, b\} \xrightarrow{S_a \geq t_a^1 \wedge S_b \geq t_b^1} \{c\}$
- $\{c\} \xrightarrow{S_c \geq t_c^1} \{a, b\}$

"Production" and "consumption" cellular contexts of node N

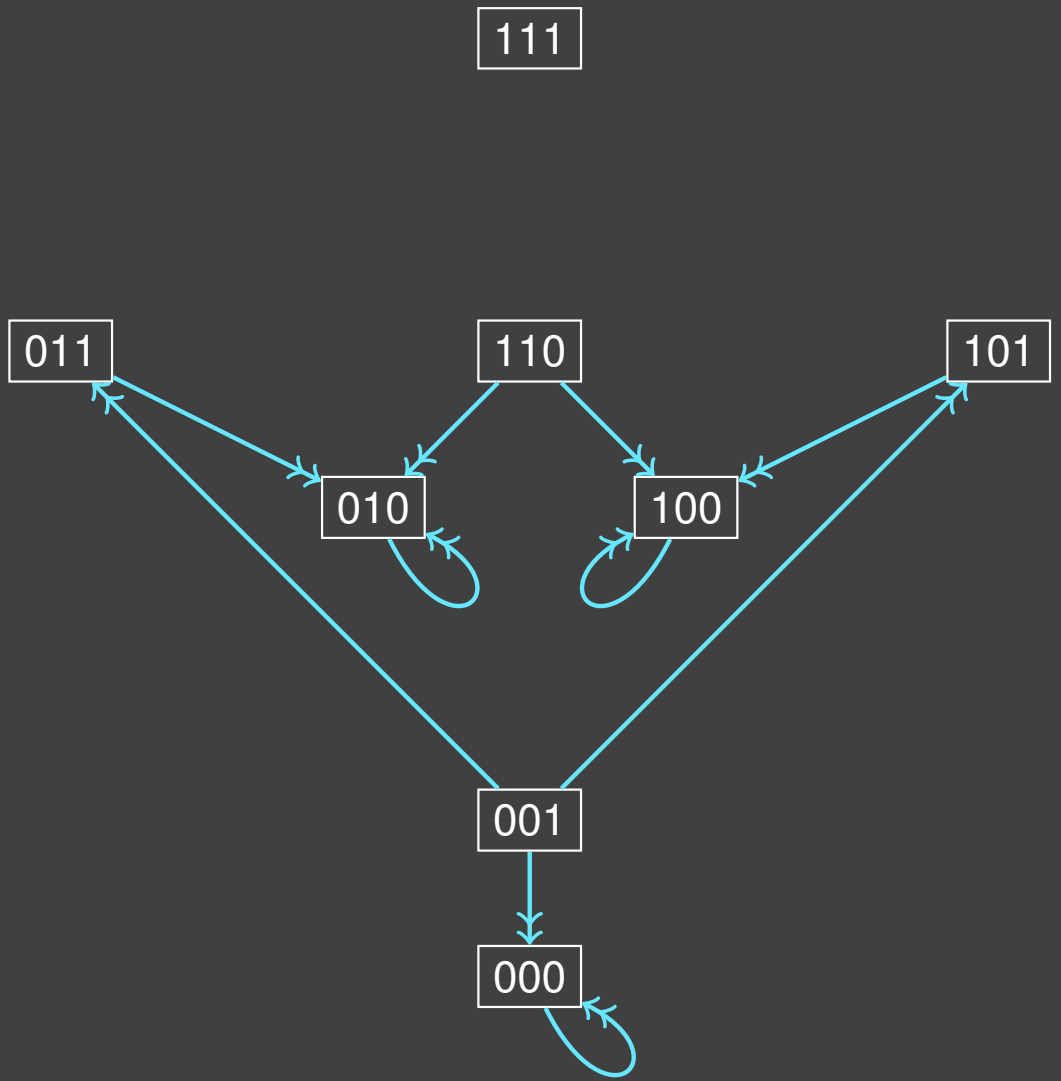
- production of $a \Leftrightarrow S_c \geq t_c^1$ (2 "production" cellular contexts for a),
- consumption of $a \Leftrightarrow S_a \geq t_a^1 \wedge S_b \geq t_b^1$,
- production of $c \Leftrightarrow S_a \geq t_a^1 \wedge S_b \geq t_b^1$,
- consumption of $c \Leftrightarrow S_c \geq t_c^1$

Tendency of N in one of these cellular contexts

- for a (idem for b) :
  - $=$ *min*: if $S_a \geq t_a^1 \wedge S_b \geq t_b^1 \wedge S_c < t_c^1$
  - $=$ *max*: if $S_c \geq t_c^1 \wedge (S_a < t_a^1 \vee S_b < t_b^1)$
  - $=$ *current value* $= S_N = S_a$: if $(S_a < t_a^1 \vee S_b < t_b^1) \wedge S_c < t_c^1$
  - $=$ *parameter* $\in \{min, current\ value, max\}$: if $S_a \geq t_a^1 \wedge S_b \geq t_b^1 \wedge S_c \geq t_c^1$

Transition : idem "genetic" + impossible to contradict the tendency of the arrival state

Semantic of discrete metabolic networks – Example on a complexation-decomplexation reaction $a + b \rightleftharpoons c$



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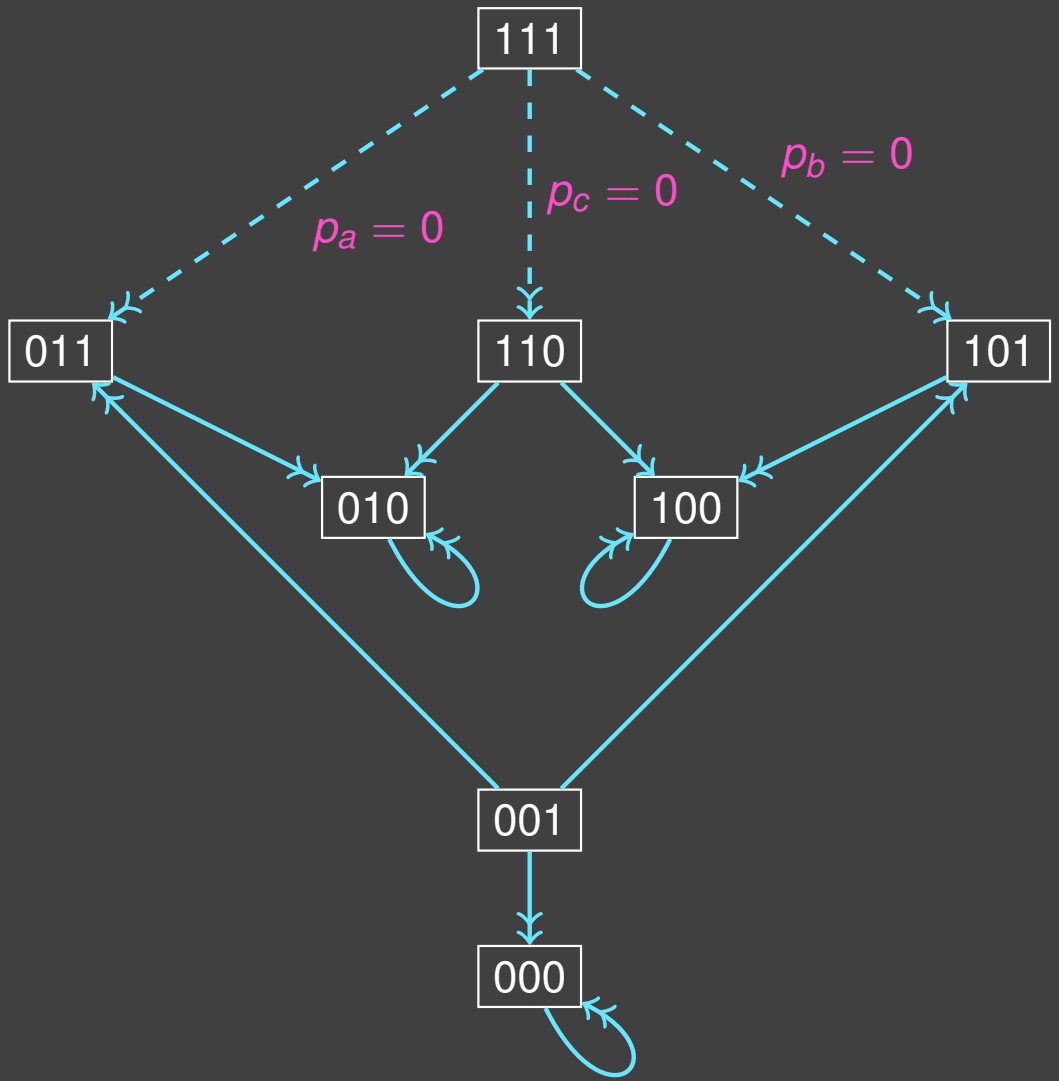

abc

$a + b \rightleftharpoons c$

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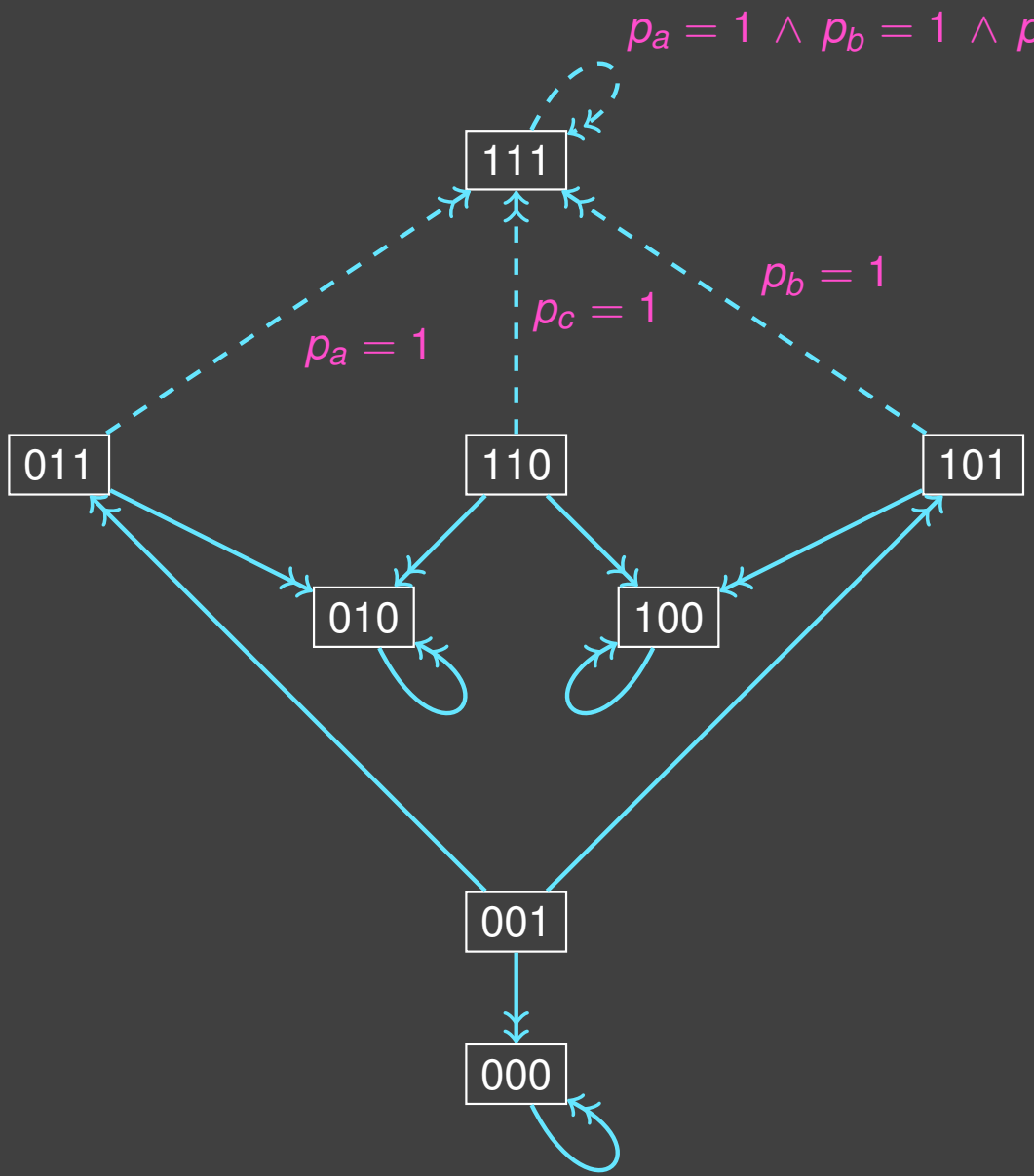

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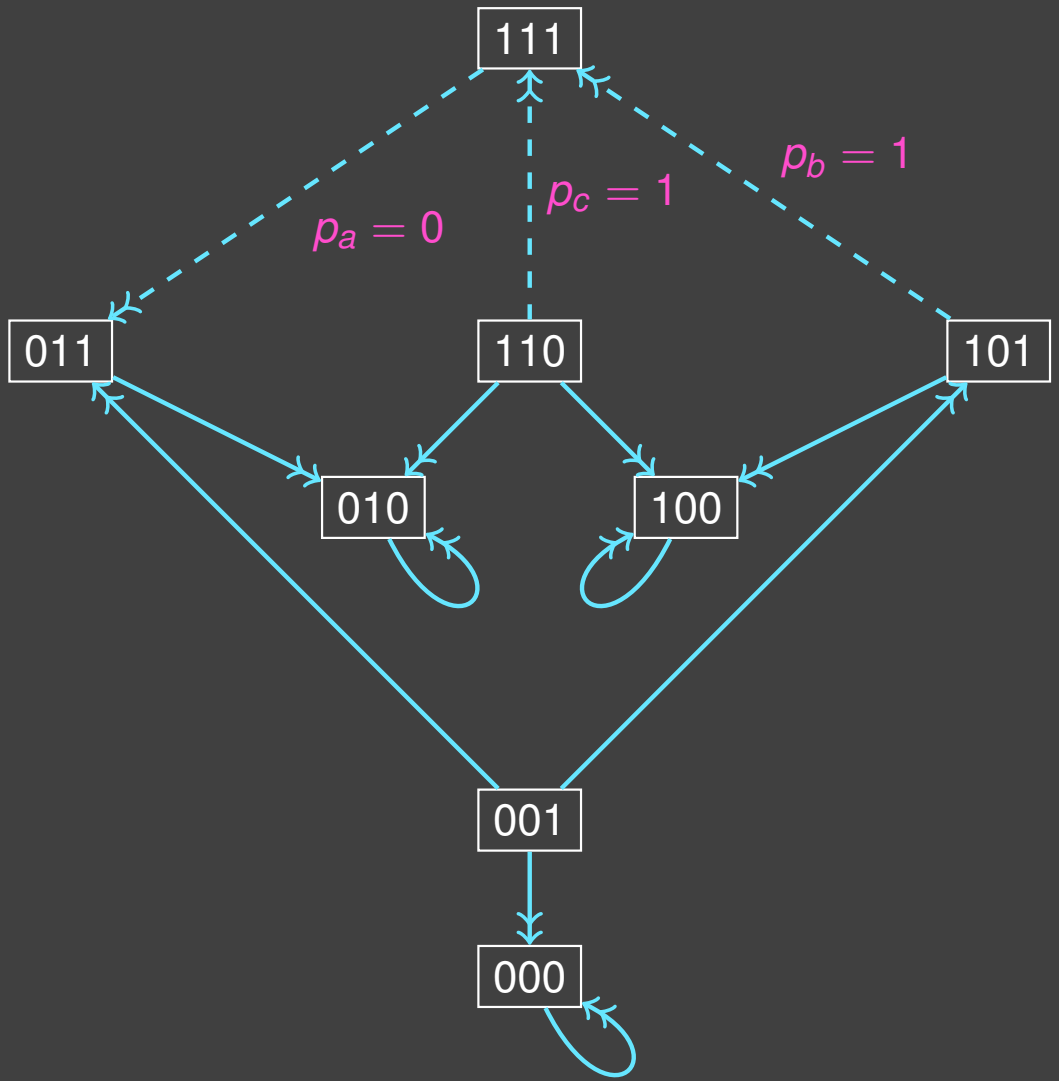

abc

$a + b \rightleftharpoons c$

Semantic of mixed networks

cellular contexts of node N

triple of cellular contexts "genetic", "production", and "consumption" (noted $Cellc_N^{i_{genetic}, i_{production}, i_{consumption}}$ or just $Cellc_N^i$).

Tendency of N in one of these cellular contexts

- if no production and consumption of N: idem genetic semantic,
- if no genetic interaction onto N: idem metabolic semantic,
- else : idem genetic semantics +
  Constraints enforcing a (non strict) increasing of the tendency from a (non empty) cellular context $Cellc_N^1$ to a (non empty) cellular context $Cellc_N^2$ if:
  - $Cellc_N^2 = Cellc_N^1 +$ one production,
  - $Cellc_N^2 = Cellc_N^1 -$ one consumption,
  - $Cellc_N^2 = Cellc_N^1 +$ one *additive* interaction (true also for genetic part).

2 programming environments to decypher biological networks

- GNBox environment
  - formalization: discrete genetic networks and biological properties
  - implementation: cooperation of 2 solvers, CP on integers and SAT
  - functionnalities: consistency, correction, property inference, optimization
  - formal entities: existence, kinetic and threhsolds of interactions, behaviors,
  - publication : F. Corblin, E. Fanchon, L. Trilling. BMC Bioinformatics 2010.
- SysBiOX environment
  - formalization : discrete mixed networks (genetic and metabolic)
  - implementation: with ASP (Answer Set Programming)

- Very general: many functionalities and easy representation of data
- Completely declarative modeling: formalizations with constraints (over formal entities)

Perspectives

- application to the toxicity control in human hepatic cells (A. Corlu, F. Morel, INSERM Rennes – J. Nicolas, IRISA-INRIA Rennes).
- application to mammal iron homeostasis (J.-M. Moulis, IMBG-CEA Grenoble).
- study of mixed network properties (as presented here).
- experiment design: language to describe
  - biological properties (objective)
  - controllable perturbations
  - observables.
- technological study for optimization, property inference, and relaxation of constraints (ASP, SMT).