From Logical Regulatory Graphs to Petri Nets to SBML

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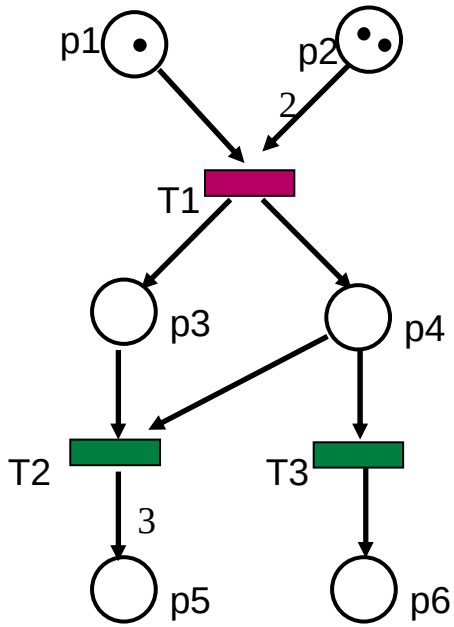
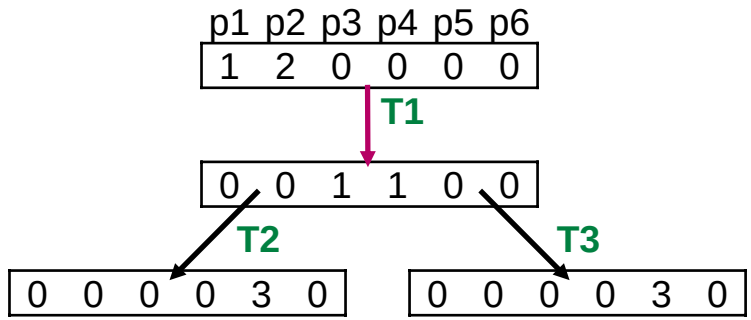
Outline

- Why Petri nets for biological networks ?
- Systematic rewriting rules: from logical regulatory models to standard PN models
  - a means to represent logical regulatory models into the SBML format
- Some conclusions

Petri Nets, an informal introduction

- ✓ A PN is defined by its: places - transitions - arcs - initial marking
- ✓ PN formalism allows the representation of concurrency/parallelism
- ✓ The firing rule ⇒ dynamics of the system (token *game*)
- ✓ Strong mathematical foundations





Why Petri Nets for biological networks ?

Examples of properties

structural → P-invariants (conservative components)
→ T-invariants (repetitive components)
dynamical → liveness
→ boundness
→ reachability

- conservation, flux modes...
- stable states / equilibrium
- limited concentrations
- paths in the dynamics

Tools

Analytical approaches → state equations, algebraic equations, graph analysis...
Model checking
Simulation
Extensions: Stochastic PN, Higher level nets, Coloured nets, hybrid nets...

www.daimi.au.dk/PetriNets/tools/

PNML Petri Net Markup Language

Why Petri Nets for biological networks ?

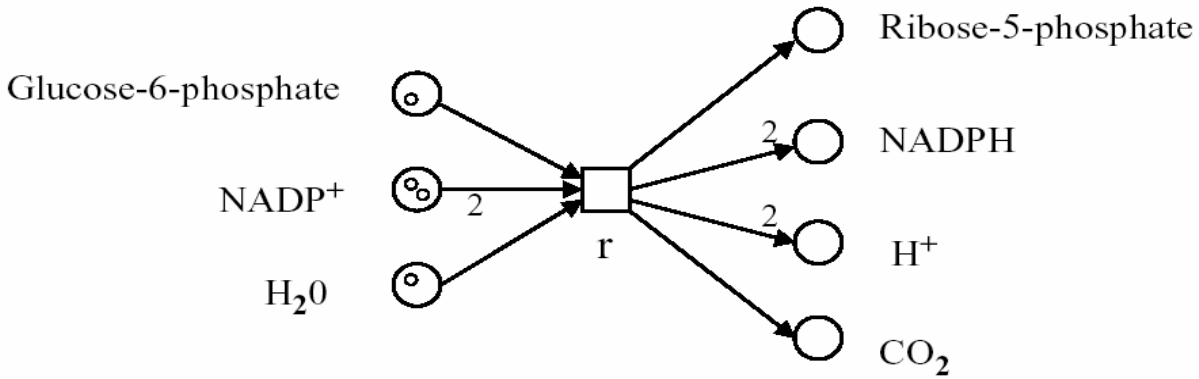
PN already successfully applied to the modelling of **metabolic networks**

places → metabolites / substrates / products / enzymes ...
transitions → reactions / catalysis ...
incidence matrix → stoichiometry

Example

Pentose Phosphate pathway

G6P + 2 $NADP^+$+H_2O → R5P + 2NADPH + H^+ + CO_2



I.Koch & M. Heiner, Qualitative Biochemical Pathway Analysis using Petri Nets

Genetic regulatory networks: arrows have a different semantic more easily represented with a logical formalism

Logical modelling of genetic regulatory networks

Genetic regulatory networks described in terms of **logical models** (with multi-level discretisation)

Implemented in **GINsim** (java, plugin architecture)

model specification, simulation and analysis

a dedicated format **GINML** (GXL extension)

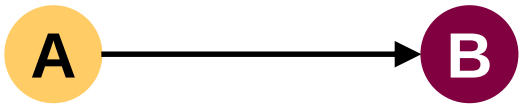
towards SBML ?

Multi-valued Regulatory Petri Nets: Towards a systematic standard PN modelling of genetic regulatory networks

Genetic regulatory networks described in terms of logical models (with multi-level discretisation)

- ➔ two complementary places for each gene
- ➔ two transitions for each logical parameter (representing the effect of inputs on a given gene)

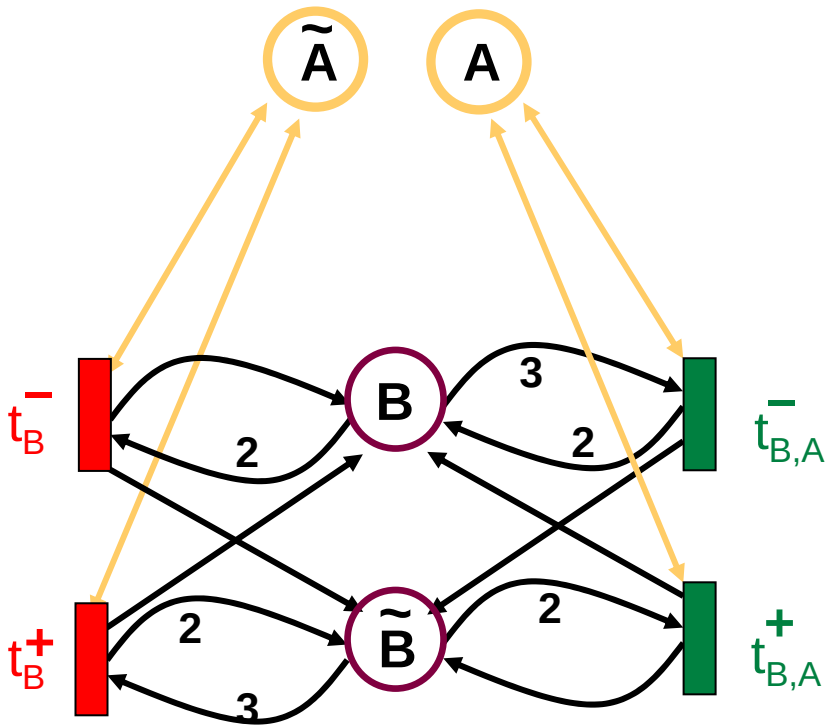
Example



$max_A=1$ $max_B=3$

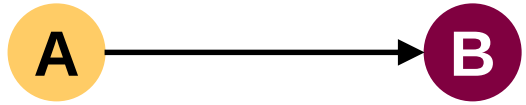
$K_B(A)=2$ $K_B(\varnothing)=1$

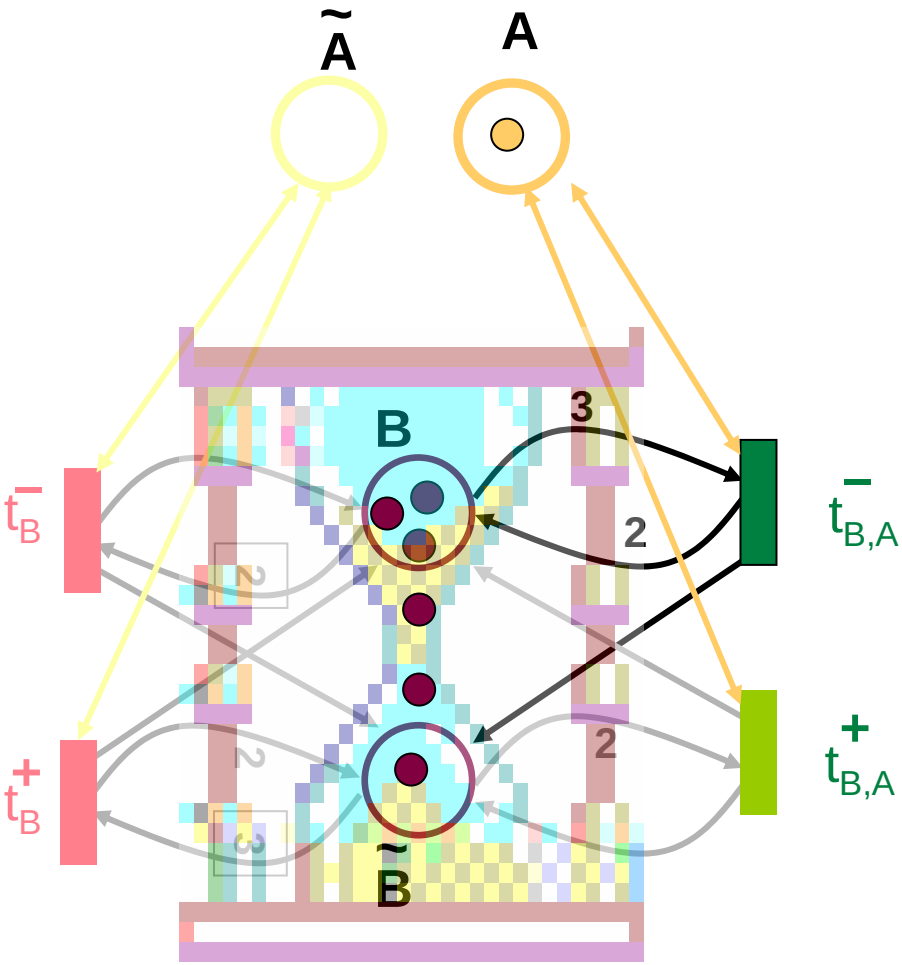
$M(A)+M(\tilde{A})=1$
$M(B)+M(\tilde{B})=3$



Multi-valued Regulatory Petri Nets

Example $max_A=1$ $max_B=3$, $K_B(A)=2$ $K_B(\varnothing)=1$





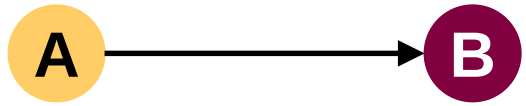
A present and B at its level 3

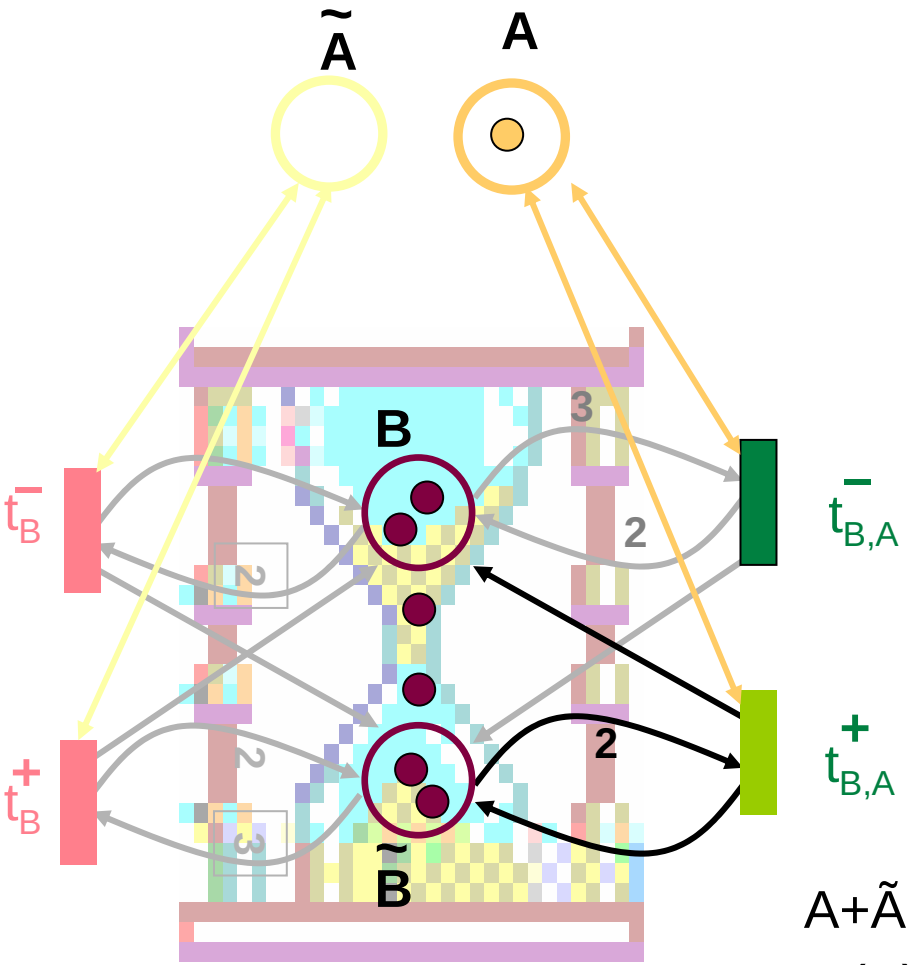
↓

B <u>decreases</u> its level to 2

Multi-valued Regulatory Petri Nets

Example $max_A=1$ $max_B=3$, $K_B(A)=2$ $K_B(\varnothing)=1$





A present and B at its level 1

↓

B increases its level to 2

$A+\tilde{A}$ → regulatory component

$M(A)$ → current amount of A

$[t^+_{A,*}, t^-_{A,*}]$ → a "regulation"

Conclusions and prospects

- Towards the modelling of mixed metabolic-genetic networks

- SBML 2 PNML
  existing attempts (Shaw et al. 2004)
  using PN tools for the analysis of biological models

- From logical models of genetic regulatory networks to Multi-valued Regulatory Petri Nets

  + PNML 2 SBML → a means to represent genetic regulatory networks into SBML ?

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