Dynamics

- only consider *valid* markings m where $m(\alpha_i) = 1 - m(\tilde{\alpha}_i)$ for all $i \in \{1, \ldots, n\}$
  - validity is conserved: marking graph of valid initial state consists only of valid states
  - boundedness
- marking graph and corresponding subgraphs of asynchronous state transition graph of f are equivalent in the following sense:
  - $x^1 \to x^2$ in asynchronous STG iff
    there is enabled transition t such that $m^1 \xrightarrow{t} m^2$ with
    $m^1(\alpha_i) = x_i^1 = 1 - m^1(\tilde{\alpha}_i)$ and $m^2(\alpha_i) = x_i^2 = 1 - m^2(\tilde{\alpha}_i)$

Remarks

- mathematical description yields automated procedure for translating network description by Boolean function into petri nets
- similar translation for multi-valued models possible
- petri net topology carries information on structure and dynamics
- counting transitions, petri net model is exponential in size (simplifications possible)
- non-determinism of petri net dynamics results in asynchronous update for the regulatory network,
  it is possible to construct petri net models yielding synchronous dynamics
- simulation, algebraic methods and model checking techniques can be used for analysis
- treatment of signalling networks similar

Combining metabolic and regulatory networks

- diversity of biological processes complicates formulation of encompassing mathematical modeling framework

  E. Simão et al., *Qualitative modelling of regulated metabolic pathways: application to the tryptophan biosynthesis in E. Coli*, Bioinformatics 21, 2005

  - integrated qualitative modeling framework – petri net model combining metabolic and gene regulatory networks

    Biosynthesis of tryptophan

    - metabolic pathway converting chorismate into tryptophan (Trp)
    - pathway enzyme (TrpE) inhibition by final product (Trp)
    - transcriptional inhibition of pathway enzyme coding operon resulting from combination of product of repressor gene *trpR* and Trp
    - importance of availability of external Trp

    $\longrightarrow$ simplified model

Tryptophan biosynthesis

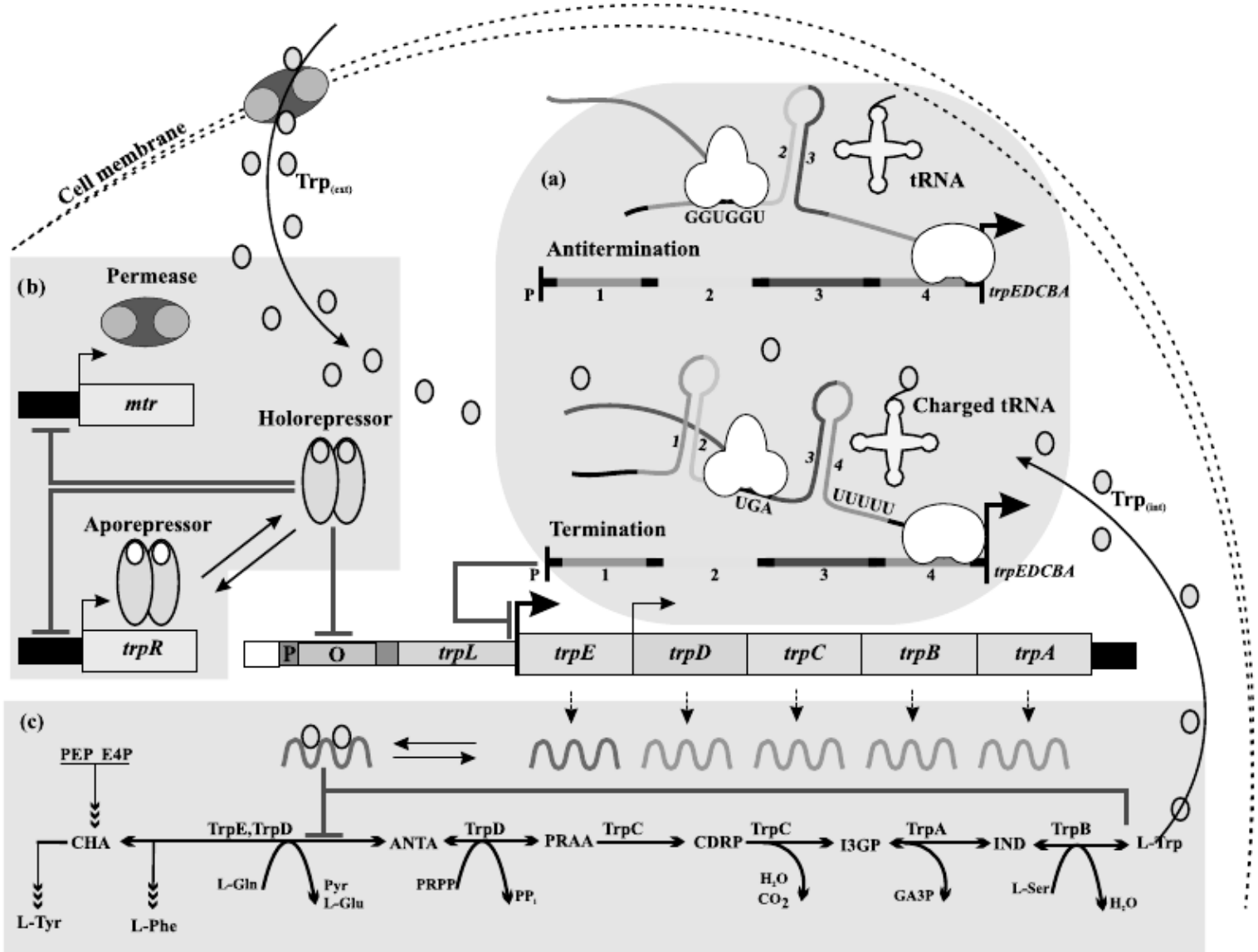
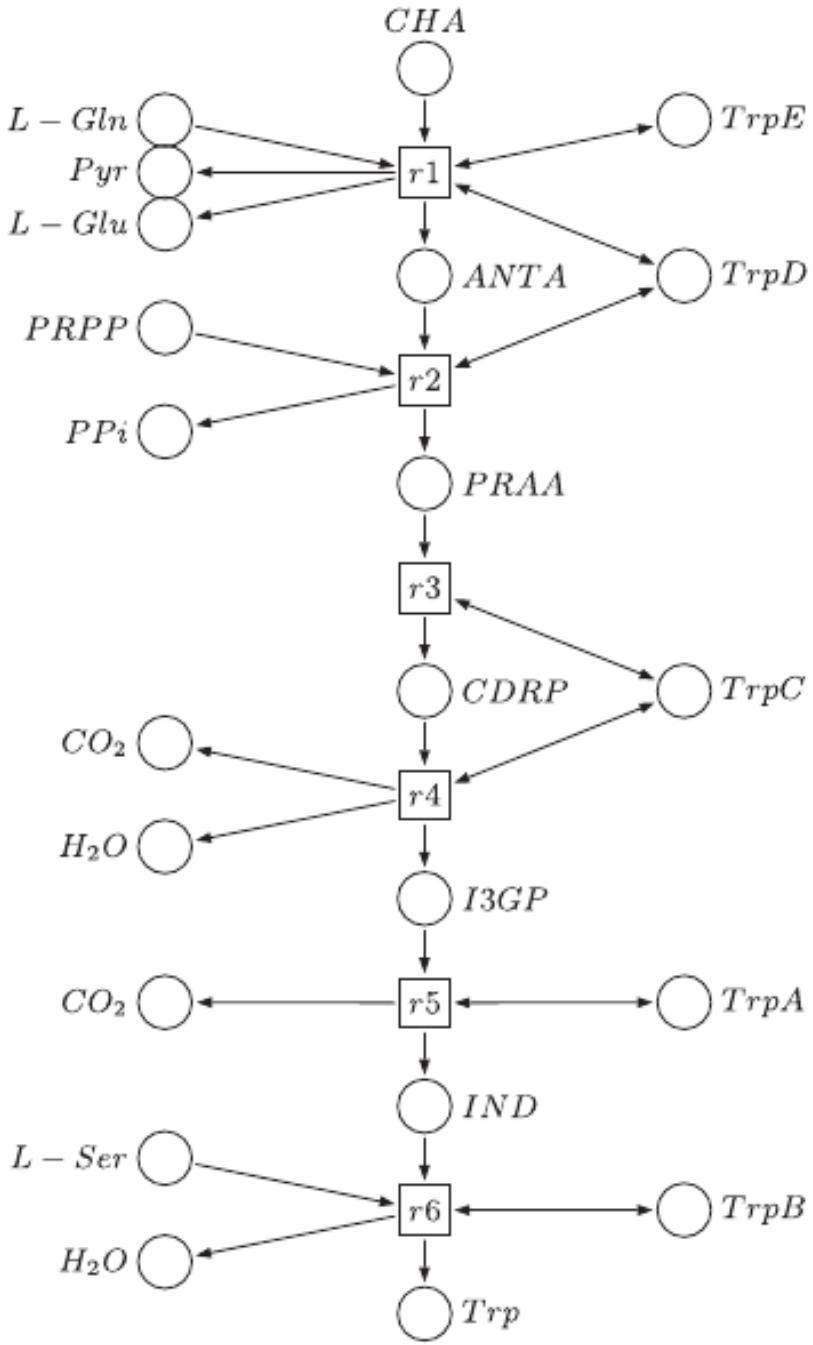


Fig. 1. Tryptophan biosynthesis is subjected to at least three regulatory mechanisms: (**a**) transcription attenuation, (**b**) transcriptional repression and (**c**) feedback enzyme inhibition [cf. (Yanofsky, 2004)].

Metabolic pathway

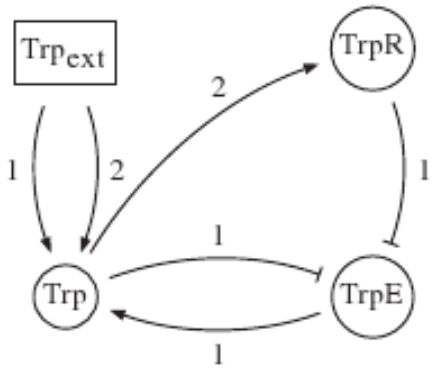
- reactions represented as transitions with reactants as input and products as output places
- enzyme catalysis: side conditions with no consumption
- stoichiometry encoded in arc weights

- simple metabolic chain conditioned by presence of enzymes and reactants

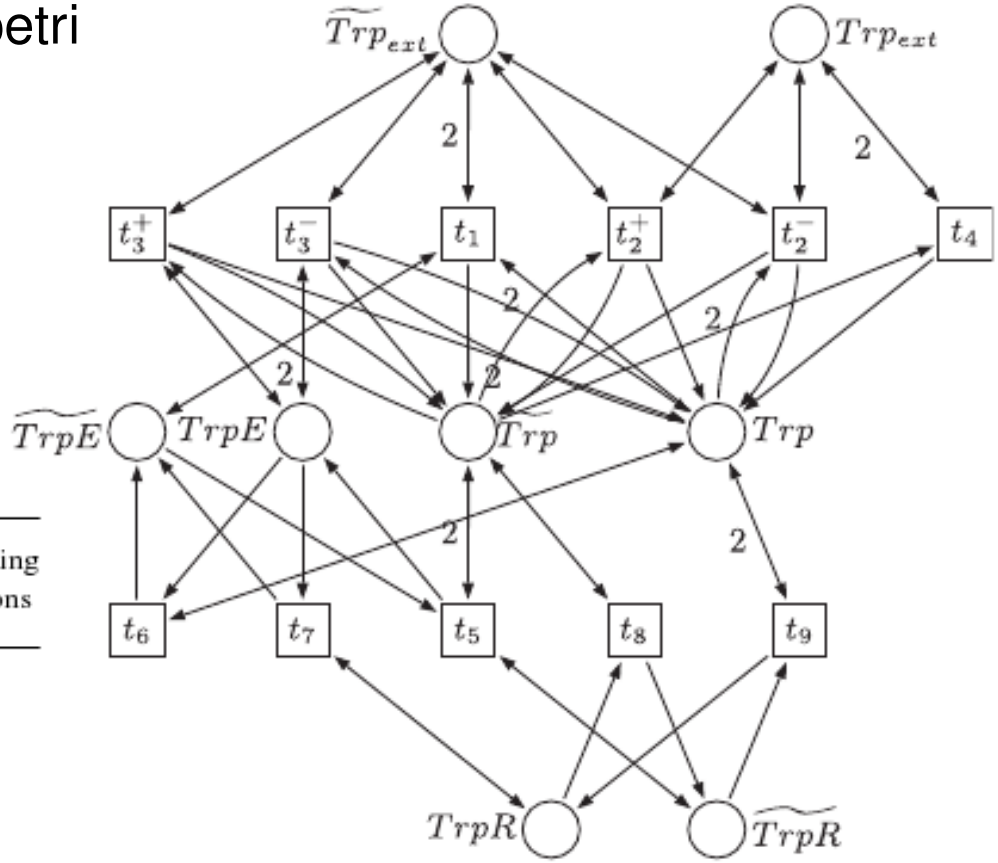


Regulatory network

Translate simplified logical model into petri net model

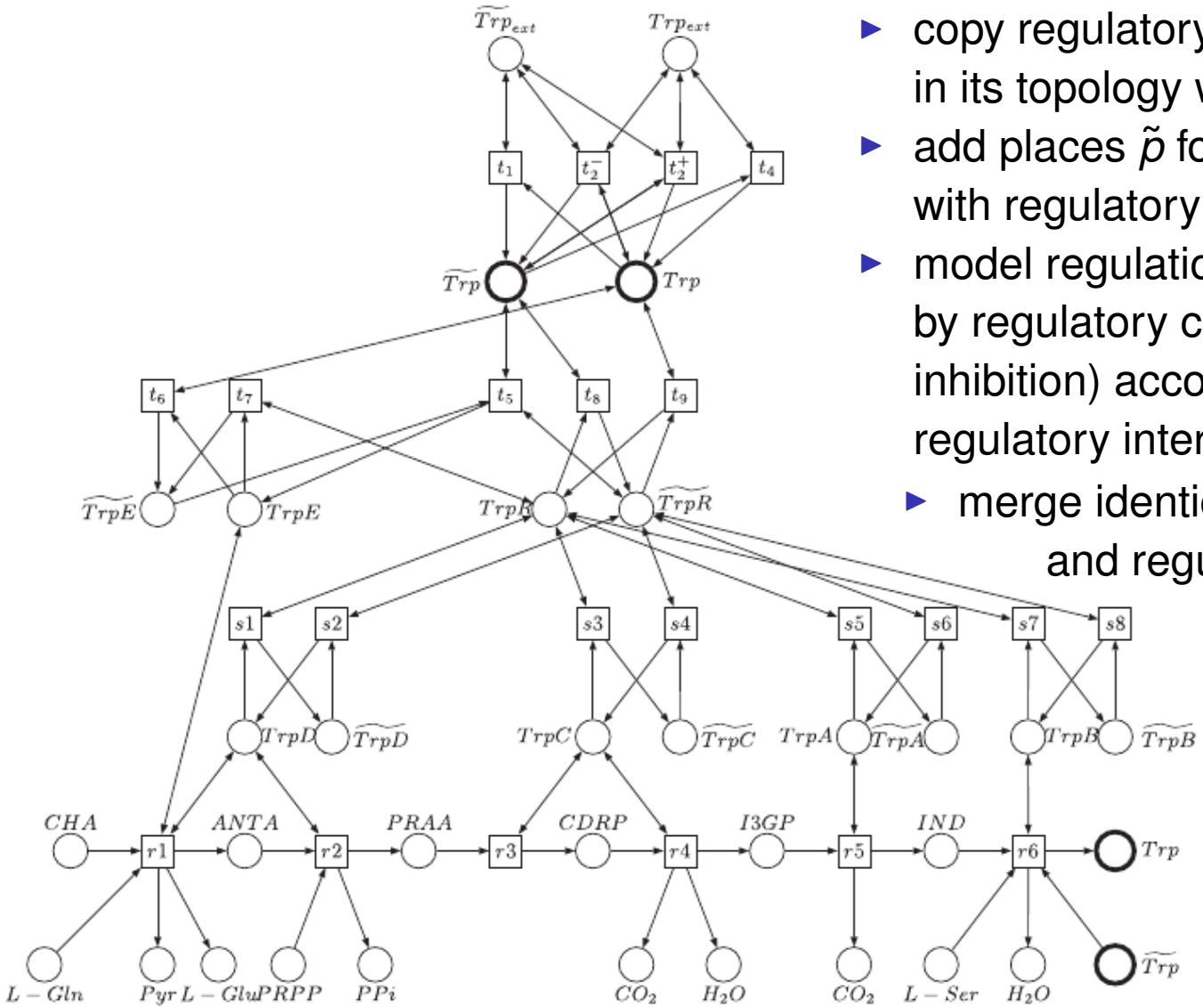


Context (input genes)	Parameter value	Corresponding PN transitions
TrpE		
$TrpR = 0$ and $Trp = 0$	1	t_5
$TrpR = 1$ and $Trp = 0$	0	t_6, t_7
$TrpR = 0$ and $Trp \geq 1$	0	
$TrpR = 1$ and $Trp \geq 1$	0	
TrpR		
$Trp \leq 1$	0	t_8
$Trp = 2$	1	t_9
Trp		
$Trp_{ext} = 0$ and $TrpE = 0$	0	t_1
$Trp_{ext} = 0$ and $TrpE = 1$	1	t_2, t_3
$Trp_{ext} = 1$ and $TrpE = 0$	1	
$Trp_{ext} = 1$ and $TrpE = 1$	1	
$Trp_{ext} = 2$ and $TrpE = 0$	2	t_4
$Trp_{ext} = 2$ and $TrpE = 1$	2	



- input vertex Trp_{ext}
- range $\{0,1,2\}$ for Trp and Trp_{ext}, $\{0,1\}$ for TrpR and TrpE

Integrated model I



- copy metabolic pathway
- copy regulatory network (but changes in its topology will be made)
- add places $\tilde{p}$ for all places communicating with regulatory network (enzymes, Trp)
- model regulation of enzymes by regulatory components (here only inhibition) according to templates for regulatory interactions
  - merge identical places in metabolic and regulatory petri net
  - identify indirect (via metabolic pathway) regulatory interactions and substitute them by explicit pathway (here influence of TrpE on Trp)

Arc weights have been omitted.

Integrated model II

Further adjustments

- add $\widetilde{\text{Trp}}$ as input place tp r6 (coherence of markings)
- add output arcs from r6 to all input compounds of the pathway (no restriction on resources)
- put priorities on transitions (delays)

Reachability analysis for three different levels of Trp_{ext} and biologically sensible initial marking

- low level: homeostatic levels of internal Trp and TrpE activity (cycle)
- intermediate level: steady state with Trp present, TrpE and TrpR inactive, all other enzymes present (unique dead marking)
- high level: Trp high, TrpR active, enzymes repressed (six dead markings, differ only in metabolic intermediates)

$\Rightarrow$ matches biological observations

Remarks

Integrated petri net models

- no automated procedure for combining models
- difficulty of "translating" tokens in more complex settings (at the interface of metabolic/regulatory/signalling networks)
- problem of handling significantly different time scales
- complexity of dynamical models unsuited for large networks

Petri nets in general

- easily accessible, flexible modeling framework allowing for efficient analysis (simulation, algebraic methods, model checking)
- well-founded mathematical theory
- availability of tools
- several extensions (colored, timed, stochastic, hybrid petri nets)

Qualitative modeling

- rigorous modeling and formal analysis in spite of limited information (lacking quantitative data, knowledge on kinetic mechanisms and components,...)
- efficient comprehensive analysis focusing on core properties (high level of abstraction)
- groundwork of and complement to quantitative models

Topics possibly mentioned in passing but deserving much more attention:

discretization of differential equation systems, deriving continuous from discrete models, hybrid modeling, reduction techniques, reverse engineering, ...