A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets

David Gilbert, Monika Heiner, Sebastian Lehrack

Bioinformatics Research Centre, University of Glasgow,
INRIA Rocquencourt/BTU Cottbus

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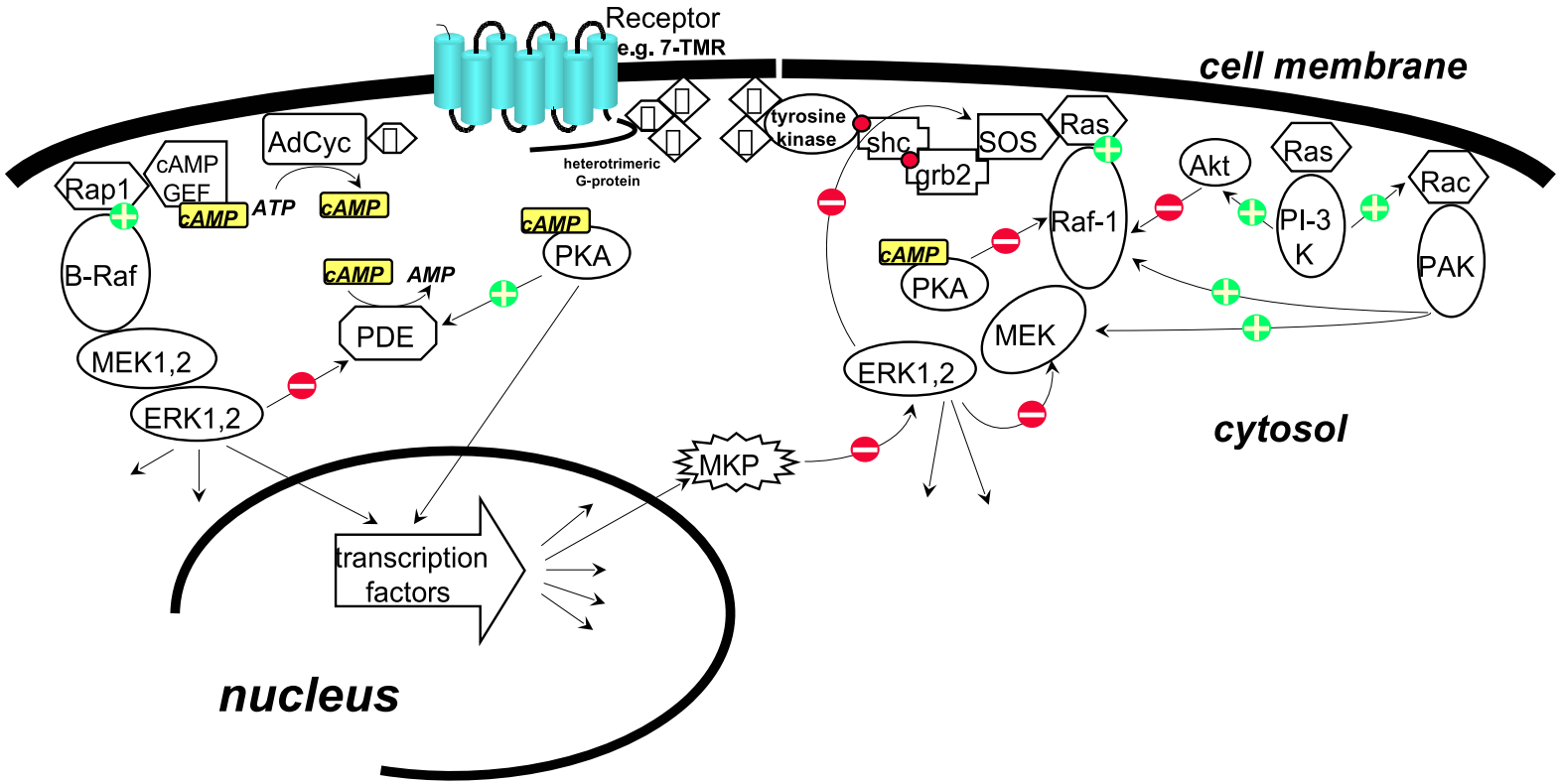
Framework

- *Biochemical pathways*



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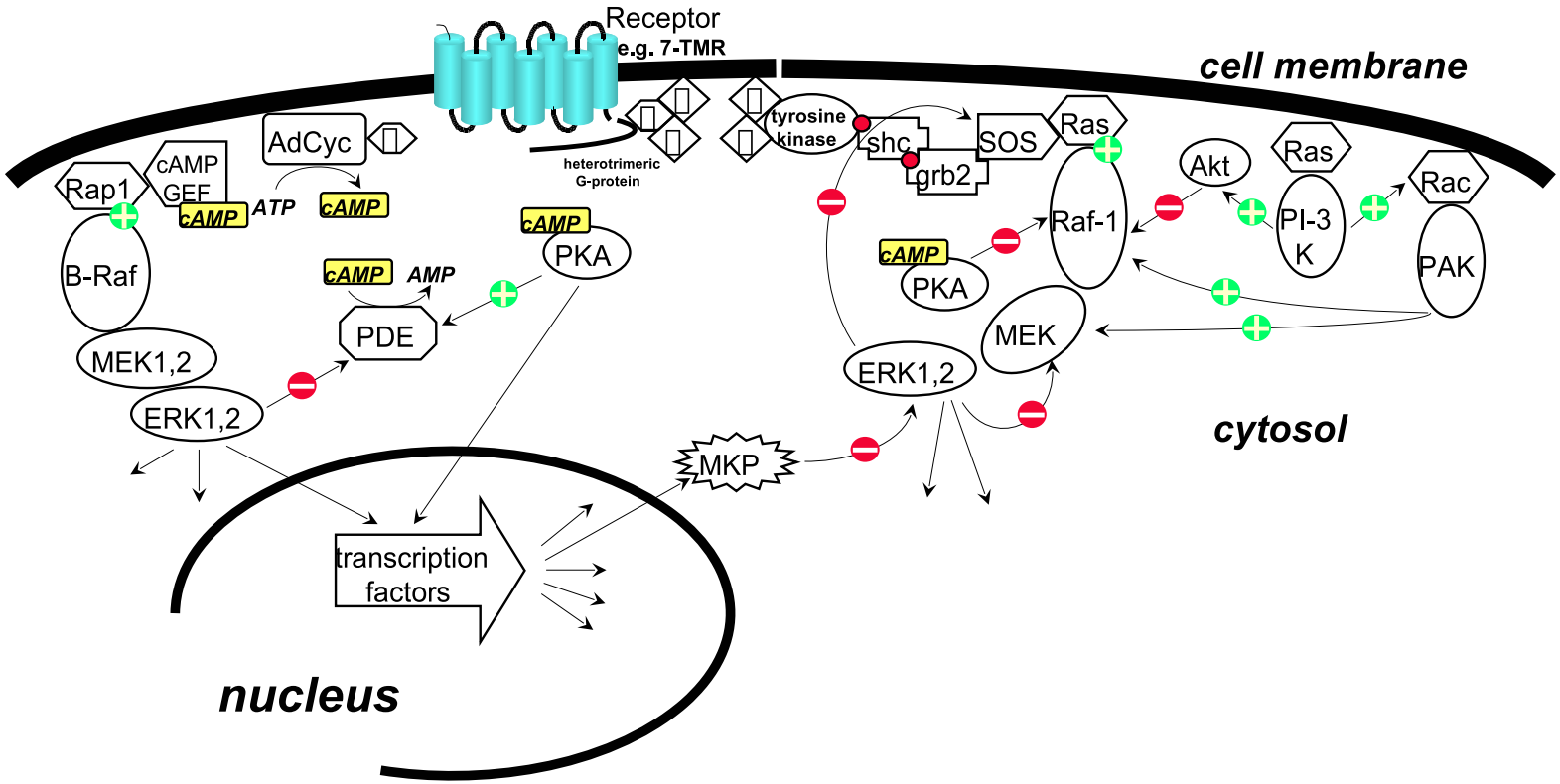
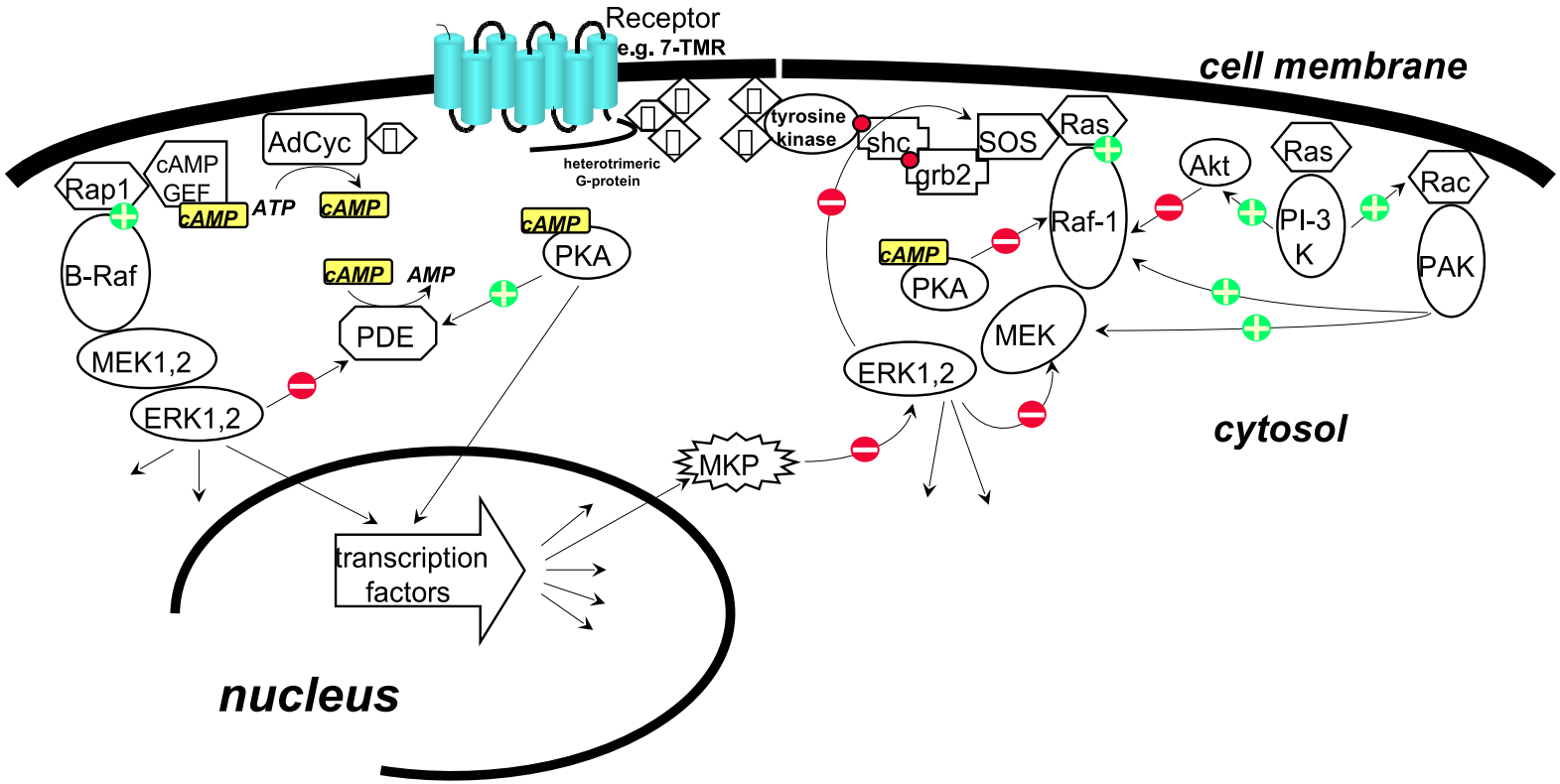


How to model this?

Framework

- *Biochemical pathways*



How to model this?

How to analyse this?

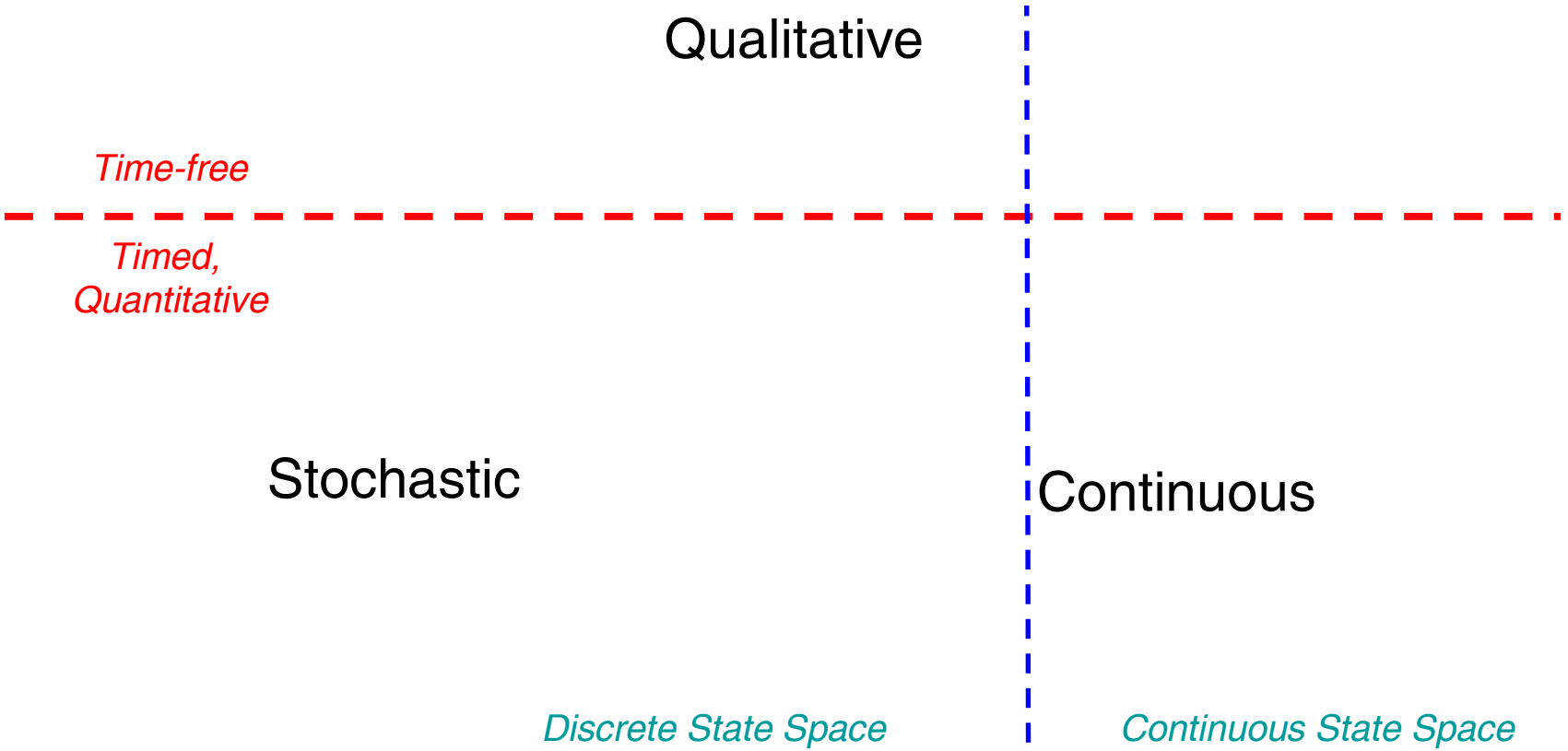
Framework

Qualitative

Stochastic

Continuous

Framework


Qualitative
Time-free
Timed,
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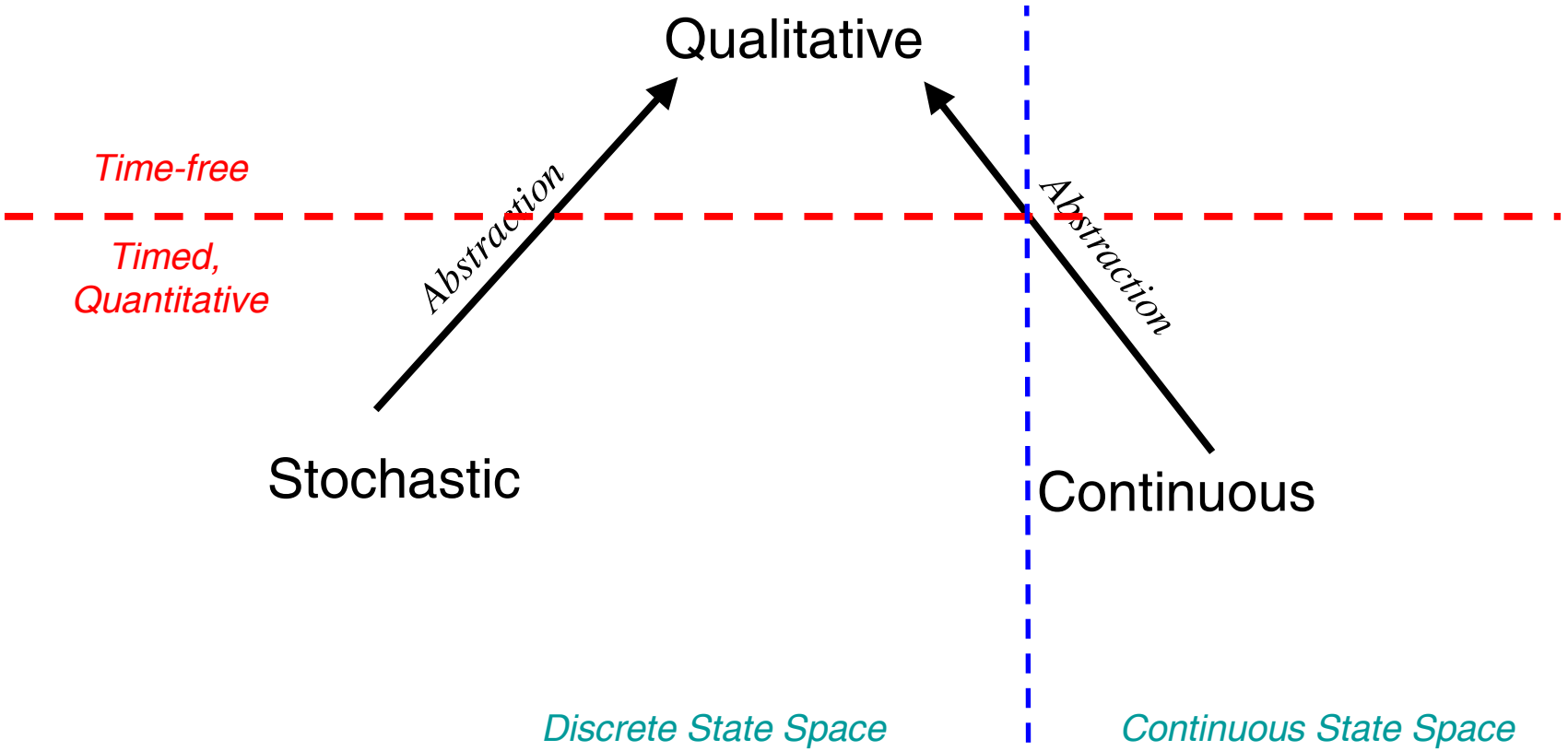
Continuous State Space

Framework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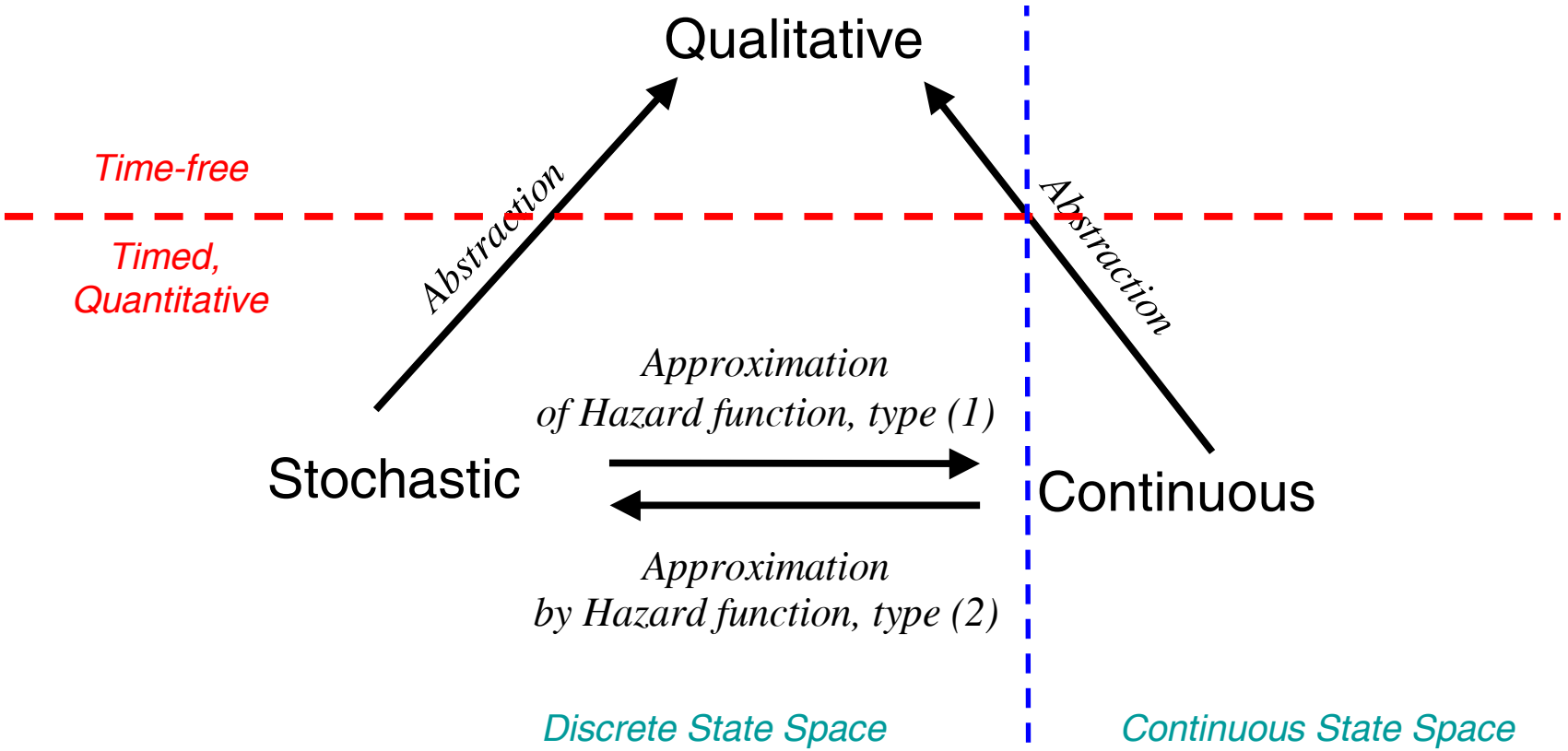
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(Qualitative) Petri net

Definition :

A **place/transition Petri net** is a quadruple $\mathcal{PN} = (P, T, f, m_0)$, where

- P, T - finite, non empty, disjoint sets *(**places**, **transitions**)*

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Interleaving Semantics : reachability graph / CTL, LTL

Definition :

A **biochemically interpreted continuous Petri net** is a quintuple $\mathcal{CPN}_{Bio} = (P, T, f, v, m_0)$, where

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- $v : T \to H$ *(**continuous firing rate functions**)* with
  - $H := \bigcup_{t \in T} \{h_t \mid h_t : \mathbb{R}^{|{}^\bullet t|} \to \mathbb{R}^+\}$
  - $v(t) = h_t$ for all transitions $t \in T$

Continuous Petri net

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Semantics : ODEs / LTLc

Definition :

A **biochemically interpreted stochastic Petri net** is a quintuple $\mathcal{SPN}_{Bio} = (P, T, f, v, m_0)$, where

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Stochastic Petri net

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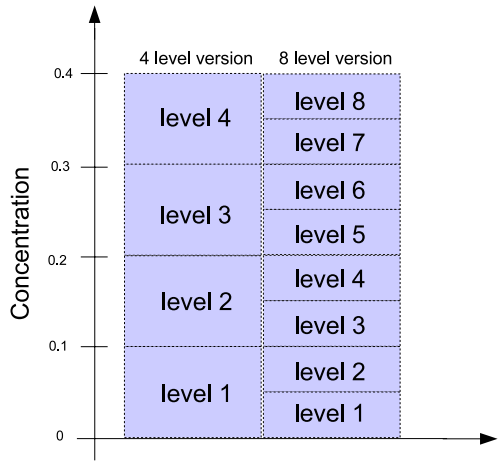
Semantics : Continuous Time Markov Chain / CSL

Interpretation of tokens :

- *tokens = molecules*
- *tokens = concentration levels* [Calder et al., CMSB 2005]



Specialised stochastic firing rate function, two examples :

- *molecules semantics*

$$h_t := c_t \cdot \prod_{p \in {}^\bullet t} \binom{m(p)}{f(p,t)} \tag{1}$$

- *concentration levels semantics*

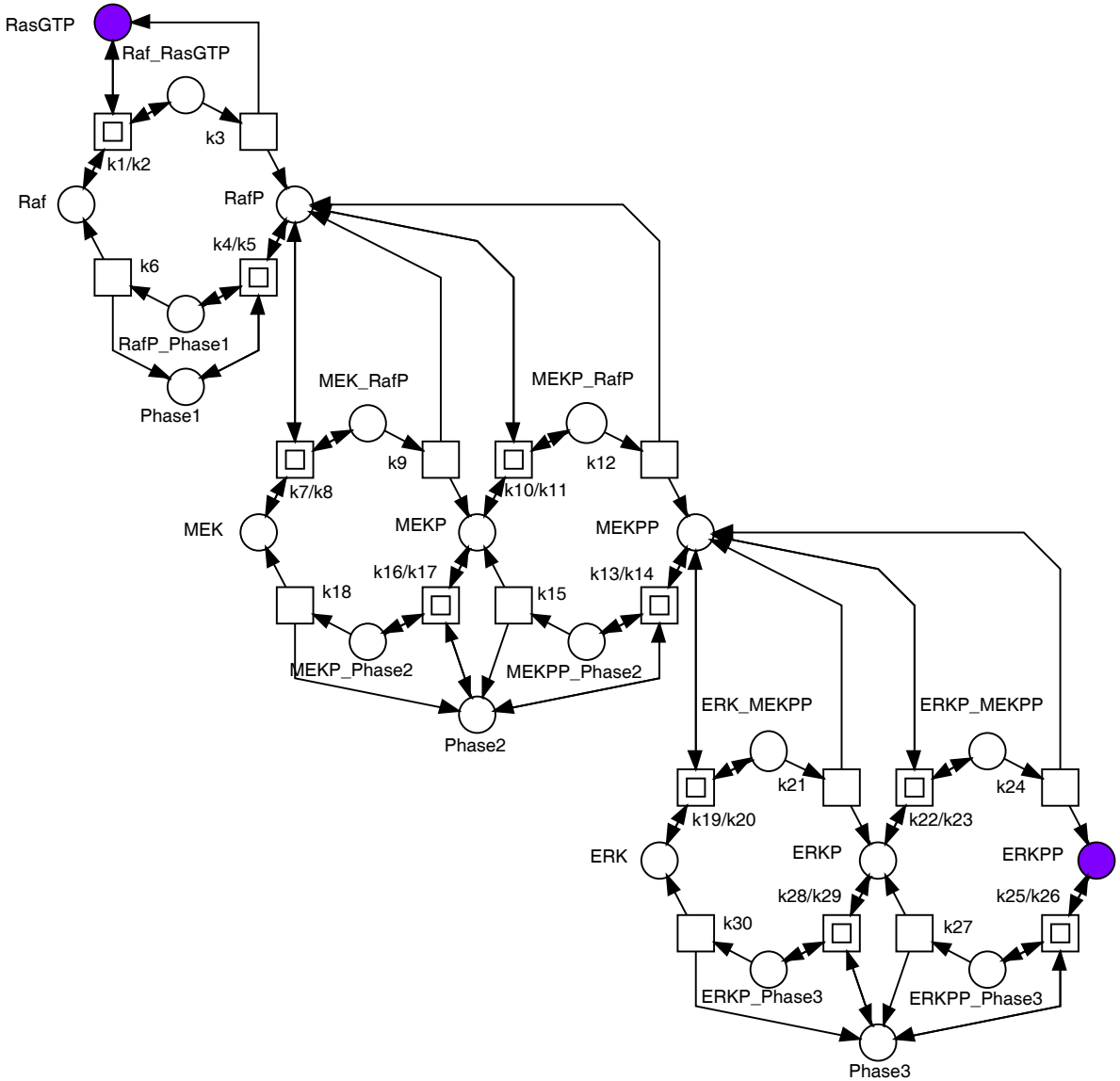
$$h_t := k_t \cdot N \cdot \prod_{p \in {}^\bullet t} \left(\frac{m(p)}{N}\right) \tag{2}$$

Running Case Study - Origin

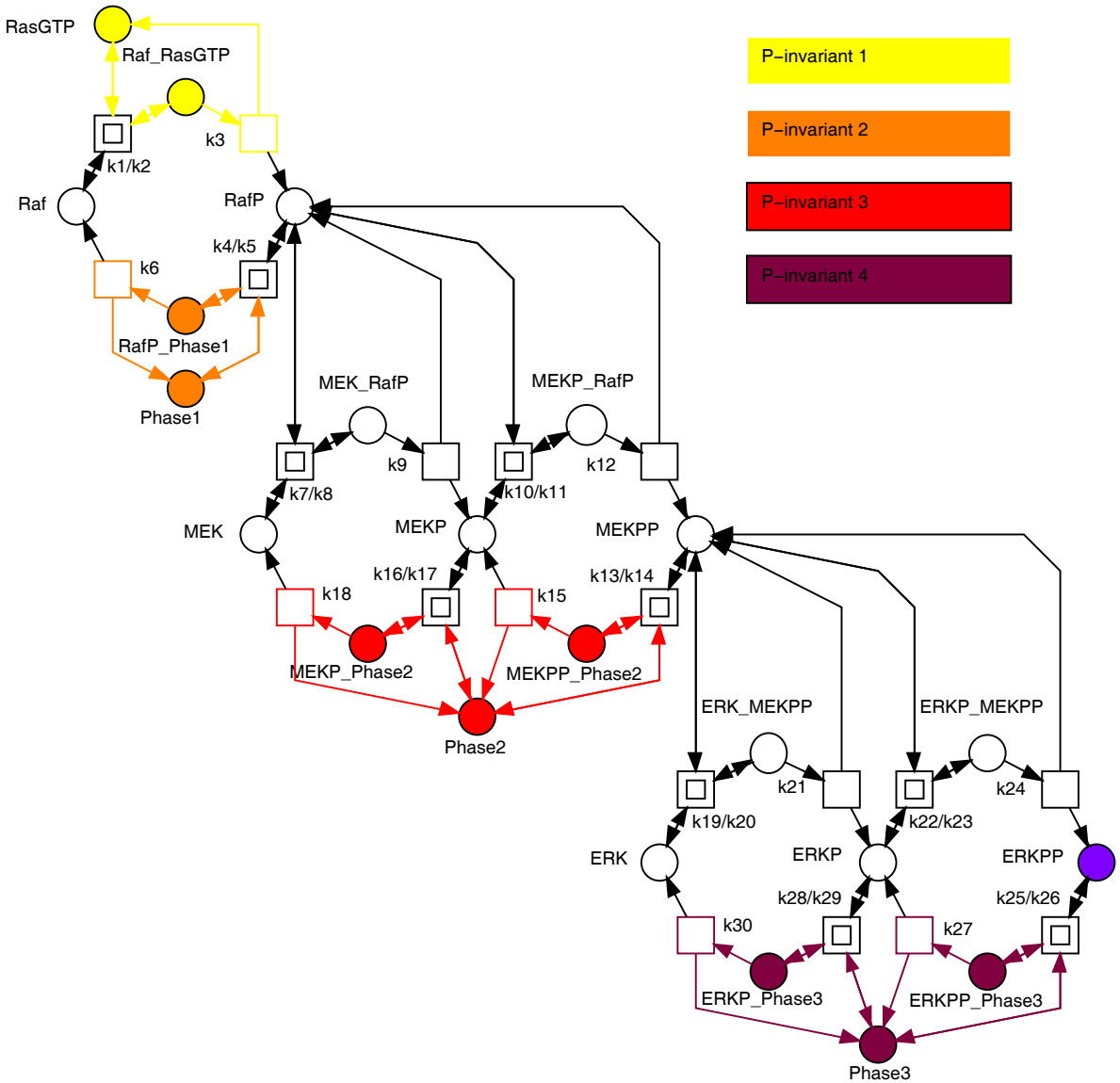
[Levchenko et al. 2000], *Supplemental Material : ODEs*

$$
\begin{aligned}
d\mathrm{Raf}/dt &= k_2 * \mathrm{Raf\_RasGTP} + k_6 * \mathrm{RafP\_Phase1} - k_1 * \mathrm{Raf} * \mathrm{RasGTP} \\
d\mathrm{RasGTP}/dt &= k_2 * \mathrm{Raf\_RasGTP} + k_3 * \mathrm{Raf\_RasGTP} - k_1 * \mathrm{Raf} * \mathrm{RasGTP} \\
d\mathrm{Raf\_RasGTP}/dt &= k_1 * \mathrm{Raf} * \mathrm{RasGTP} - k_2 * \mathrm{Raf\_RasGTP} - k_3 * \mathrm{Raf\_RasGTP} \\
d\mathrm{RafP}/dt &= k_3 * \mathrm{Raf\_RasGTP} + k_{12} * \mathrm{MEKP\_RafP} + k_9 * \mathrm{MEK\_RafP} + \\
&\quad k_5 * \mathrm{RafP\_Phase1} + k_8 * \mathrm{MEK\_RafP} + k_{11} * \mathrm{MEKP\_RafP} - \\
&\quad k_7 * \mathrm{RafP} * \mathrm{MEK} - k_{10} * \mathrm{MEKP} * \mathrm{RafP} - k_4 * \mathrm{Phase1} * \mathrm{RafP} \\
d\mathrm{RafP\_Phase1}/dt &= k_4 * \mathrm{Phase1} * \mathrm{RafP} - k_5 * \mathrm{RafP\_Phase1} - k_6 * \mathrm{RafP\_Phase1} \\
d\mathrm{MEK\_RafP}/dt &= k_7 * \mathrm{RafP} * \mathrm{MEK} - k_8 * \mathrm{MEK\_RafP} - k_9 * \mathrm{MEK\_RafP} \\
d\mathrm{MEKP\_RafP}/dt &= k_{10} * \mathrm{MEKP} * \mathrm{RafP} - k_{11} * \mathrm{MEKP\_RafP} - k_{12} * \mathrm{MEKP\_RafP} \\
d\mathrm{MEKP\_Phase2}/dt &= k_{16} * \mathrm{Phase2} * \mathrm{MEKP} - k_{18} * \mathrm{MEKP\_Phase2} - k_{17} * \mathrm{MEKP\_Phase2} \\
d\mathrm{MEKPP\_Phase2}/dt &= k_{13} * \mathrm{MEKPP} * \mathrm{Phase2} - k_{15} * \mathrm{MEKPP\_Phase2} - k_{14} * \mathrm{MEKPP\_Phase} \\
d\mathrm{ERK}/dt &= k_{20} * \mathrm{ERK\_MEKPP} + k_{30} * \mathrm{ERKP\_Phase3} - k_{19} * \mathrm{MEKPP} * \mathrm{ERK} \\
d\mathrm{ERK\_MEKPP}/dt &= k_{19} * \mathrm{MEKPP} * \mathrm{ERK} - k_{20} * \mathrm{ERK\_MEKPP} - k_{21} * \mathrm{ERK\_MEKPP} \\
d\mathrm{ERKP\_MEKPP}/dt &= k_{22} * \mathrm{MEKPP} * \mathrm{ERKP} - k_{24} * \mathrm{ERKP\_MEKPP} - k_{23} * \mathrm{ERKP\_MEKPP} \\
\textit{etcetera} &= \ldots
\end{aligned}
$$

Running Case Study



Running Case Study - P-invariants



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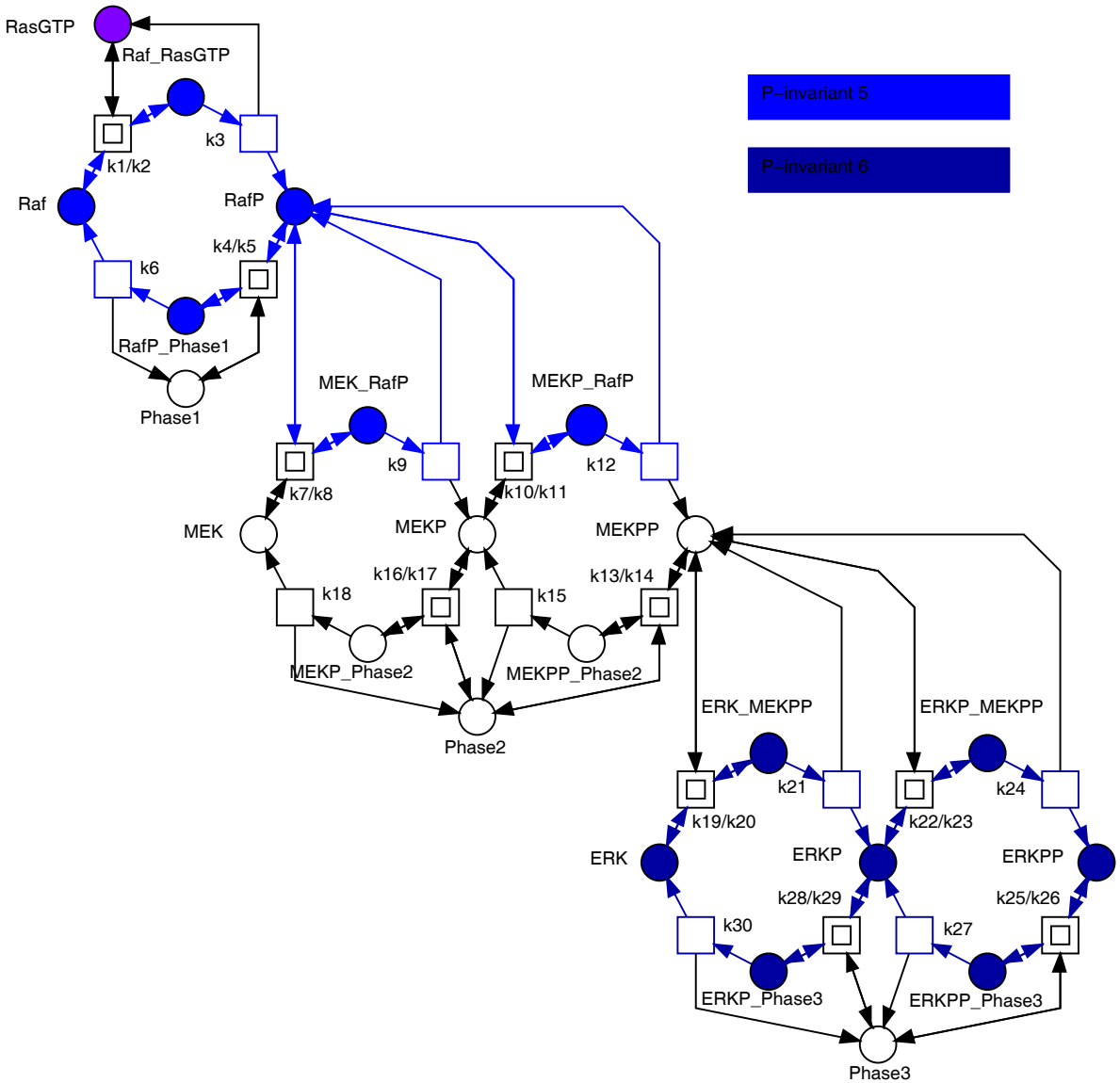

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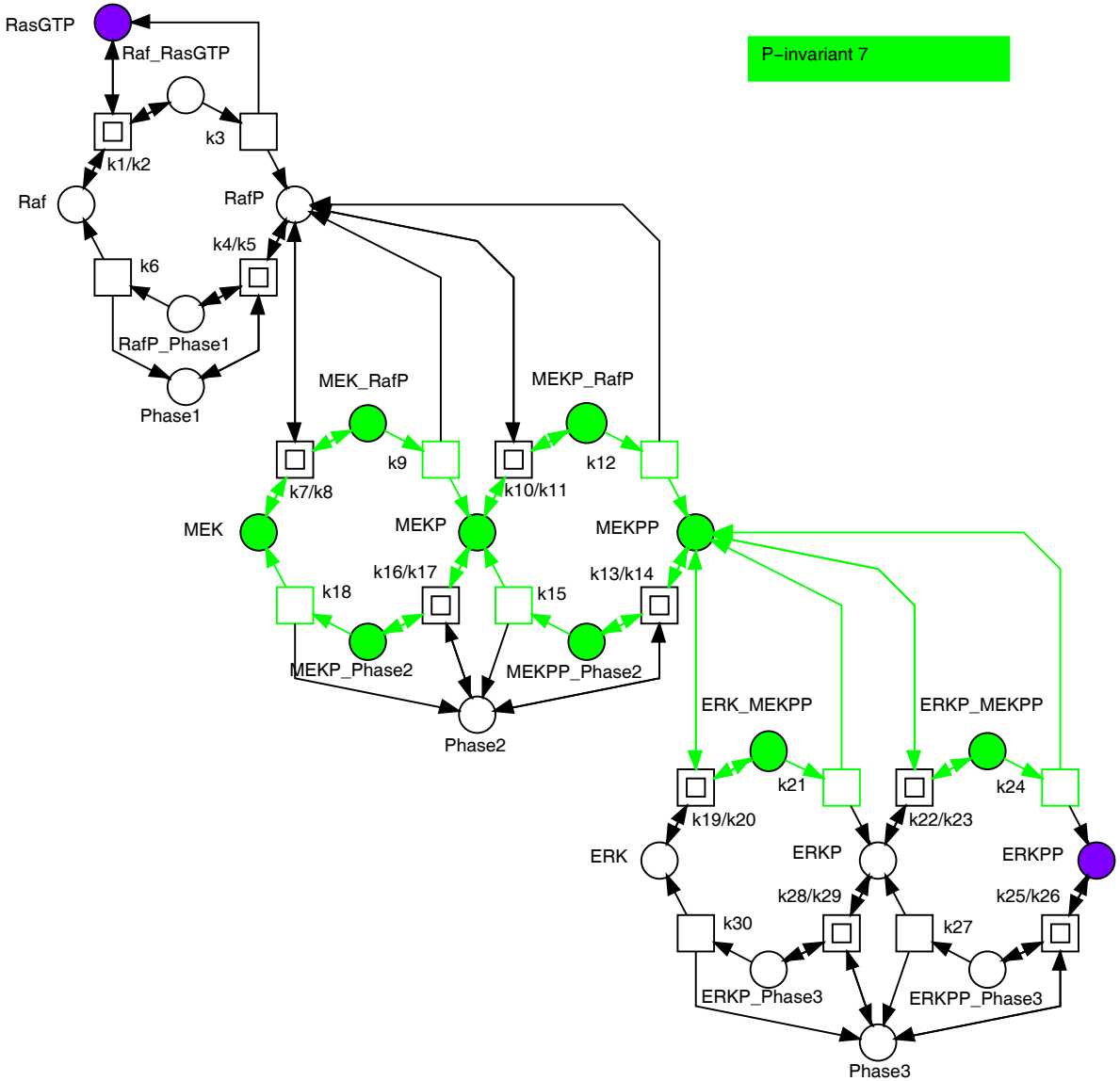
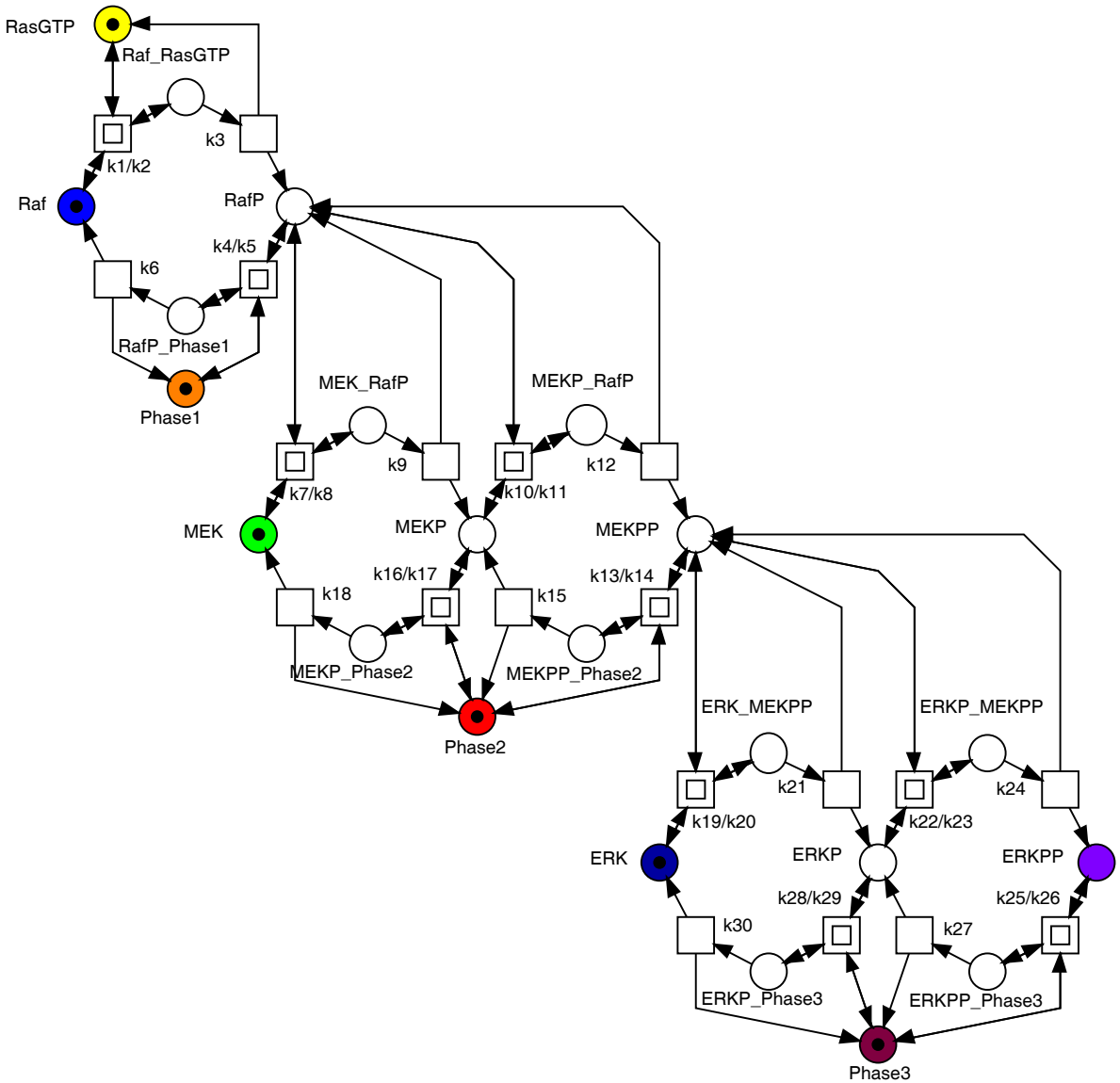
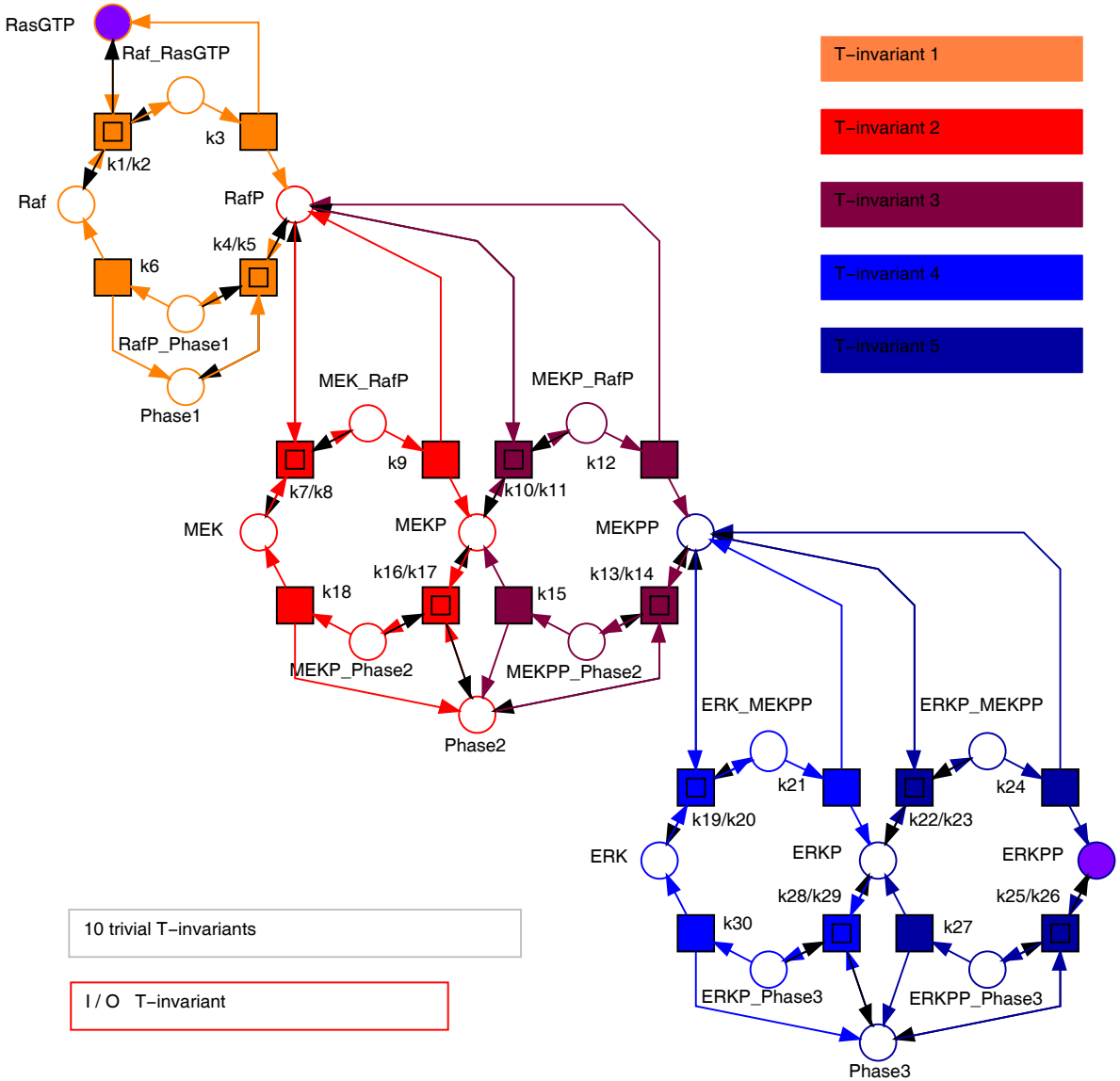


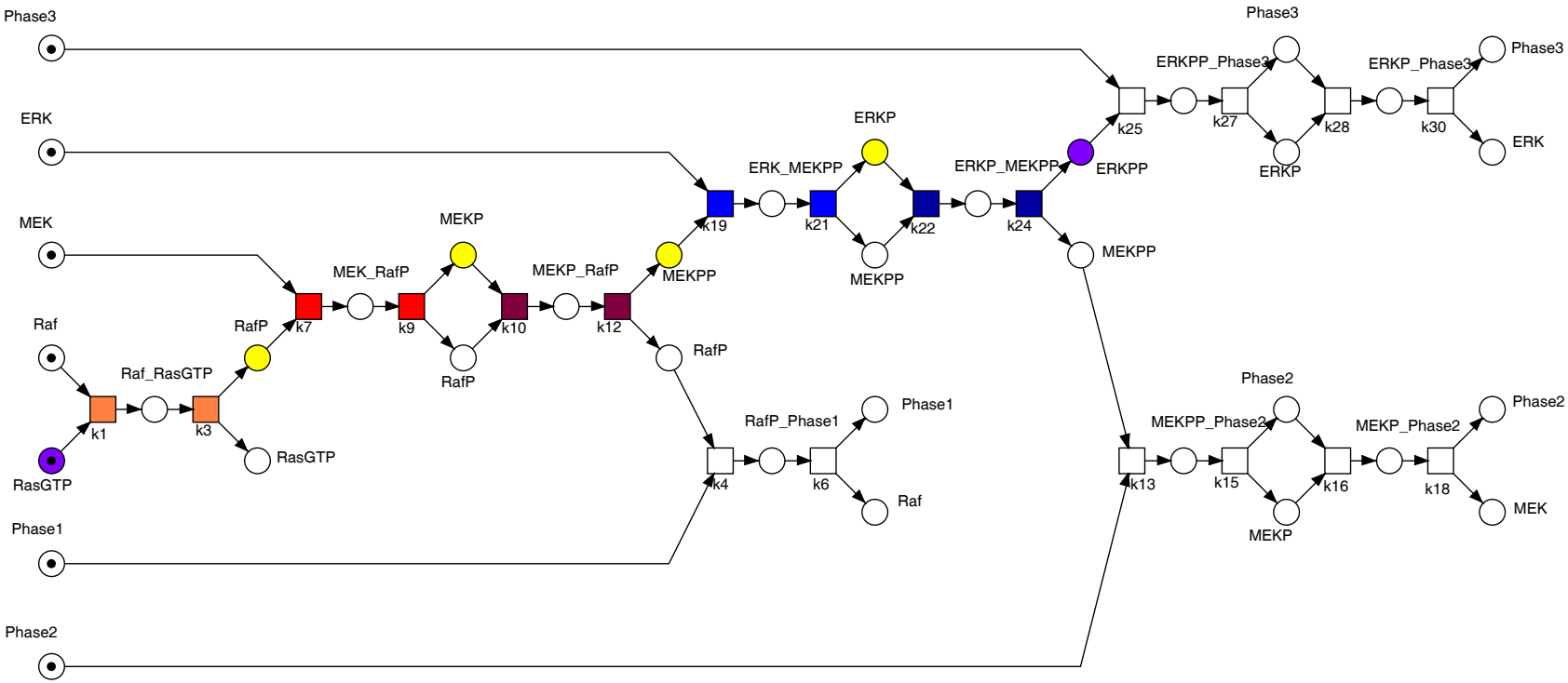
Running Case Study - initial marking



Running Case Study - T-invariants



Running Case Study - partial order run of I/O T-invariant



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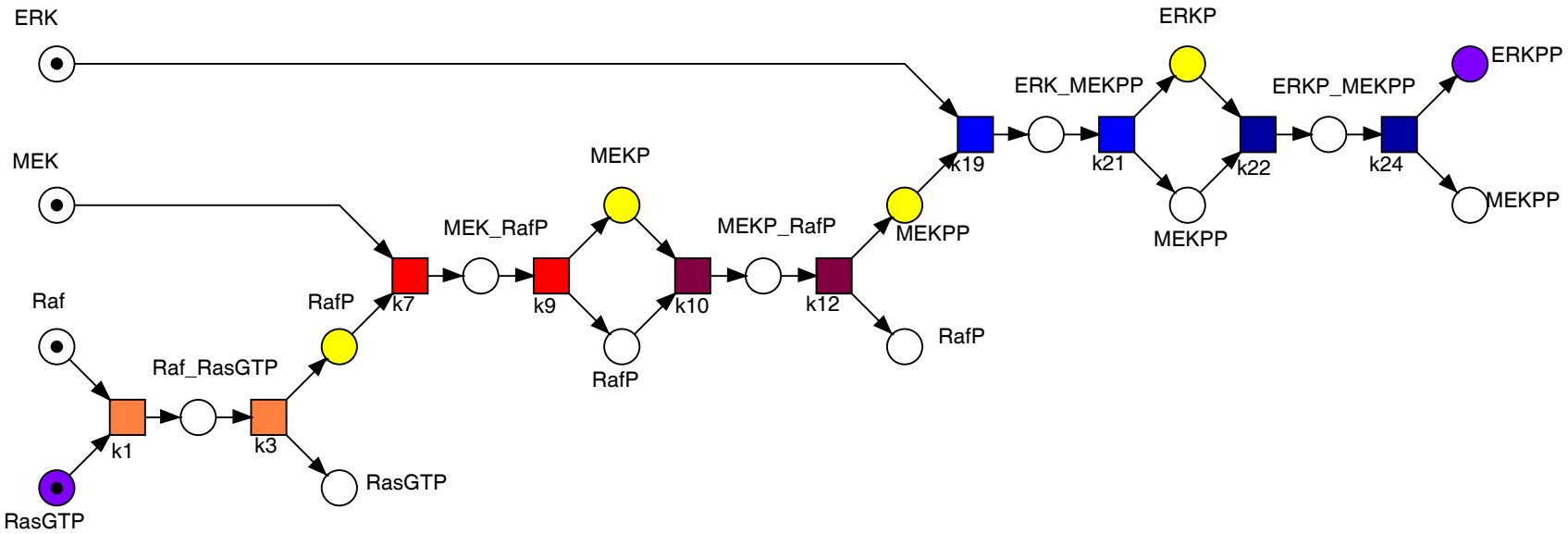
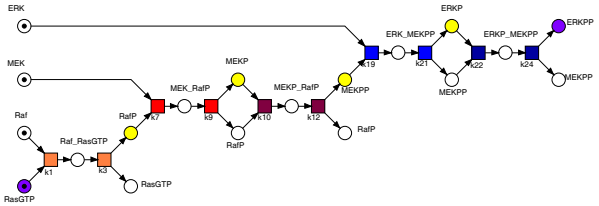


Qualitative Model Checking (CTL)



property Q1 :

The signal sequence predicted by the partial order run of the I/O T-invariant is the only possible one ;
i.e., starting at the initial state, it is necessary to pass through RafP, MEKP, MEKPP and ERKP in order to reach ERKPP.

$$\neg \, [\, \mathbf{E} \, (\, \neg \, \mathrm{RafP} \, \mathbf{U} \, \mathrm{MEKP} \,) \vee$$
$$\mathbf{E} \, (\, \neg \, \mathrm{MEKP} \, \mathbf{U} \, \mathrm{MEKPP} \,) \vee$$
$$\mathbf{E} \, (\, \neg \, \mathrm{MEKPP} \, \mathbf{U} \, \mathrm{ERKP} \,) \vee$$
$$\mathbf{E} \, (\, \neg \, \mathrm{ERKP} \, \mathbf{U} \, \mathrm{ERKPP} \,) \quad]$$

Stochastic Model Checking - Preparation

- *isomorphy of reachability graph and CTMC,*
  thus all qualitative properties still valid

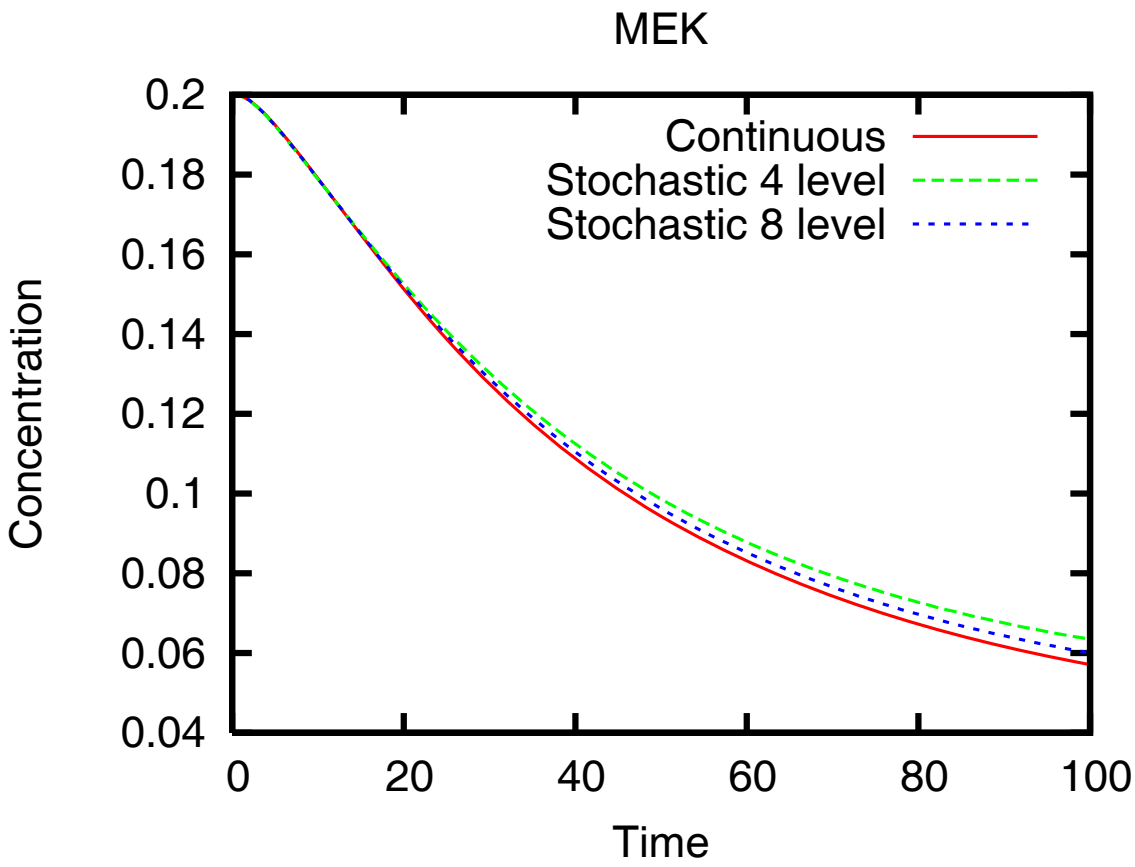
- *How many levels needed for quantitative evaluation ?*
  - state space(1 levels) = 118 (Boolean interpretation)
  - state space(4 levels) = 24,065
  - state space(8 levels) = 6,110,643

- *equivalence check*

$$C_{RafP}(t) = \frac{0.1}{s} \cdot \underbrace{\sum_{i=1}^{4s} \left(i \cdot P(L_{RafP}(t) = i) \right)}_{\textit{expected value of } L_{RafP}(t)}$$

Stochastic Model Checking - Preparation

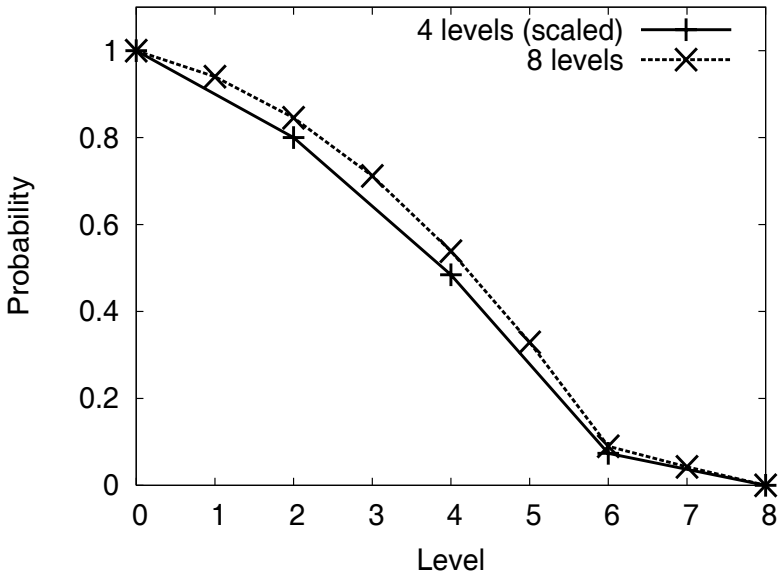
- *equivalence check, results, e.g. for MEK :*



property S1 :

What is the probability of the concentration of RafP increasing, when starting in a state where the level is already at L ?

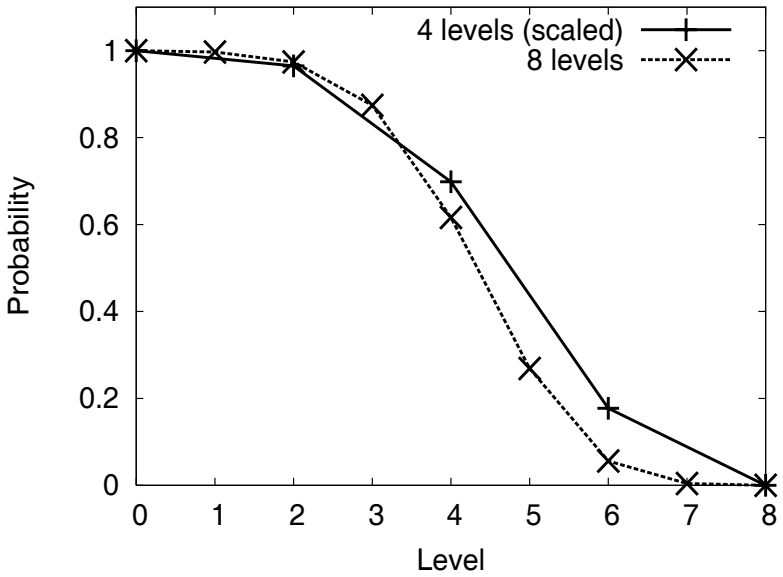
$$\mathbf{P}_{=?}\,[\,(\,\mathrm{RafP}\;=\;\mathrm{L}\,)\;\mathbf{U}^{<=100}\;(\,\mathrm{RafP}>\mathrm{L}\,)\{\,\mathrm{RafP}=\mathrm{L}\,\}\,]$$



property S2 :

What is the probability that RafP is the first species to react ?

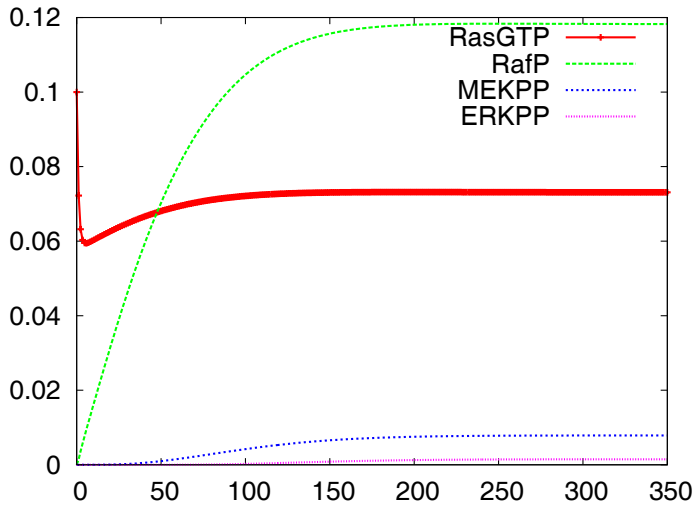
$$\mathbf{P}_{=?}\,[\,((\,\mathrm{MEKPP}\,=\,0\,)\wedge(\,\mathrm{ERKPP}\,=\,0\,))\,\mathbf{U}^{<=100}\,(\,\mathrm{RafP}>\,\mathrm{L}\,)$$
$$\{\,(\,\mathrm{MEKPP}\,=\,0\,)\wedge(\,\mathrm{ERKPP}\,=\,0\,)\;\wedge(\,\mathrm{RafP}=\,0\,)\,\}\,]$$



property C1 :

The concentration of RafP rises to a significant level, while the concentrations of MEKPP and ERKPP remain close to zero ; i.e. RafP is really the first species to react.

$$((\mathrm{MEKPP} < 0.001) \wedge (\mathrm{ERKPP} < 0.0002)) \ \mathbf{U} \ (\mathrm{RafP} > 0.06)$$



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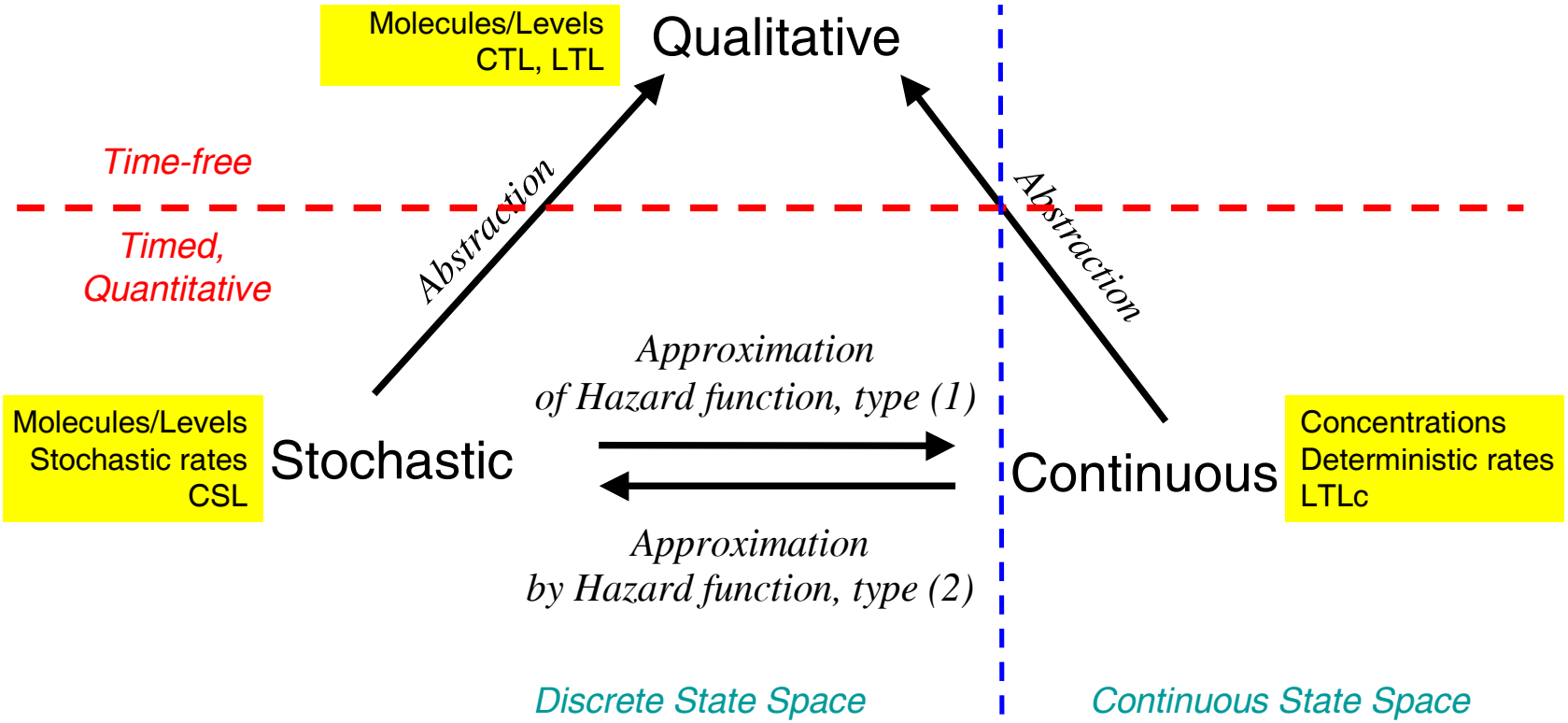
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- *continuous analysis*
  - BioNessie *(Glasgow)*
  - MATLAB
  - Biocham, LTLc model checker

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  - qualitative & stochastic & continuous model checking
- **not bound to the Petri net perspective**

Thanks !

all data files and analysis results available at
www-dssz.informatik.tu-cottbus.de/examples/levchenko

laptop demonstration available

drg@dcs.gla.ac.uk

monika.heiner@tu-cottbus.de