Calculi for Biological Systems

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University of Edinburgh

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Outline

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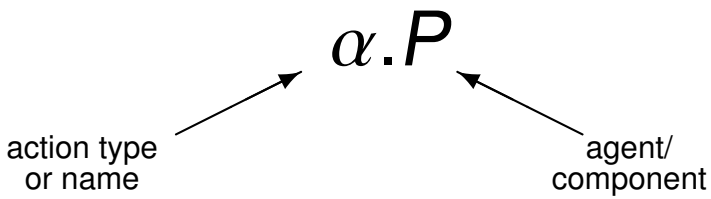
Process Algebra

- Models consist of agents which engage in actions.



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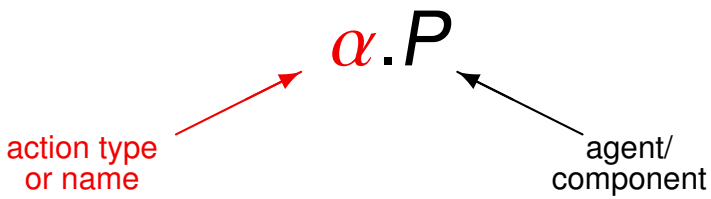

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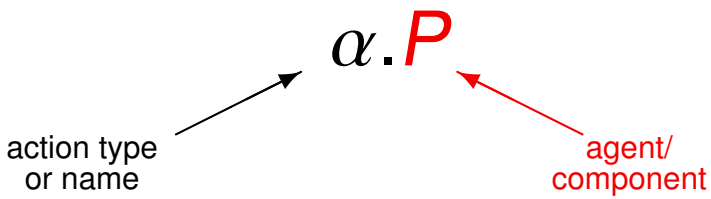

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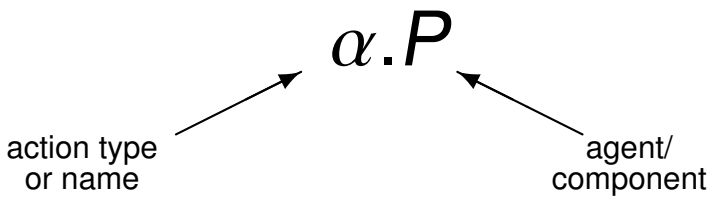

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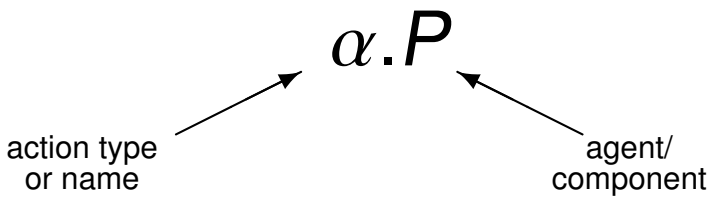

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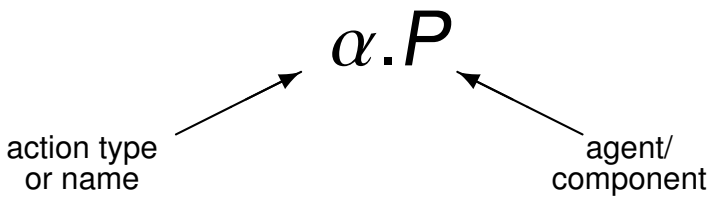

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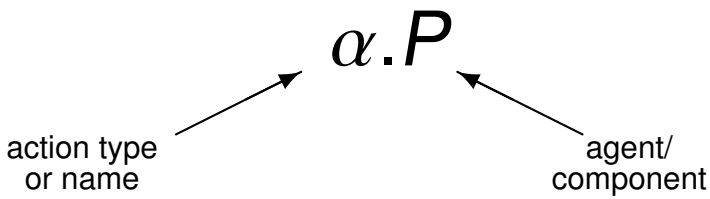

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Consider a web server which offers html pages for download:

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Clients are web browsers, in a domain with a local cache of frequently requested pages. Thus any display request might result in an access to the server or in a page being loaded from the cache.

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A simple version of the Web can be considered to be the interaction of these components:

$$WEB \stackrel{def}{=} (Browser \parallel Browser) \mid Server$$

Dynamic behaviour

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- This can be viewed as a graph in which each node is a state of the model (comprised of the local states of each of the components) and the arcs represent the actions which can cause the move from one state to another.
- The language is also equipped with observational equivalence which can be used to compare models.

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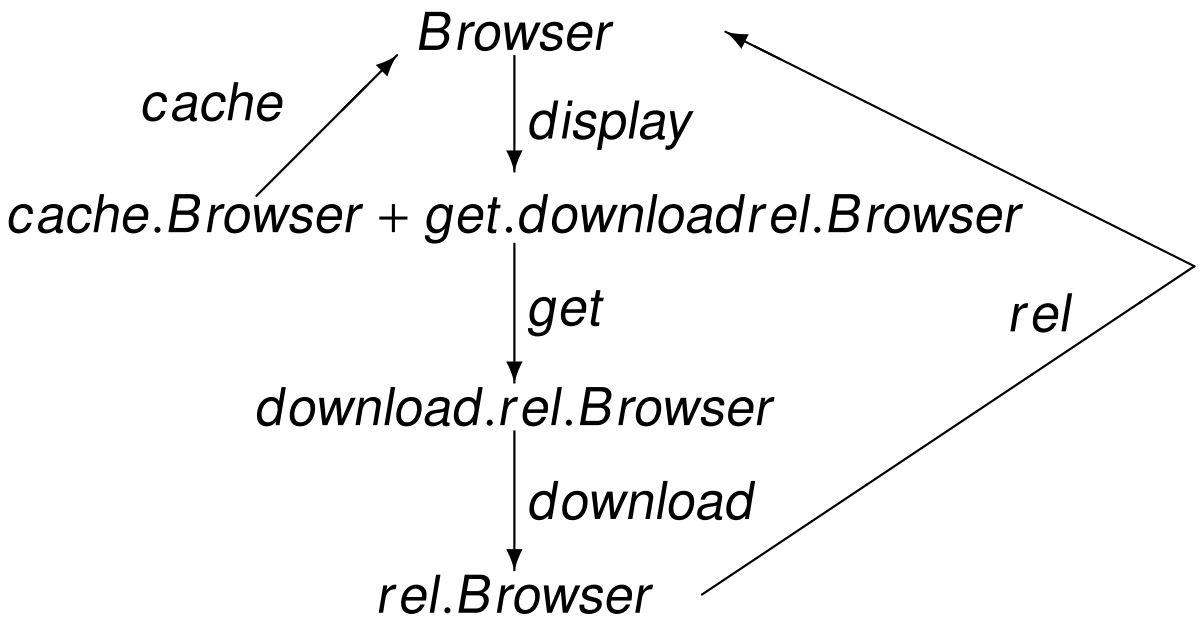

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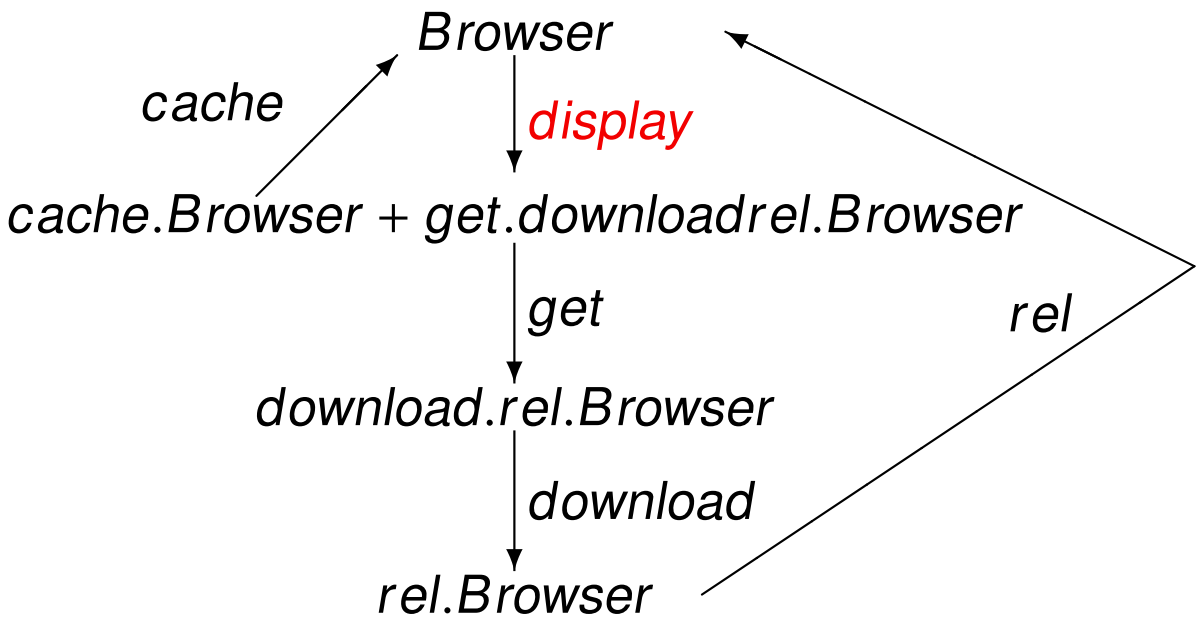

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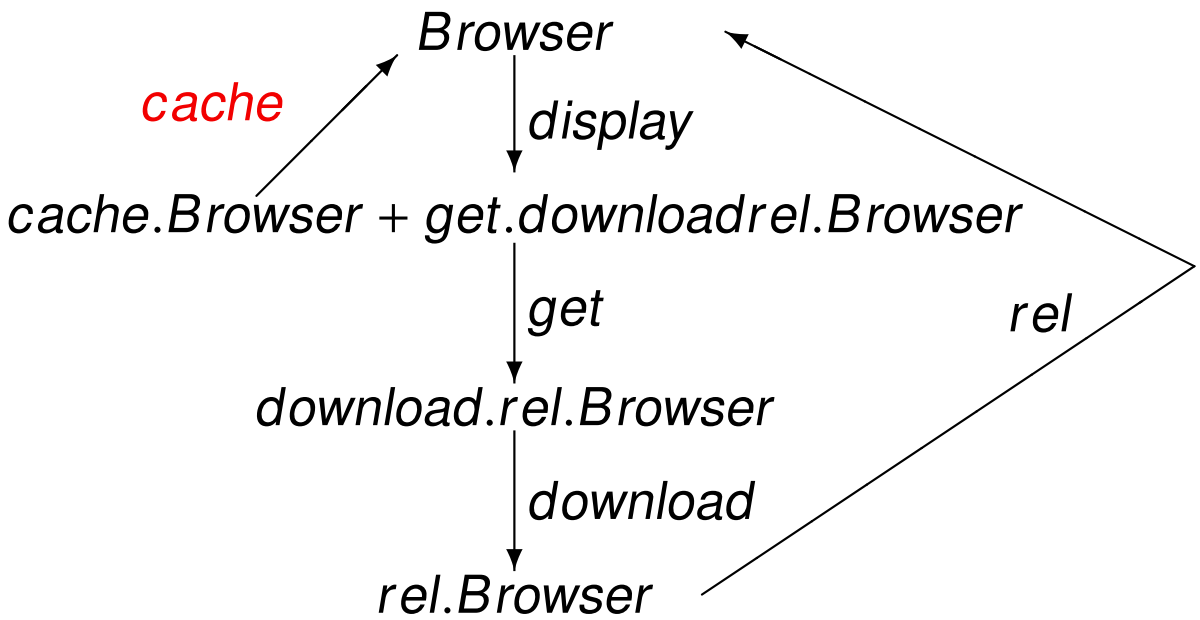

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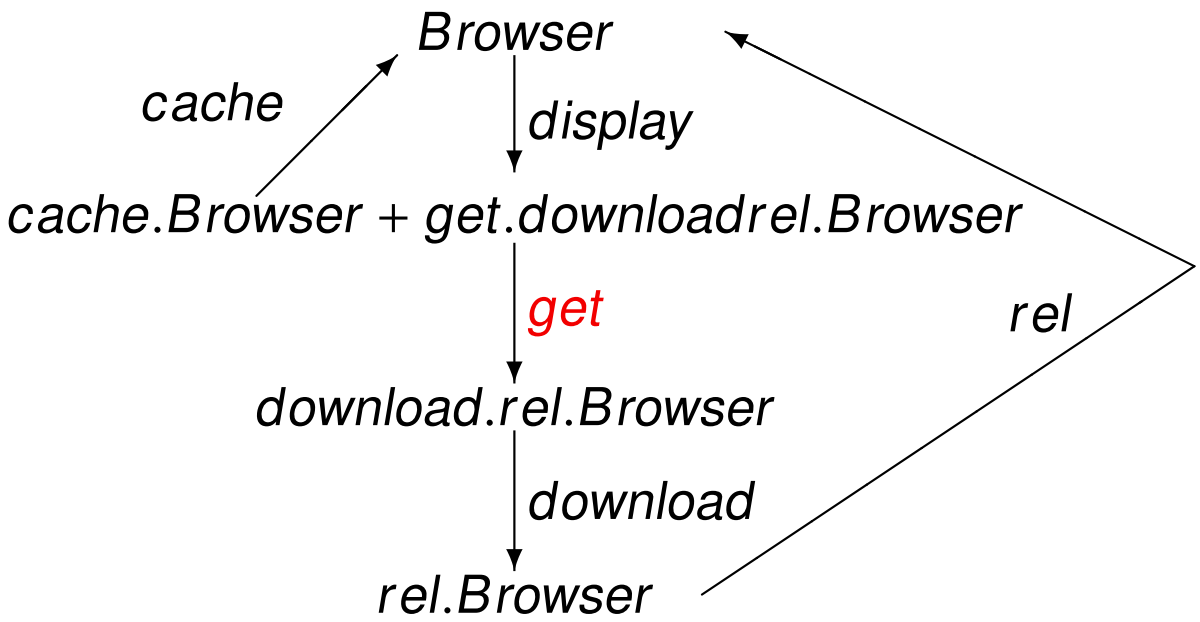

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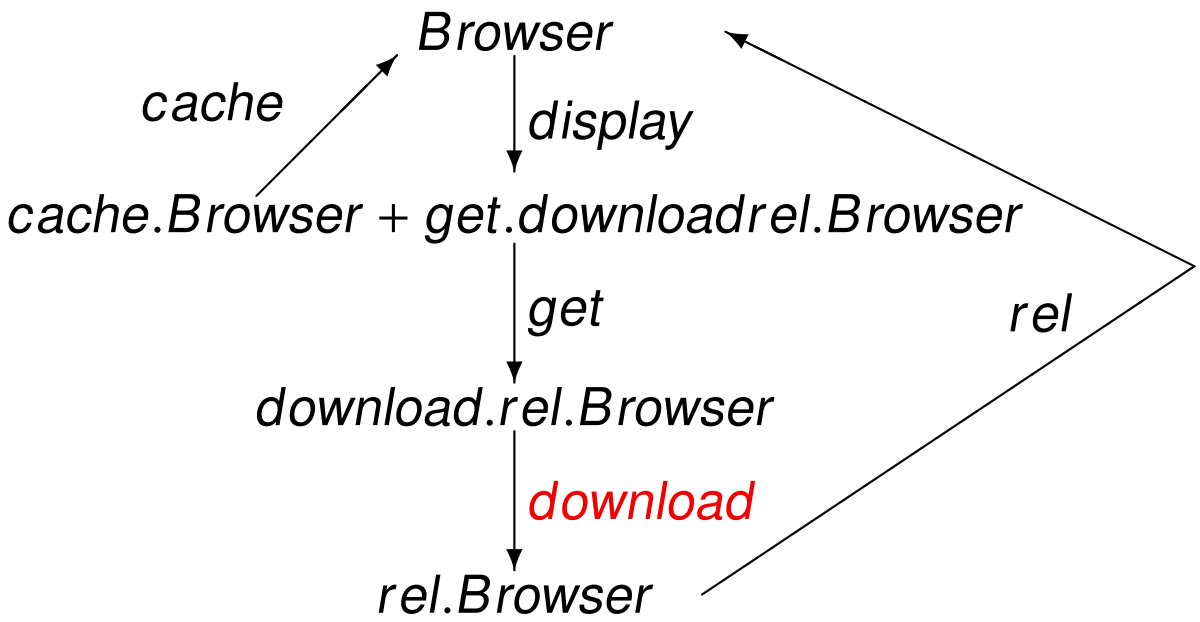

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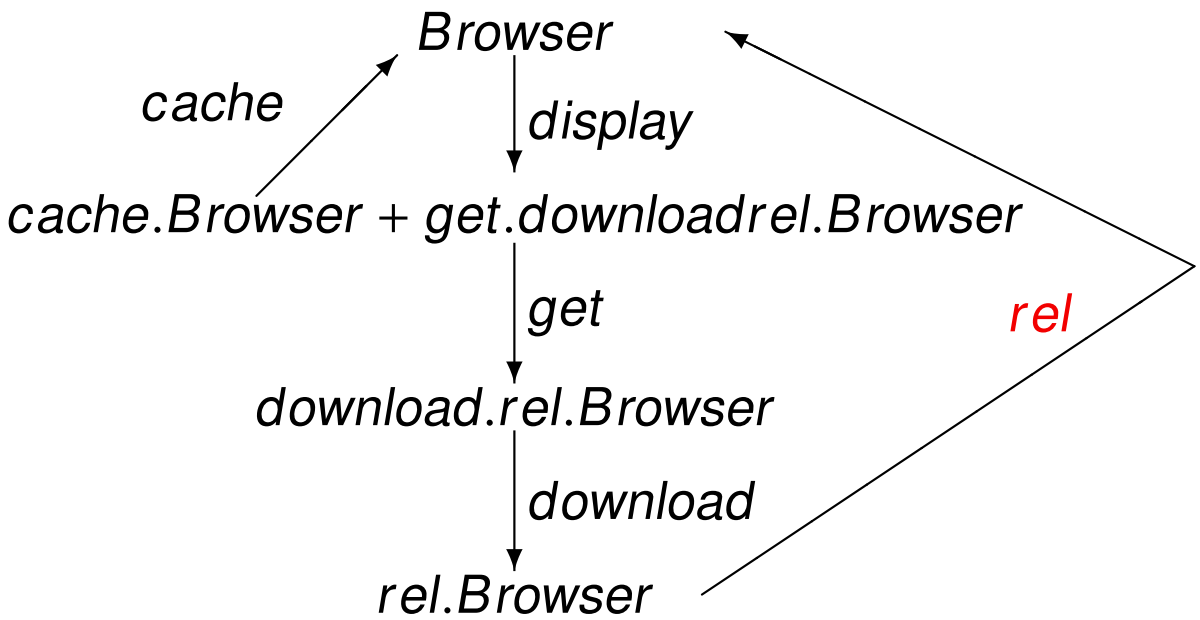

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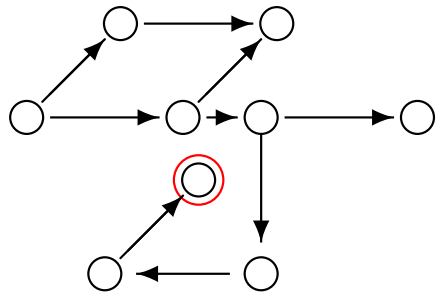
Will the system arrive in a particular state?



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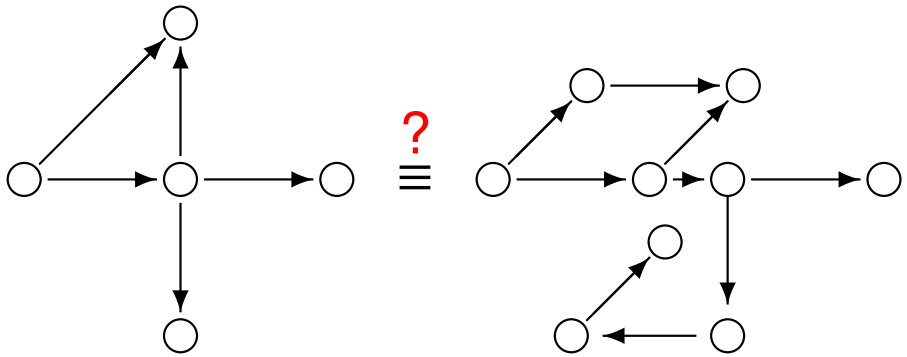

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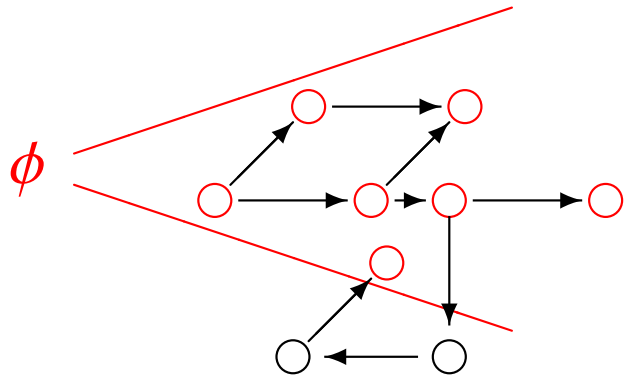
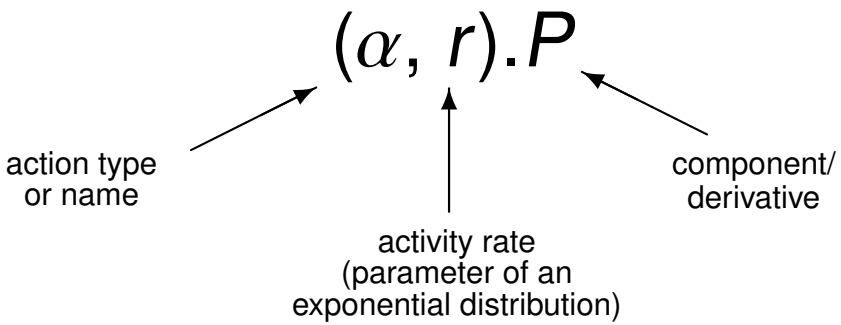
Does a given property ϕ hold within the system?



Stochastic Process Algebra

- Models are constructed from components which engage in activities.



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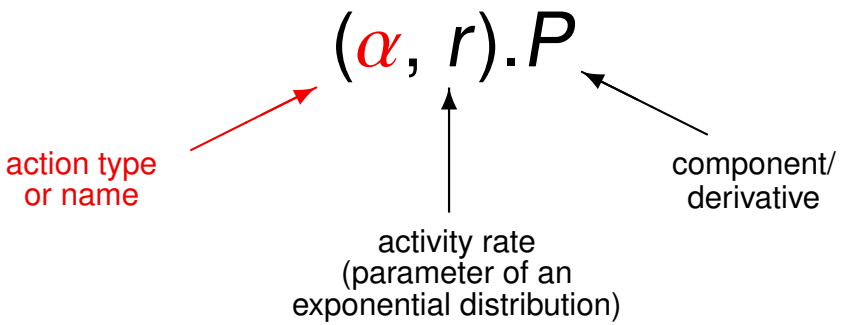

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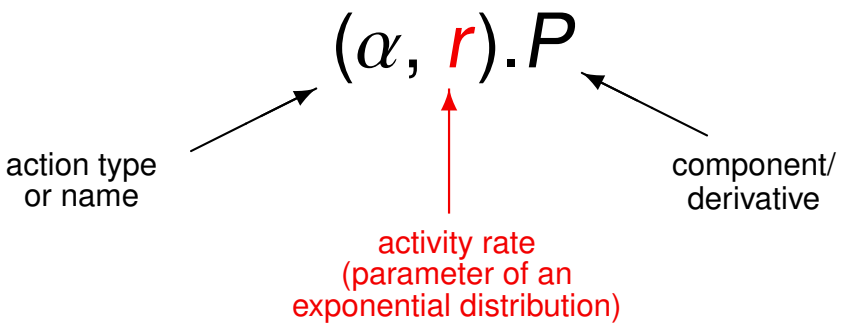

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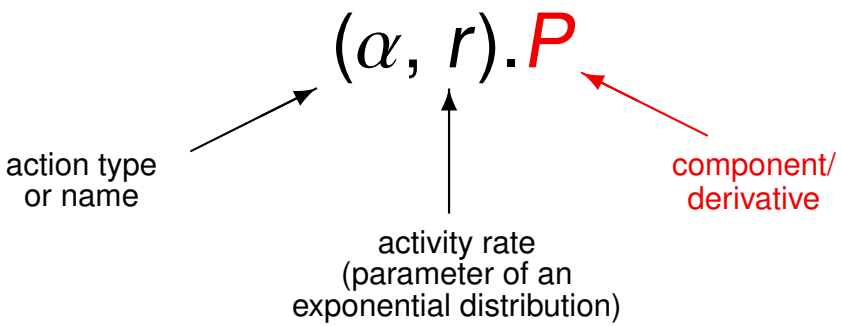

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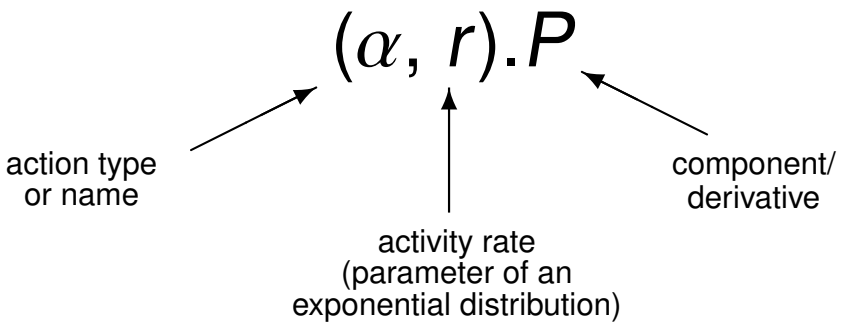

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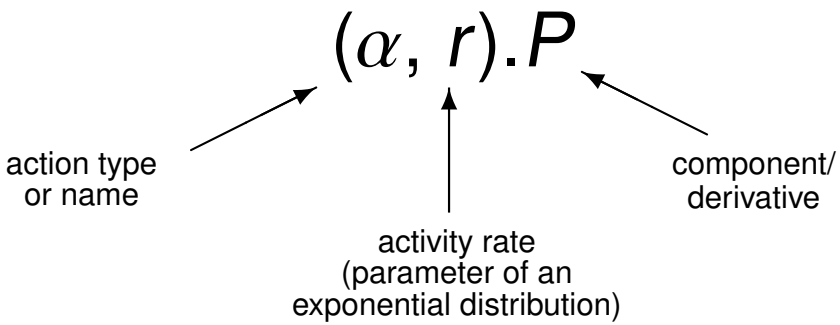

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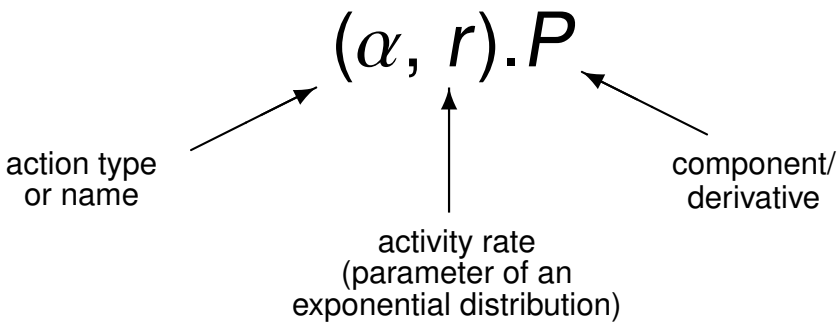

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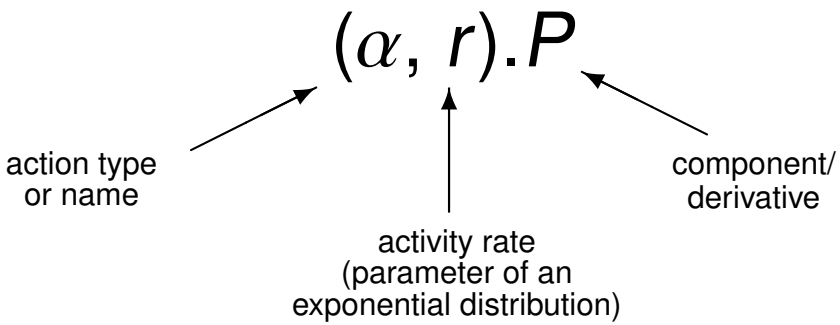

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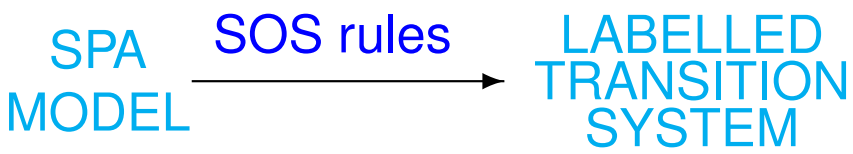

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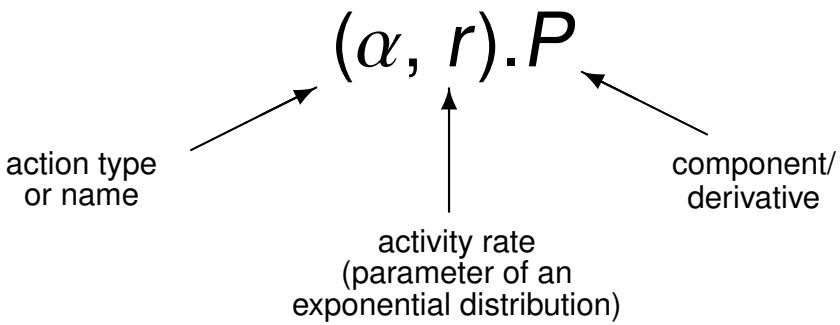

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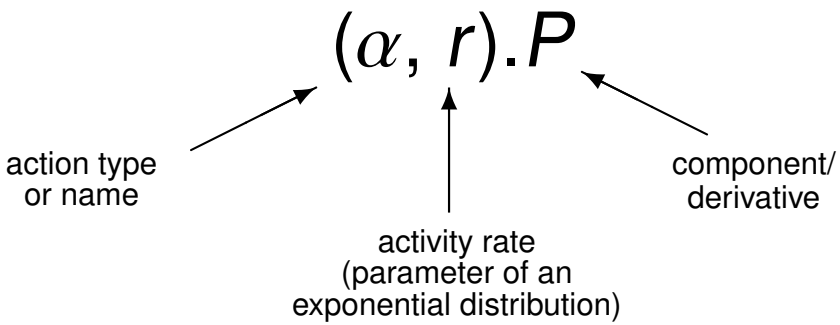

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PEPA

$$
\begin{aligned}
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\end{aligned}
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CHOICE: $S + S$ competing components (race policy)

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HIDING:	P/L	abstraction $\alpha \in L \Rightarrow \alpha \rightarrow \tau$

Example revisited

The behaviour of the server is the same but now quantitative information is recorded for each operation:

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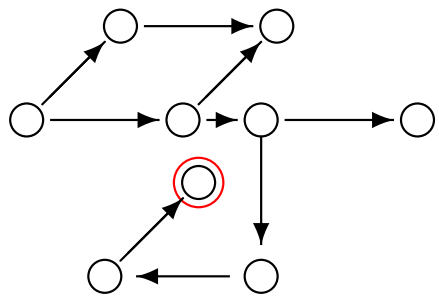
Reachability analysis

How long will it take for the system to arrive in a particular state?



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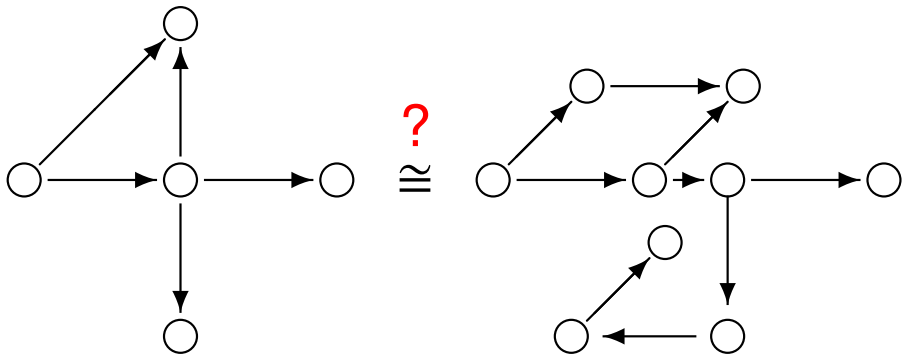
Specification matching

With what probability
does system behaviour
match its specification?



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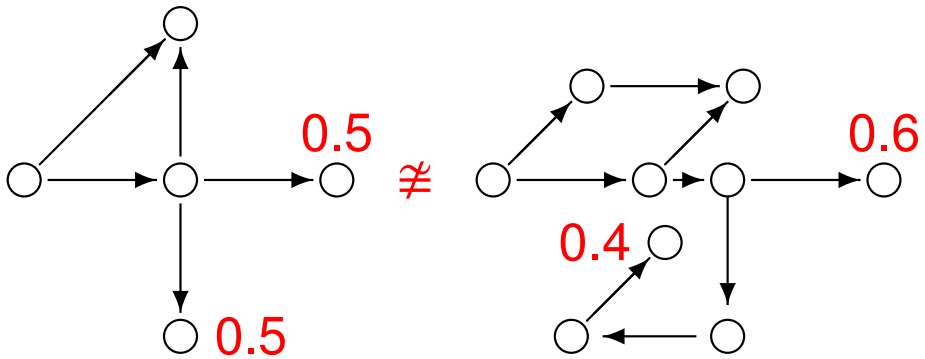
Specification matching

Does the "*frequency profile*" of the system match that of the specification?

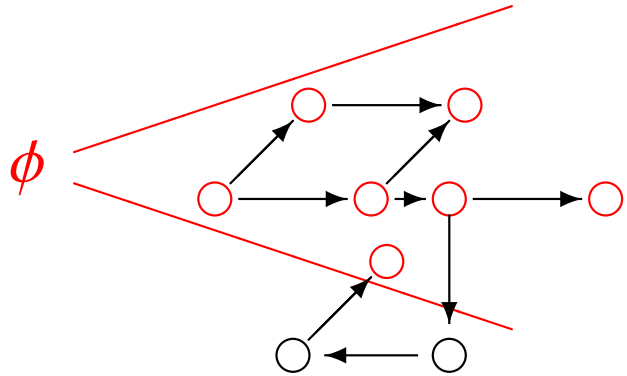


Integrated analysis

- Qualitative verification can now be complemented by quantitative verification:

Model checking

Does a given property ϕ hold within the system with a given probability?

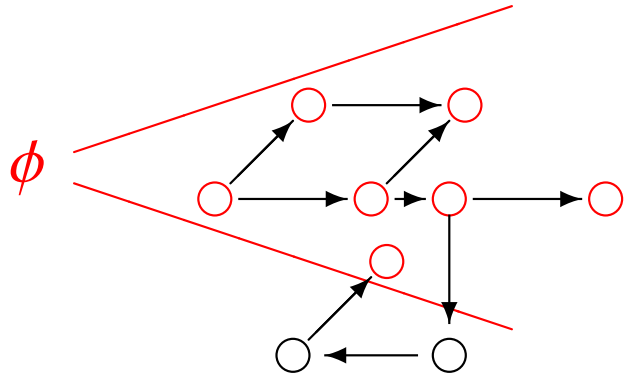


Integrated analysis

- Qualitative verification can now be complemented by quantitative verification:

Model checking

For a given starting state
how long is it until
a given property ϕ holds?



SPA Languages

SPA

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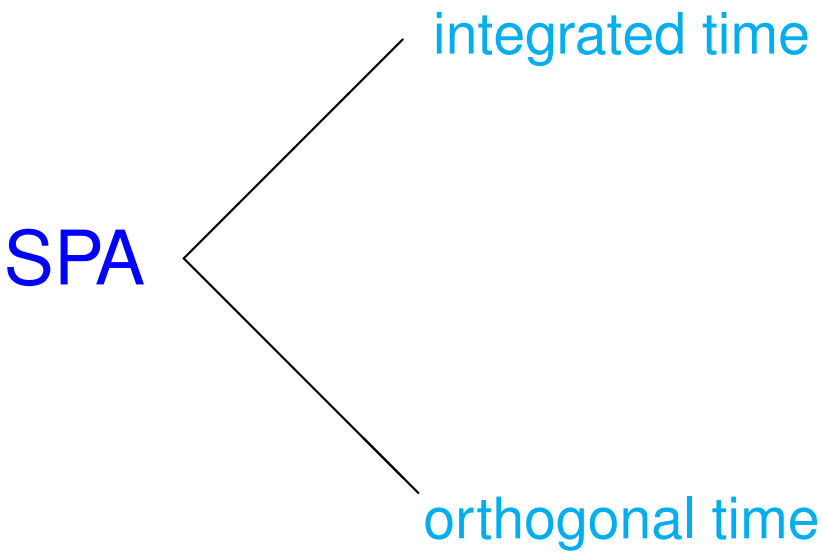

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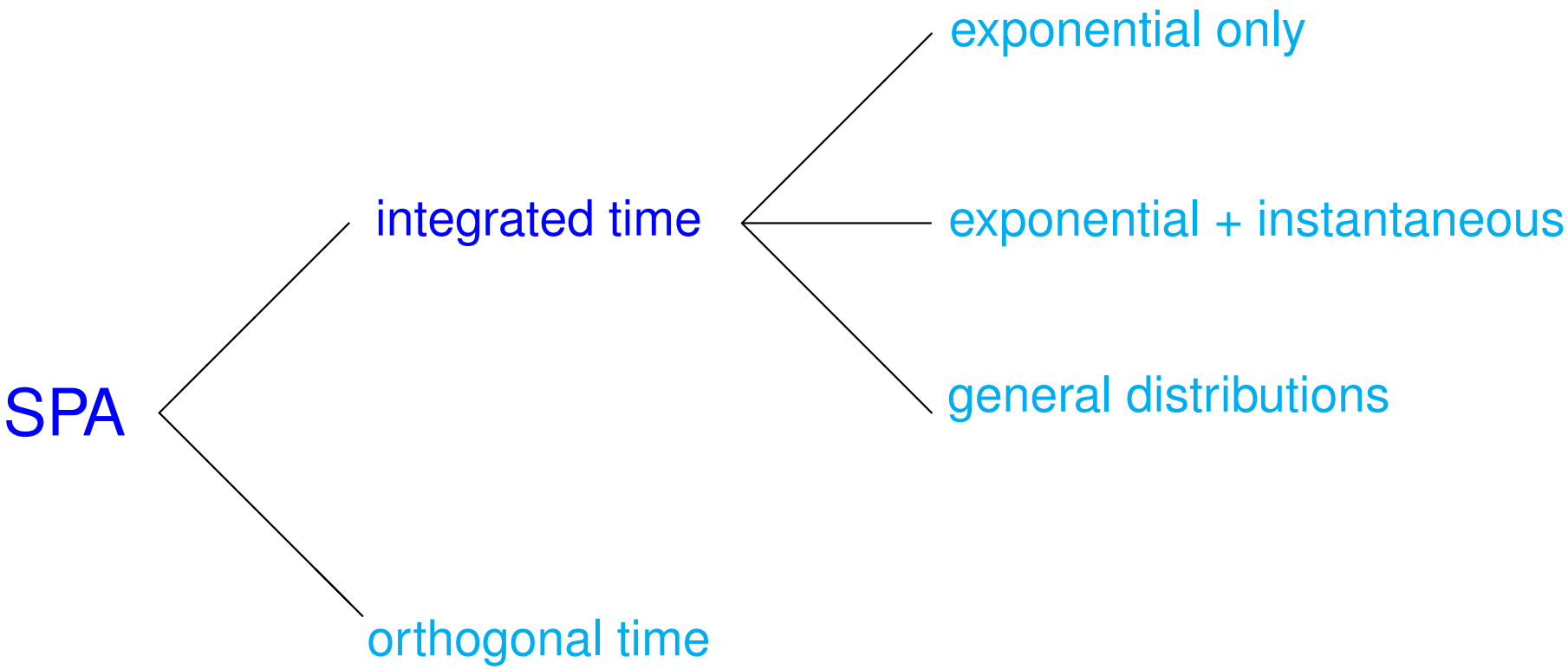

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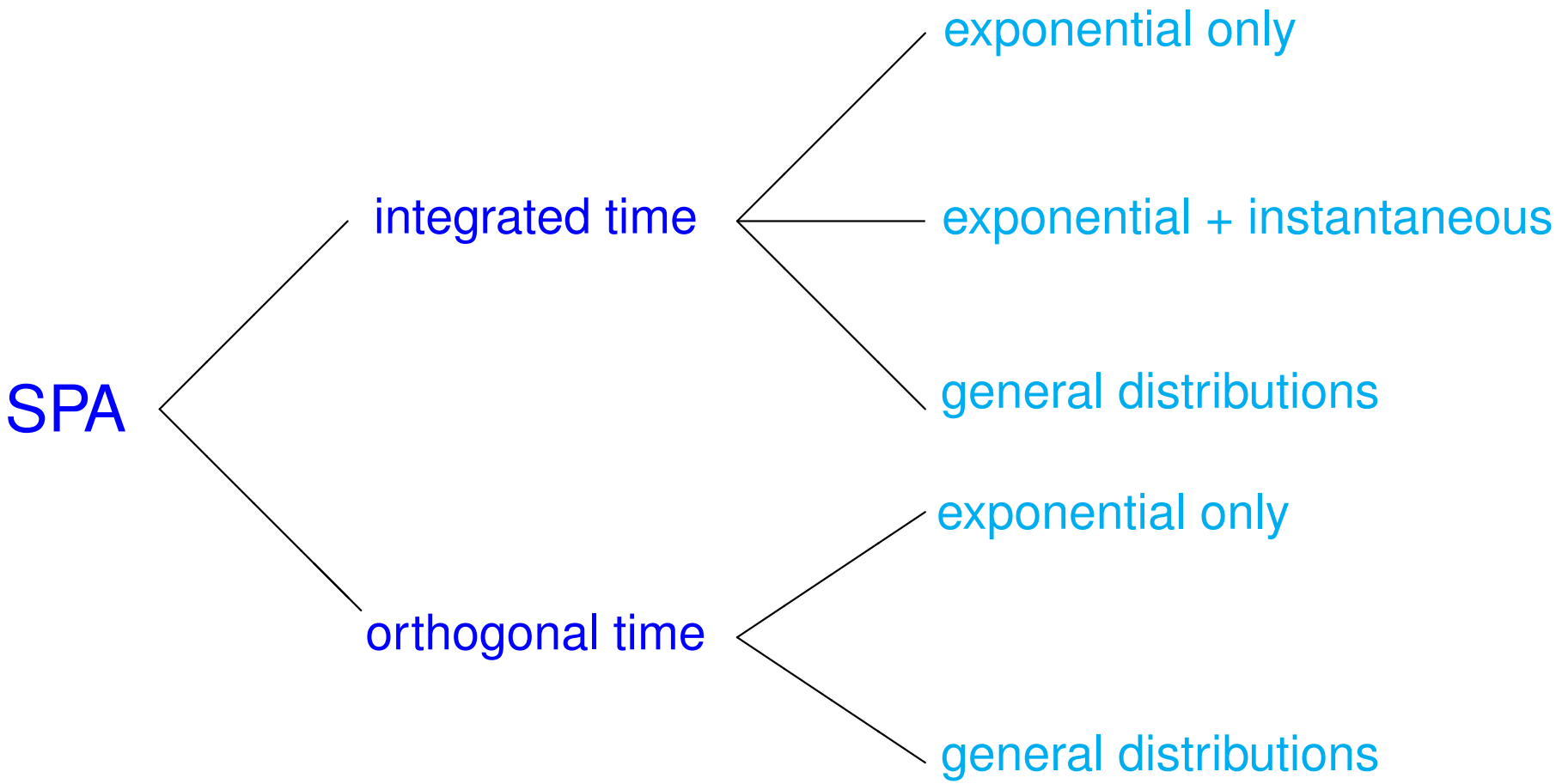

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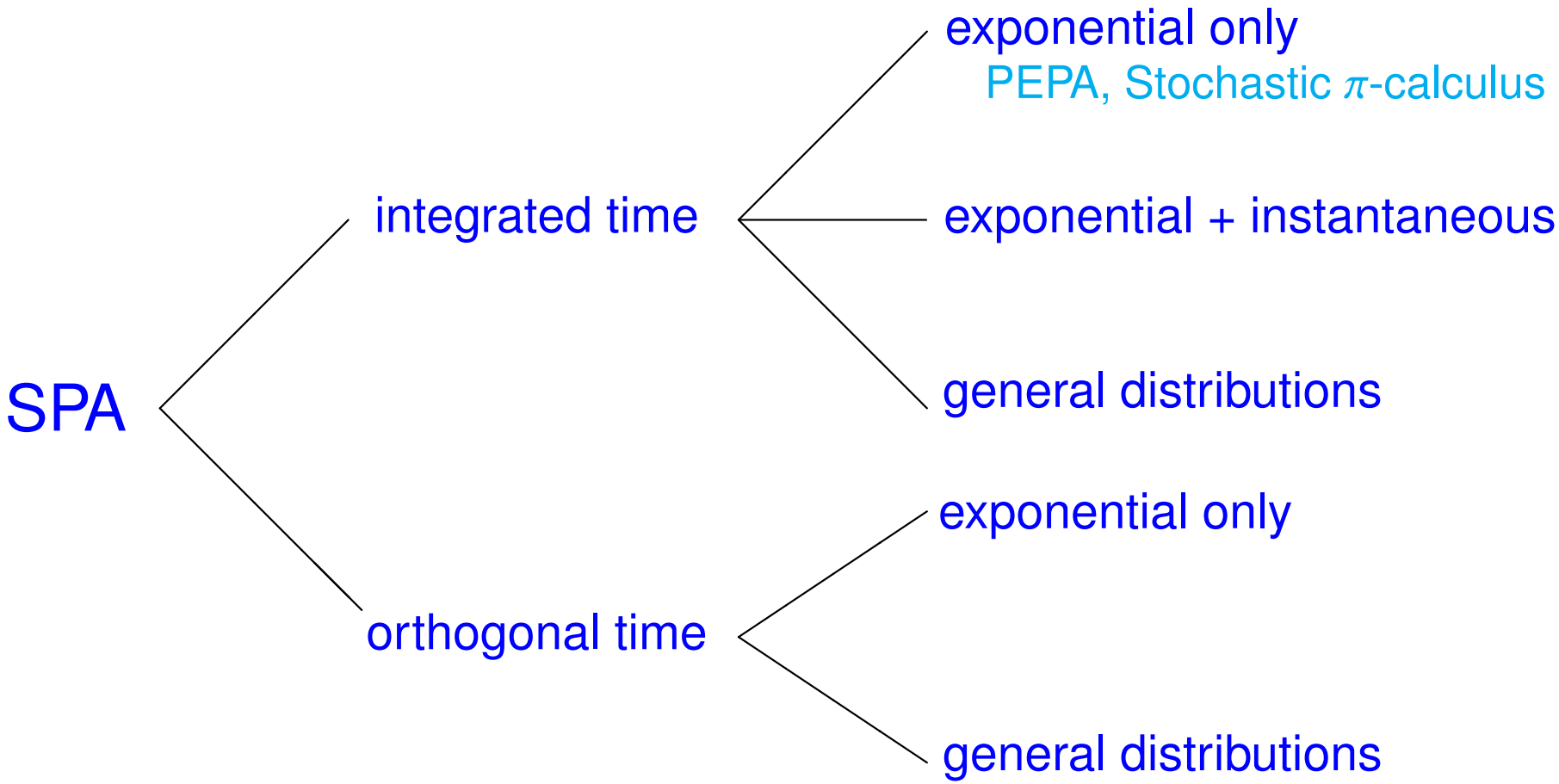

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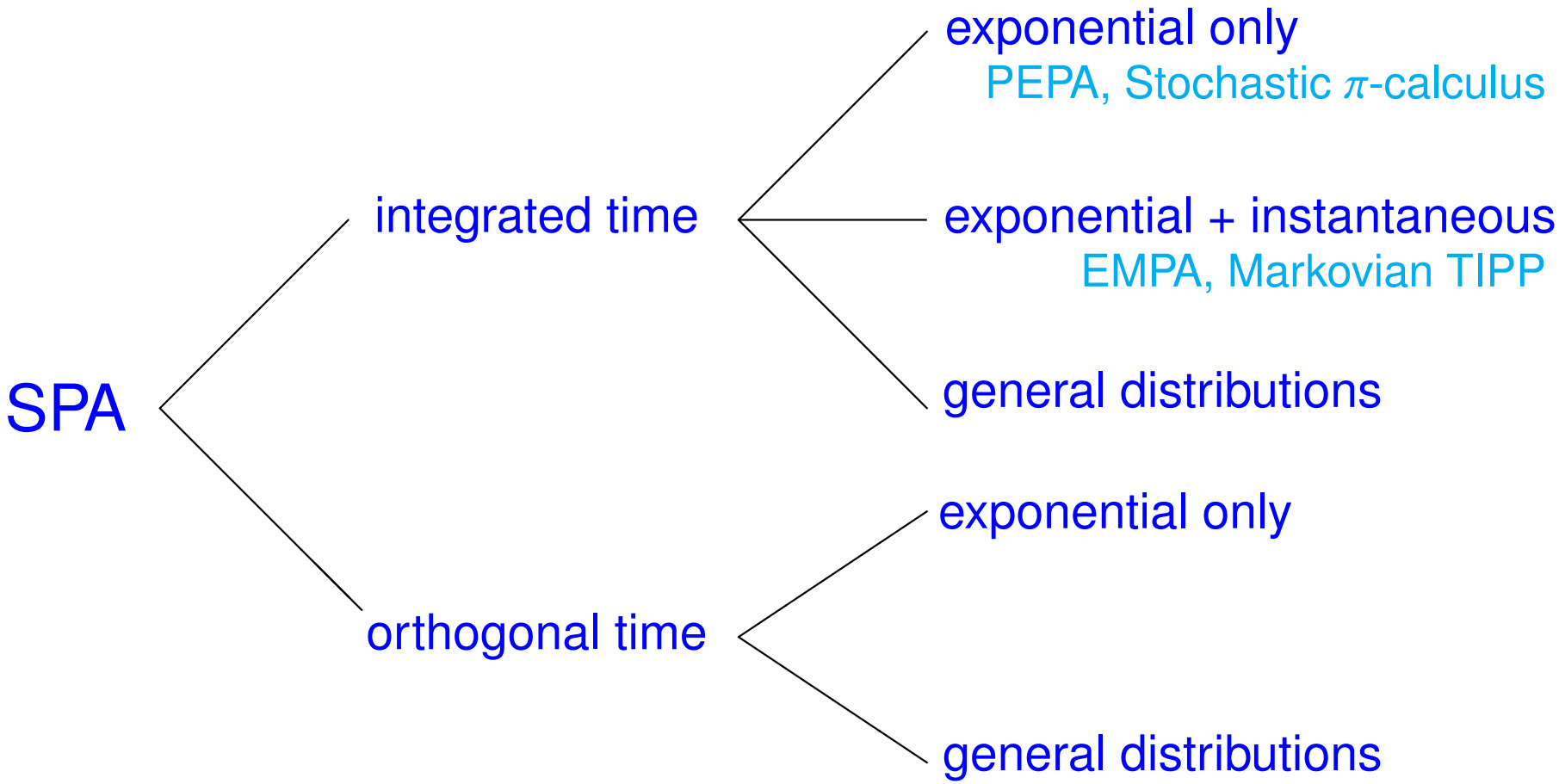

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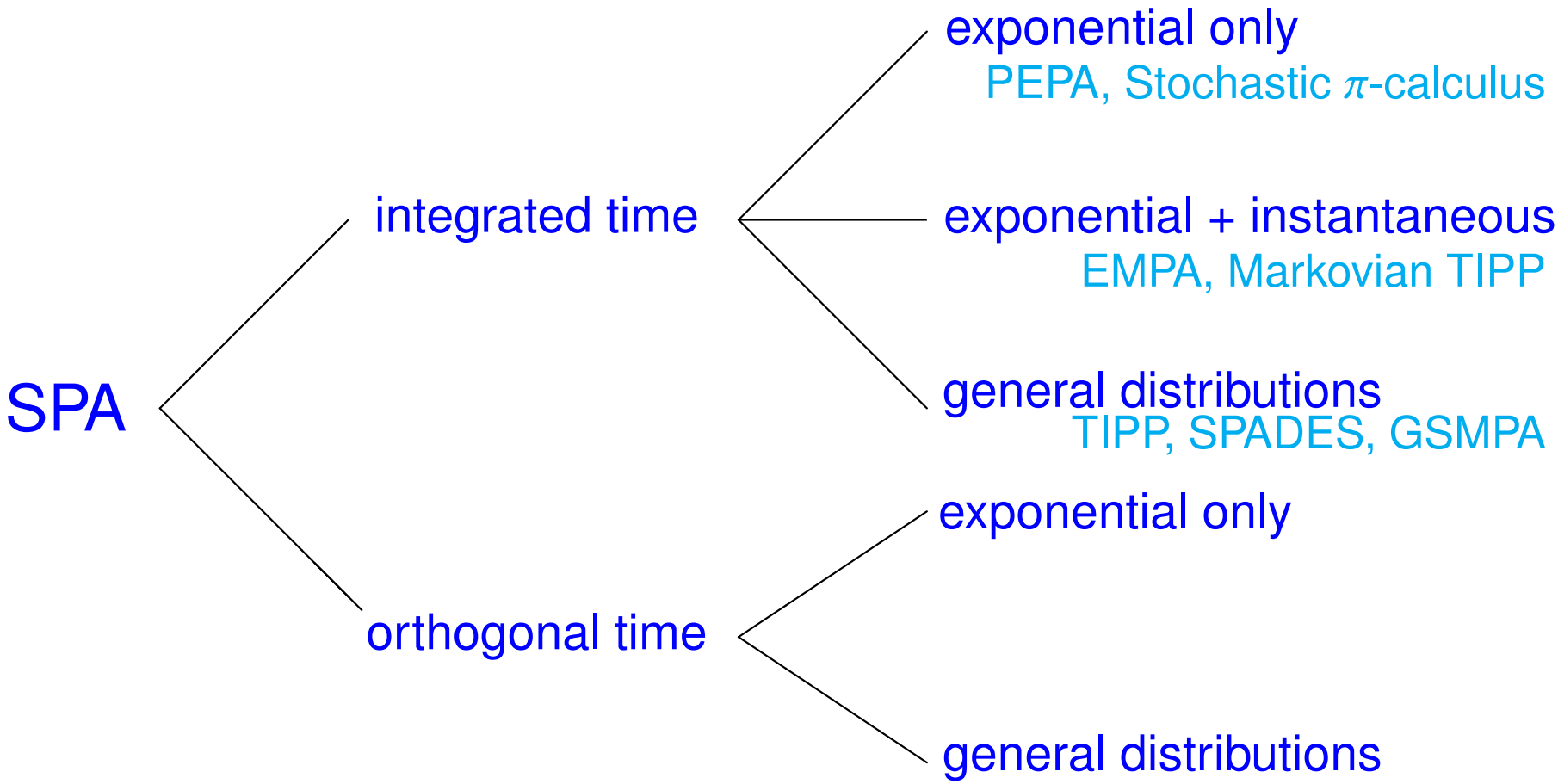

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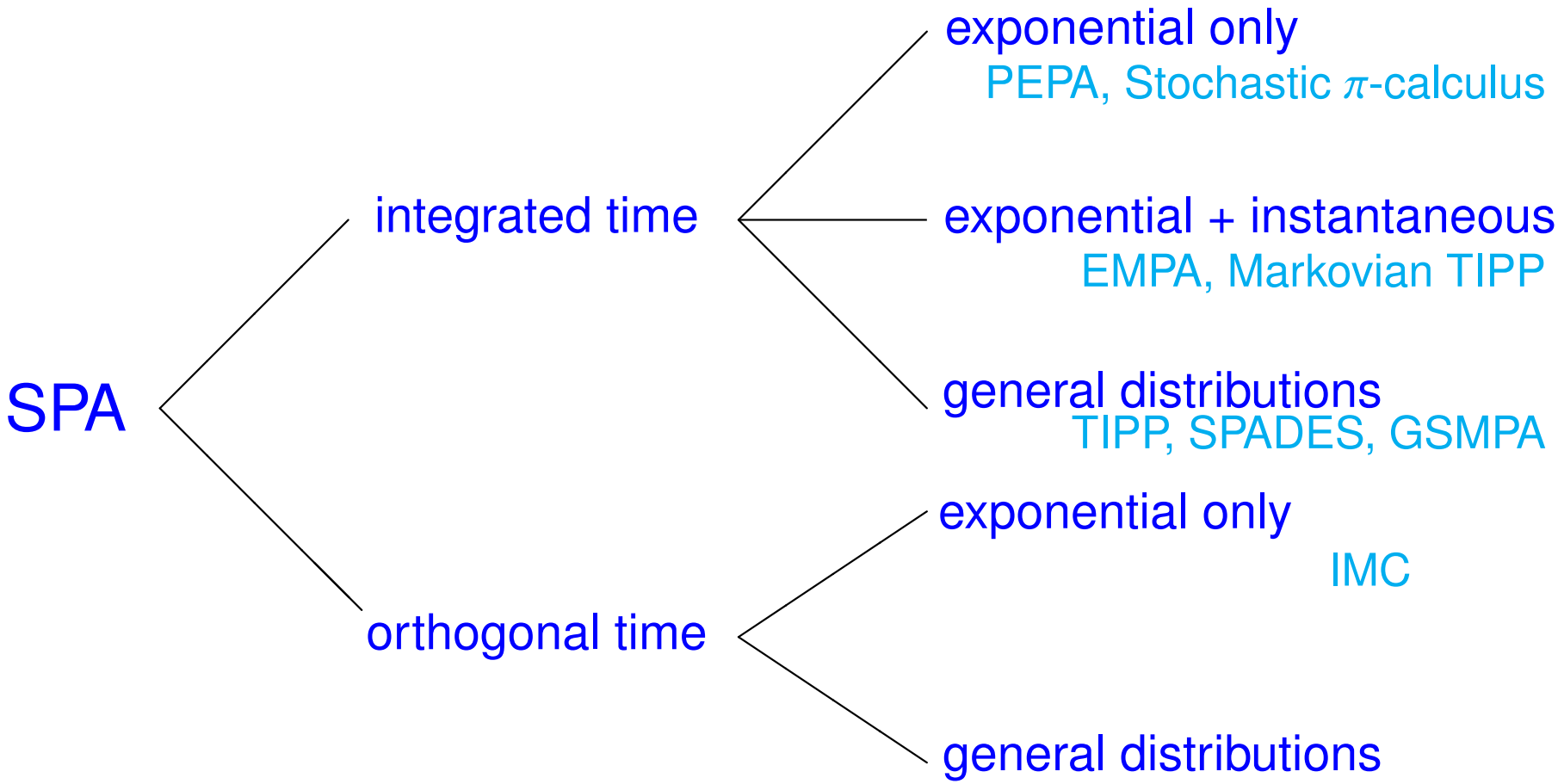

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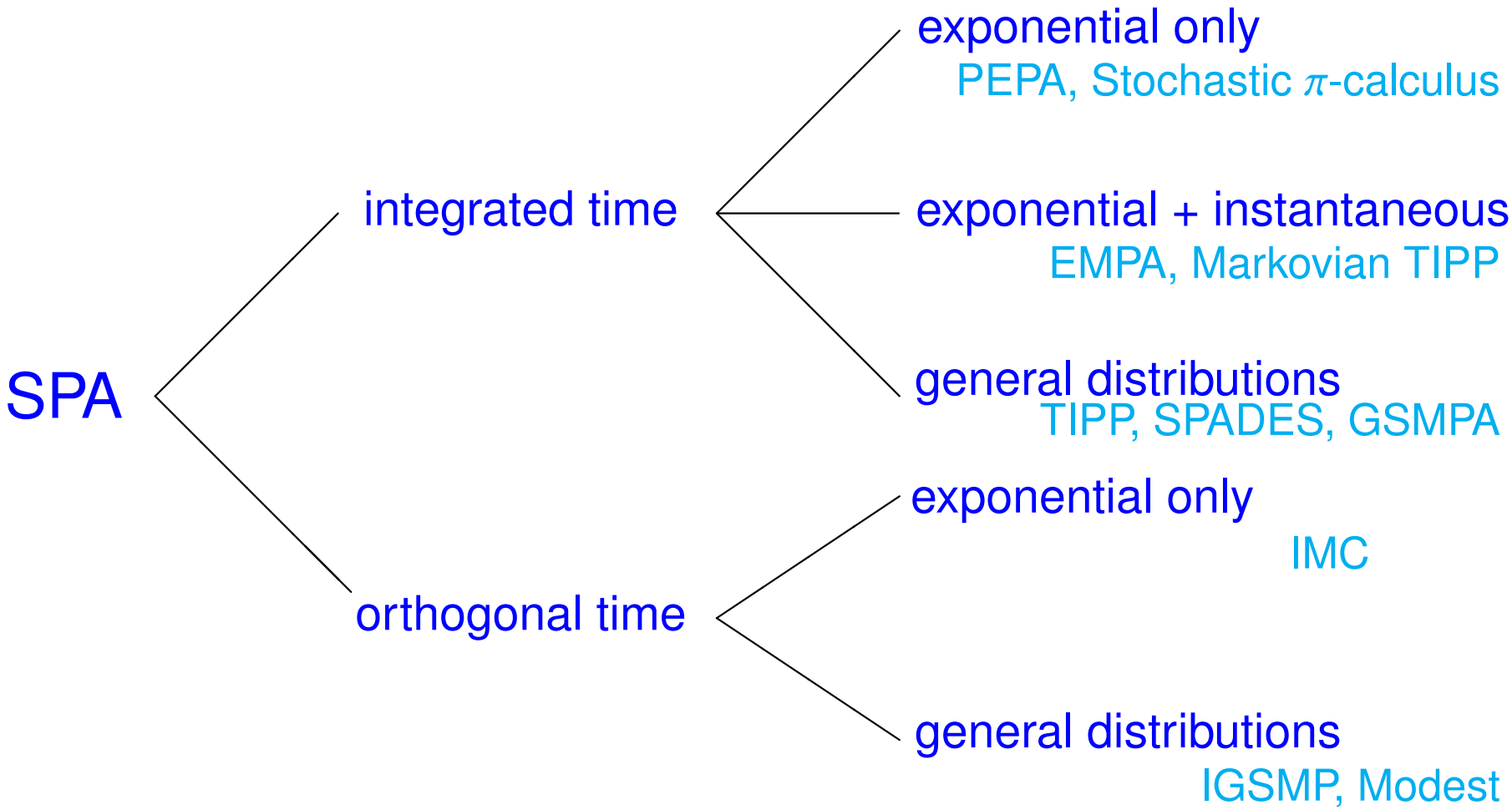

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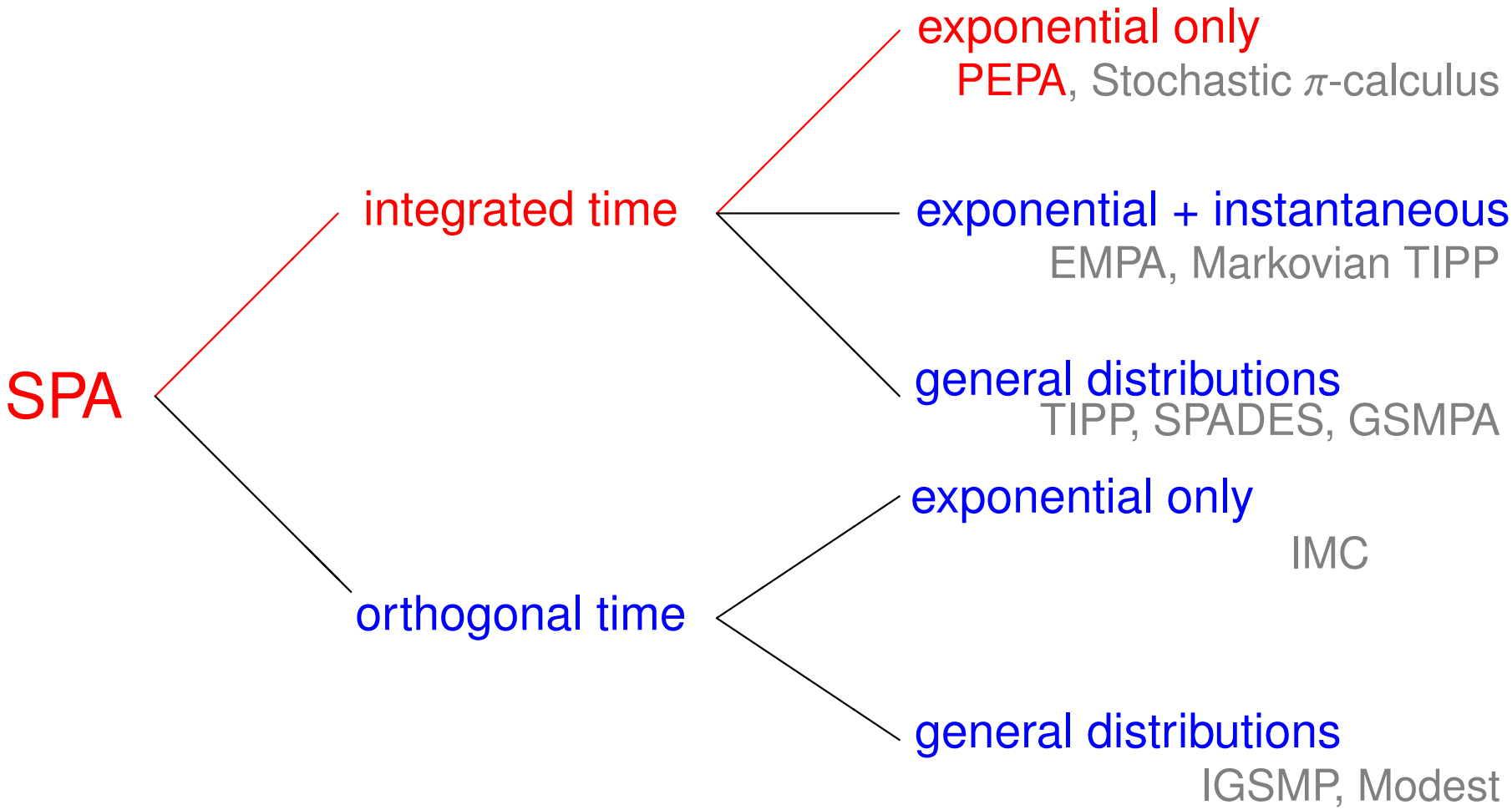

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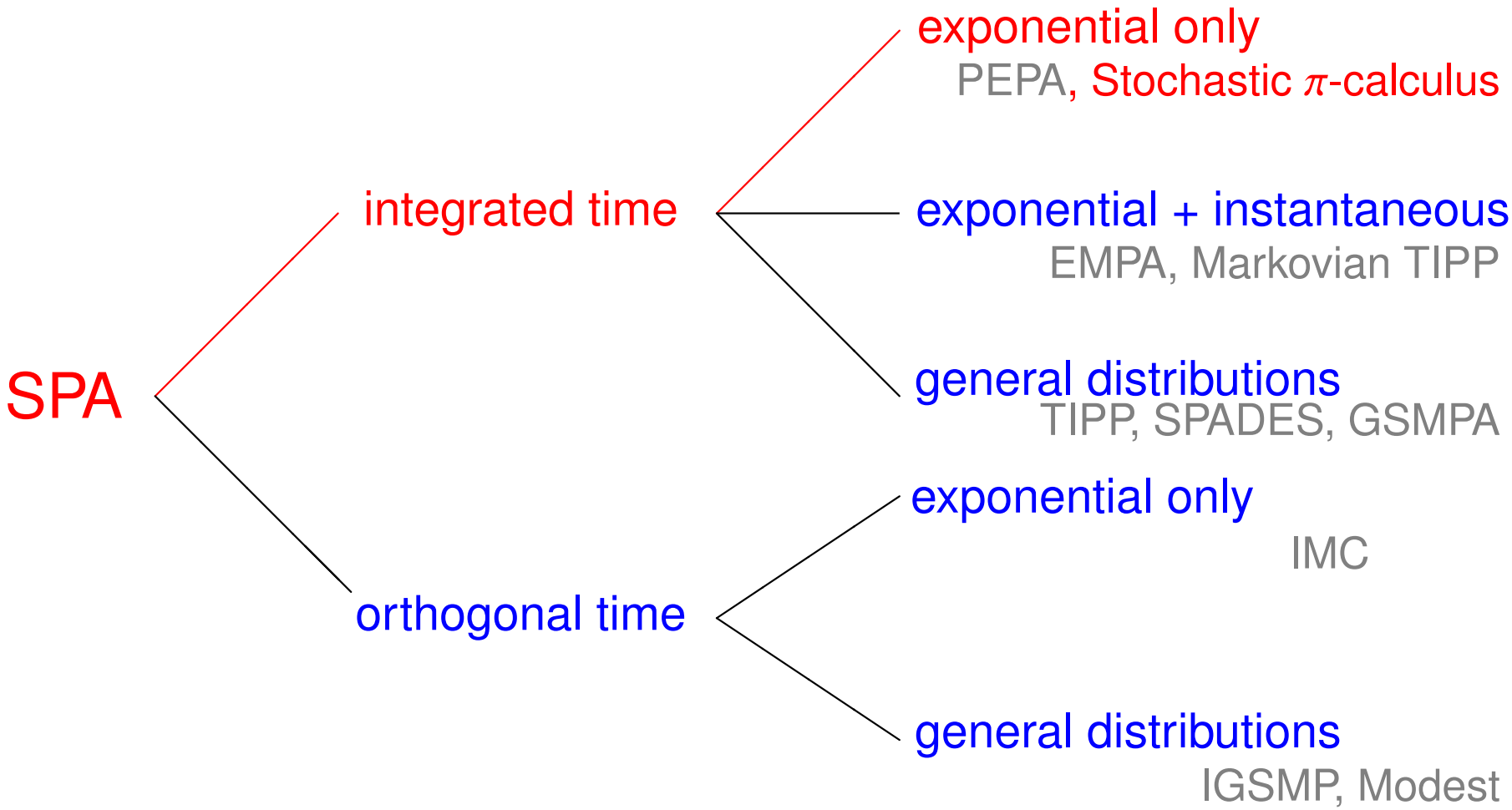
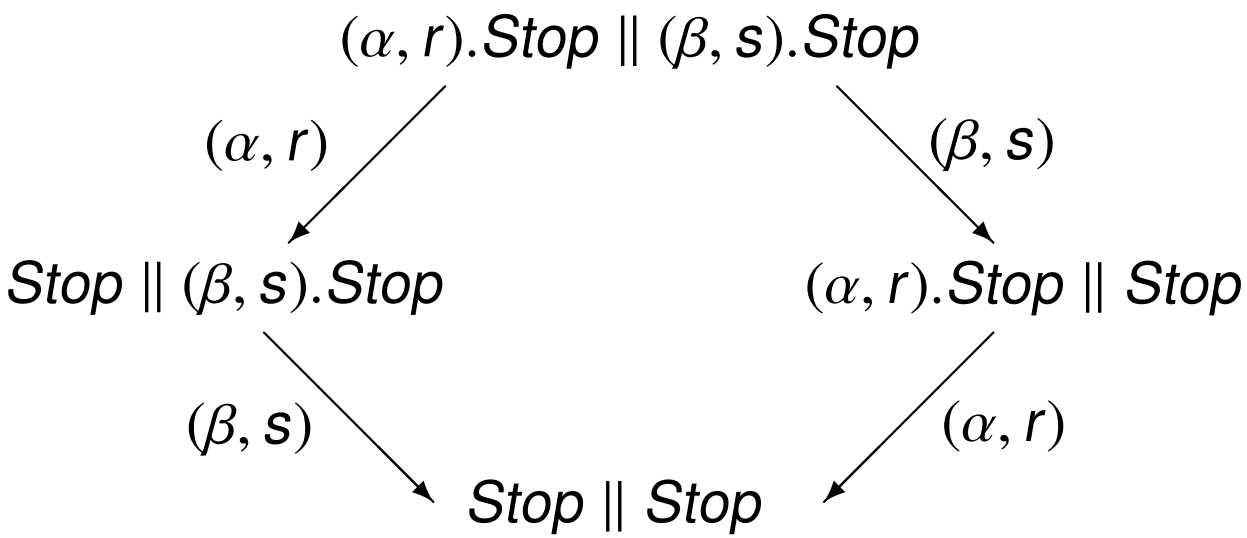


The Importance of Being Exponential



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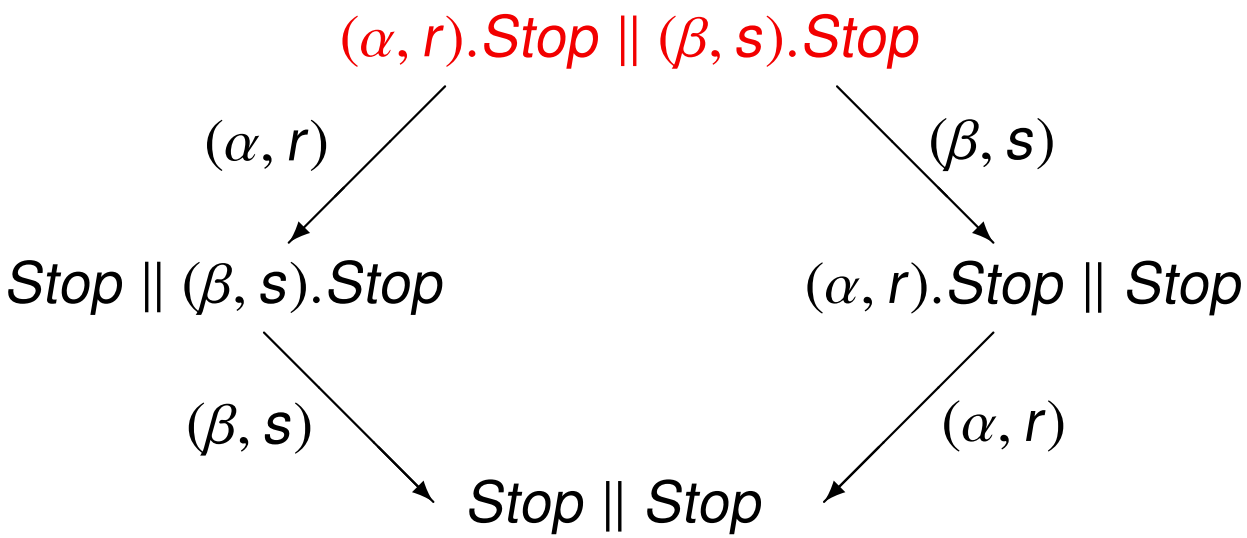

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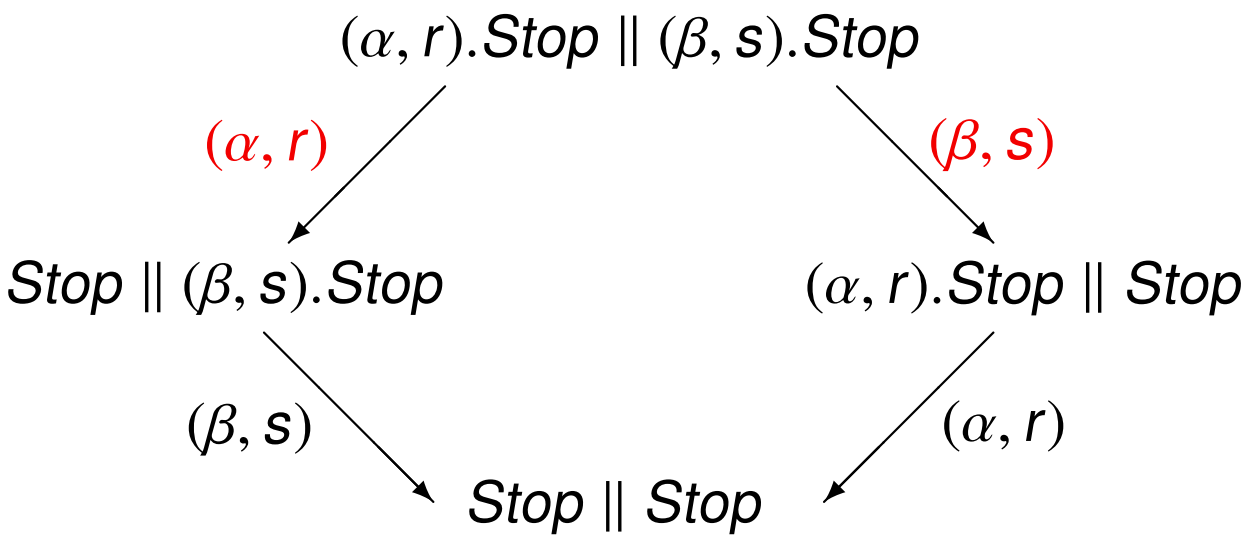

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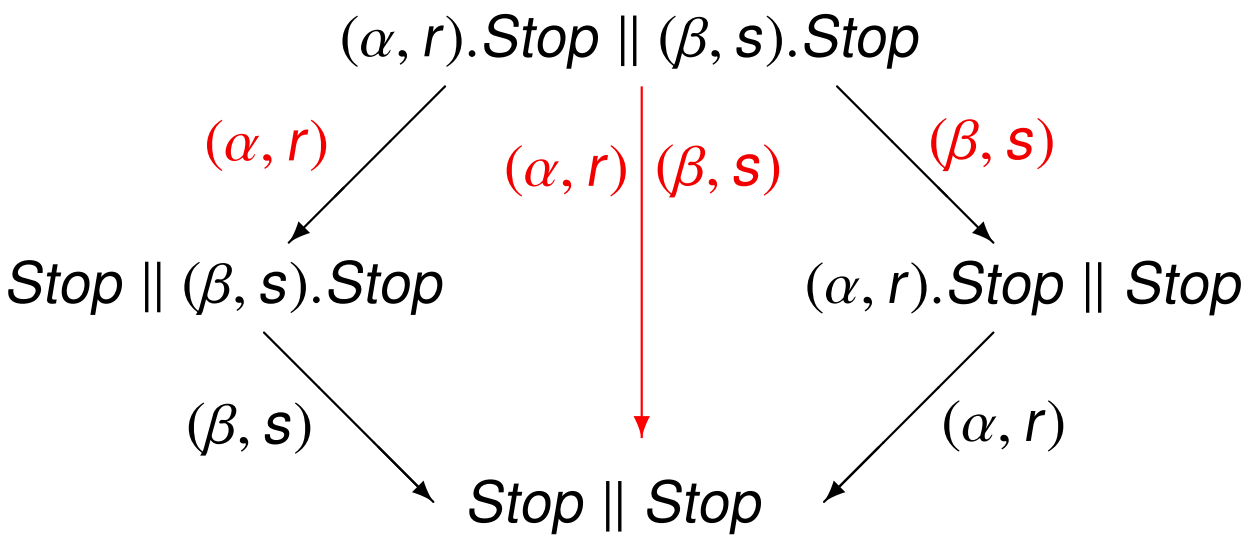

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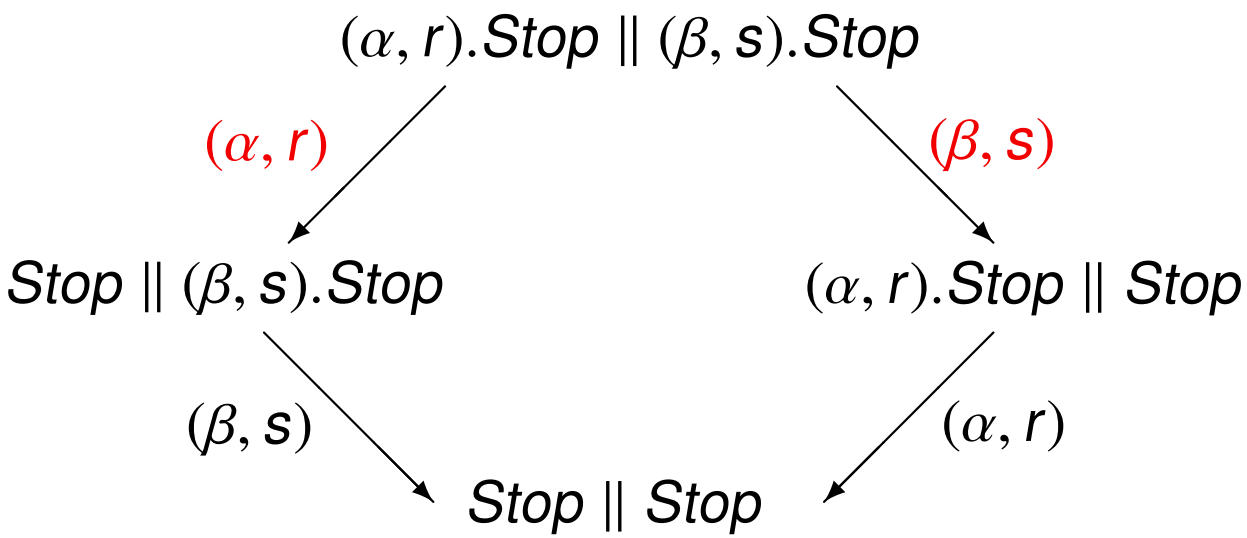

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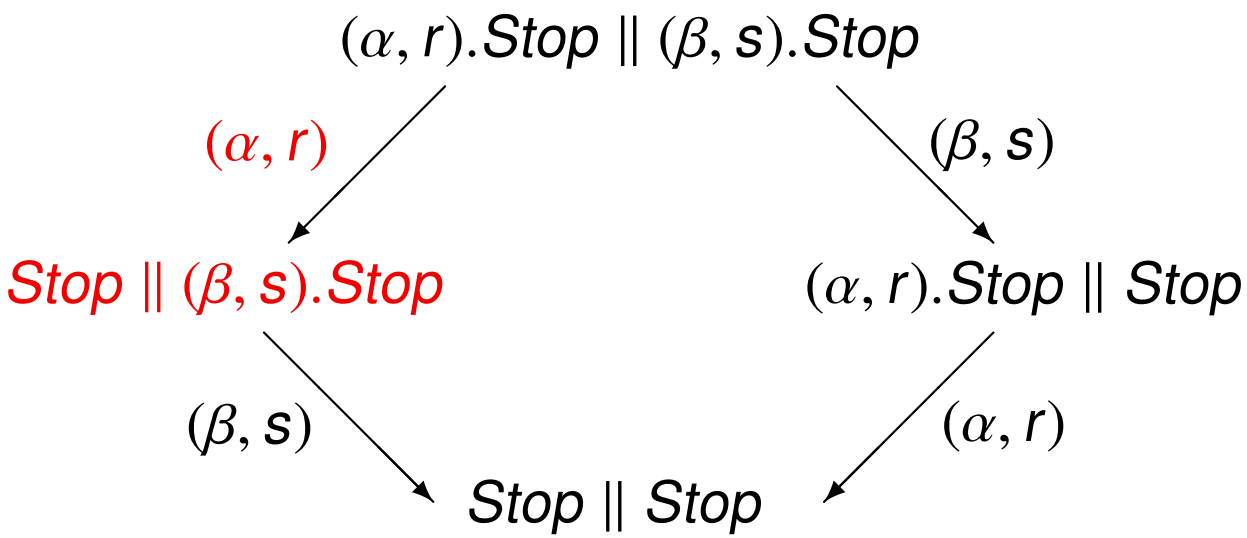

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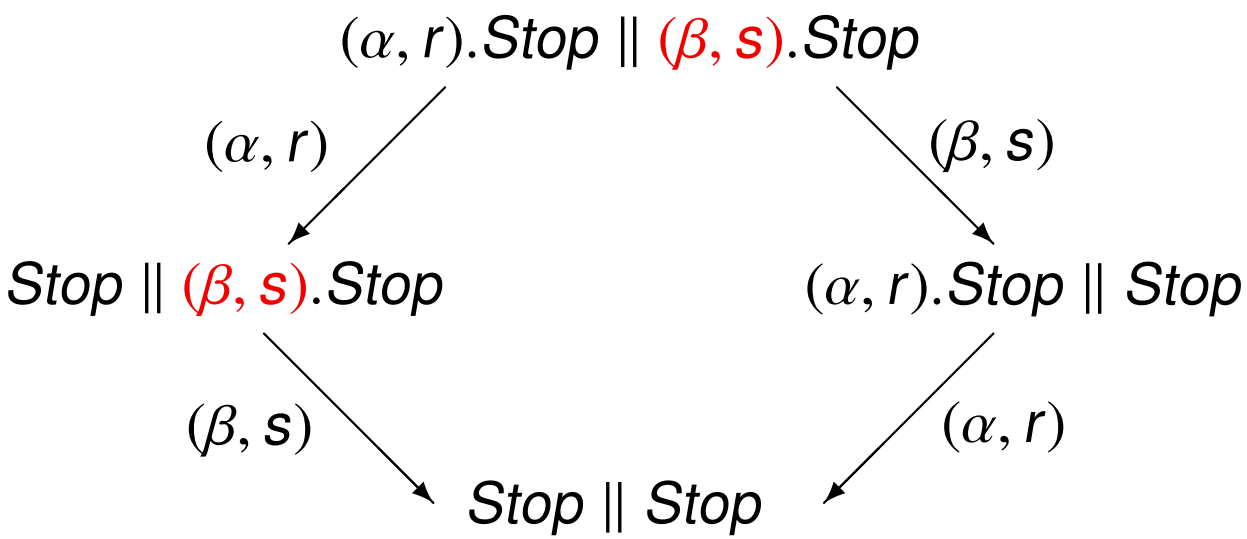

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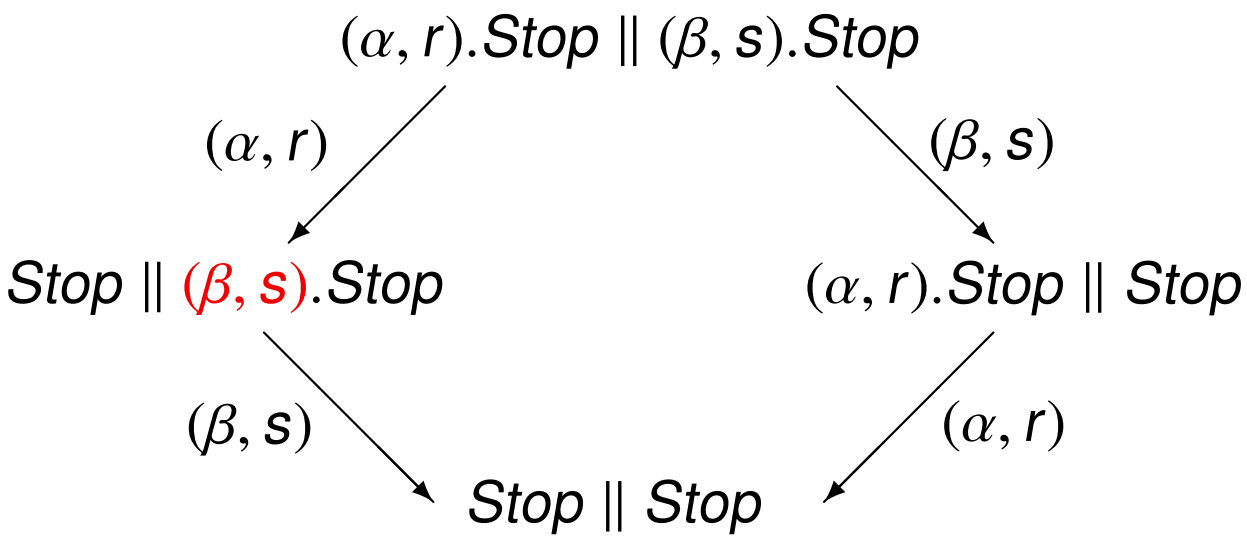
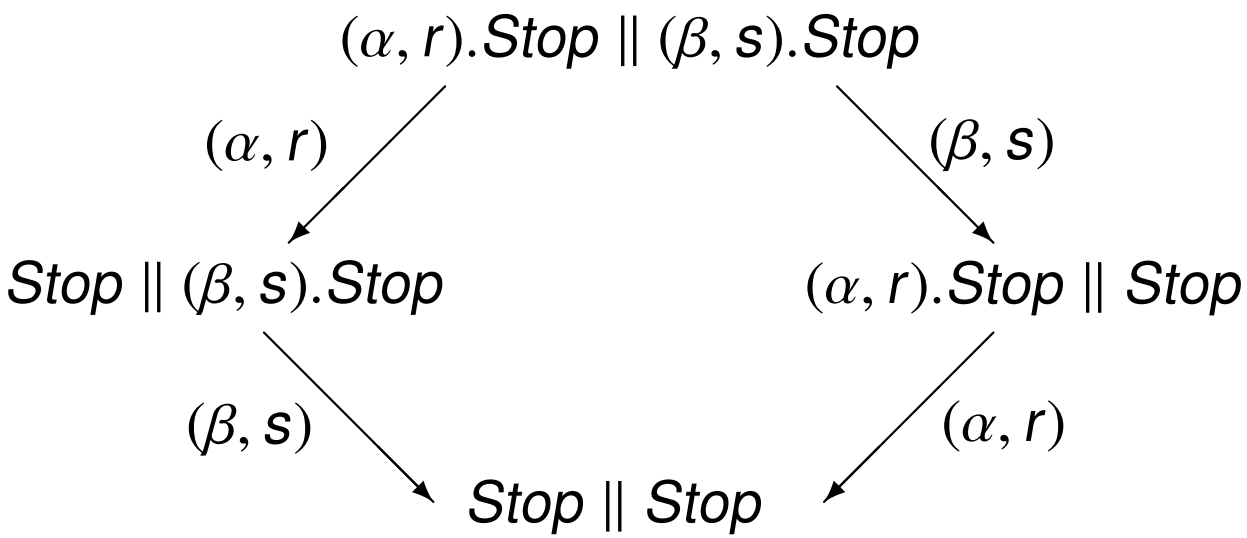


The memoryless property of the negative exponential distribution means that residual times do not need to be recorded.

The Importance of Being Exponential



We retain the expansion law of classical process algebra:

$$(\alpha, r).Stop \parallel (\beta, s).Stop =$$
$$(\alpha, r).(\beta, s).(Stop \parallel Stop) + (\beta, s).(\alpha, r).(Stop \parallel Stop)$$

only if the negative exponential distribution is assumed.

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- When the activities of the process algebra have a duration the definition of parallel composition becomes more complex.

Who Synchronises...?

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We will see examples of both CCS-style and CSP-style synchronisation.

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- The rate of a synchronised or shared activity must then be chosen, reflecting the capacities of the components involved.
- The different SPA languages have adopted a number of different solutions to this problem.

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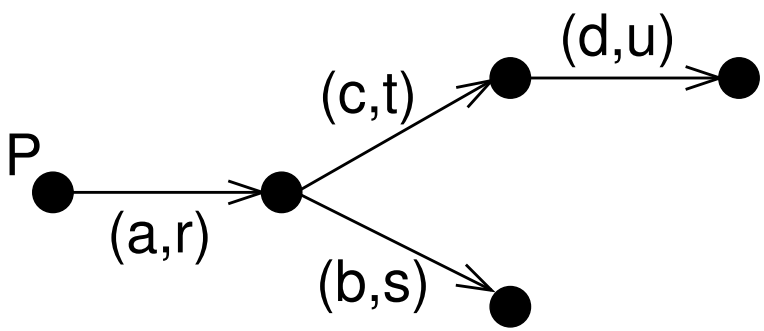
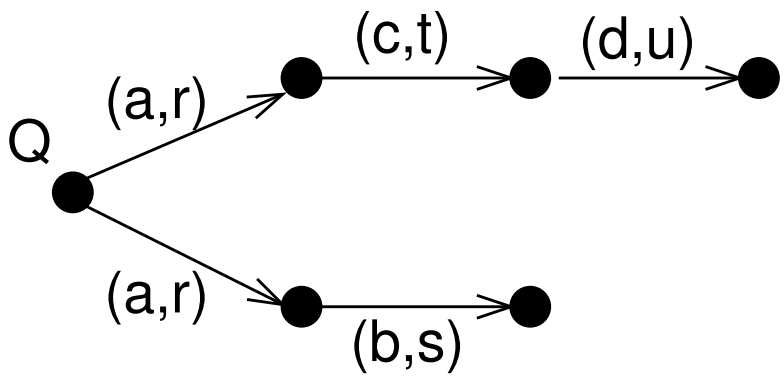
- We will see that a different solution is appropriate in the context of biological systems.

Equivalence Relations

In process algebra equivalence relations are defined based on the notion of observability:





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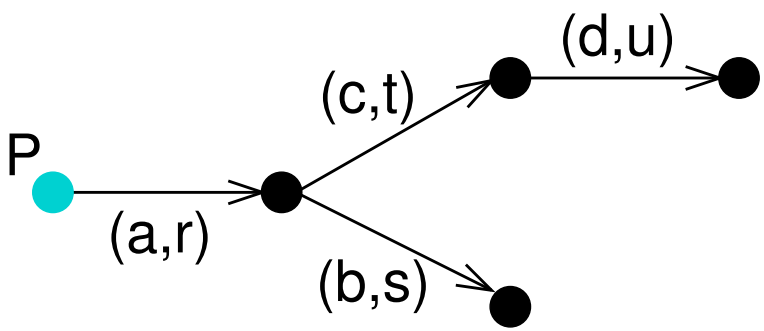

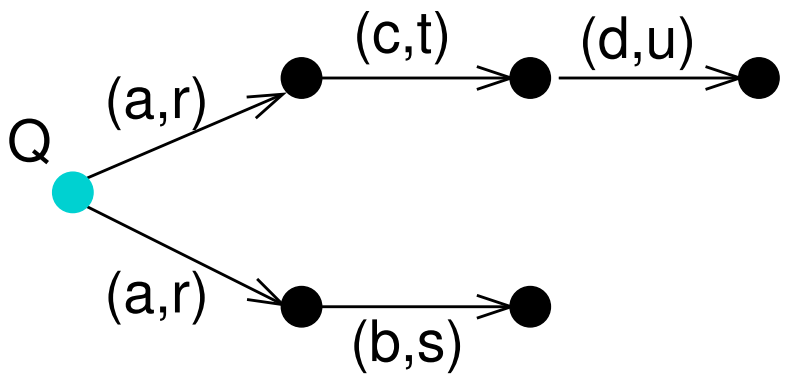

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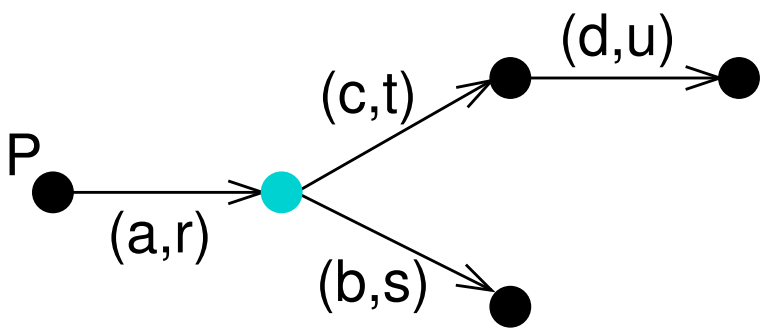

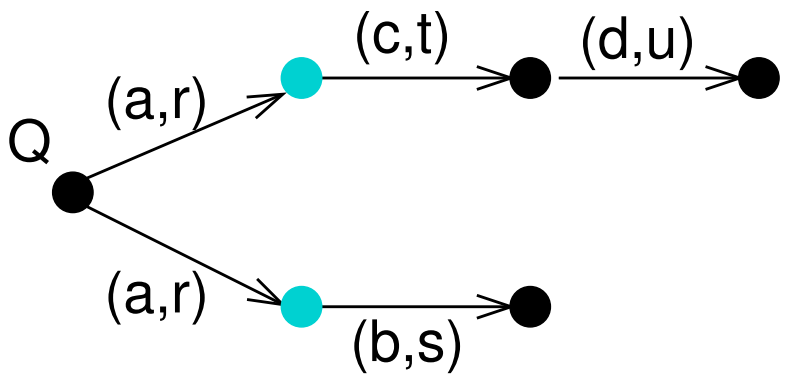

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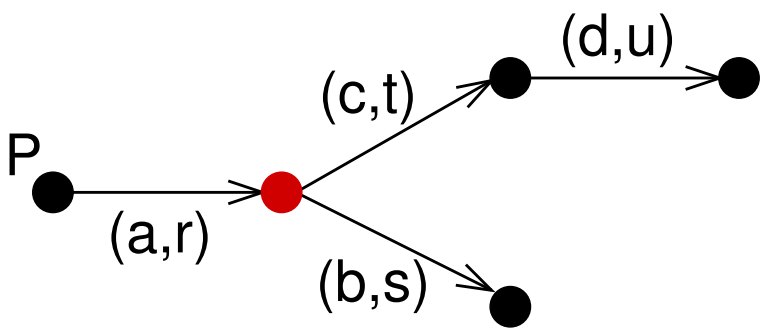

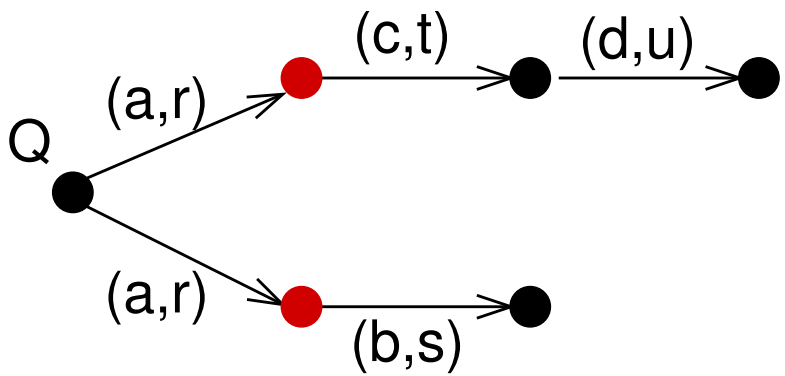

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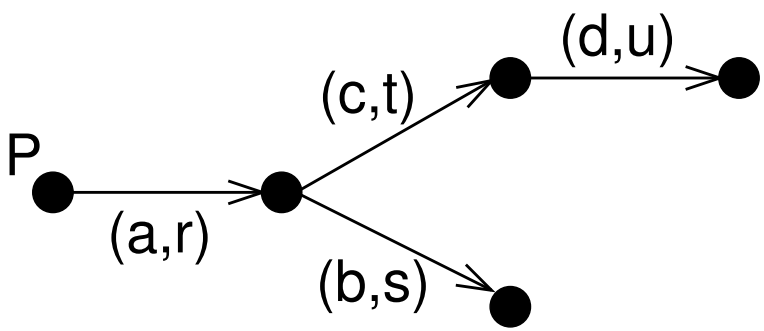

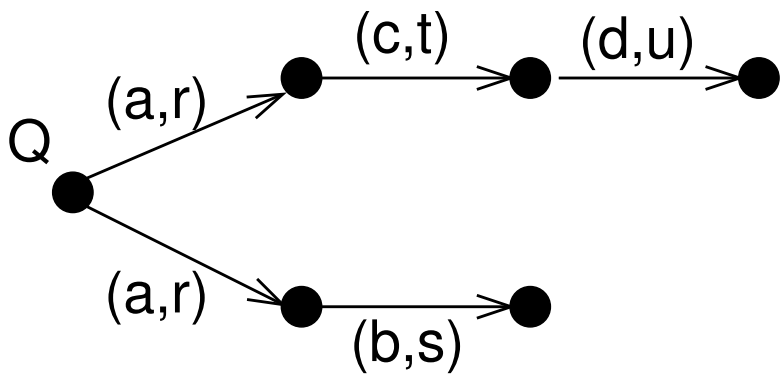

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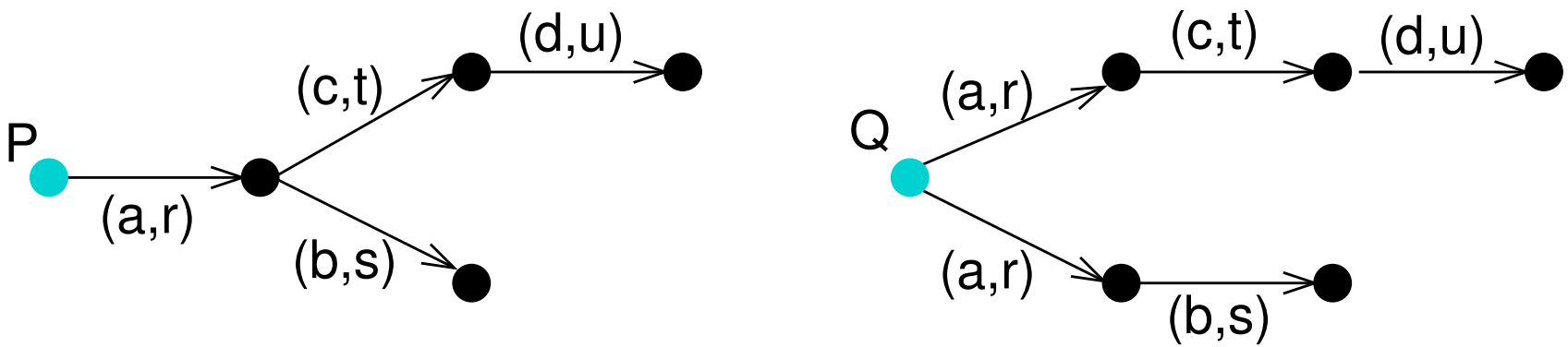

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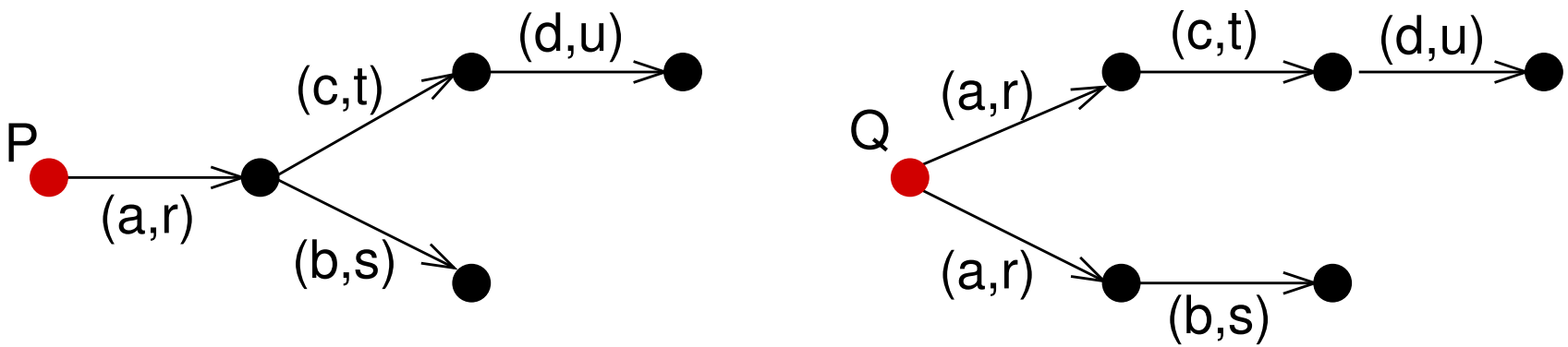

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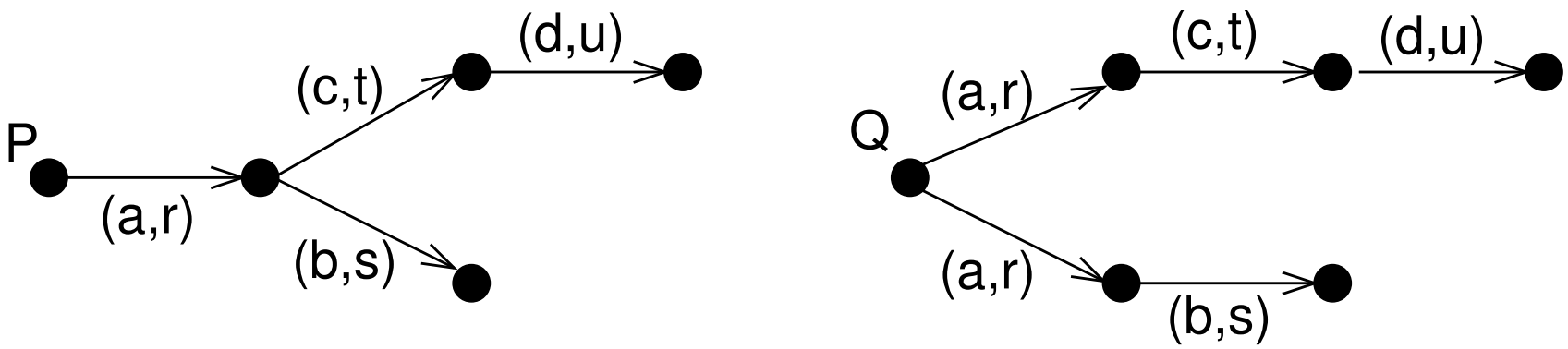

In SPA observation is assumed to include the ability to record timing information over a number of runs.

The resulting equivalence relation is a bisimulation in the style of Larsen and Skou, and coincides with the Markov process notion of lumpability.

Exploiting equivalence relations

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- Equivalence between models: The behaviour of two alternative models/components may be compared. Equivalent ones may be used interchangeably. This is of particular value when one model is easier to solve than the other e.g. if it has a smaller state space. This is termed model simplification.

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- Equivalence between models: The behaviour of two alternative models/components may be compared. Equivalent ones may be used interchangeably. This is of particular value when one model is easier to solve than the other e.g. if it has a smaller state space. This is termed model simplification.
- Equivalence within a model: The behaviour of individual states within the state space of a single model may be compared. This can lead to the formation of equivalence classes and a more abstract representation may then be chosen with one representative of each equivalence class. This is termed model aggregation.

Aggregation and lumpability

Model aggregation: use a state-state equivalence to establish a partition of the state space of a model, and replace each set of states by one macro-state, i.e. take a different stochastic representation of the same model.

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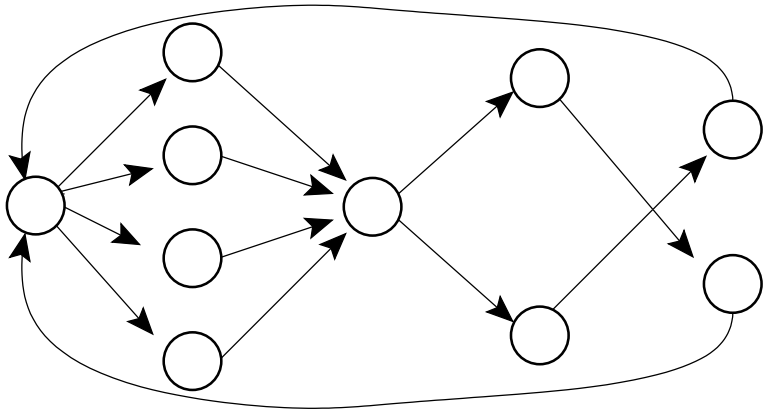

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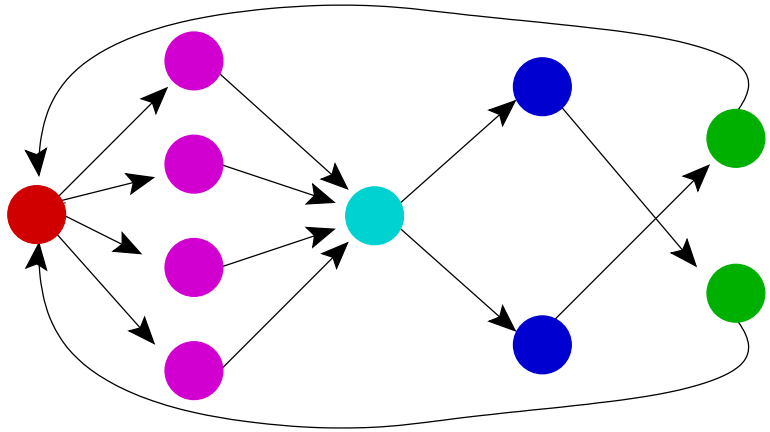

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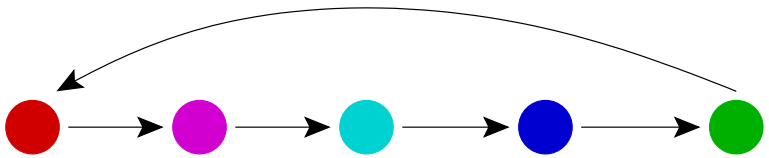
Model aggregation: use a state-state equivalence to establish a partition of the state space of a model, and replace each set of states by one macro-state, i.e. take a different stochastic representation of the same model.

A lumpable partition is the only partition of a Markov process which preserves the Markov property.



PEPA Case Studies (1)

- Multiprocessor access-contention protocols (Gilmore, Hillston and Ribaudo, Edinburgh and Turin)
- Protocols for fault-tolerant systems (Clark, Gilmore, Hillston and Ribaudo, Edinburgh and Turin)
- Multimedia traffic characteristics (Bowman et al, Kent)
- Database systems (The STEADY group, Heriot-Watt University)
- Software Architectures (Pooley, Bradley and Thomas, Heriot-Watt and Durham)
- Switch behaviour in active networks (Hillston, Kloul and Mokhtari, Edinburgh and Versailles)

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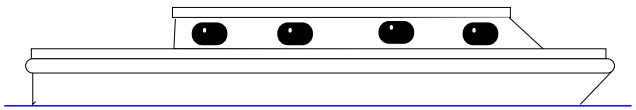

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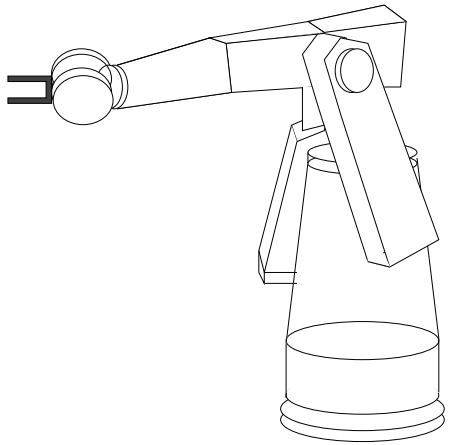

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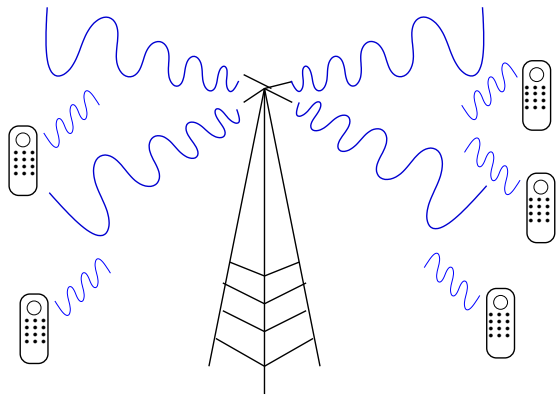

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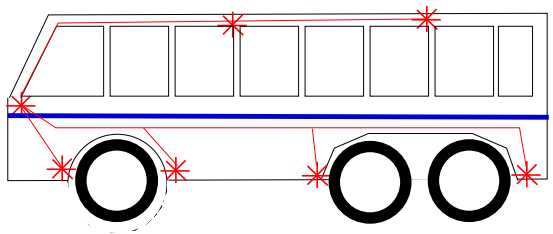
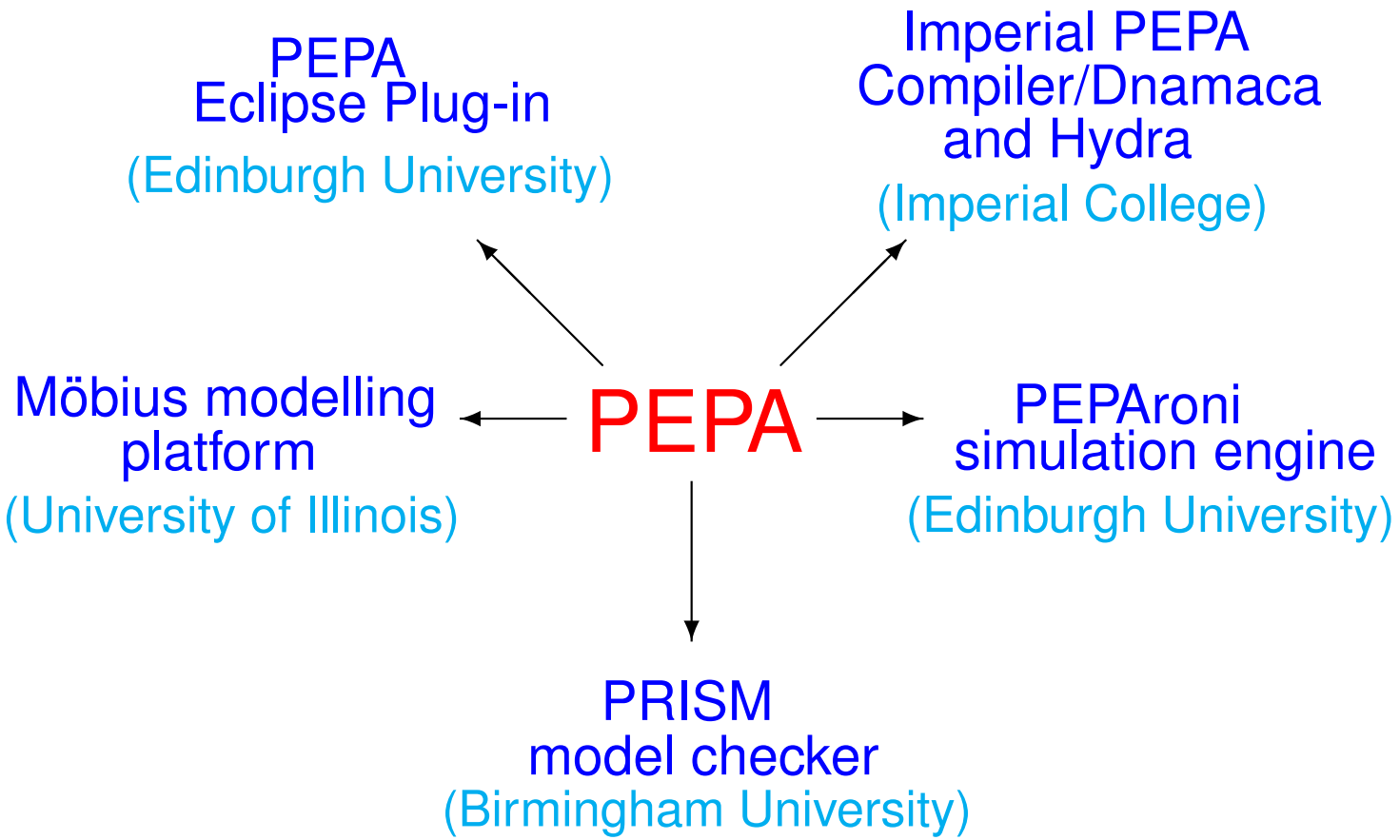


Tool Support



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Outline

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- There are well-established techniques for reasoning about the behaviours and properties of models, supported by software. These include qualitative and quantitative analysis, and model checking.

Molecular processes as concurrent computations

Concurrency	**Molecular Biology**	**Metabolism**	**Signal Transduction**
Concurrent computational processes	Molecules	Enzymes and metabolites	Interacting proteins
Synchronous communication	Molecular interaction	Binding and catalysis	Binding and catalysis
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- Calculi defined specifically by observing biological structures and phenomena, such as BioAmbients, Brane Calculi and Beta-binders.

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- There has also been some work on a graphical notation associated with the SPIM tool.

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- The successor of CSS-R is the Reversible CCS (RCCS). This calculus allows processes to backtrack if this is in agreement with a defined notion of casual equivalence.

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- Unlike the stochastic π-calculus and CCS-R, the calculus is not limited to binary interactions so any kind of reactions can be represented.
- Moreover the rate can be expressed by a generic function, thus general kinetic laws can be captured.

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- A stochastic version has recently been defined and used in applications.

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- The semantics give rules on joining and splitting boxes, as well as the affinity between interaction sites.

Mapping biological systems to process algebra

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Alternative mappings from the process algebra to underlying mathematics are then readily available.

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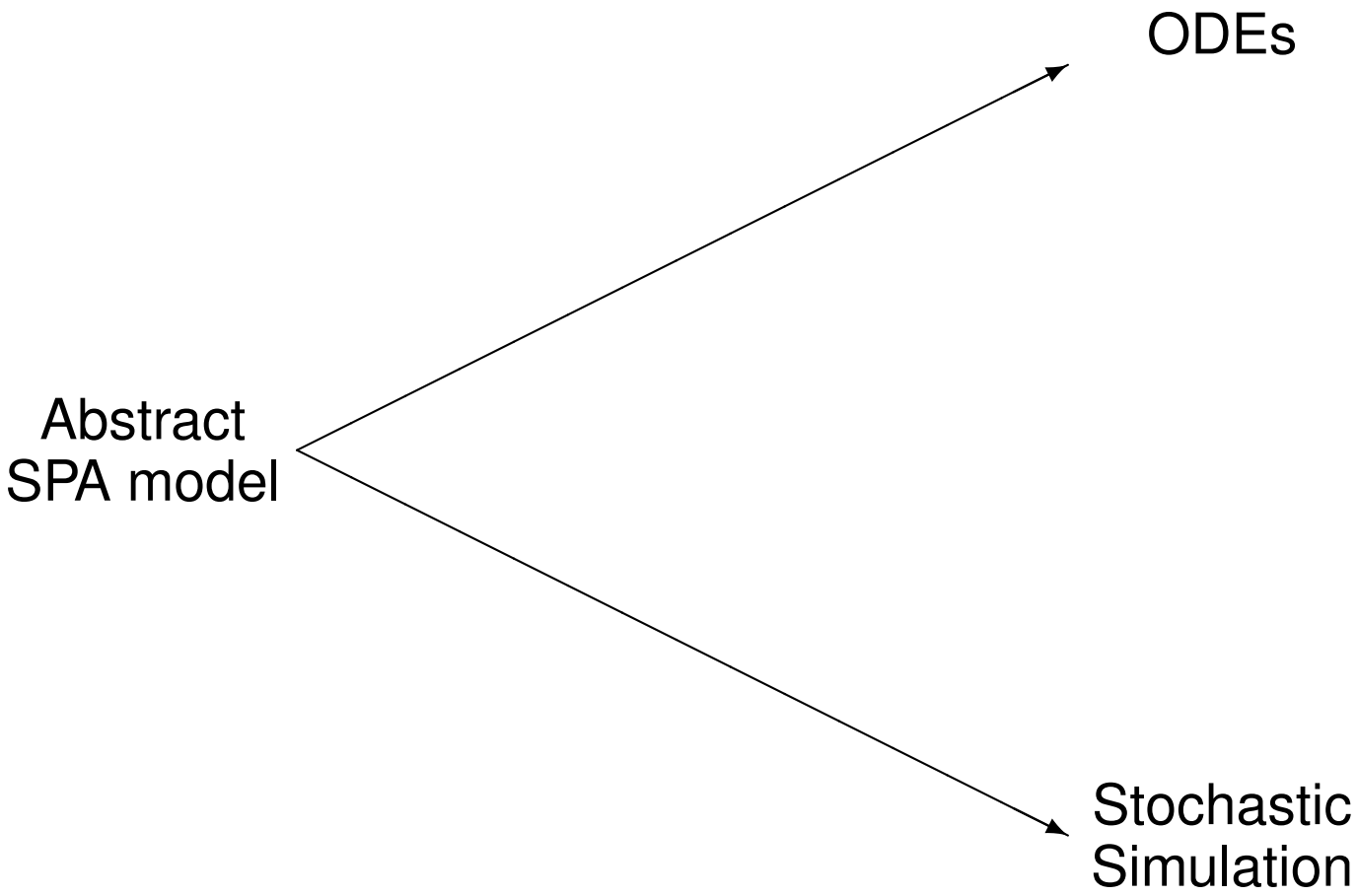

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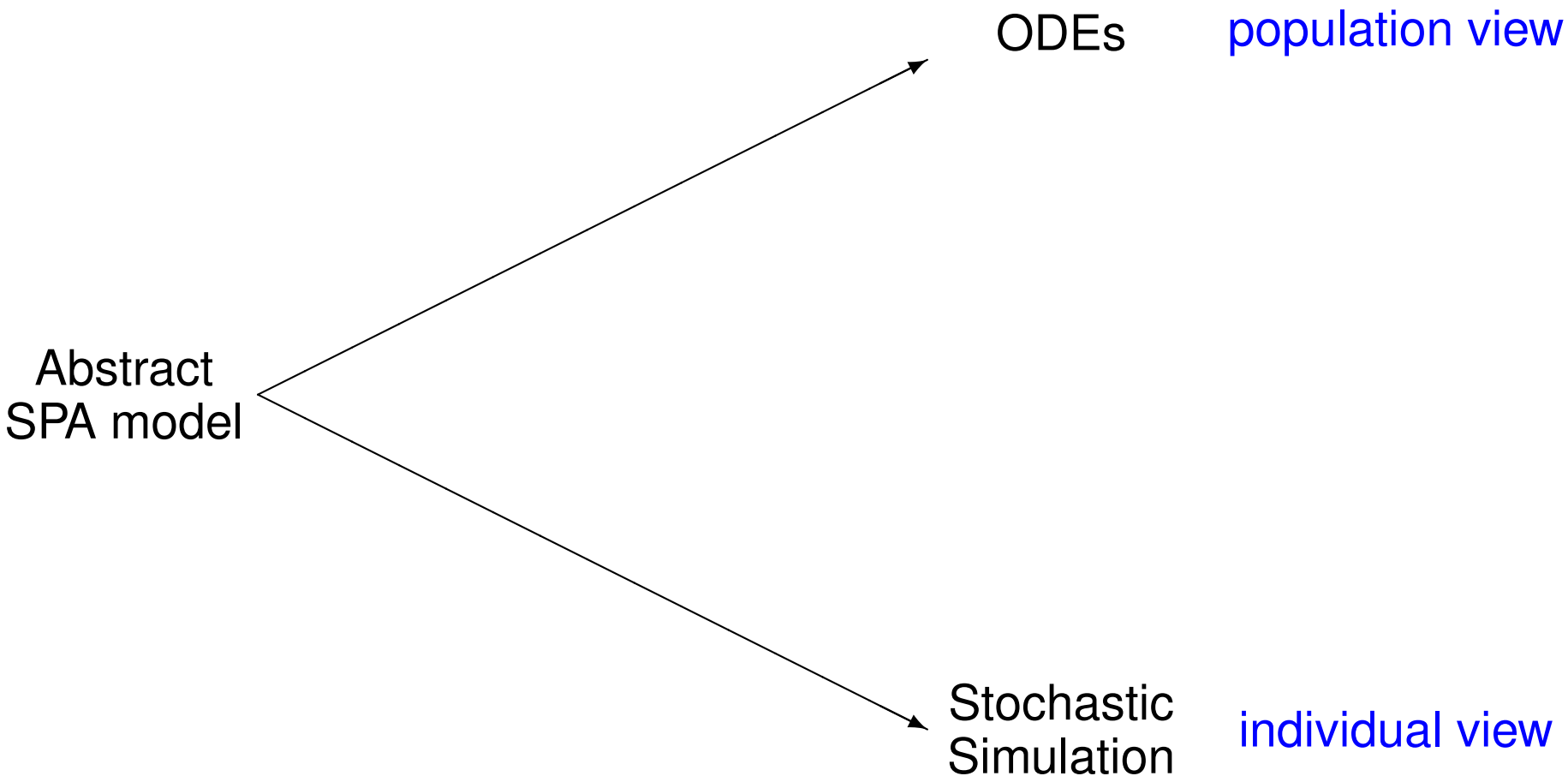

Discretising the population view

We can discretise the continuous range of possible concentration values into a number of distinct states. These form the possible states of the component representing the reagent.

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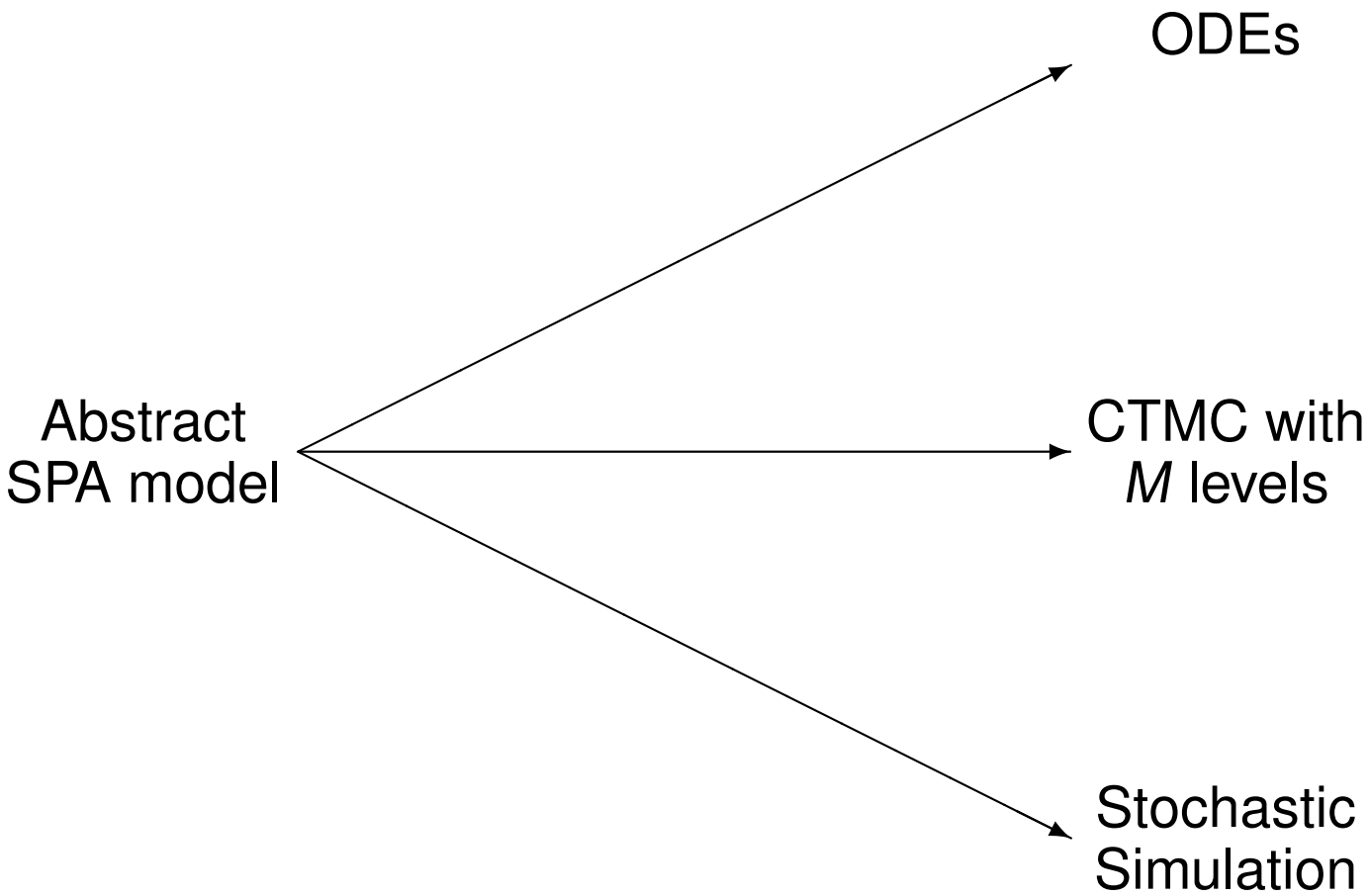

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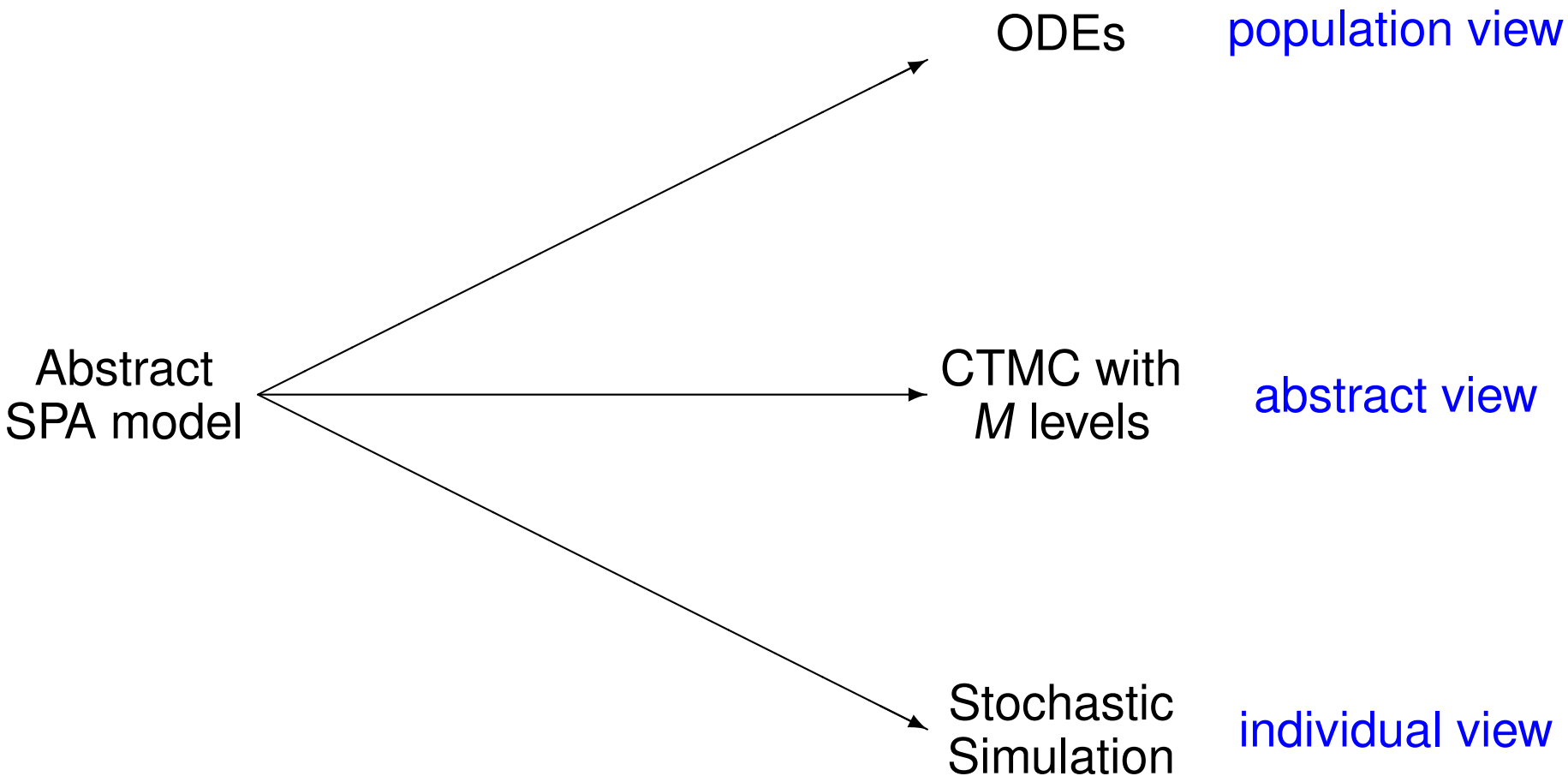

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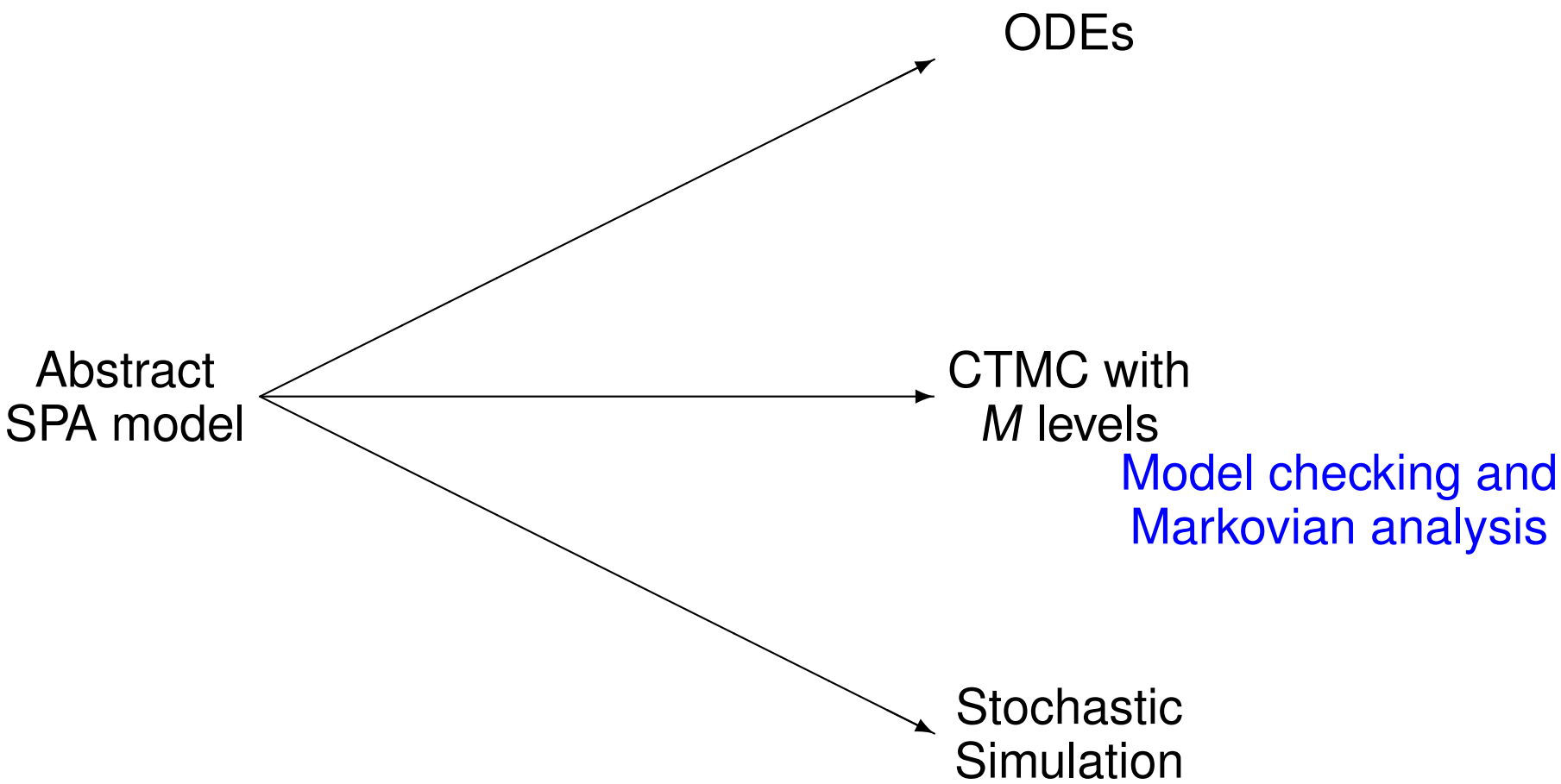

Stochastic Process Algebra

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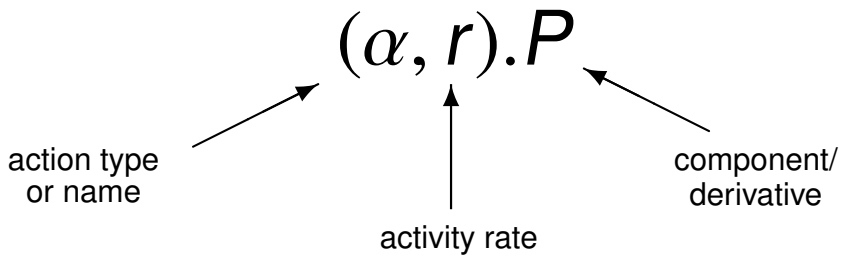

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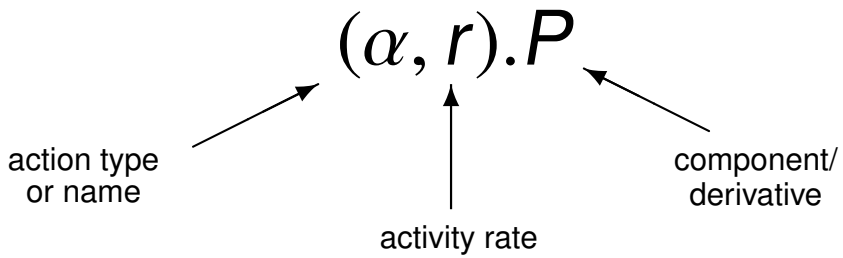

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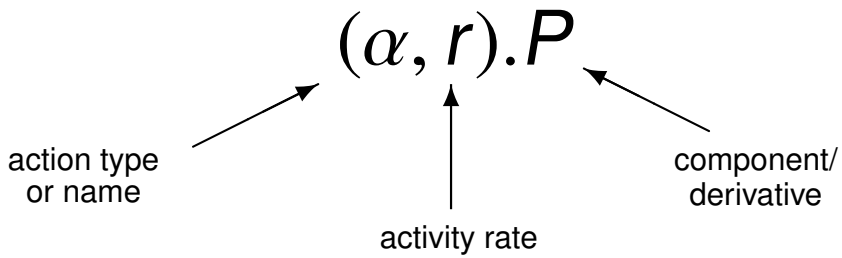

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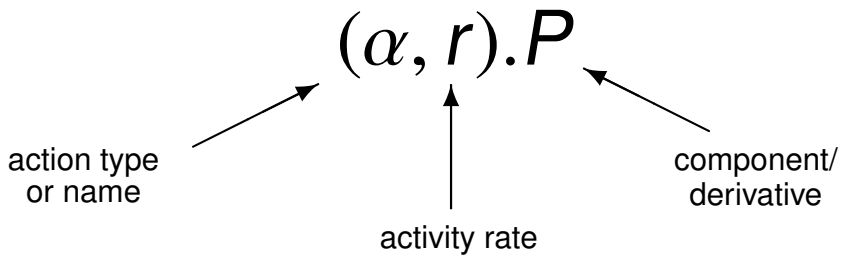

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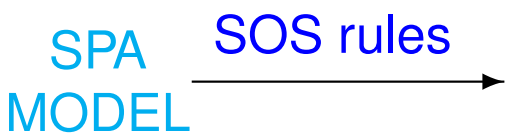

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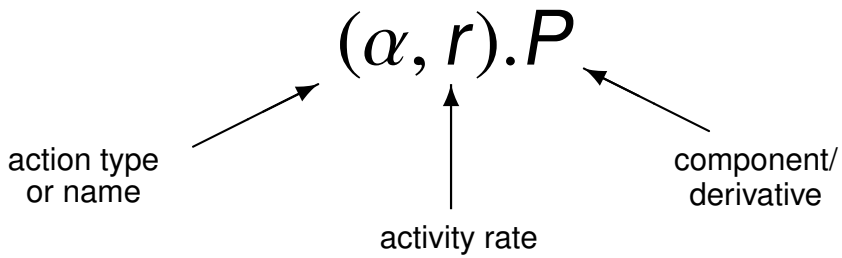

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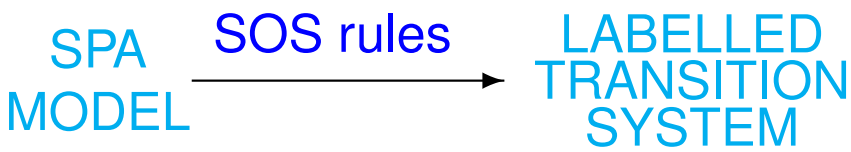

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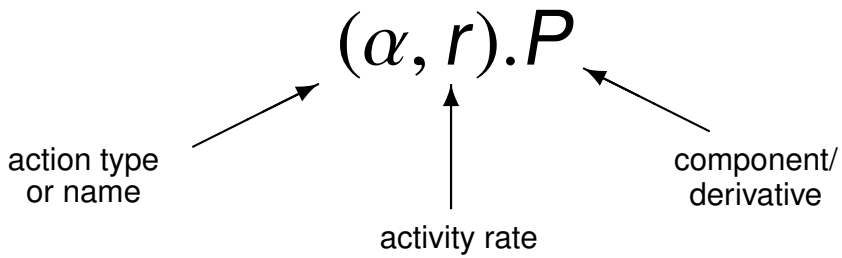

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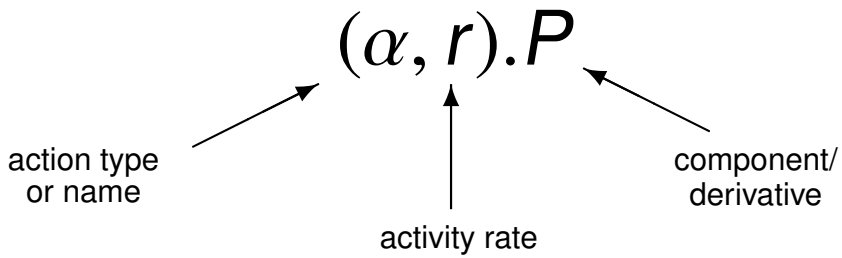

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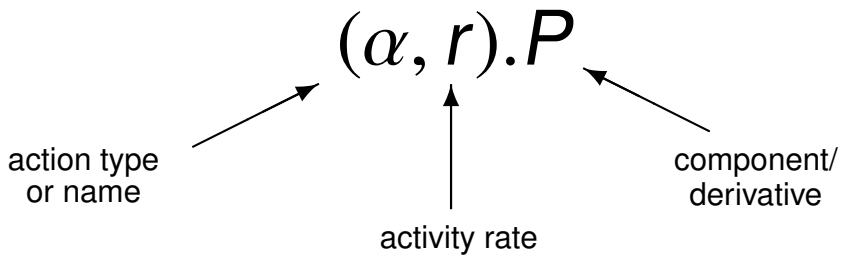

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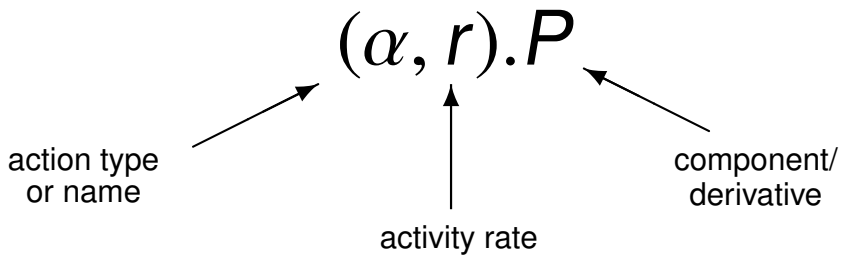

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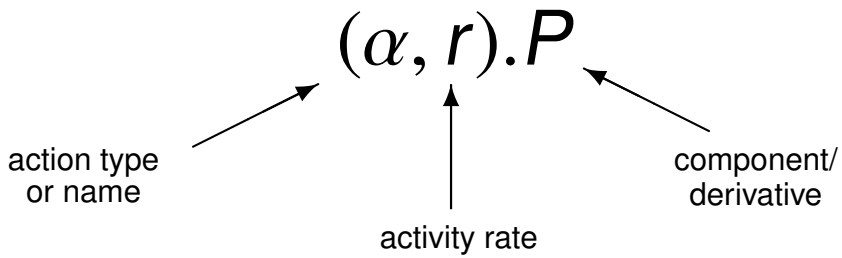

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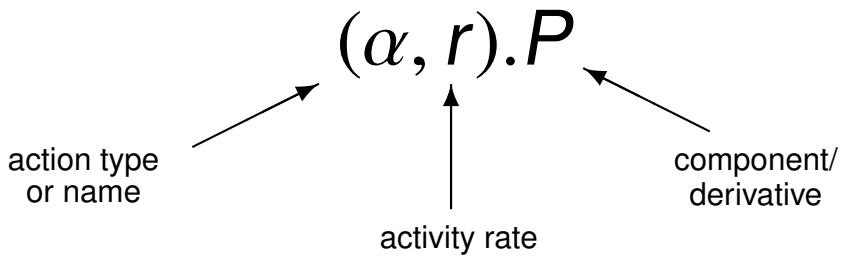

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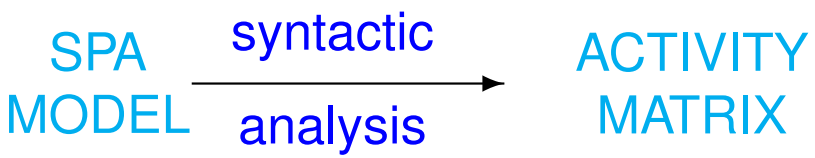

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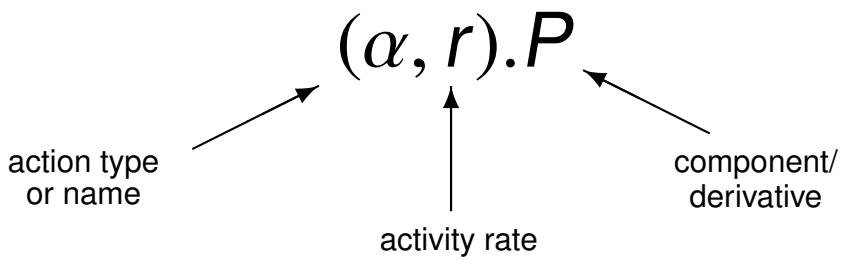

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SPA MODEL —syntactic analysis→ ACTIVITY MATRIX —continuous interpretation→

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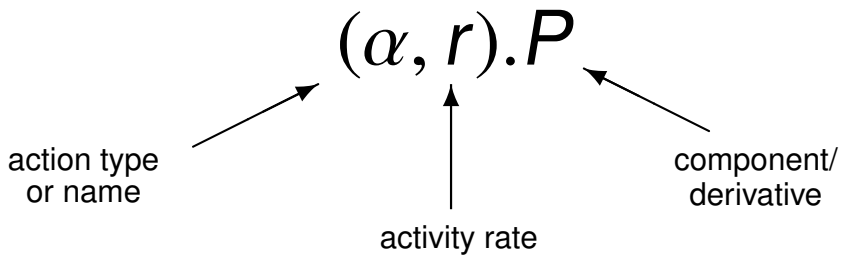

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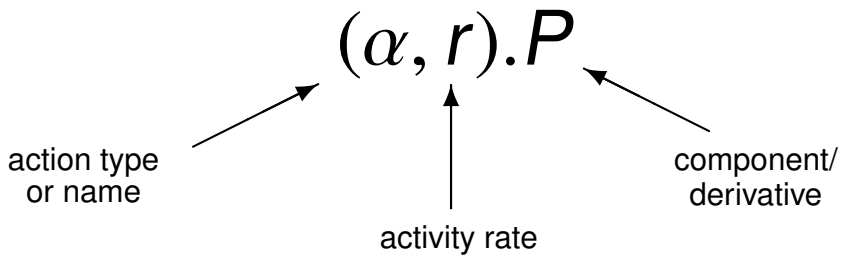

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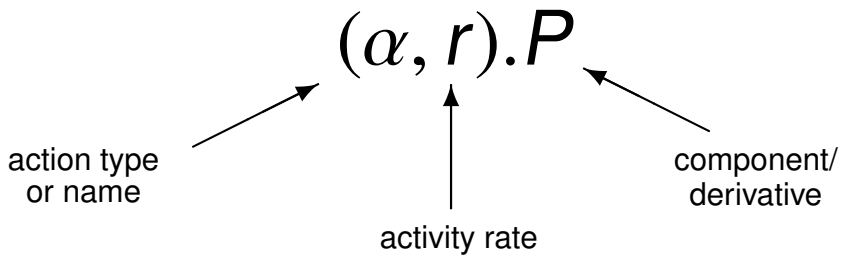

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SPA
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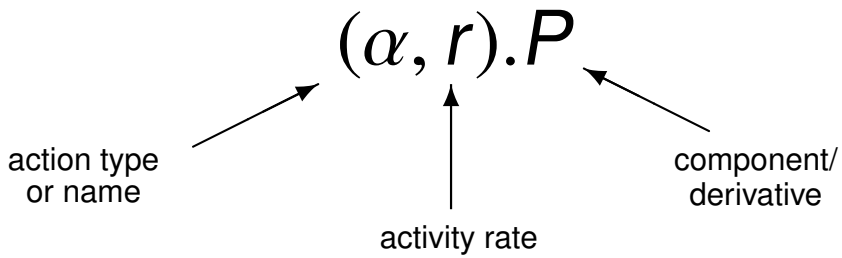

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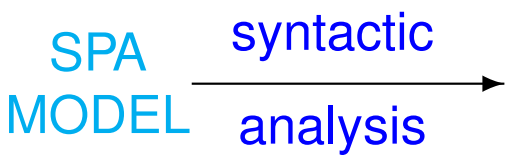

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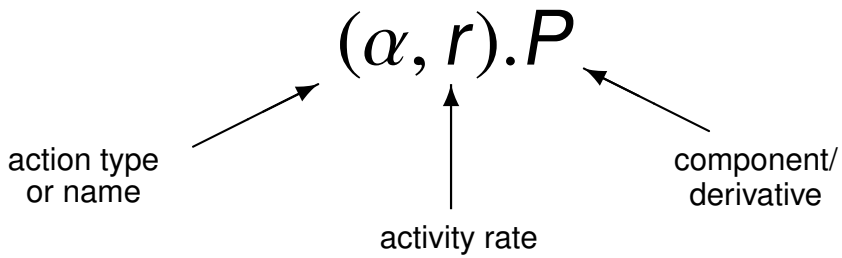

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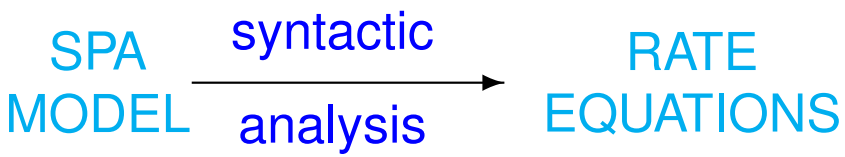

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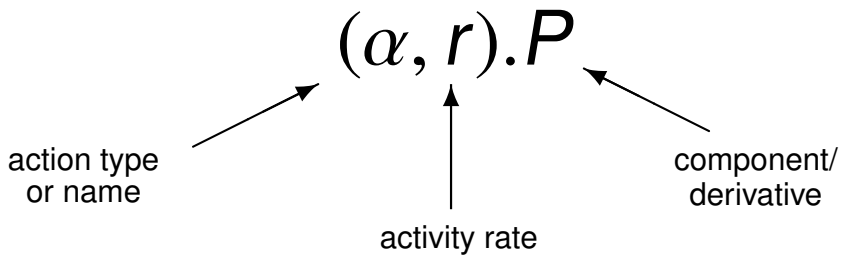

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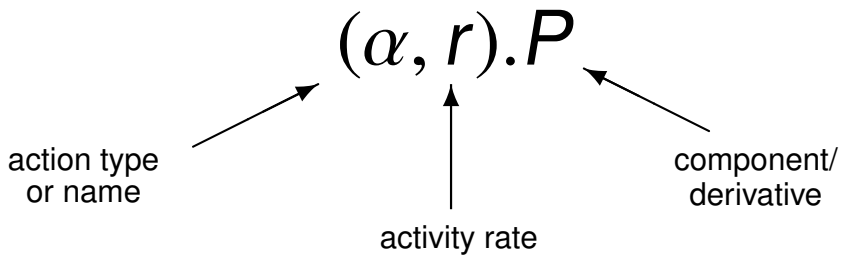

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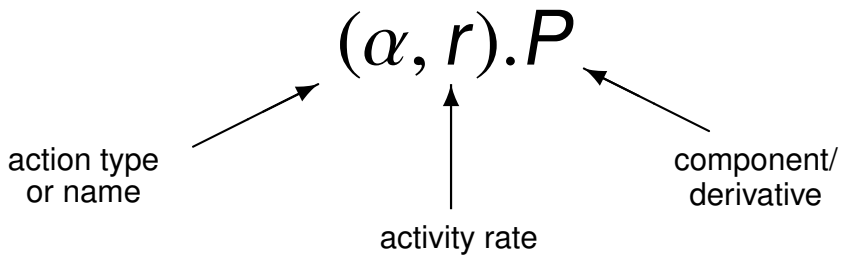

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- In models with levels, each level of granularity gives rise to a CTMC, and the behaviour of this sequence of Markov processes converges to the behaviour of the system of ODEs.
- Some analyses which can be carried out via numerical solution of the CTMC are not readily available from ODEs or stochastic simulation.

Outline

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- stoichiometry — the multiplicity in which an entity participates in a reaction;
- general kinetic laws — while mass action is widely used other kinetics are also commonly employed.
- multiway reactions — although thermodynamics arguments can be made that there are never more than two reagents involved in a reaction, in practice it is often useful to model at a more abstract level.

Illustration

Consider a conversion of a substrate S, with stoichiometry 2, to a product P which is under the influence of an enzyme E, i.e.

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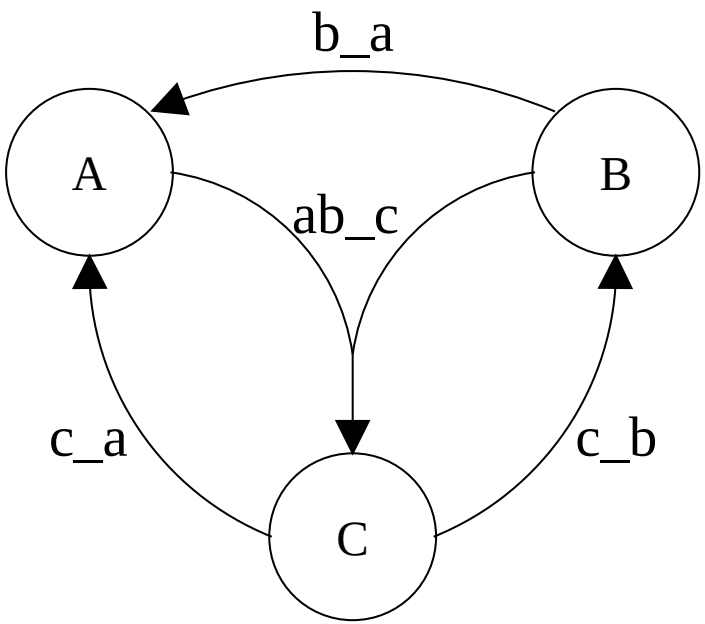
- The representation of an action within a component (species) records the stoichiometry of that entity with respect to that reaction. The role of the entity is also distinguished.
- Multi-way reactions are possible in Bio-PEPA since it has CSP-style synchronisation rather than CCS-style synchronisation. Thus a multi-way reaction is abstracted as a multi-syncronisation.

Reagent-centric modelling [CGH04]

Role	*Impact on reaction rate*	*Impact on reagent*
Reactant	positive impact, e.g. proportional to current concentration	decreases level
Product	no impact, except at saturation	increases level
Enzyme	positive impact, e.g. proportional to current concentration	level unchanged
Inhibitor	negative impact, e.g. inversely proportional to current concentration	level unchanged

Bio-PEPA reagent-centric example



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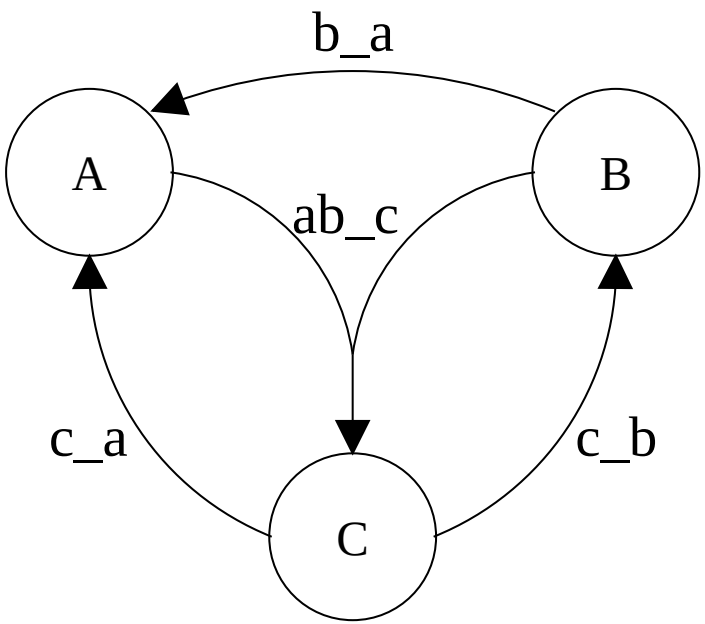

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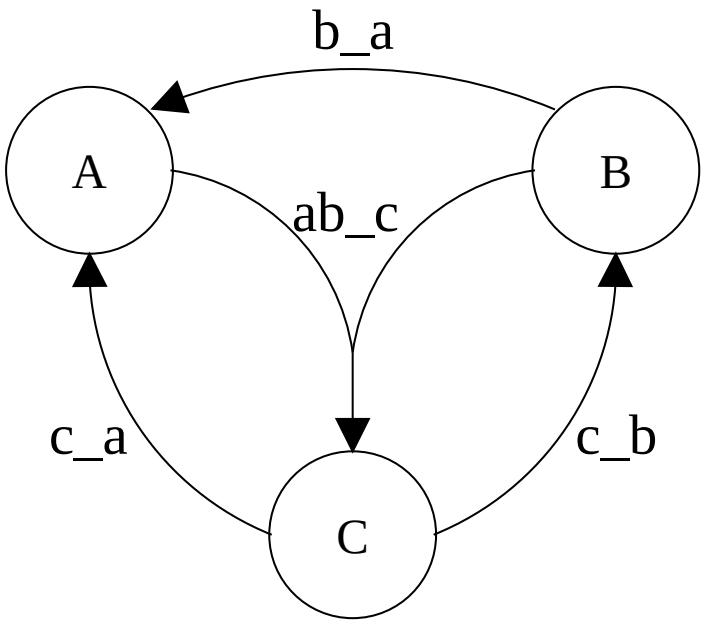

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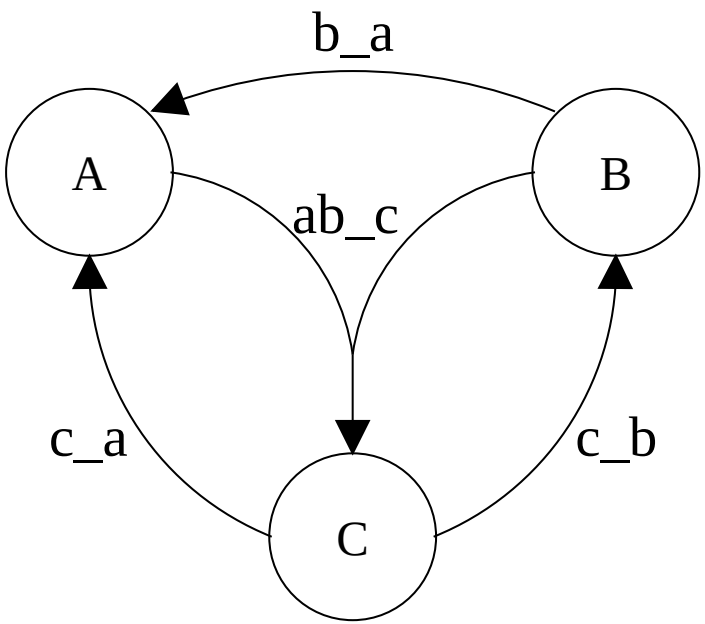

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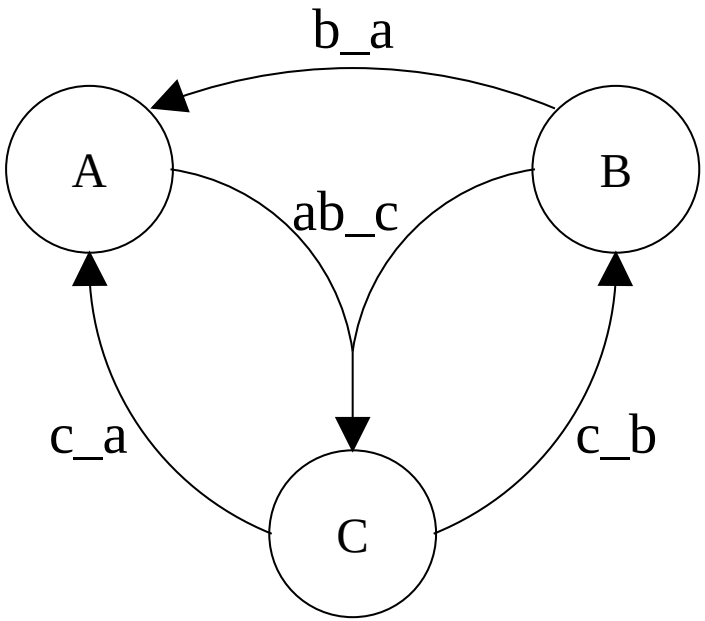

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- A component varying its state corresponds to it varying its concentration.
- This is captured by an integer parameter associated with the species and the effect of a reaction is to vary that parameter by a number of levels corresponding to the stoichiometry of this species in the reaction.

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- The form of the CTMC, which we term the CTMC with levels, will depend on the granularity of the model.
- As the granularity tends to zero the behaviour of this CTMC with levels tends to the behaviour of the ODEs. [CDHC08]

The syntax

Sequential component (species component)

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with $op = \odot, \oplus$, or $\ominus$

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$$\texttt{Constant} \quad \frac{S(l) \xrightarrow{(\alpha,S:[op(l,\kappa)])} S'(l')}{C(l) \xrightarrow{(\alpha,C:[op(l,\kappa)])} S'(l')} \quad \text{with } C \stackrel{def}{=} S$$

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$$\texttt{coopFinal} \quad \frac{P_1 \xrightarrow{(\alpha,v_1)} P_1' \quad P_2 \xrightarrow{(\alpha,v_2)} P_2'}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha,v_1 \,@\, v_2)} P_1' \underset{\mathcal{L}}{\bowtie} P_2'} \quad \text{with } \alpha \in \mathcal{L}$$

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The transition system and the CTMC are defined via the SOS.

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Binding of the inhibitor to the enzyme prevents binding of the substrate and vice versa.

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with functional rate

$$f_\alpha = f_{CI}((w, K_M, K_I), S, E, I) = \frac{w \times S \times E}{S + K_M(1 + \frac{I}{K_I})}$$

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From a biological perspective we are investigating the situations in which biologists regard models or elements of models to be equivalent, particularly when this is employed for model simplification.

Bisimulation

Definition

A binary relation $\mathcal{R} \subseteq \mathcal{C} \times \mathcal{C}$ is a strong bisimulation with respect to $\rightarrow_S$, if $(P, Q) \in \mathcal{R}$ implies for all $\alpha \in \mathcal{A}$:

- if $P \xrightarrow{\gamma_1}_S P'$ then, for some Q' and γ_2, $Q \xrightarrow{\gamma_2}_S Q'$ with $(P', Q') \in \mathcal{R}$ and
  1. $action(\gamma_1) = action(\gamma_2) = \alpha$
  2. $rate(\gamma_1) = rate(\gamma_2)$
- symmetric definition for $Q \xrightarrow{\gamma_2}_S Q'$

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Each of these kinds of analysis can be of help for studying different aspects of the biological model. Moreover we are exploring how they can be used in conjunction.

Outline

The biological model

Consider a genetic network with negative feedback through dimers.

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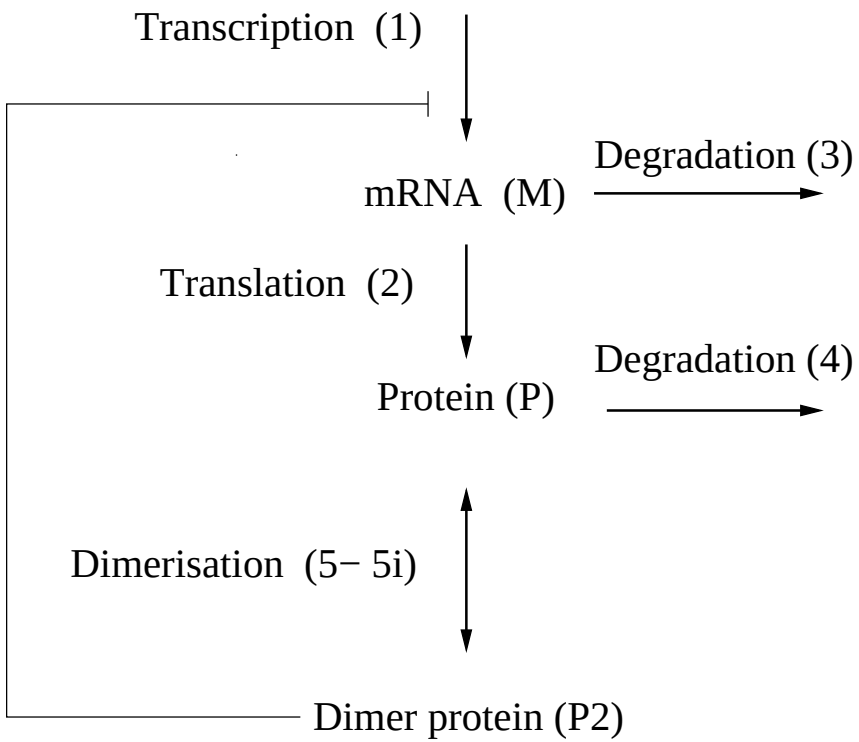

Simple genetic network model

The biological entities are:

- the *mRNA molecule* (*M*),
- the protein in monomer form (*P*) and
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All the reactions are described by mass action kinetics with the exception of the first reaction, that has an inhibition kinetics.

Translation into Bio-PEPA

Definition of the list $\mathcal{N}$

$$[M : N_M, M_M; \quad P : N_P, M_P; \quad P2 : N_{P2}, M_{P2}]$$

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Definition of functional rates

$$f_{\alpha_1} = fl((v, K_M), [P2, CF]) = \frac{v \times CF}{K_M + P2}$$

$$f_{\alpha_2} = fMA(k_2, [M]) \qquad f_{\alpha_3} = fMA(k_3, [M]) \qquad f_{\alpha_4} = fMA(k_4, [P])$$

$$f_{\alpha_5} = fMA(k_5, [P]) \qquad f_{\alpha_{5i}} = fMA(k_{5i}, [P2])$$

Translation into Bio-PEPA (cont.)

Definition of the system components

$$
\begin{array}{lcl}
\mathrm{M} & = & (\alpha_2,1) \oplus \mathrm{M} + (\alpha_3,1) \downarrow \mathrm{M} + (\alpha_1,1) \uparrow \mathrm{M}; \\
\mathrm{P} & = & (\alpha_4,1) \downarrow \mathrm{P} + (\alpha_5,2) \downarrow \mathrm{P} + (\alpha_{5i},2) \uparrow \mathrm{P}) + (\alpha_2,0) \uparrow \mathrm{P}; \\
\mathrm{P2} & = & (\alpha_1,1) \ominus \mathrm{P2} + (\alpha_{5i},1) \downarrow \mathrm{P2} + (\alpha_5,1) \uparrow \mathrm{P2}; \\
\mathrm{Res} & = & (\alpha_3,1) \odot \mathrm{Res} + (\alpha_4,1) \odot \mathrm{Res}; \\
\mathrm{CF} & = & (\alpha_1,1) \odot \mathrm{CF};
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Definitions of the system

$$((((CF(1) \underset{\{\alpha_1\}}{\bowtie} M(0)) \underset{\{\alpha_2\}}{\bowtie} P(0)) \underset{\{\alpha_5,\alpha_{5i}\}}{\bowtie} P2(0)) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} Res(0)$$

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For **2 levels**, the CTMC consists of **8 states** and **18 transitions**.

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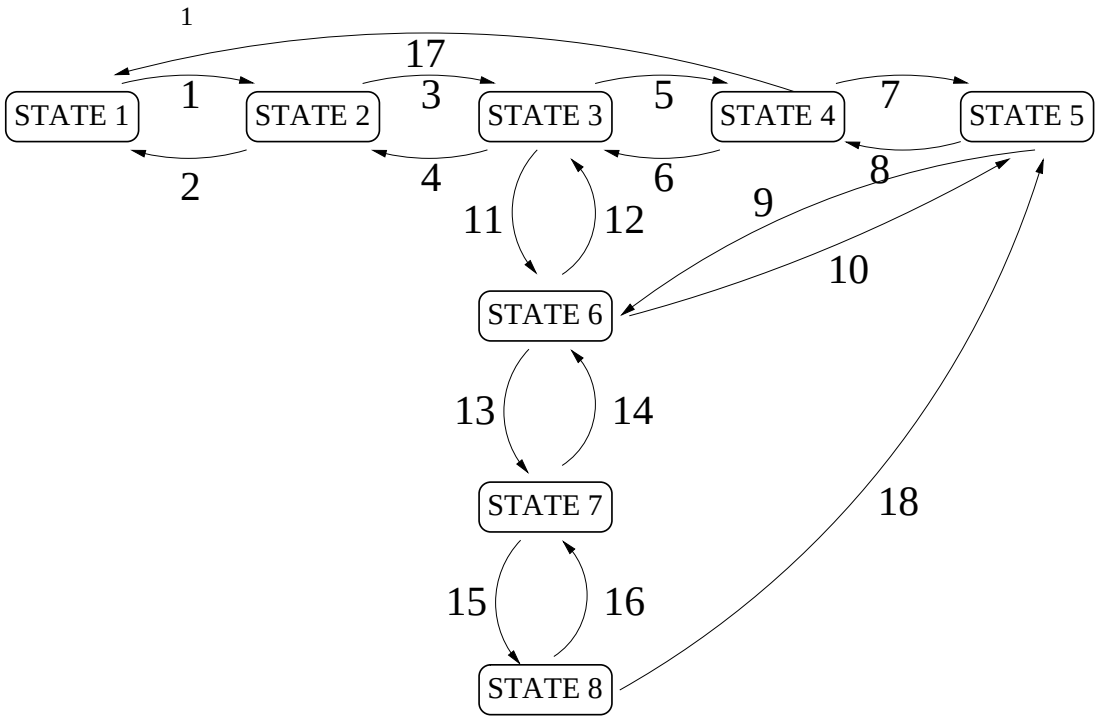

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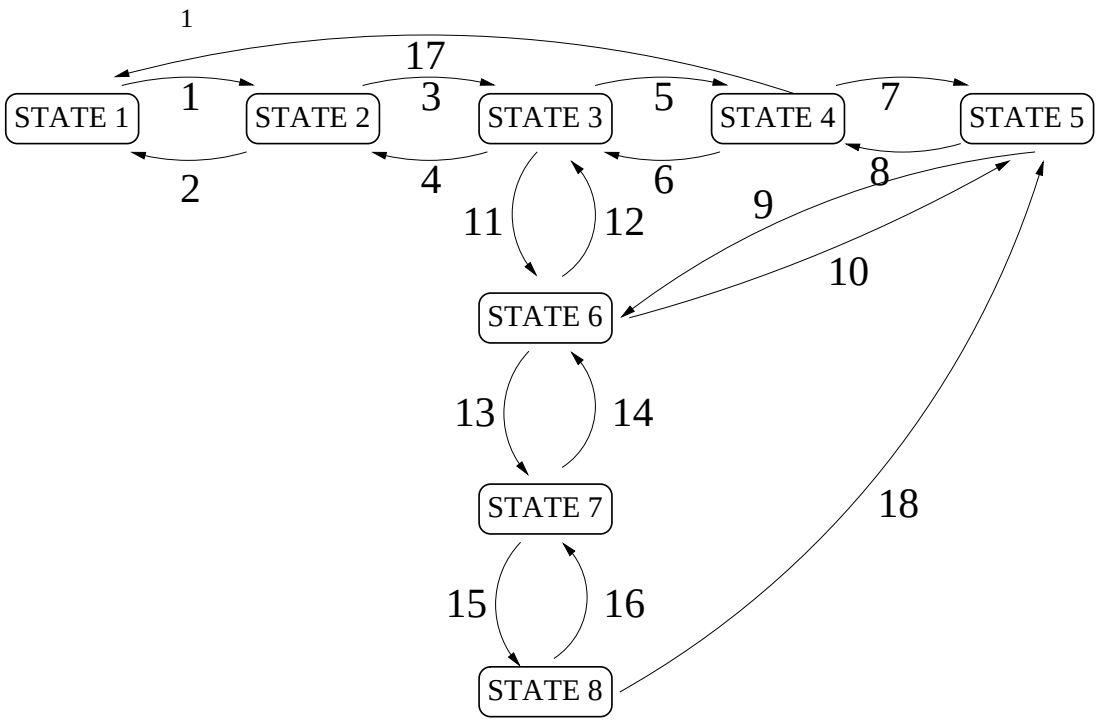

States are $(CF(l_1), M(l_2), P(l_3), P2(l_4), RES(l_5))$, with levels $l_1 \ldots l_5$.

Derivation of ODEs and Gillespie model

The stoichiometry matrix D associated with the system is

	R1	R2	R3	R4	R5	R6	
CF	0	0	0	0	0	0	x_{CF}
Res	0	0	0	0	0	0	x_{Res}
M	+1	0	-1	0	0	0	x_1
P	0	+1	0	-1	-2	+2	x_2
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P	0	+1	0	-1	-2	+2	x_2
P2	0	0	0	0	+1	-1	x_3

The kinetic law vector is

$$w^T = (\frac{v \times x_{CF}}{K + x_3};\quad k_2 \times x_1; k3 \times x_1;\quad k4 \times x_2;\quad k5 \times {x_2}^2;\quad ki5 \times x_3)$$

Derivation of ODEs (2)

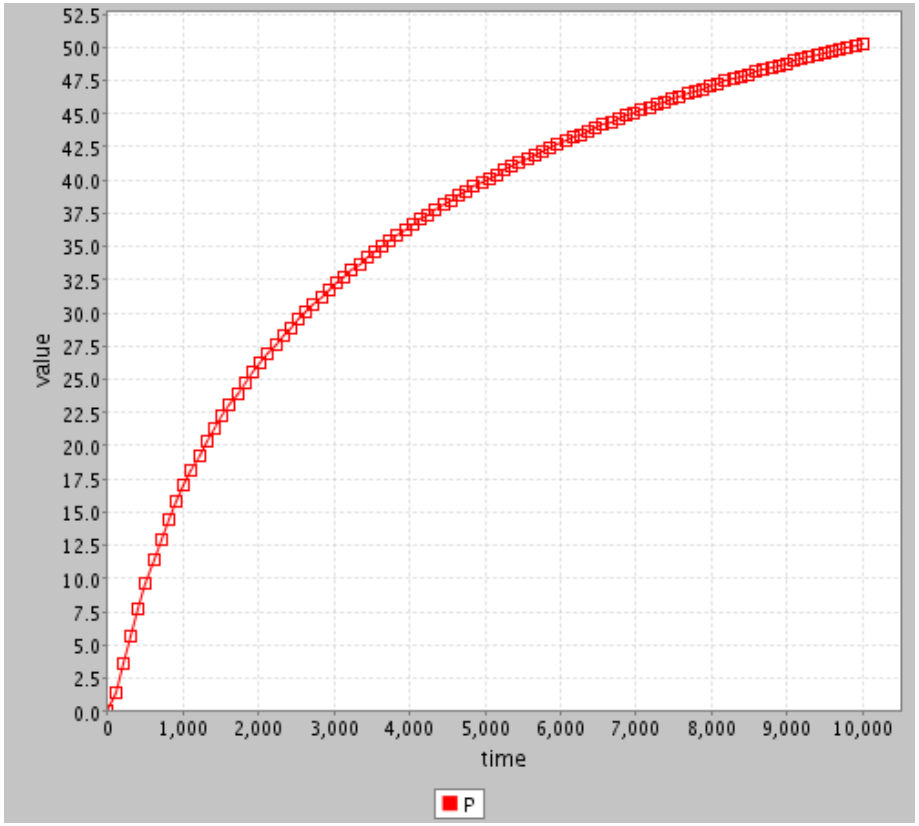
The system of ODEs is obtained as $\frac{d\bar{x}}{dt} = D \times w$:

$$\begin{aligned}
\frac{dx_1}{dt} &= \frac{v \times 1}{K + x_3} - k3 \times x_1 \\
\frac{dx_2}{dt} &= k2 \times x_1 - k4 \times x_2 - 2 \times k5 \times {x_2}^2 + 2 \times ki5 \times x_3 \\
\frac{dx_2}{dt} &= k5 \times {x_2}^2 - ki5 \times x_3
\end{aligned}$$

Derivation of Gillespie model

The derivation of the Gillespie model is made by creating molecules corresponding to each species and defining the possible reactions with appropriate adjustment of kinetic rates.

Simulation results



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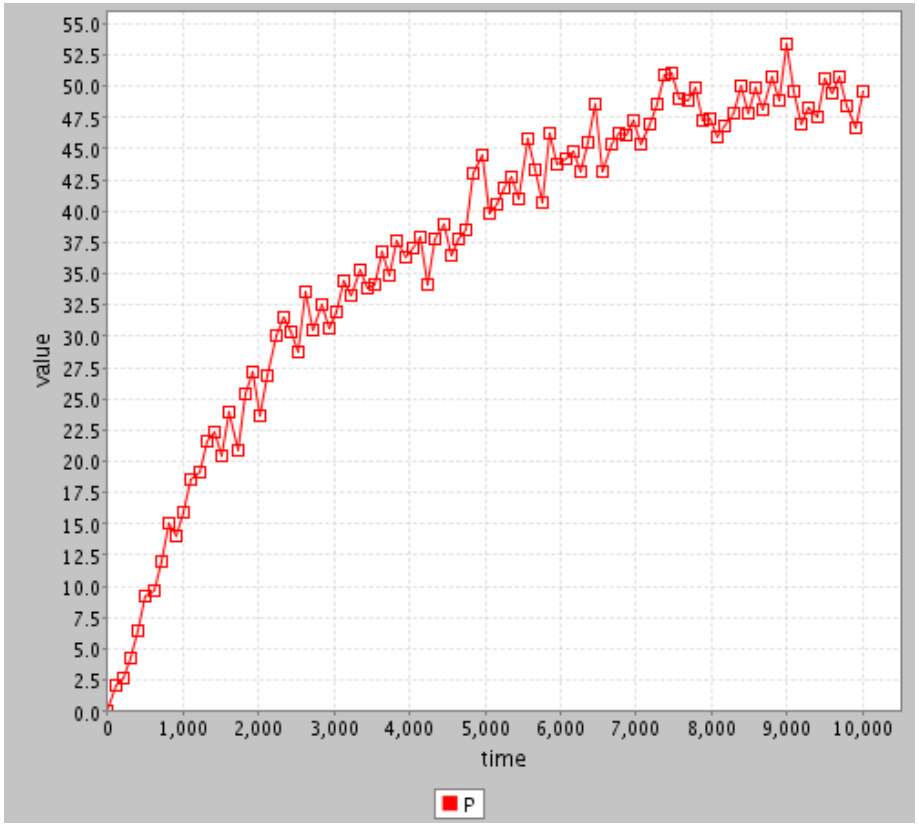

Stochastic simulation results (10 runs)

PRISM model

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For example, the protein is represented as:

module p
$p : [0..Np]$ **init** 0;
$[a2]p < Np \rightarrow (p' = p + 1)$;
$[a4]p > 0 \rightarrow (p' = p - 1)$;
$[a5]p > 0 \rightarrow (p' = p - 2)$;
$[a5i]p < Np \rightarrow (p' = p + 2)$;
endmodule

PRISM model (2)

An additional (dummy) module is needed to capture the kinetic rates.

module Functional_rates
dummy: bool **init** true;
$[a1]dummy = true \rightarrow \frac{v}{(1+(p2/k))} : (dummy' = dummy);$
$[a2]dummy = true \rightarrow r2 : (dummy' = dummy);$
$[a3]dummy = true \rightarrow r3 : (dummy' = dummy);$
$[a4]dummy = true \rightarrow r4 : (dummy' = dummy);$
$[a5]dummy = true \rightarrow r5 : (dummy' = dummy);$
$[a5i]dummy = true \rightarrow r5i : (dummy' = dummy);$
endmodule

PRISM analysis

- **Proportion of monomer P in total P (in terms of levels)**.
  We need to define a reward structure in the PRISM file as:

  rewards
  $true : \frac{p}{(p+p2)};$
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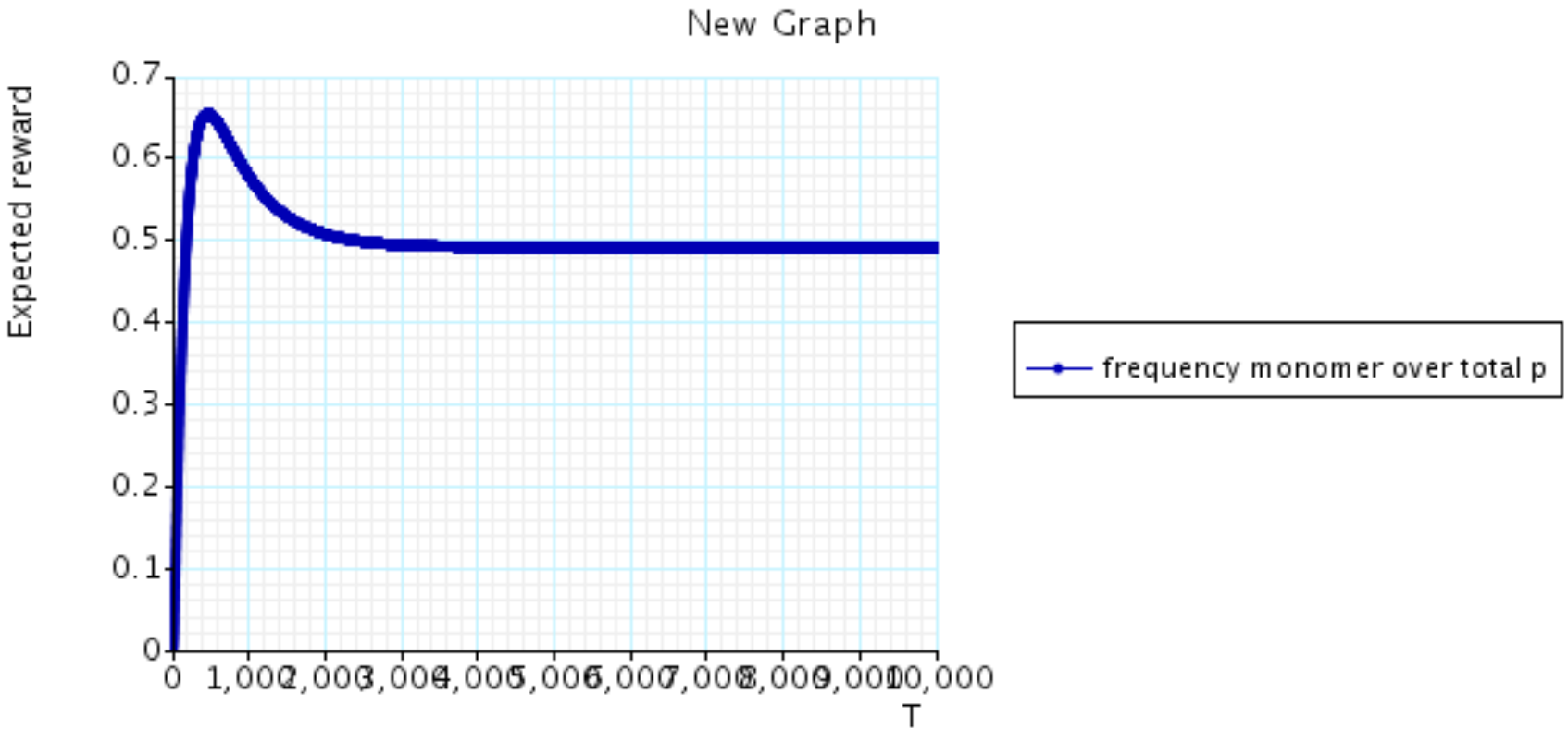
- **Probability that P is at level i at time T**

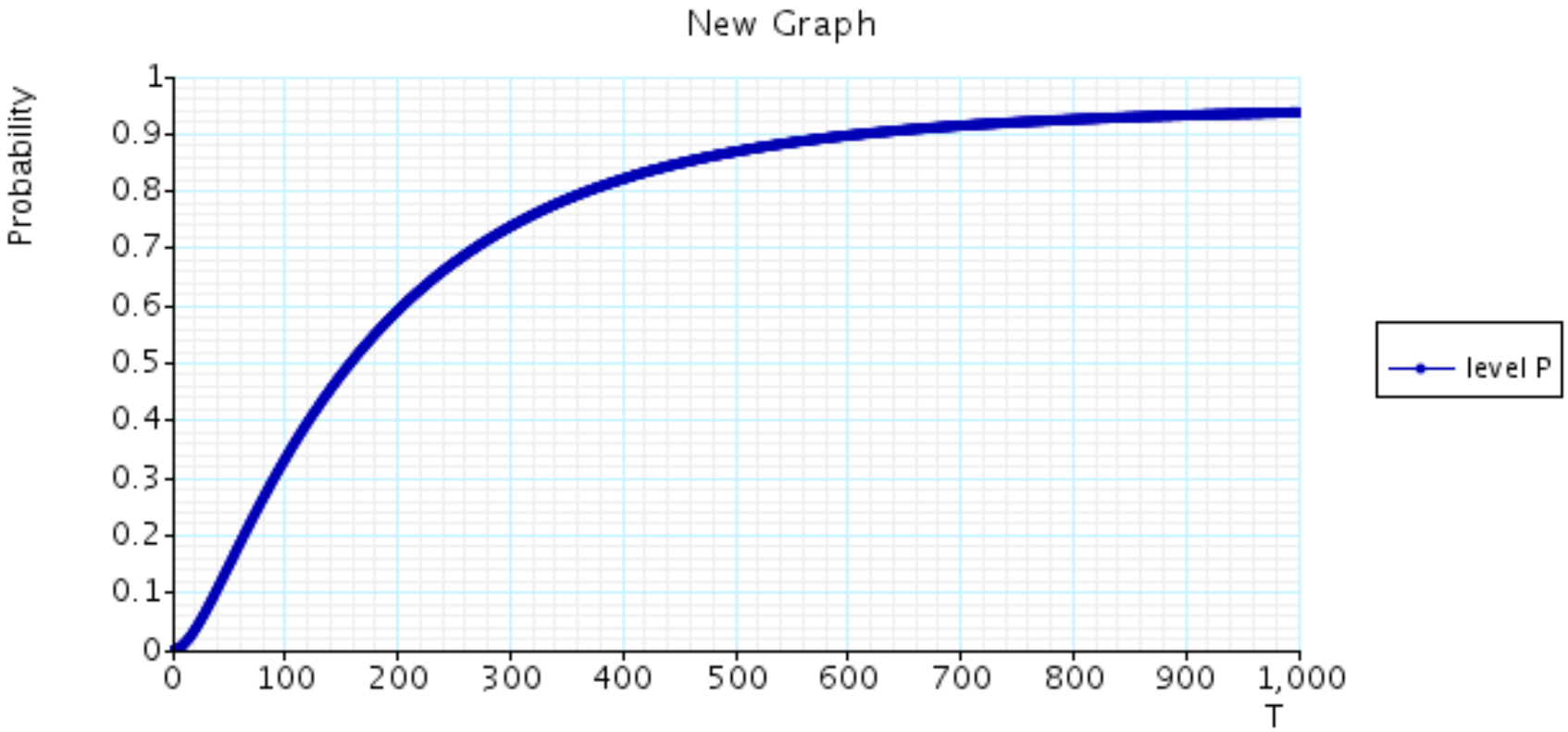
  $$P =?[trueU[T, T]p = i]$$

PRISM results



monomer frequency

PRISM results



Probability monomer protein is at high level over time

Goldbeter's model [Goldbeter 91]

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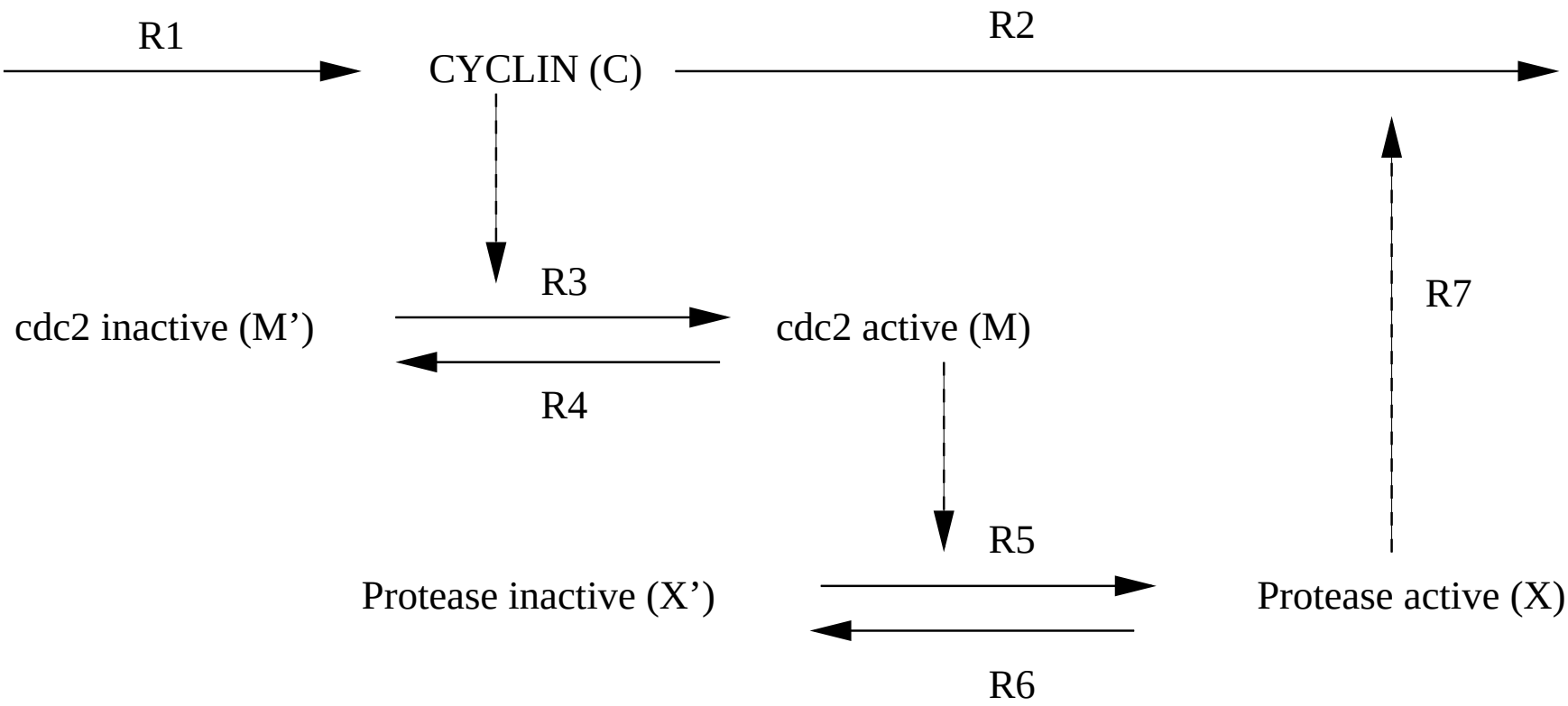
- This protease promotes cyclin degradation.
- This leads to a negative feedback loop.
- In the model most of the kinetic laws are of kind Michaelis-Menten and this can be reflected in the Bio-PEPA model

The biological model



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- cyclin protease, in both active (i.e. phosphorylated) and inactive form (i.e. dephosphorylated). The variable are X and X'.

Reactions

id	desc.	react.	prod.	mod.	kinetic laws
R1	creation of cyclin	-	C	-	vi
R2	degradation of cyclin	C	-	-	$kd \times C$
R3	activation of cdc2 kinase	M'	M	-	$\frac{C*V_{M1}}{(K_c+C)} \frac{M'}{(K_1+M')}$
R4	deactivation of cdc2 kinase	M	M'	-	$\frac{M \times V_2}{(K_2+M)}$
R5	activation of cyclin protease	X'	X	M	$\frac{X' \times M \times V_{M3}}{(K_3+X')}$
R6	deactivation of cyclin protease	X	X'	-	$\frac{X \times V_4}{K_4+X}$
R7	X triggered degradation of cyclin	C	-	X	$\frac{C \times v_d \times X}{C+K_d}$

R1 and R2 have Mass-Action kinetics, whereas all others are Michaelis-Menten.

The Bio-PEPA model

Definition of the list $\mathcal{N}$:.

$$\mathcal{N} = [Res : 0, 1;\ CF : 1, 1;\ C : M_C, N_c;\ M : M_M, N_M;\ M' : M_{M'}, N_{M'};\ X : M_X, N_X;\ X' : M_{X'}, N_{X'}] \quad (1)$$

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Res and *CF* represent degradation and synthesis respectively.

Definition of functional rates ($\mathcal{F}$:)

$$f_{\alpha_1} = fMA(v_i); \qquad f_{\alpha_2} = fMA(k_d);$$

$$f_{\alpha_3} = fMM'((V_1, K_c, K_1), M', C) = \frac{v_1 \times C}{K_c + C} \frac{M'}{K1 + M'};$$

$$f_{\alpha_4} = fMM(V_2, K_2); \qquad f_{\alpha_5} = fMM(V_3, K_3);$$

$$f_{\alpha_6} = fMM(V_4, K_4); \qquad f_{\alpha_7} = fMM(V_d, K_d);$$

The Bio-PEPA model (2)

Definition of species components (*Comp*):

$$
\begin{array}{lcl}
C & = & (\alpha_1, 1)\uparrow C + (\alpha_2, 1)\downarrow C + (\alpha_7, 1)\downarrow C + (\alpha_3, 1) \oplus C; \\
M' & = & (\alpha_4, 1)\uparrow M' + (\alpha_3, 1)\downarrow M'; \\
M & = & (\alpha_3, 1)\uparrow M + (\alpha_4, 1)\downarrow M + (\alpha_5, 1) \oplus M; \\
X' & = & (\alpha_6, 1)\uparrow X' + (\alpha_5, 1)\downarrow X'; \\
X & = & (\alpha_5, 1)\uparrow X + (\alpha_6, 1)\downarrow X + (\alpha_7, 1) \oplus X; \\
Res & = & (\alpha_2, 1) \odot Res; \quad CF = (\alpha_1, 1) \odot CF;
\end{array}
$$

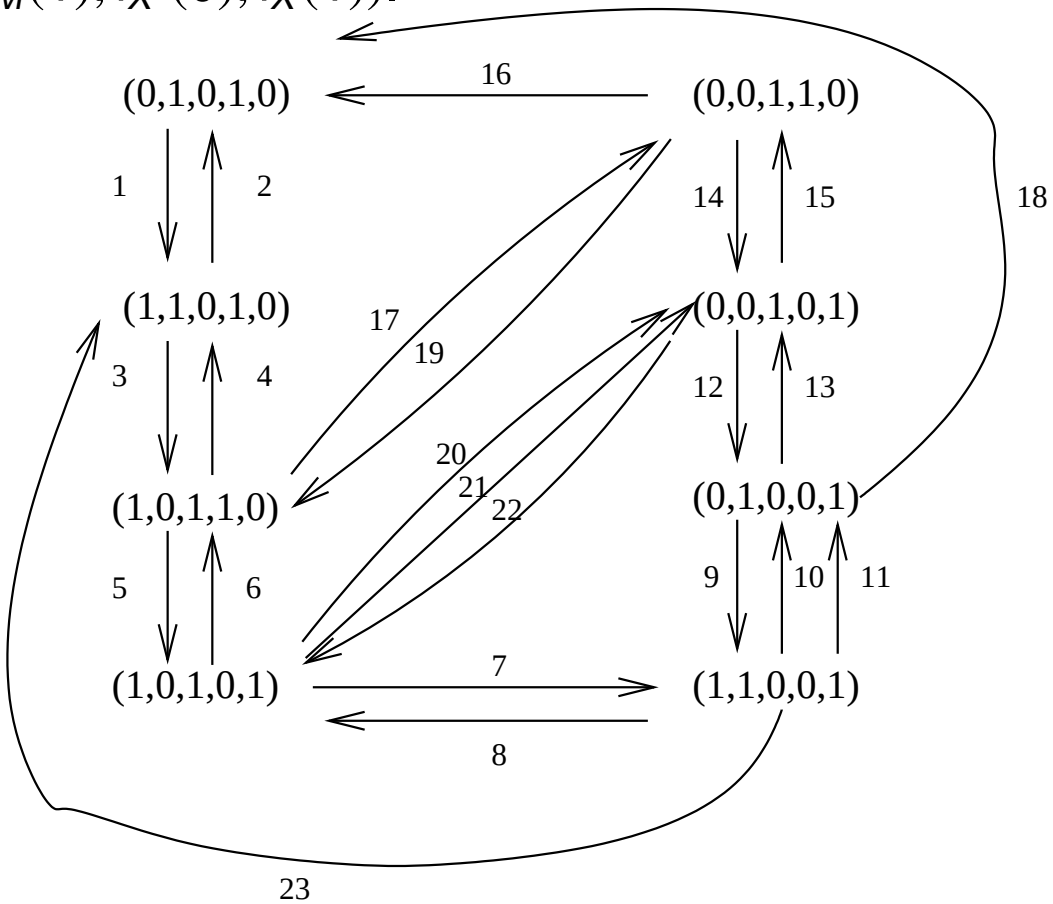
Definition of the model component (*P*):

$$
C(l_{0C}) \underset{\{\alpha_3\}}{\bowtie} M(l_{0M}) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} M'(l_{0M'}) \underset{\{\alpha_5,\alpha_7\}}{\bowtie} X(l_{0X}) \underset{\{\alpha_5,\alpha_6\}}{\bowtie} X'(l_{0X'})
$$

$$
\underset{\{\alpha_2\}}{\bowtie} Deg(0) \underset{\{\alpha_1\}}{\bowtie} CF(1)
$$

Analysis

Assume two levels for each species and the initial state $(l_C(1), l_{M'}(0), l_M(1), l_{X'}(0), l_X(1))$.



ODEs

The stoichiometry matrix D:

	R1	R2	R3	R4	R5	R6	R7	
C	+1	0	0	0	0	0	-1	x_C
M'	0	0	-1	+1	0	0	0	$x_{M'}$
M	0	0	+1	-1	0	0	0	x_M
X'	0	0	0	0	-1	+1	0	$x_{X'}$
X	0	0	0	0	+1	-1	0	x_X

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M'	0	0	-1	+1	0	0	0	$x_{M'}$
M	0	0	+1	-1	0	0	0	x_M
X'	0	0	0	0	-1	+1	0	$x_{X'}$
X	0	0	0	0	+1	-1	0	x_X

The vector that contains the kinetic laws is:

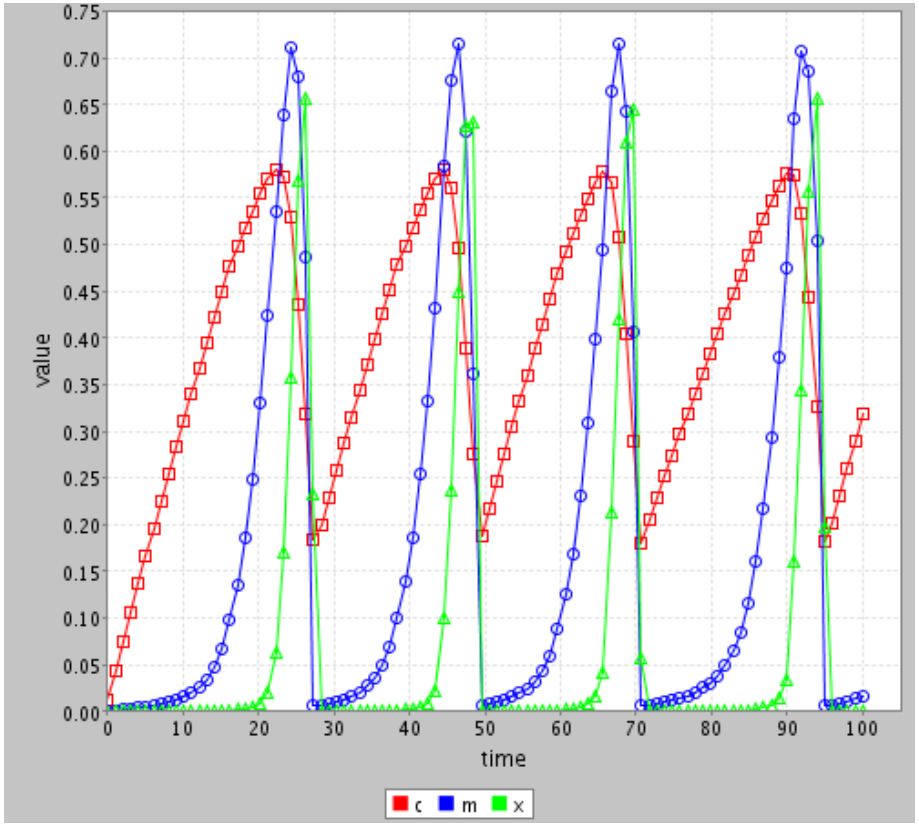
$$w = \Big(v_i \times 1, k_d \times x_C, \frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})}, \frac{V_2 \times x_M}{(K_2 + x_M)}, \frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})}, \frac{V_4 \times x_X}{(K_4 + x_X)}, \frac{v_d \times x_C \times x_X}{(K_d + x_C)}\Big)$$

ODEs (2)

The system of ODEs is obtained as $\frac{d\bar{x}}{dt} = D \times w$, where $\bar{x}^T =: (x_C, x_{M'}, x_M, x_{X'}, x_X)$ is the vector of the species variables:

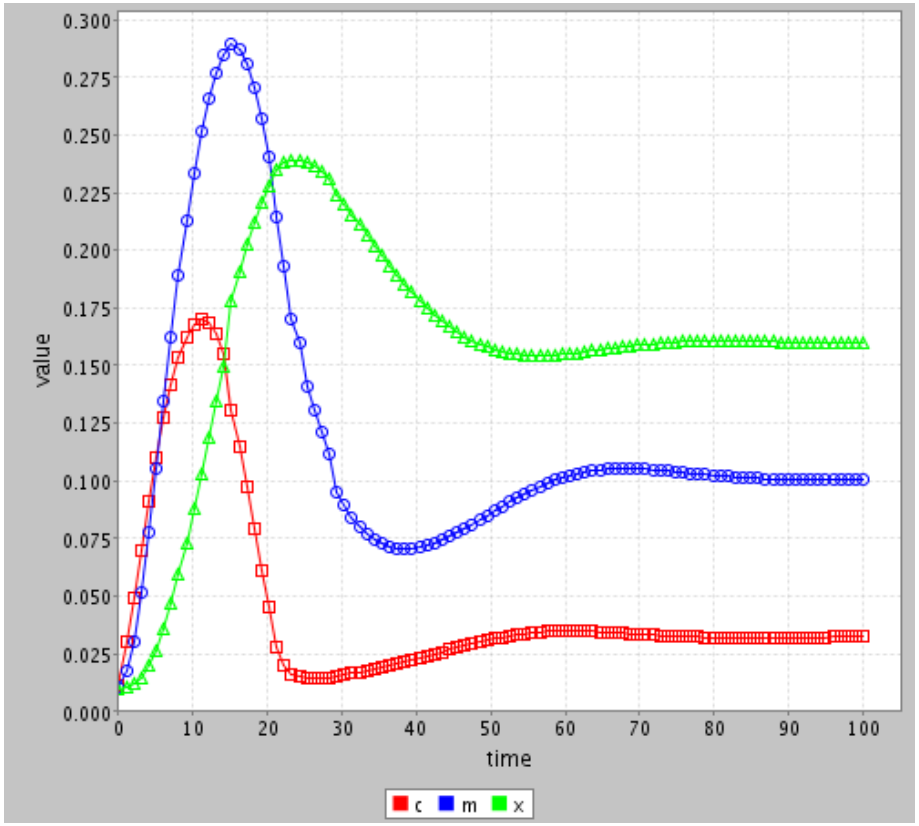
$$
\begin{aligned}
\frac{dx_C}{dt} &= v_i \times 1 - k_d \times x_C - \frac{v_d \times x_C \times x_X}{(K_d + x_C)} \\
\frac{dx_{M'}}{dt} &= -\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} + \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_M}{dt} &= +\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} - \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_{X'}}{dt} &= -\frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})} + \frac{V_4 \times x_X}{(K_4 + x_X)} \\
\frac{dx_X}{dt} &= \frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})} - \frac{V_4 \times x_X}{(K_4 + x_X)}
\end{aligned}
$$

ODE results



$$K_1 = K_2 = K_3 = K_4 = 0.02\mu M$$

ODE results



$$K_1 = K_2 = K_3 = K_4 = 40\mu M$$

Extended model

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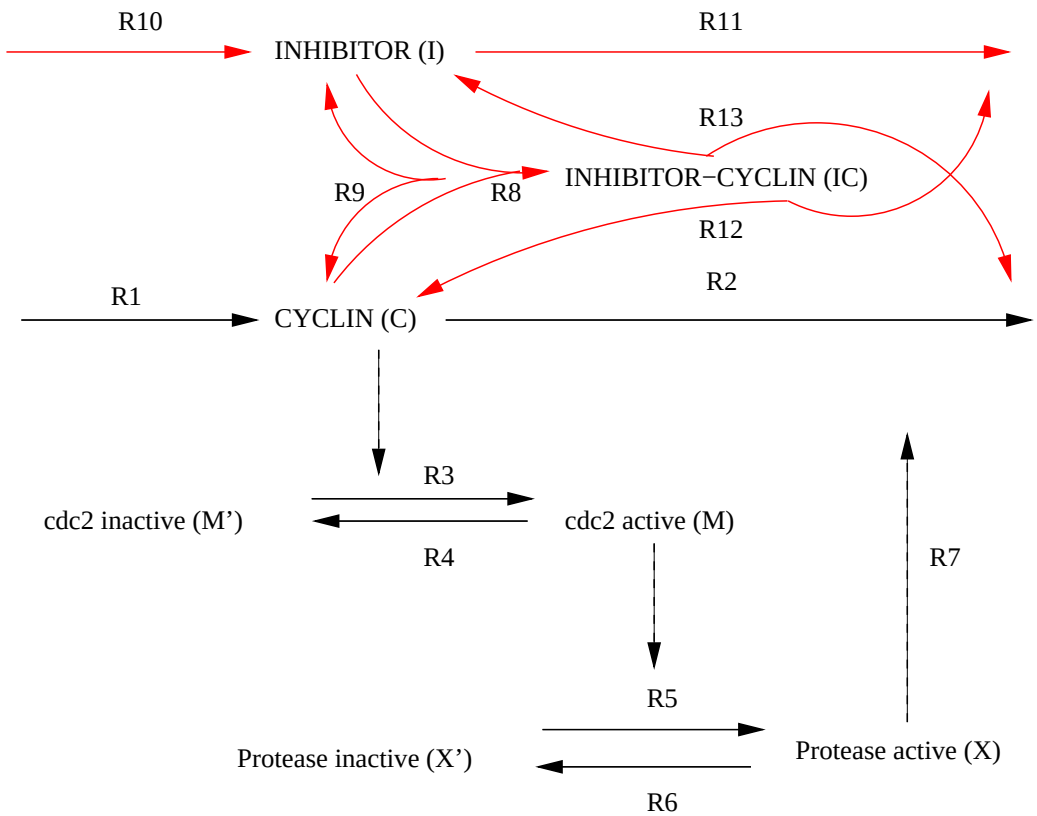
Several possible extension were presented; we consider one of them.

Extension of Goldbeter's model



Extended Bio-PEPA model

$$
\begin{aligned}
C &= \cdots + (\alpha_8, 1)\downarrow C + (\alpha_9, 1)\uparrow C + (\alpha_{12}, 1)\uparrow C; \\
&\vdots \qquad\qquad \vdots \\
Res &= \cdots + (\alpha_{11}, 1) \odot Res; \quad CF = \cdots + (\alpha_{10}, 1) \odot CF; \\
I &= (\alpha_8, 1)\downarrow I + (\alpha_9, 1)\uparrow I + (\alpha_{10}, 1)\uparrow I + (\alpha_{11}, 1)\downarrow I + (\alpha_{13}, 1)\uparrow I; \\
IC &= (\alpha_8, 1)\uparrow IC + (\alpha_9, 1)\downarrow IC + (\alpha_{12}, 1)\downarrow IC + (\alpha_{13}, 1)\downarrow IC;
\end{aligned}
$$

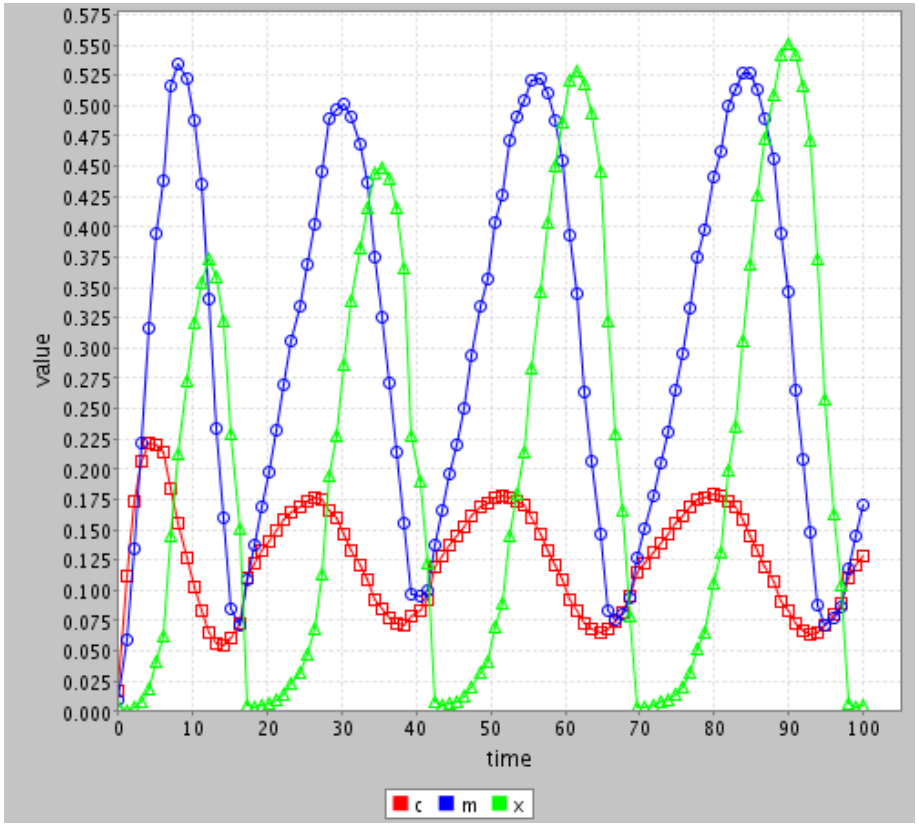
New functional rates

$$
\begin{aligned}
f_{\alpha_8} &= v_s; \\
f_{\alpha_9} &= fMA(d_1); \\
f_{\alpha_{10}} &= fMA(a_1); \\
f_{\alpha_{11}} &= fMA(a_2); \\
f_{\alpha_{12}} &= fMA(\theta \times d_1); \\
f_{\alpha_{13}} &= fMA(\theta \times k_d)
\end{aligned}
$$

Complete Bio-PEPA model

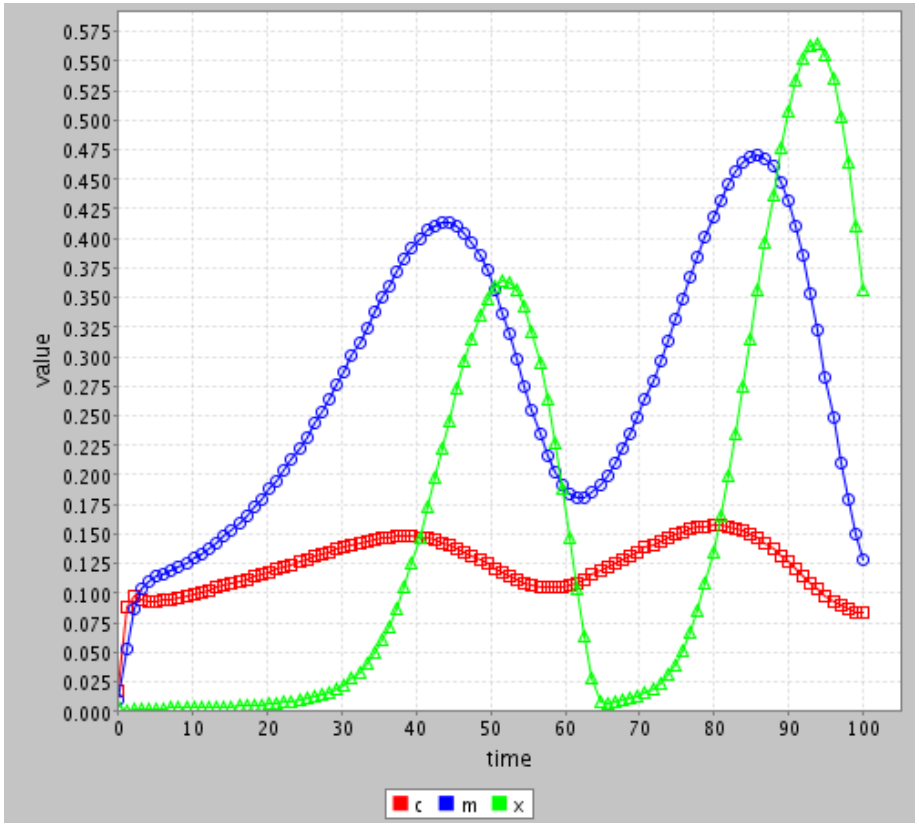
$$C(l_{0C}) \underset{\{\alpha_3\}}{\bowtie} M(l_{0M}) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} M'(l_{0M'}) \underset{\{\alpha_5,\alpha_7\}}{\bowtie} X(l_{0X}) \underset{\{\alpha_5,\alpha_6\}}{\bowtie} X'(l_{0X'}) \underset{\{\alpha_2\}}{\bowtie}$$
$$Deg(0) \underset{\{\alpha_1\}}{\bowtie} CF(1)$$
$$\underset{\{\alpha_8,\alpha_9,\alpha_{10},\alpha_{11}\}}{\bowtie} I(l_{0I}) \underset{\{\alpha_8,\alpha_9,\alpha_{12},\alpha_{13}\}}{\bowtie} IC(l_{0IC})$$

New ODE results



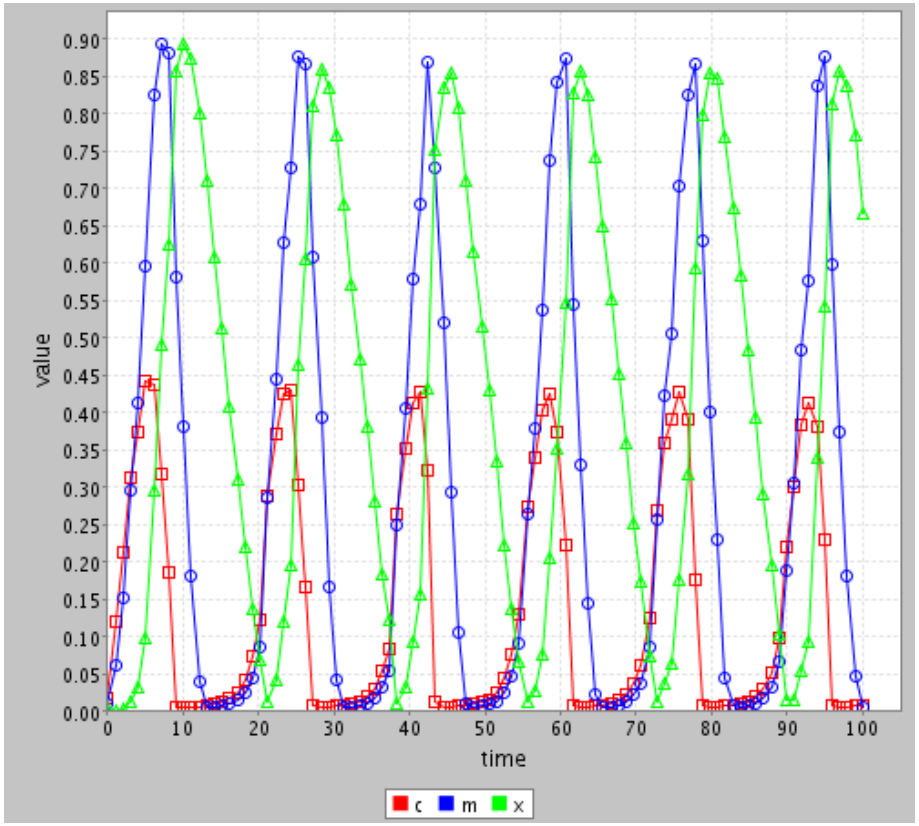
$a_1 = a_2 = 0.3$ and $v_s = 0.6$

New ODE results



$a_1 = a_2 = 0.7$ and $v_s = 1.4$

New ODE results



$a_1 = a_2 = 0.05$ and $v_s = 0.1$

Outline

Conclusion: SPA for Systems Biology

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However, such molecular mappings typically generate state spaces which are too large for other SPA analysis techniques.

Conclusions: Bio-PEPA

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Bio-PEPA allows us to represent explicitly features of biological networks, such as stoichiometry and general kinetic laws.

Moreover the reagent-centric, abstract style of modelling supports an integrative approach in which several different approaches to analysis may be applied to the same model.

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Moveover we can undertake additional analysis based on the discretised population view.

The abstract Markovian models allow quantities of interest such as "response times" to be expressed as probability distributions rather than single estimates. This may allow better reflection of wet lab data which also shows variability.

Future directions

There are number of areas for on-going and future work. For example:

- The definition of bisimulations and equivalences.
- The extent to which the process algebra compositional structure can be exploited during model analysis, particularly in conjunction with model checking techniques.
- The issue of coping with unknown and uncertain values in experimental data.
- *...and many more...*

Acknowledgements

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Thank you