Calculi for Biological Systems

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University of Edinburgh

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Outline

- Process Calculi
  - SPA
- SPA for Systems Biology
- Bio-PEPA
  - Model definition
  - The syntax and semantics
  - Equivalences and Analysis
- Examples
  - Genetic network with negative feedback loop
  - Goldbeter's model
- Conclusions

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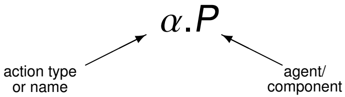
Process Algebra

- Models consist of agents which engage in actions.



$\alpha.P$

action type or name

agent/ component

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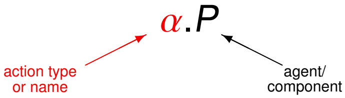

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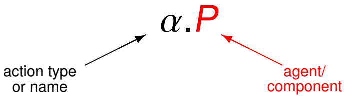

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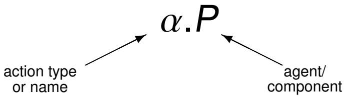

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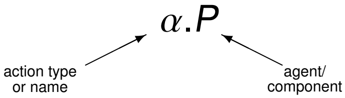

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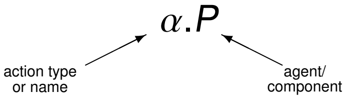

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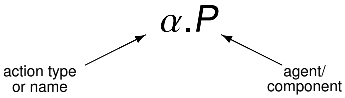

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Example

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:

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

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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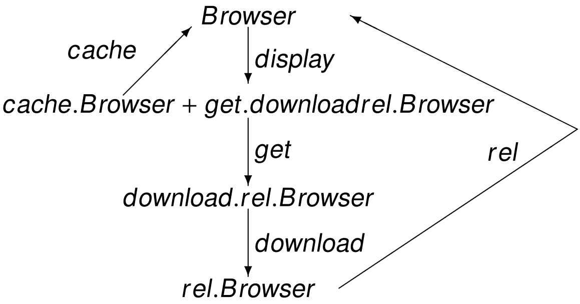

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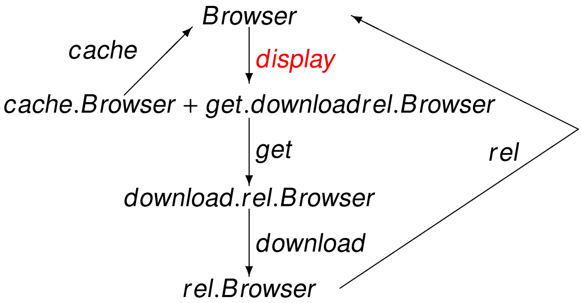

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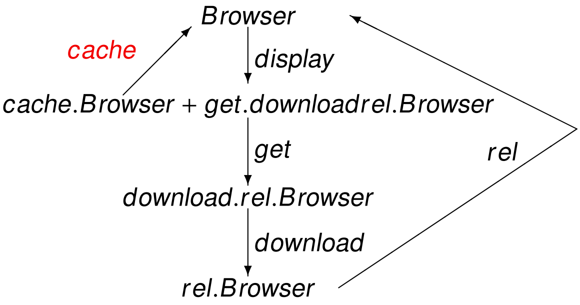

Browser

cache

display

cache.Browser + get.downloadrel.Browser

get

rel

download.rel.Browser

download

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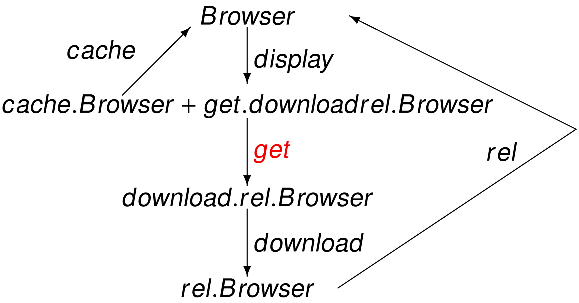

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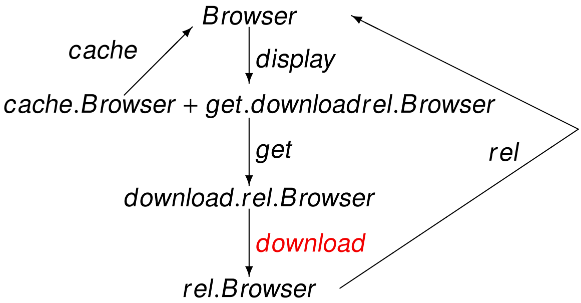

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cache

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get

rel

download.rel.Browser

download

rel.Browser

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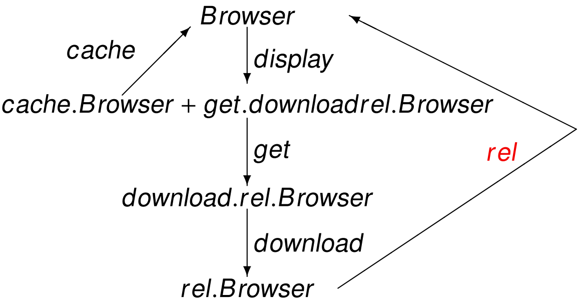

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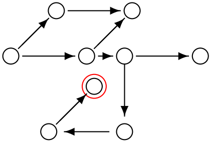
Will the system arrive in a particular state?



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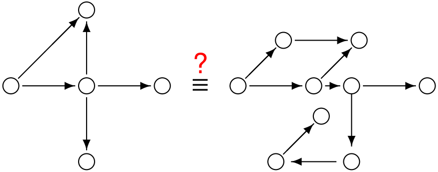

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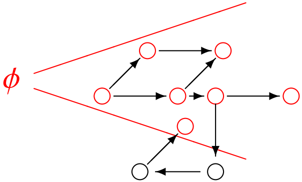
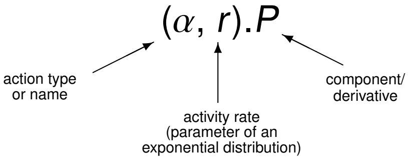


Stochastic Process Algebra

- Models are constructed from components which engage in activities.



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action type or name

activity rate (parameter of an exponential distribution)

component/ derivative

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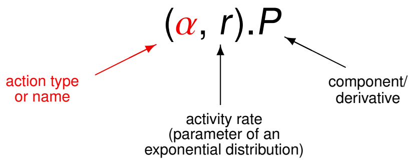

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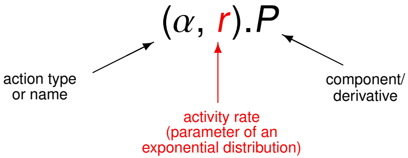

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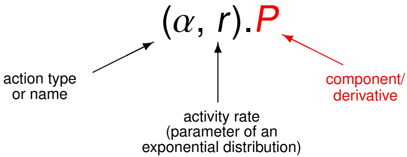

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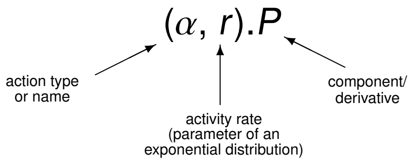

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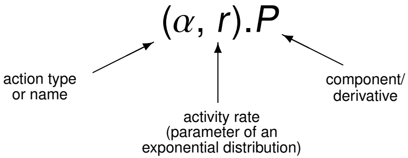

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SPA
MODEL

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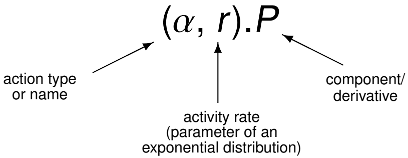

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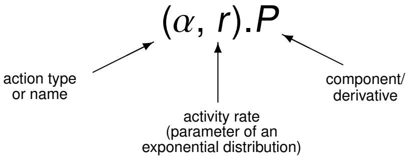

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$$\text{SPA MODEL} \xrightarrow{\text{SOS rules}} \text{LABELLED TRANSITION SYSTEM}$$

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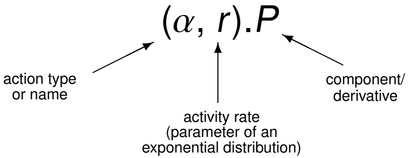

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SPA MODEL $\xrightarrow{\text{SOS rules}}$ LABELLED TRANSITION SYSTEM $\xrightarrow[\text{diagram}]{\text{state transition}}$

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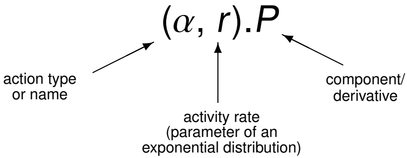

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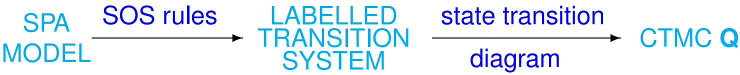

SPA MODEL $\xrightarrow[\text{}]{\text{SOS rules}}$ LABELLED TRANSITION SYSTEM $\xrightarrow[\text{diagram}]{\text{state transition}}$ CTMC **Q**

PEPA

$$
\begin{array}{lcl}
S & ::= & (\alpha, r).S \mid S + S \mid A \\
P & ::= & S \mid P \underset{L}{\bowtie} P \mid P/L
\end{array}
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PREFIX: $(\alpha, r).S$ designated first action

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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:

$$Server \overset{def}{=} (get, \top).(download, \mu).(rel, \top).Server$$

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In addition to duration we also incorporate information about the relative frequencies of the different actions which take place after a display request:

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The configuration is recorded as before; using the PEPA cooperation the actions which must be shared are explicitly named:

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Integrated analysis

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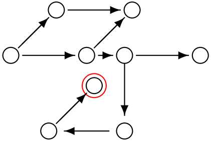
Reachability analysis

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



Integrated analysis

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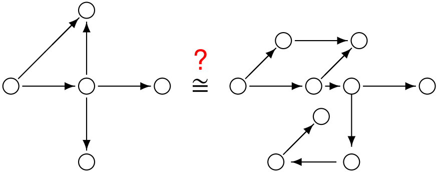
Specification matching

With what probability does system behaviour match its specification?



Integrated analysis

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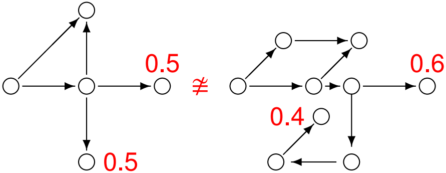
Specification matching

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



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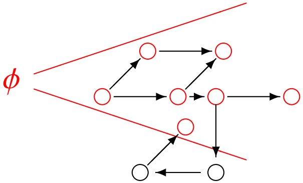
Model checking

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



Integrated analysis

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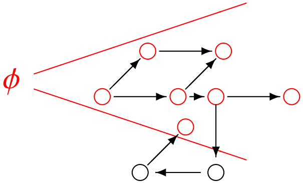
Model checking

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



SPA Languages

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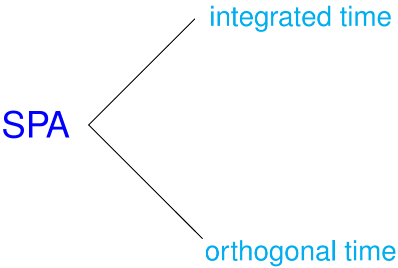
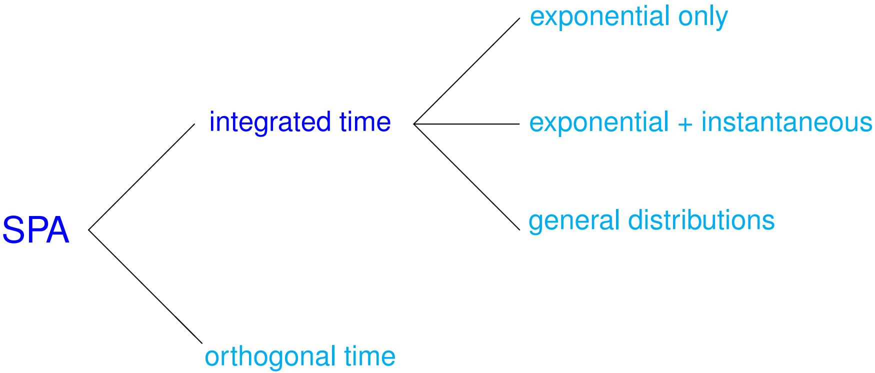

SPA

integrated time

orthogonal time

SPA Languages



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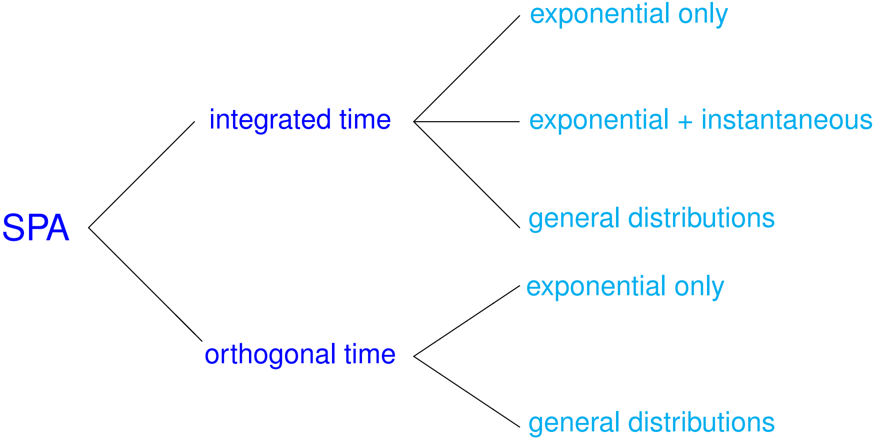

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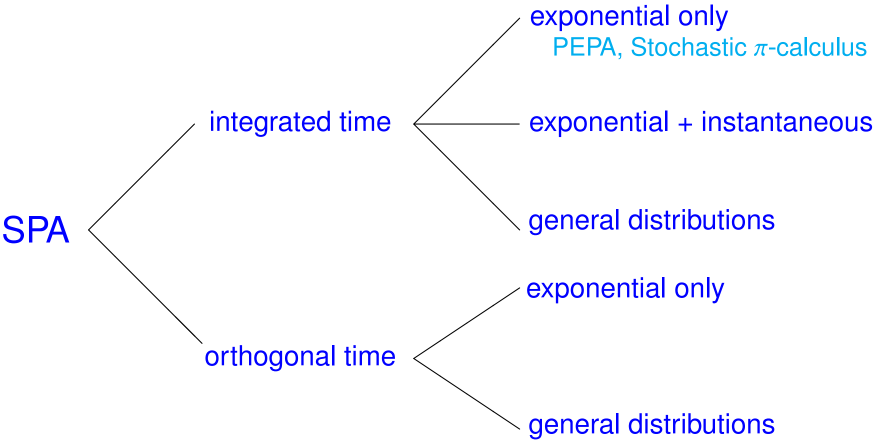

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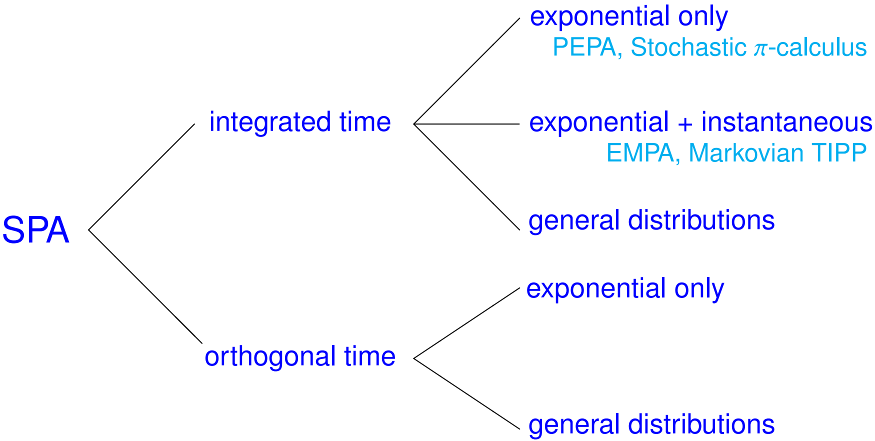

SPA

integrated time

exponential only

PEPA, Stochastic π-calculus

exponential + instantaneous

EMPA, Markovian TIPP

general distributions

orthogonal time

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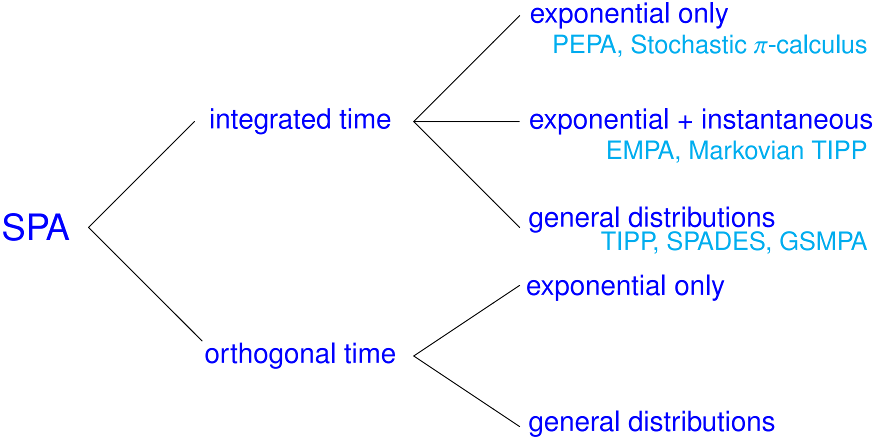
SPA Languages



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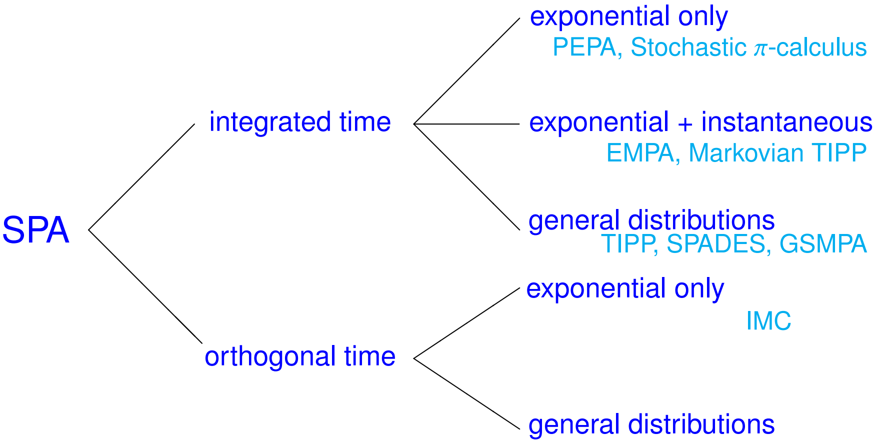

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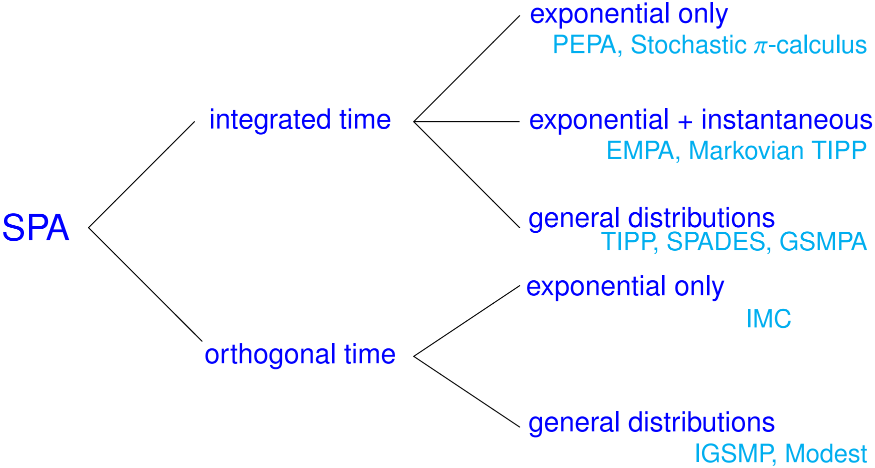

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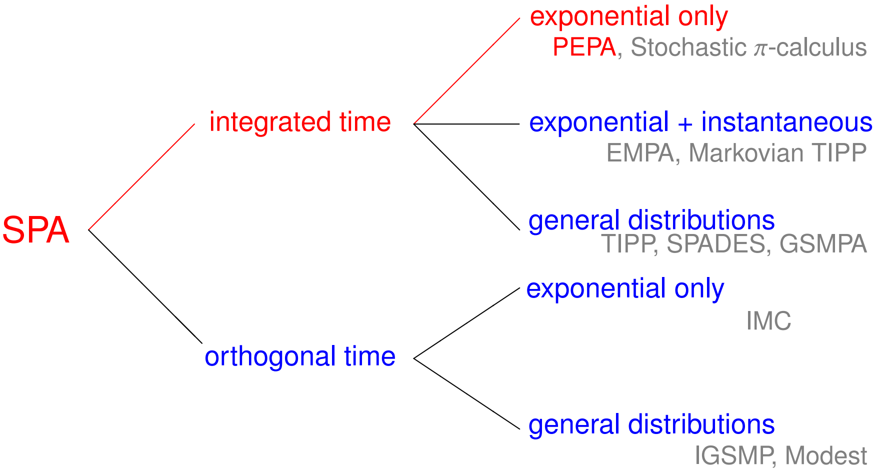

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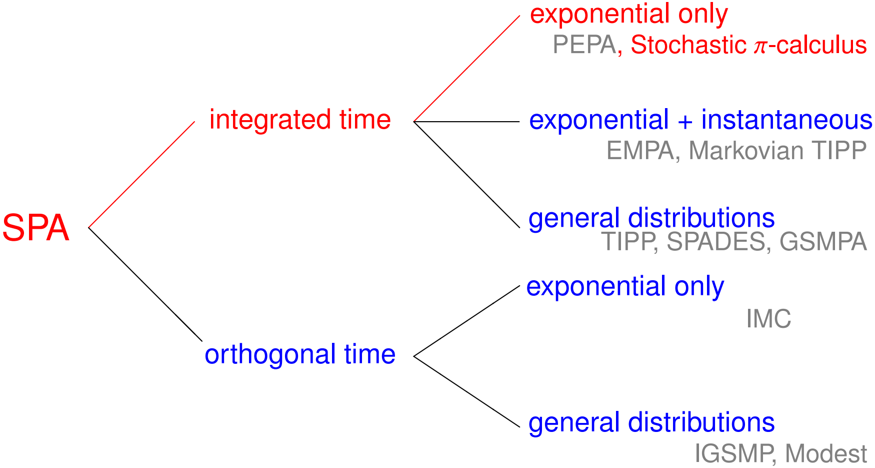

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The Importance of Being Exponential

$$\begin{tikzcd}
 & (\alpha, r).\mathit{Stop} \parallel (\beta, s).\mathit{Stop} \arrow[dl, "{(\alpha, r)}"'] \arrow[dr, "{(\beta, s)}"] & \\
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The memoryless property of the negative exponential distribution means that residual times do not need to be recorded.

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We retain the expansion law of classical process algebra:

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

only if the negative exponential distribution is assumed.

Parallel Composition

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- In classical process algebra is it often associated with communication.
- When the activities of the process algebra have a duration the definition of parallel composition becomes more complex.

Who Synchronises...?

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- Actions are partitioned into input and output pairs.

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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.

Cooperation in PEPA

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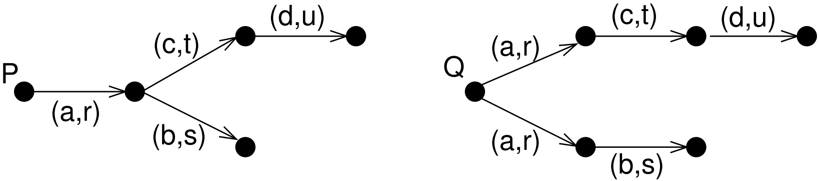
- Synchronisation, or cooperation cannot make a component exceed its bounded capacity.
- Thus the apparent rate of a cooperation is the minimum of the apparent rates of the co-operands.
- We will see that a different solution is appropriate in the context of biological systems.

Equivalence Relations

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



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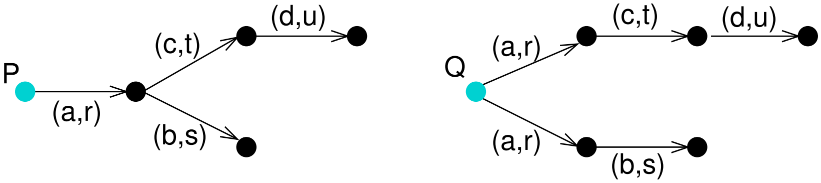

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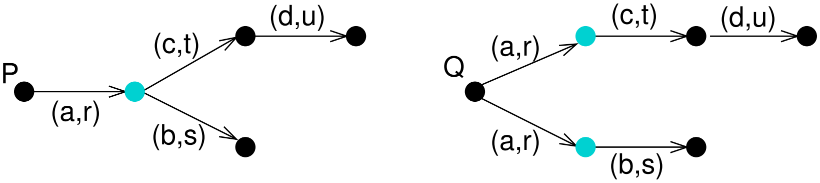

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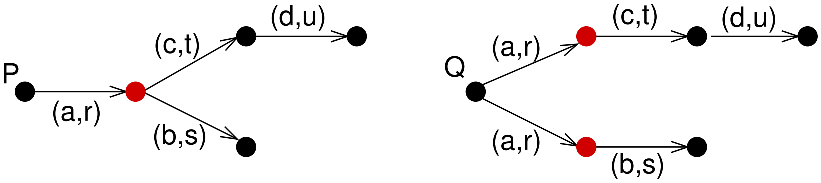

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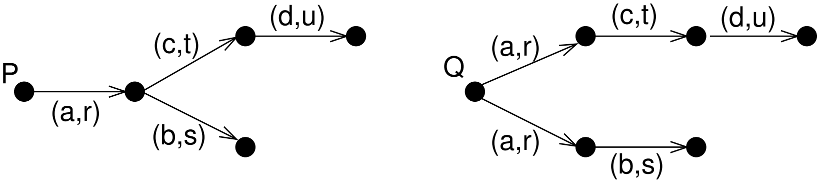

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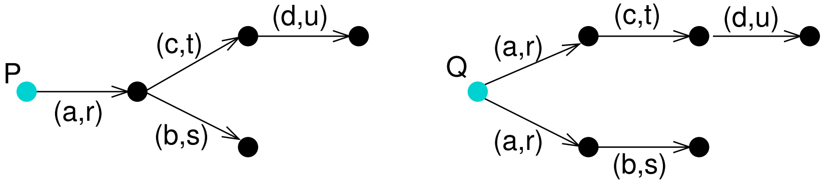

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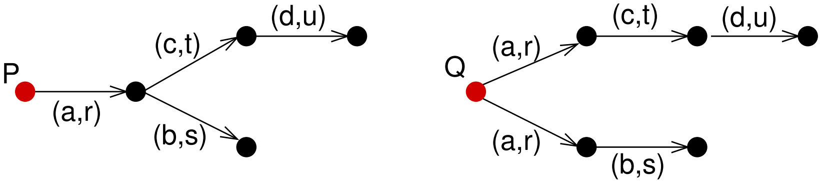

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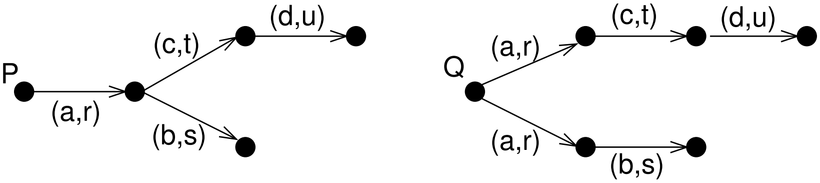

In SPA observation is assumed to include the ability to record timing information over a number of runs.

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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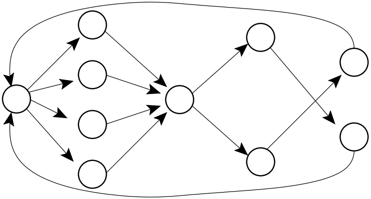

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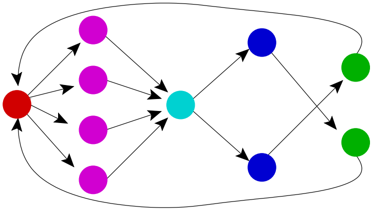

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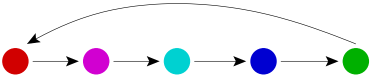
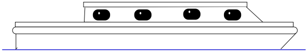


PEPA Case Studies (1)

- 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)

PEPA Case Studies (2)

- Locks and movable bridges in inland shipping in Belgium (Knapen, Hasselt)



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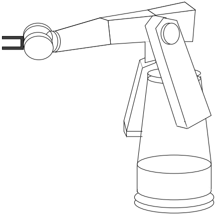

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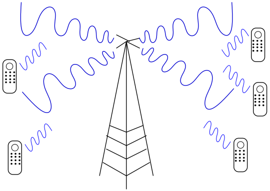

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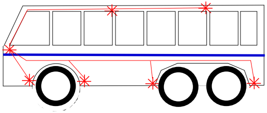
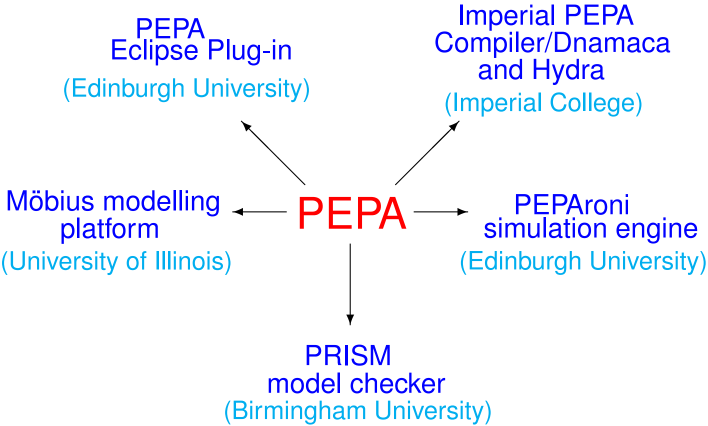
- Automotive diagnostic expert systems (Console, Picardi and Ribaudo, Turin)



Tool Support



PEPA

PEPA
Eclipse Plug-in
(Edinburgh University)

Imperial PEPA
Compiler/Dnamaca
and Hydra
(Imperial College)

Möbius modelling
platform
(University of Illinois)

PEPAroni
simulation engine
(Edinburgh University)

PRISM
model checker
(Birmingham University)

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- Stochastic model checking is available via the PRISM model checker, assessing the probable validity of properties expressed in CSL (Continuous Stochastic Logic).

Outline

Process Calculi

SPA

SPA for Systems Biology

Bio-PEPA

Model definition

The syntax and semantics

Equivalences and Analysis

Examples

Genetic network with negative feedback loop

Goldbeter's model

Conclusions

Using Stochastic Process Algebras

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- Equivalence relations allow formal comparison of high-level descriptions.
- 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
Transition or mobility	Biochemical modification or relocation	Metabolite synthesis	Protein binding, modification or sequestration

[Regev *et al* 2000]

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Calculi for Systems Biology

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- Calculi defined originally in computer science and then applied in biology, such as the biochemical stochastic π-calculus, SCCP, CCS-R and PEPA;
- Calculi defined specifically by observing biological structures and phenomena, such as BioAmbients, Brane Calculi and Beta-binders.

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- Two tools: BioSPI and SPIM which implement slightly different versions of the language.
- 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.

Biology-specific process calculi

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Thus each of the new calculi places emphasis on the location of components and how this impacts on their potential interactions.

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

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- Processes are encapsulated into boxes, that mimic biological membranes, and have interaction sites, motifs, depicting where molecules can bind together.
- The semantics give rules on joining and splitting boxes, as well as the affinity between interaction sites.

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

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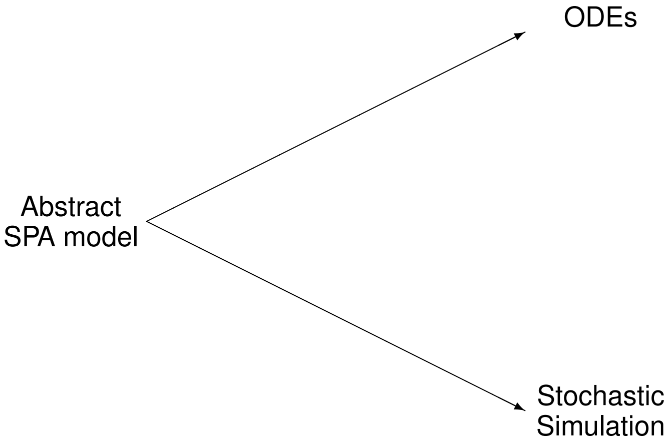
Alternative Representations



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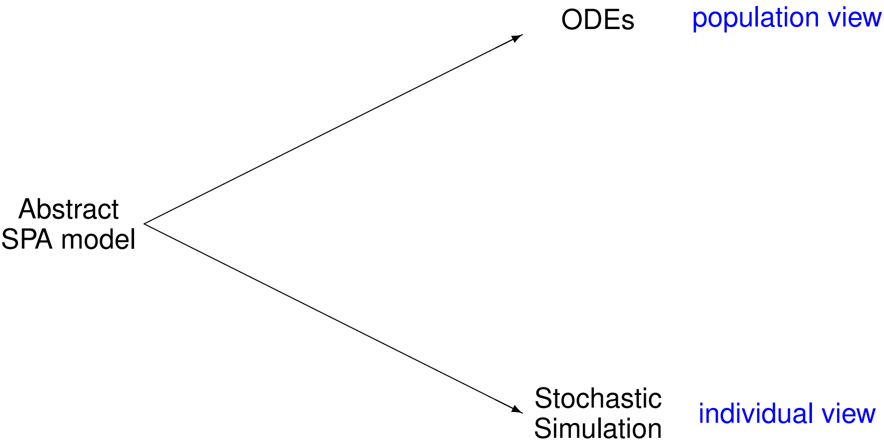


Abstract SPA model

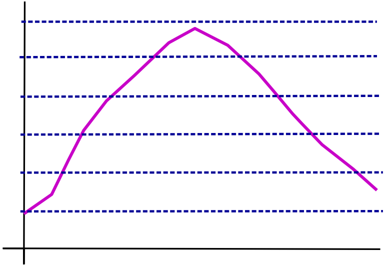
ODEs

population view

Stochastic Simulation

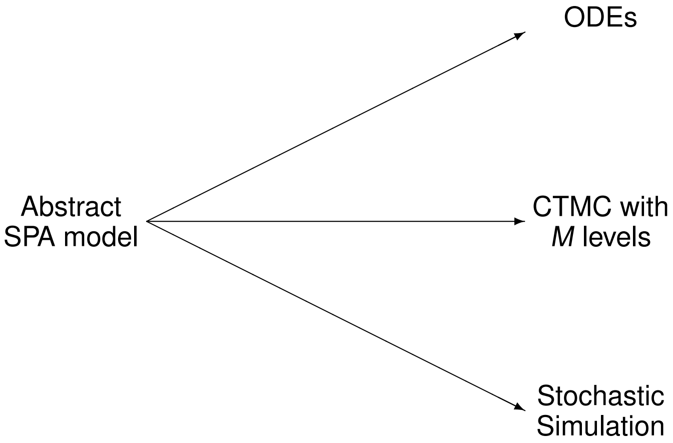
individual view

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.

Alternative Representations



Abstract SPA model

ODEs

CTMC with *M* levels

Stochastic Simulation

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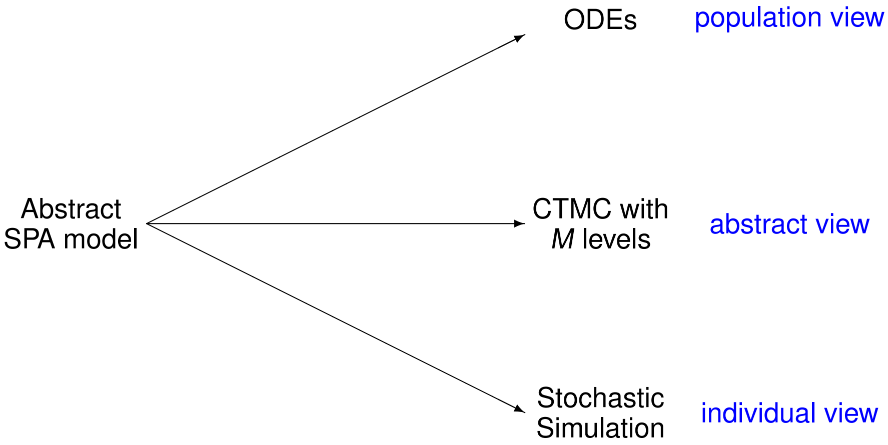


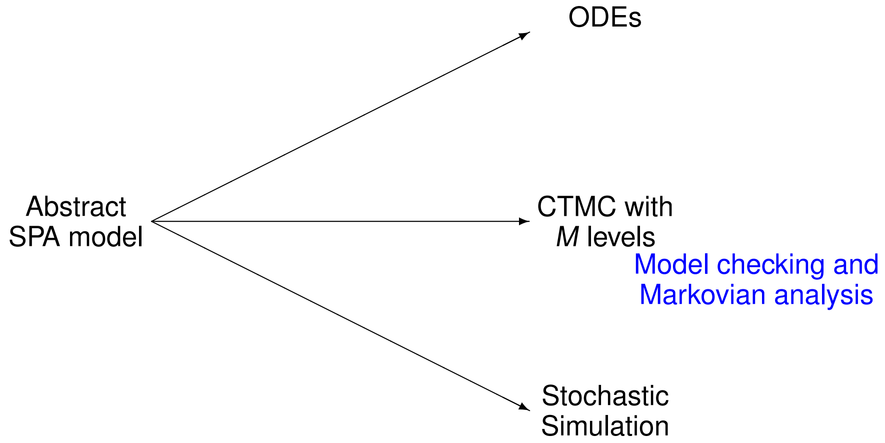
Abstract SPA model

ODEs population view

CTMC with *M* levels abstract view

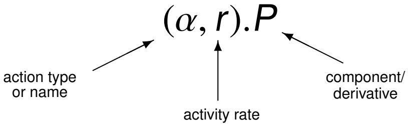
Stochastic Simulation individual view

Alternative Representations



Stochastic Process Algebra

- Models are constructed from components which engage in activities.



$$(\alpha, r).P$$

action type
or name

activity rate

component/
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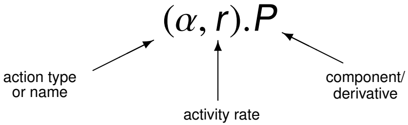

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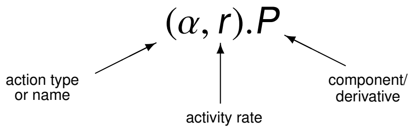

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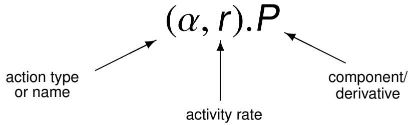

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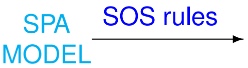

SPA MODEL

SOS rules

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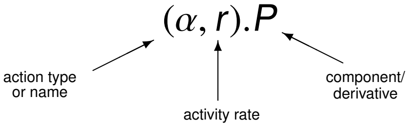

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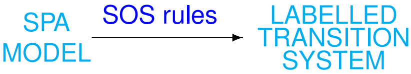

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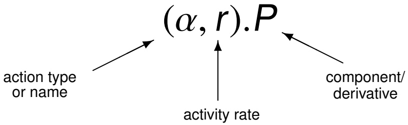

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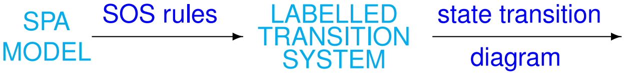

SPA MODEL

SOS rules

LABELLED TRANSITION SYSTEM

state transition

diagram

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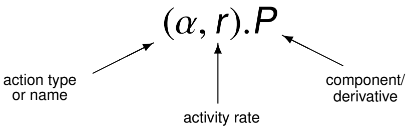

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$$\text{SPA MODEL} \xrightarrow{\text{SOS rules}} \text{LABELLED TRANSITION SYSTEM} \xrightarrow[\text{diagram}]{\text{state transition}} \text{CTMC } \mathbf{Q}$$

Q is the infinitesimal generator matrix characterising the CTMC.

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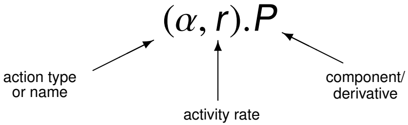

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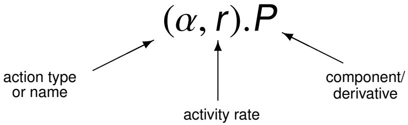

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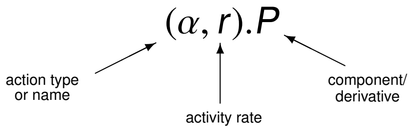

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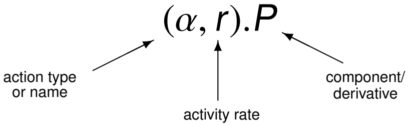

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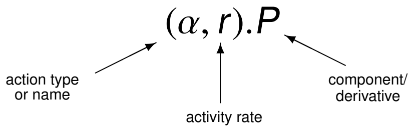

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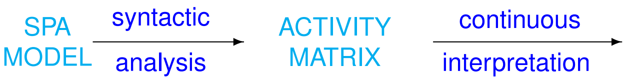

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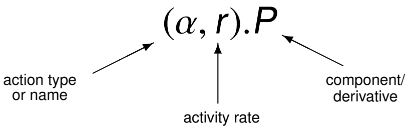

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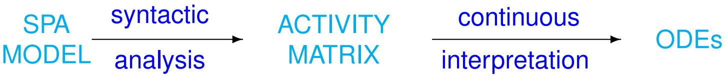

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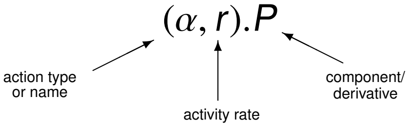

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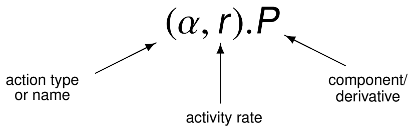

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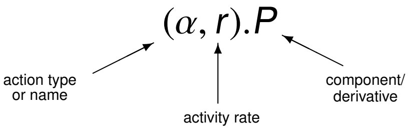

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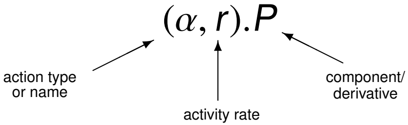

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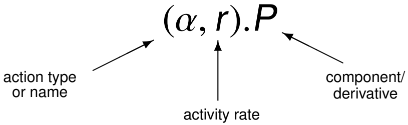

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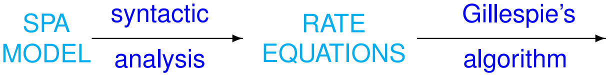

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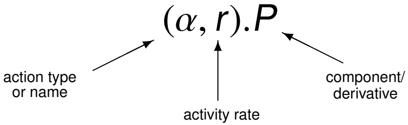

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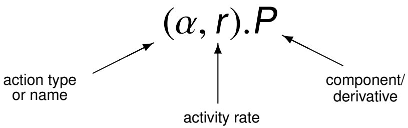

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- In models with levels, each level of granularity gives rise to a CTMC, and the behaviour of this sequence of Markov processes converges to the behaviour of the system of ODEs.

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- When a molecular mapping is used in general a CTMC state space is too large to permit anything but stochastic simulation.
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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

Process Calculi

SPA

SPA for Systems Biology

Bio-PEPA

Model definition

The syntax and semantics

Equivalences and Analysis

Examples

Genetic network with negative feedback loop

Goldbeter's model

Conclusions

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Particular problems are encountered with:

- 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.

$$2S \xrightarrow{E} P$$

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In process algebras such as the stochastic π-calculus this must be broken up into a sequence of unary and binary reactions, e.g.:

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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.

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- We define the same step size *h* for all the species, with few exceptions. This follows from the law of conservation of mass.
- If l_i is the concentration level for the species *i*, the concentration is taken to be $x_i = l_i \times h$.

Reagent-centric modelling (2)

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

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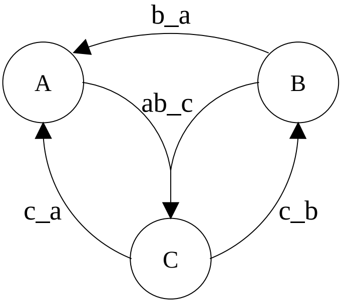
- The form of the CTMC derived from Bio-PEPA, which we term the CTMC with levels, will depend on the granularity of the model.
- As the granularity tends to zero the behaviour of this CTMC with levels tends to the behaviour of the ODEs [CDHC08].

Bio-PEPA reagent-centric example



$$
\begin{aligned}
A &\overset{def}{=} (ab\_c,1)\downarrow A + (b\_a,1)\uparrow A \\
&\quad + (c\_a,1)\uparrow A \\
B &\overset{def}{=} (ab\_c,1)\downarrow B + (b\_a,1)\downarrow B \\
&\quad + (c\_b,1)\uparrow B \\
C &\overset{def}{=} (c\_a,1)\downarrow C + (c\_b,1)\downarrow C \\
&\quad + (ab\_c,1)\uparrow C
\end{aligned}
$$

$$
\left(A(l_{A0}) \underset{\{ab\_c,b\_a\}}{\bowtie} B(l_{B0})\right) \underset{\{ab\_c,c\_a,c\_b\}}{\bowtie} C(l_{C0})
$$

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- The state of the system at any time consists of the local states of each of its sequential/species components.

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- A component varying its state corresponds to it varying its concentration level.
- 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.

The syntax

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Model component

$$P \overset{def}{=} P \underset{\mathcal{L}}{\bowtie} P \mid S(l)$$

The Bio-PEPA system

A Bio-PEPA system $\mathcal{P}$ is a 6-tuple $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, Comp, P \rangle$, where:

- $\mathcal{V}$ is the set of compartments;
- $\mathcal{N}$ is the set of quantities describing each species (step size, number of levels, location, ...);
- $\mathcal{K}$ is the set of parameter definitions;
- $\mathcal{F}_R$ is the set of functional rate definitions;
- *Comp* is the set of definitions of sequential components;
- P is the model component describing the system.

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2. stochastic relation, that gives us the rates associated with each action.

Semantics: prefix rules

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$$\texttt{prefixReac} \qquad ((\alpha,\kappa){\downarrow}S)(l) \xrightarrow{(\alpha,[S:\downarrow(l,\kappa)])}_{c} S(l-\kappa) \quad \kappa \leq l \leq N$$

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$$\texttt{prefixMod} \qquad ((\alpha,\kappa)\; op\; S)(l) \xrightarrow{(\alpha,[S:op(l,\kappa)])}_c S(l) \quad 0 \le l \le N$$

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

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$$\texttt{Choice1} \qquad \frac{S_1(l) \xrightarrow{(\alpha,v)}_c S'_1(l')}{(S_1 + S_2)(l) \xrightarrow{(\alpha,v)}_c S'_1(l')}$$

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Choice2 $$\frac{S_2(l)\xrightarrow{(\alpha,v)}_c S^{'}{}_2(l')}{(S_1 + S_2)(l)\xrightarrow{(\alpha,v)}_c S^{'}{}_2(l')}$$

Constant $$\frac{S(l)\xrightarrow{(\alpha,S:[op(l,\kappa))]}_c S'(l')}{C(l)\xrightarrow{(\alpha,C:[op(l,\kappa))]}_c S'(l')}$$ with $C \overset{def}{=} S$

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Semantics: rates and transition system

In order to derive the rates we consider the *stochastic relation* $\rightarrow_S \subseteq \mathcal{P} \times \Gamma \times \mathcal{P}$, with $\gamma \in \Gamma := (\alpha, r)$ and $r \in \mathbb{R}^+$.

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r_{α_j} represents the parameter of an exponential distribution and the dynamic behaviour is determined by a race condition.
The rate r_{α_j} is defined as $f_{\alpha_j}(v, \mathcal{N})/h$.

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The species components are then composed together to describe the behaviour of the system.

Example: Michaelis-Menten

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Example: Competitive Inhibition

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Under QSSA (the intermediate species *SE* and *EI* are constant) we can approximate the reactions above by a unique reaction

$$S \xrightarrow{E,I:f_I} P \qquad \text{with rate } f_I = \frac{w \times S \times E}{S + K_M(1 + \frac{I}{K_I})}$$

where w: turnover number (catalytic constant),
K_M: Michaelis constant and K_I: inhibition constant.

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with functional rate

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From the 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.

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- a ODE system for simulation and other kinds of analysis
- a Gillespie model for stochastic simulation
- a PRISM model for model checking

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

Process Calculi

SPA

SPA for Systems Biology

Bio-PEPA

Model definition

The syntax and semantics

Equivalences and Analysis

Examples

Genetic network with negative feedback loop

Goldbeter's model

Conclusions

The biological model

Consider a genetic network with negative feedback through dimers.

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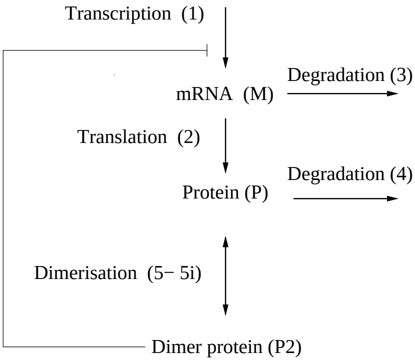

Species and reactions

The biological entities are:

- the *mRNA molecule* (*M*),
- the protein in monomer form (*P*) and
- the protein in dimeric form (*P2*).

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- the *mRNA molecule* (*M*),
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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 $\mathcal{N}$

$$[M : N_M, h_M; \quad P : N_P, h_P; \quad P2 : N_{P2}, h_{P2}]$$

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$$[M : N_M, h_M; \quad P : N_P, h_P; \quad P2 : N_{P2}, h_{P2}]$$

Definition of functional rates

$$\begin{aligned}
f_{\alpha_1} &= \frac{v}{K_M + P2} \\
f_{\alpha_2} &= fMA(k_2) \qquad f_{\alpha_3} = fMA(k_3) \qquad f_{\alpha_4} = fMA(k_4) \\
f_{\alpha_5} &= fMA(k_5) \qquad f_{\alpha 5\_Inv} = fMA(k_{5\_Inv})
\end{aligned}$$

Translation into Bio-PEPA (cont.)

Definition of the system components

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

Translation into Bio-PEPA (cont.)

Definition of the system components

$$
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\mathrm{M} & = & (\alpha_1,1)\uparrow \mathrm{M} + (\alpha_2,1)\oplus \mathrm{M} + (\alpha_3,1)\downarrow \mathrm{M};\\
\mathrm{P} & = & (\alpha_2,2)\uparrow \mathrm{P} + (\alpha_4,1)\downarrow \mathrm{P} + (\alpha_5,2)\downarrow \mathrm{P} + (\alpha_{5\_\mathit{Inv}},2)\uparrow \mathrm{P});\\
\mathrm{P2} & = & (\alpha_1,1)\ominus \mathrm{P2} + (\alpha_{5\_\mathit{Inv}},1)\downarrow \mathrm{P2} + (\alpha_5,1)\uparrow \mathrm{P2};\\
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\end{array}
$$

Definitions of the system

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

Analysis: the CTMC with levels

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

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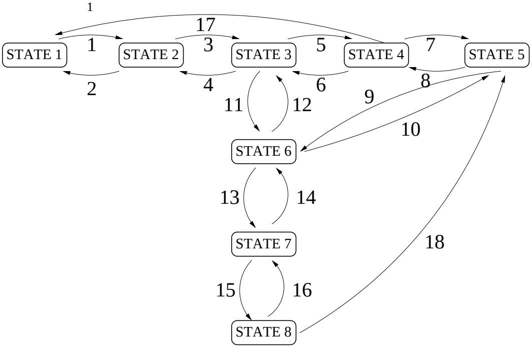

Analysis: the CTMC with levels

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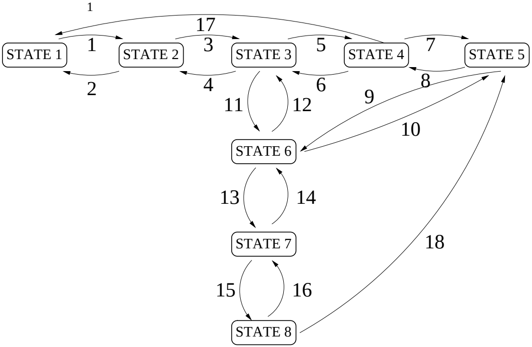

States are $(CF(l_1), M(l_2), P(l_3), P2(l_4), RES(l_5))$, with levels $l_1 \ldots l_5$.

Analysis: derivation of the ODE system

The stoichiometry matrix *D* associated with the system is

	α_1	α_2	α_3	α_4	α_5	α_{5_Inv}	
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
P2	0	0	0	0	+1	-1	x_3

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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

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

Analysis: derivation of ODEs (cont.)

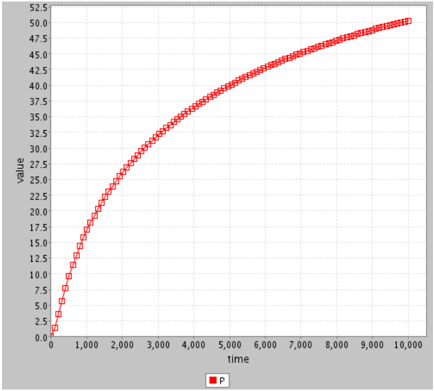
The system of ODEs is obtained as $\frac{d\bar{x}}{dt} = D \times w$:

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

Analysis: stochastic simulation

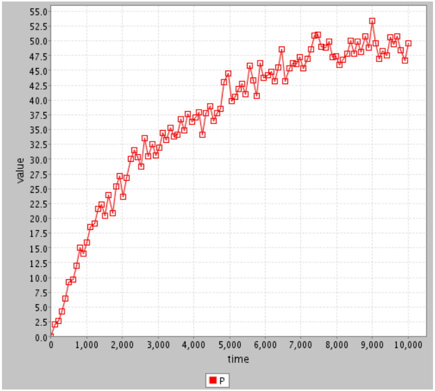
The derivation of the Gillespie model is made by creating molecules corresponding to each species and defining the possible reactions with appropriate adjustment of kinetic rates.

Simulation results



ODE results

Simulation results



Stochastic simulation results (10 runs)

PRISM model

Each species is represented as a PRISM module.

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For example, the protein is represented as:

module p
p: [0..Np] init 0;
$[Translation]\ p < Np \rightarrow (p' = p + 1);$
$[DegradationP]\ p > 0 \rightarrow (p' = p - 1);$
$[Dimerization]\ p > 1 \rightarrow (p' = p - 2);$
$[DimerizationInv]\ p < (Np - 1) \rightarrow (p' = p + 2);$
endmodule

PRISM model (cont.)

An additional module is needed to capture the kinetic rates.

module Functional_rates
dummy: bool **init** true;
$[\mathit{Transcription}]\ m < Nm \rightarrow (v/(K + p2 * h_{p2}) * h_{p2}) : (\mathit{dummy}' = \mathit{dummy});$
$[\mathit{Translation}]\ m > 0 \rightarrow (k2 * m * h_m/h_m) : (\mathit{dummy}' = \mathit{dummy});$
$[\mathit{DegradationmRNA}]\ m > 0 \rightarrow (k3 * m * h_m/h_m) : (\mathit{dummy}' = \mathit{dummy});$
$[\mathit{DegradationP}]\ p > 0 \rightarrow (k4 * p * h_p/h_p) : (\mathit{dummy}' = \mathit{dummy});$
$[\mathit{Dimerization}]\ p > 1 \rightarrow (k5 * p * h_p * p * h_p/h_p)(\mathit{dummy}' = \mathit{dummy});$
$[\mathit{DimerizationInv}]\ p2 > 0 \rightarrow (k5\_Inv * p2 * h_{p2}/h_{p2}) : (\mathit{dummy}' = \mathit{dummy});$
endmodule

PRISM analysis

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:

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  $true : \frac{p}{(p+p2)};$
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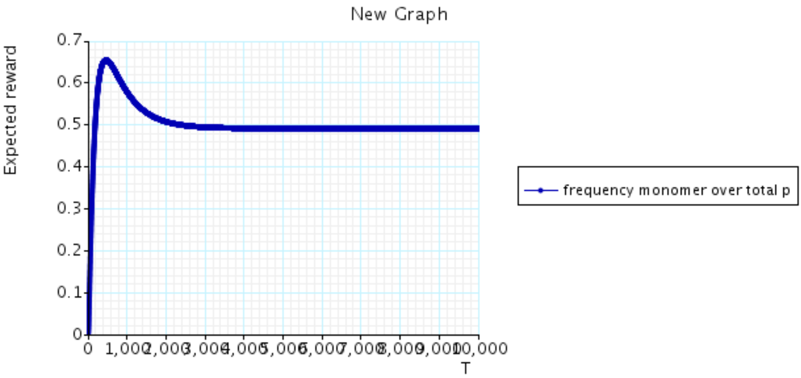
  $$R = ?[I = T]$$

- **Probability that P is at level i at time T**

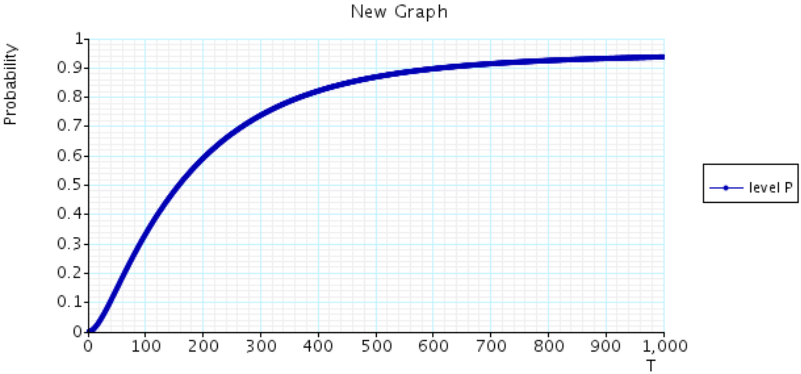
  $$P = ?[trueU[T, T]p = i]$$

PRISM results



monomer frequency

PRISM results



Probability monomer protein is at high level over time

Goldbeter's model [Goldbeter 91]

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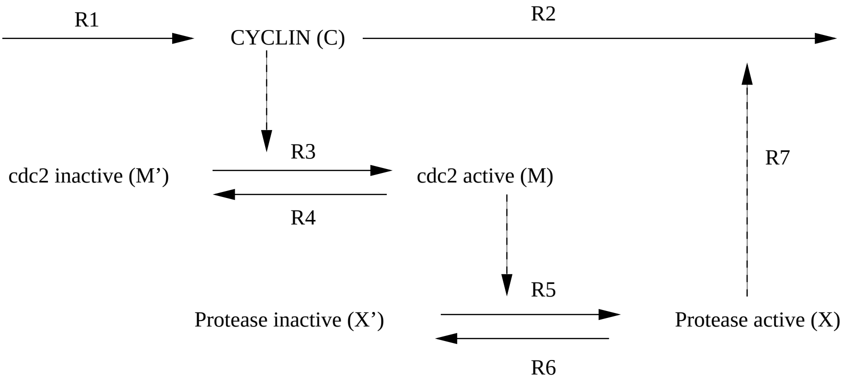
- The cyclin promotes the activation of a cdk (cdc2) which in turn activates a cyclin protease.
- This protease promotes cyclin degradation.
- This leads to a negative feedback loop.
- In the model most of the kinetic laws are of kind Michaelis-Menten and this can be reflected in the Bio-PEPA model.

The biological model



The biological model (2)

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- cyclin, the protein protagonist of the cycle, C;
- cdc2 kinase, in both active (i.e. dephosphorylated) and inactive form (i.e. phosphorylated). The variables used to represent them are M and M', respectively;
- 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.

Translation into Bio-PEPA

Definition of the set $\mathcal{N}$:

$$\mathcal{N} = [Res : 1, 1;\ CF : 1, 1;\ C : h_C, N_c;\ M : h_M, N_M; \\ M' : h_{M'}, N_{M'};\ X : h_X, N_X, ;\ X' : h_{X'}, N_{X'}]$$

Res and *CF* represent degradation and synthesis respectively.

Translation into Bio-PEPA

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Res and *CF* represent degradation and synthesis respectively.
Definition of functional rates ($\mathcal{F}$):

$$\begin{array}{lllllll} f_{\alpha_1} & = & fMA(v_i); & & f_{\alpha_2} & = & fMA(k_d); \\ f_{\alpha_4} & = & fMM(V_2, K_2); & & f_{\alpha_5} & = & fMM(V_3, K_3); \\ f_{\alpha_6} & = & fMM(V_4, K_4); & & f_{\alpha_7} & = & fMM(V_d, K_d); \end{array}$$

$$f_{\alpha_3} = \frac{v_1 \times C}{K_c + C} \frac{M'}{K1 + M'}$$

The Bio-PEPA system (2)

Definition of species components (*Comp*):

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

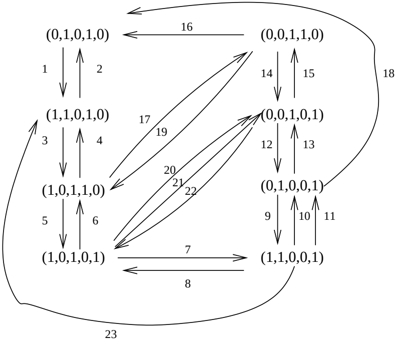
Definition of the model component (*P*):

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

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

Analysis: CTMC with 2 levels

Assume two levels for each species and initially C, M and X present (level 1) and the other elements not present (level 0).
The initial state is $(l_C(1), l_{M'}(0), l_M(1), l_{X'}(0), l_X(1))$.



Analysis: 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

Analysis: ODEs

The stoichiometry matrix D:

$$
\begin{array}{c|c|c|c|c|c|c|c|c}
 & \mathrm{R1} & \mathrm{R2} & \mathrm{R3} & \mathrm{R4} & \mathrm{R5} & \mathrm{R6} & \mathrm{R7} & \\
\hline
\mathrm{C} & +1 & 0 & 0 & 0 & 0 & 0 & -1 & x_C \\
M' & 0 & 0 & -1 & +1 & 0 & 0 & 0 & x_{M'} \\
\mathrm{M} & 0 & 0 & +1 & -1 & 0 & 0 & 0 & x_M \\
X' & 0 & 0 & 0 & 0 & -1 & +1 & 0 & x_{X'} \\
\mathrm{X} & 0 & 0 & 0 & 0 & +1 & -1 & 0 & x_X
\end{array}
$$

The vector that contains the kinetic laws is:

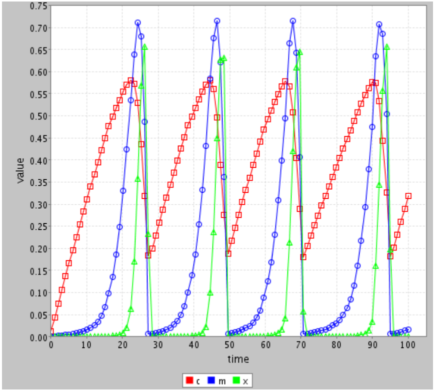
$$
\begin{aligned}
w = \Big(v_i \times 1, k_d \times x_C, \frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})}, \frac{V_2 \times x_M}{(K_2 + x_M)}, \\
\frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})}, \frac{V_4 \times x_X}{(K_4 + x_X)}, \frac{v_d \times x_C \times x_X}{(K_d + x_C)}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

Analysis: 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:

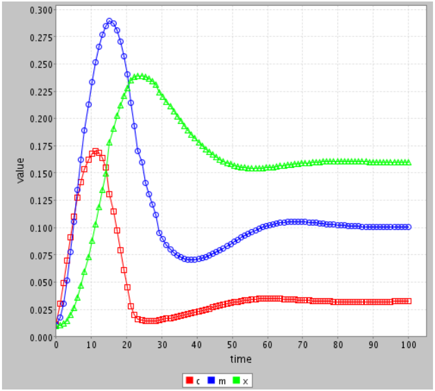
$$\begin{aligned}
\frac{dx_C}{dt} &= v_i \times 1 - k_d \times x_C - \frac{v_d \times x_C \times x_X}{(K_d + x_C)} \\
\frac{dx_{M'}}{dt} &= -\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} + \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_M}{dt} &= +\frac{V_{M1} \times x_C}{K_c + x_C}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

ODE results



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

ODE results



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

Extension of the Goldbeter's model

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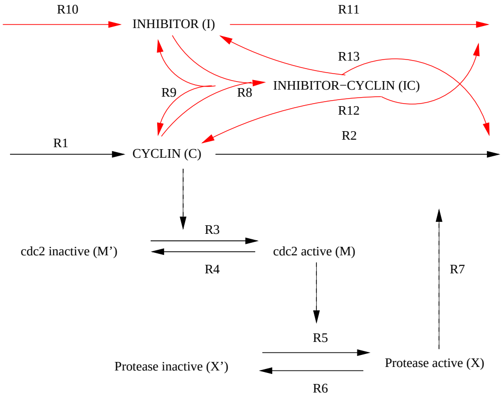
Several possible extensions were presented; we consider one of them.

Schema of the extended model



Extended Bio-PEPA system

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

New functional rates

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

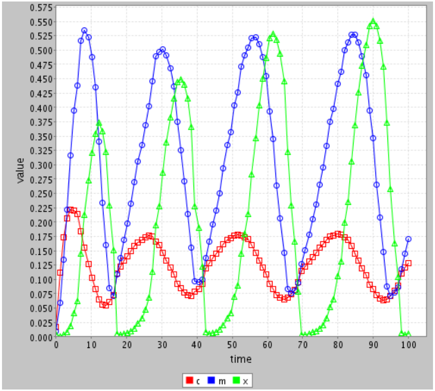
Complete Bio-PEPA system

$$C(l_{0C}) \underset{\{\alpha_3\}}{\bowtie} M(l_{0M}) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} M^{'}(l_{0M'}) \underset{\{\alpha_5,\alpha_7\}}{\bowtie} X(l_{0X}) \underset{\{\alpha_5,\alpha_6\}}{\bowtie} X^{'}(l_{0X'}) \underset{\{\alpha_2\}}{\bowtie}$$

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

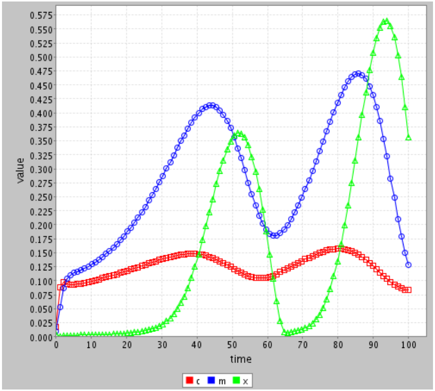
$$\underset{\{\alpha_8,\alpha_9,\alpha_{10},\alpha_{11}\}}{\bowtie} I(l_{0I}) \underset{\{\alpha_8,\alpha_9,\alpha_{12},\alpha_{13}\}}{\bowtie} IC(l_{0IC})$$

New ODE results



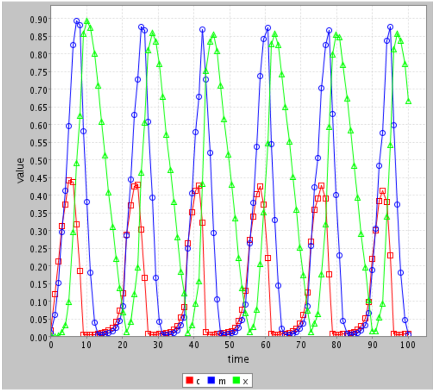
$a_1 = a_2 = 0.3$ and $v_s = 0.6$

New ODE results



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

New ODE results



$$a_1 = a_2 = 0.05 \text{ and } v_s = 0.1$$

Outline

Process Calculi

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

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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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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...*

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