The Bio-PEPA project

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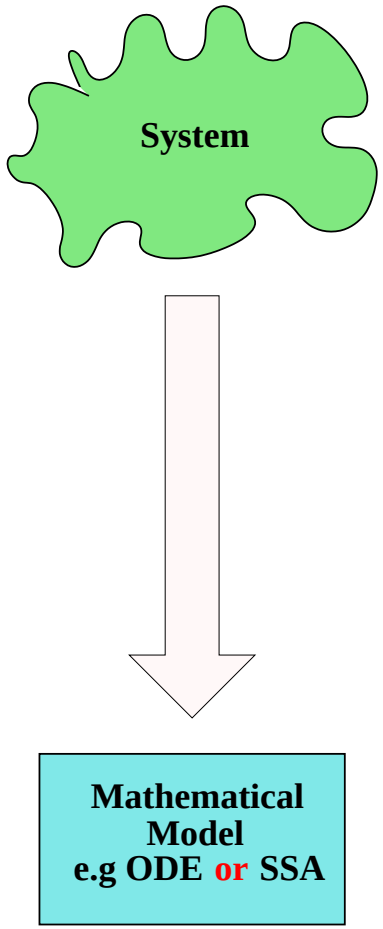
24th February 2009

Joint work with Federica Ciocchetta, Adam Duguid, Vashti Galpin, Stephen Gilmore, Maria Luisa Guerriero and Laurence Loewe.

Integrated Analysis



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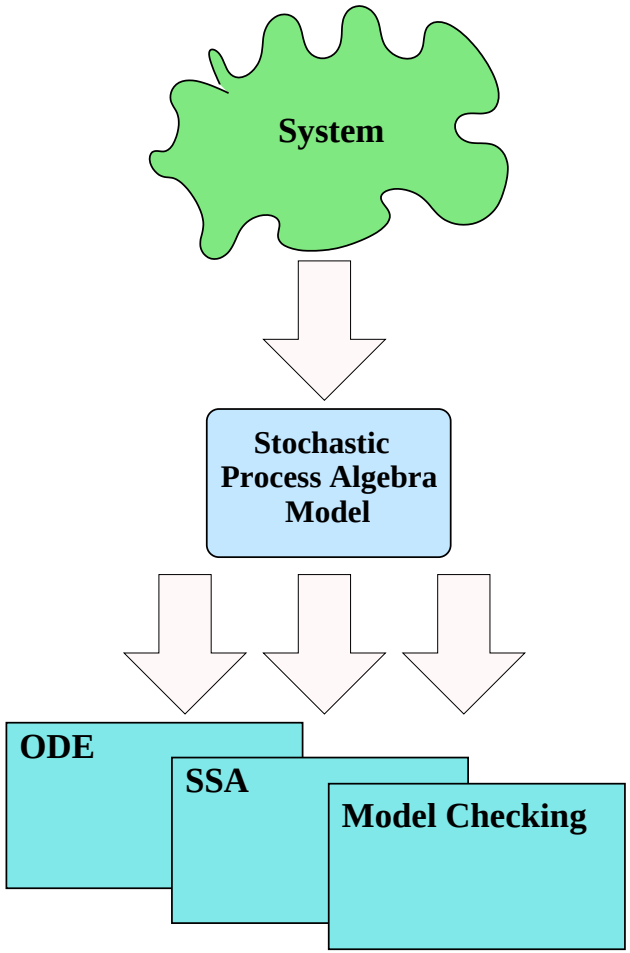

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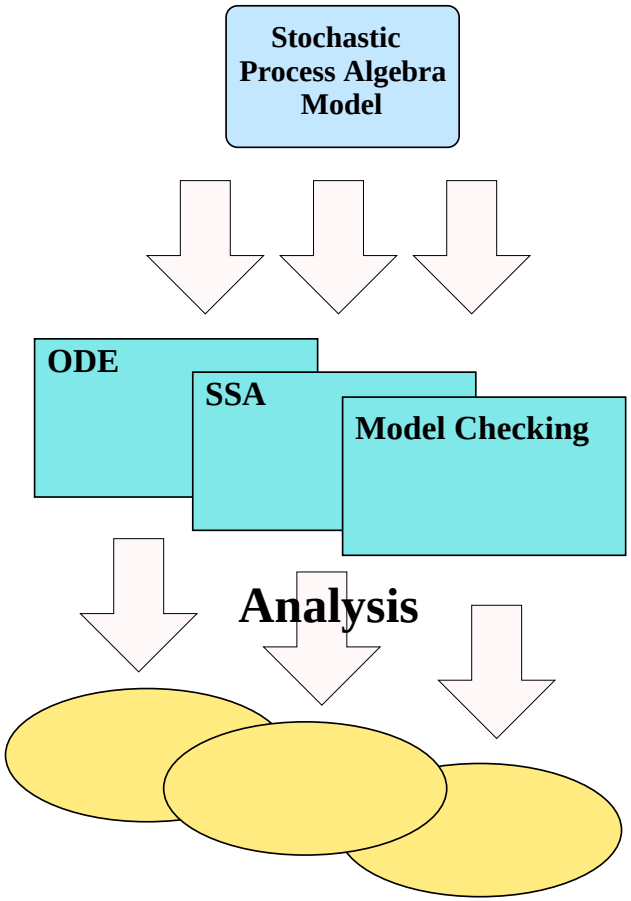

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We also wanted to be able to capture more of the biological features expressed in the models such as those found in the BioModels database.

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  This suggests that it can be useful to use semi-quantitative models rather than quantitative ones.

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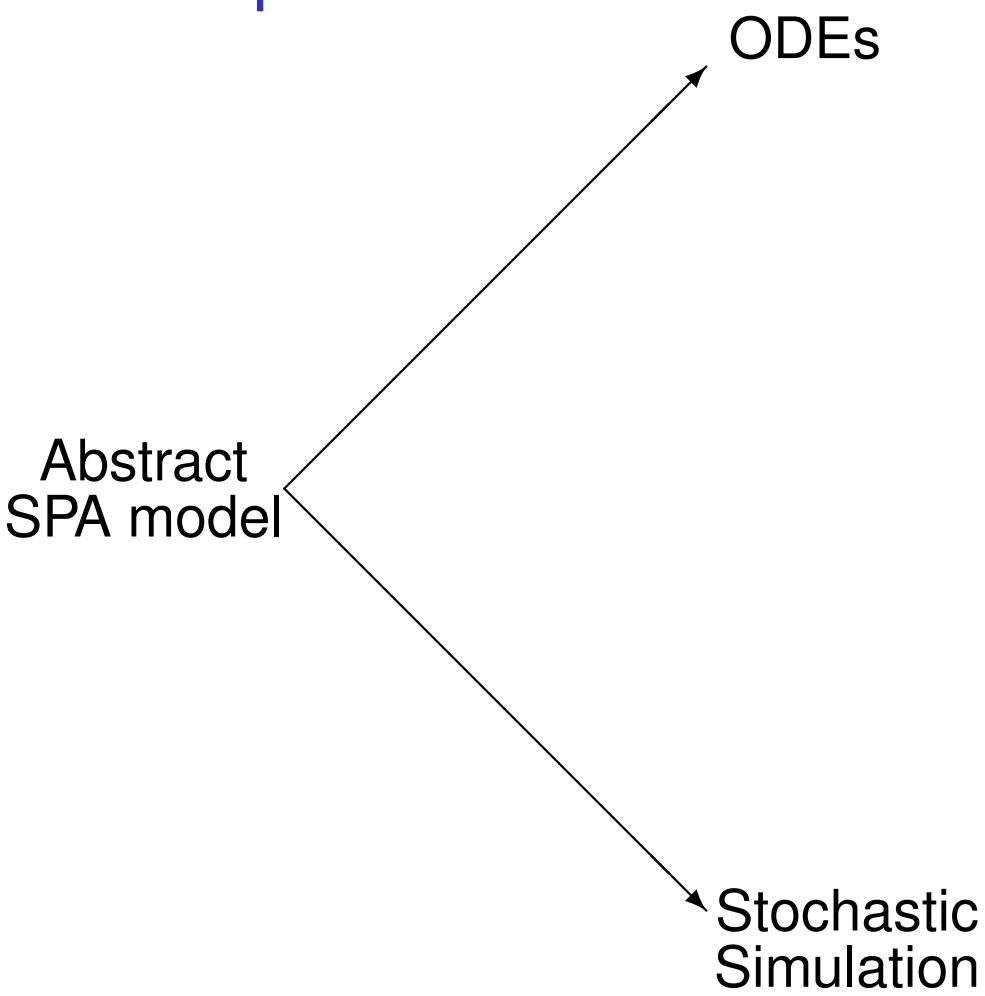

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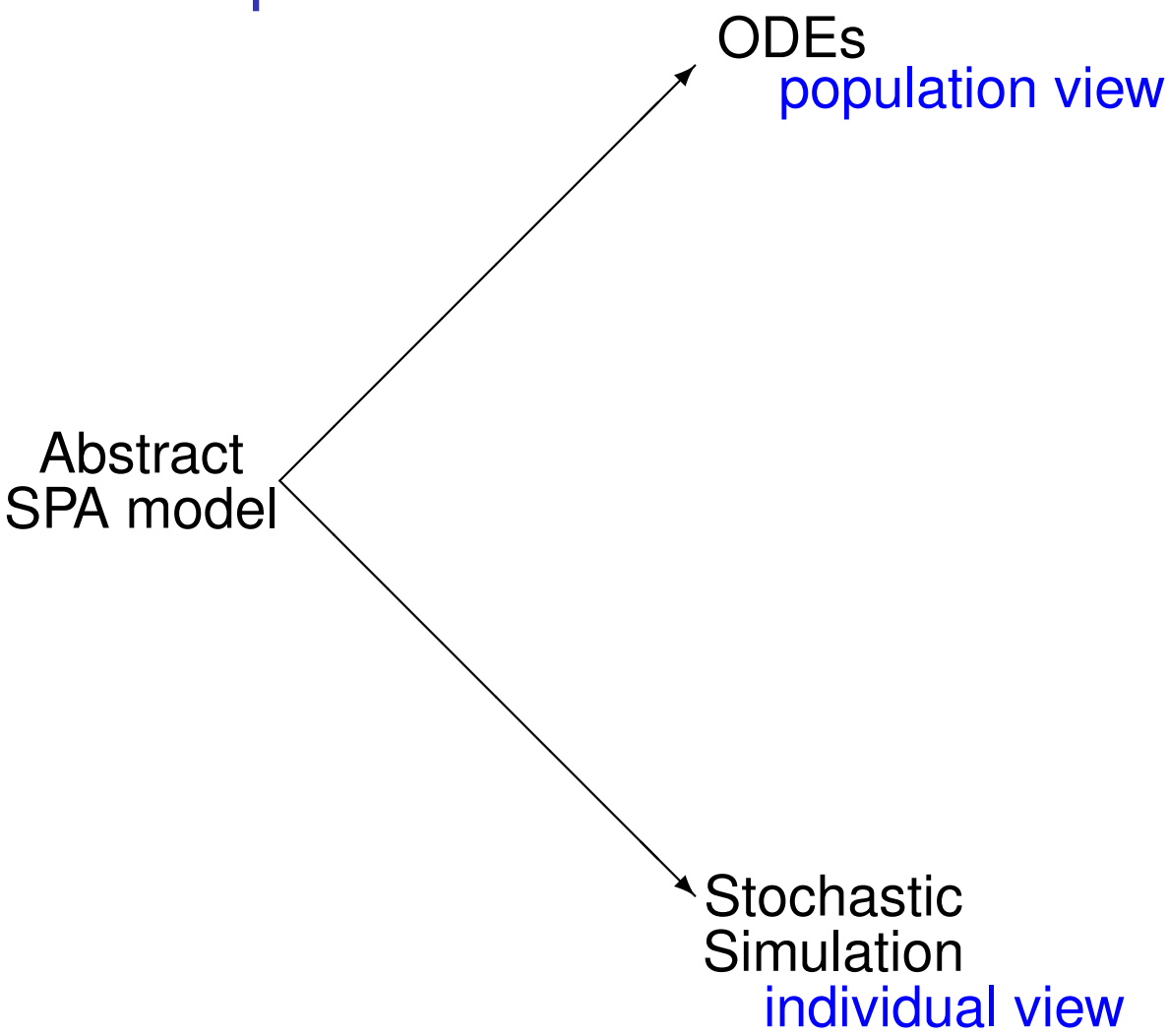

Discretising the population view

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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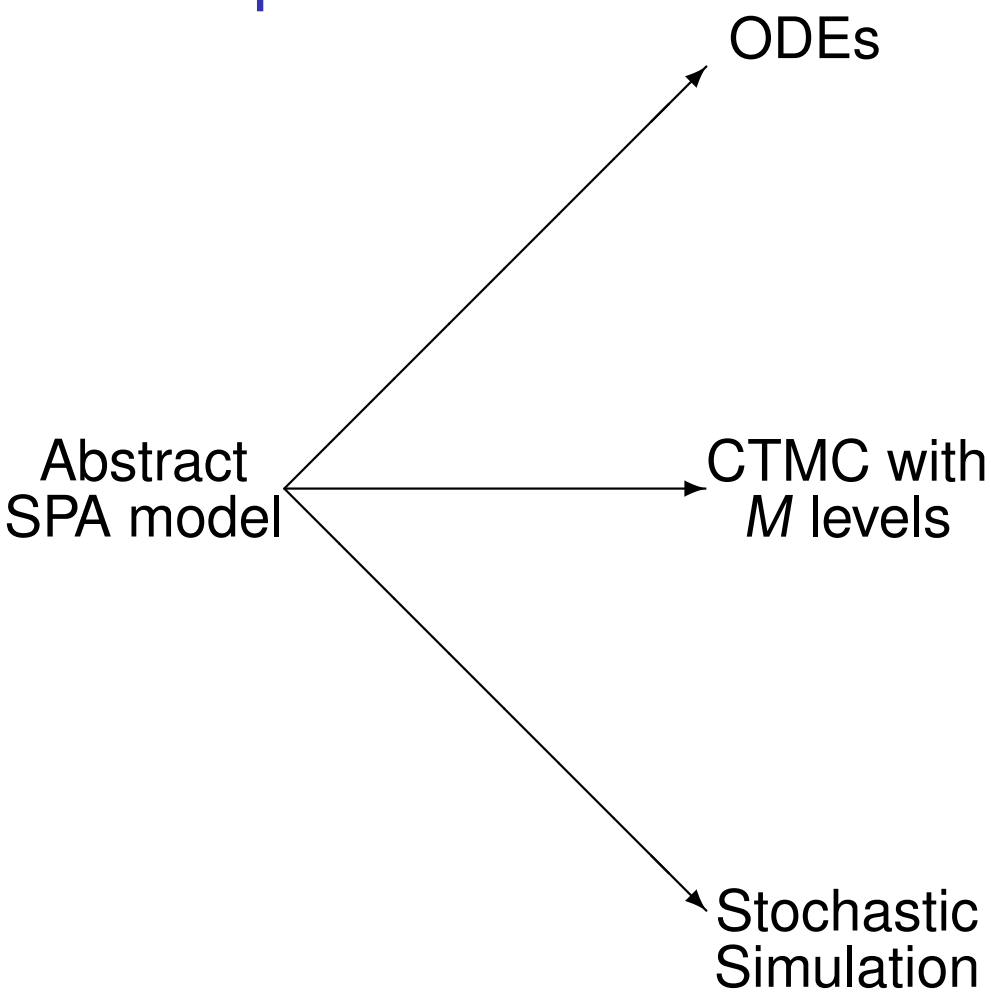

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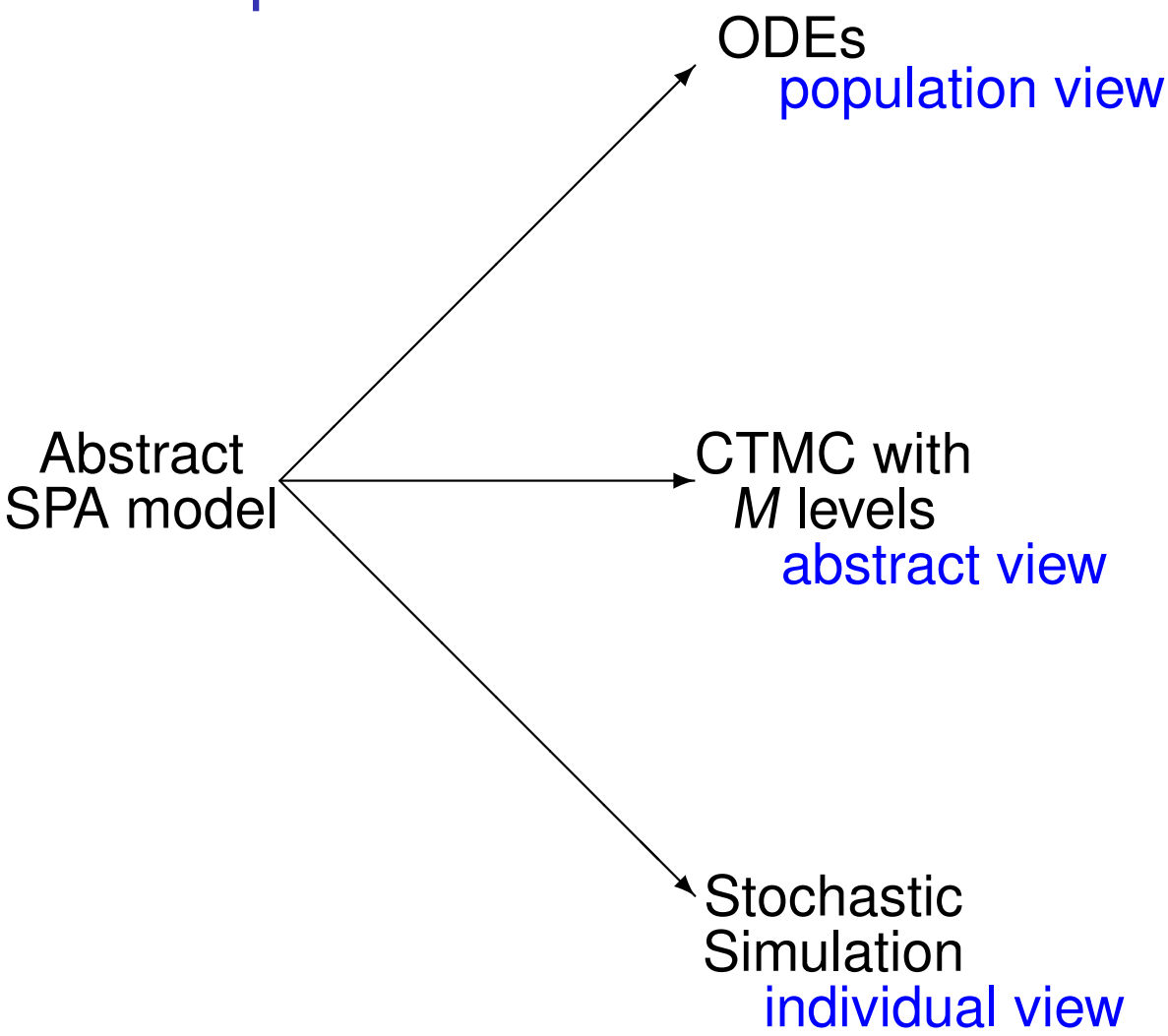

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Particular problems are encountered with:

- stoichiometry — the multiplicity in which an entity participates in a reaction;
- general kinetic laws — although mass action is widely used other kinetics are also commonly employed.
- multiway reactions — although thermodynamic 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.

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- Unique rates are associated with each reaction (action) type, separately from the specification of the logical behaviour. These rates may be specified by functions.
- 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.
- The local states of components are quantitative rather than functional, i.e. distinct states of the species are represented as distinct components, not derivatives of a single component.

The syntax

Sequential component (species component)

$$S ::= (\alpha, \kappa) \text{ op } S \mid S + S \mid C \qquad \text{where op} = \downarrow \mid \uparrow \mid \oplus \mid \ominus \mid \odot$$

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The parameter l is abstract, recording quantitative information about the species.

Depending on the interpretation, this quantity may be:

- number of molecules (SSA),
- concentration (ODE) or
- a level within a semi-quantitative model (CTMC).

The Bio-PEPA system

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

Semantics

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We define two relations over the processes:

1. capability relation, that supports the derivation of quantitative information;
2. stochastic relation, that gives the rates associated with each action.

Semantics: prefix rules

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

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

Semantics: constant and choice rules

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

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

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

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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$$\frac{P \xrightarrow{(\alpha_j, v)}_c P'}{\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, Comp, P \rangle \xrightarrow{(\alpha_j, r_{\alpha_j})}_s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, Comp, P' \rangle}$$

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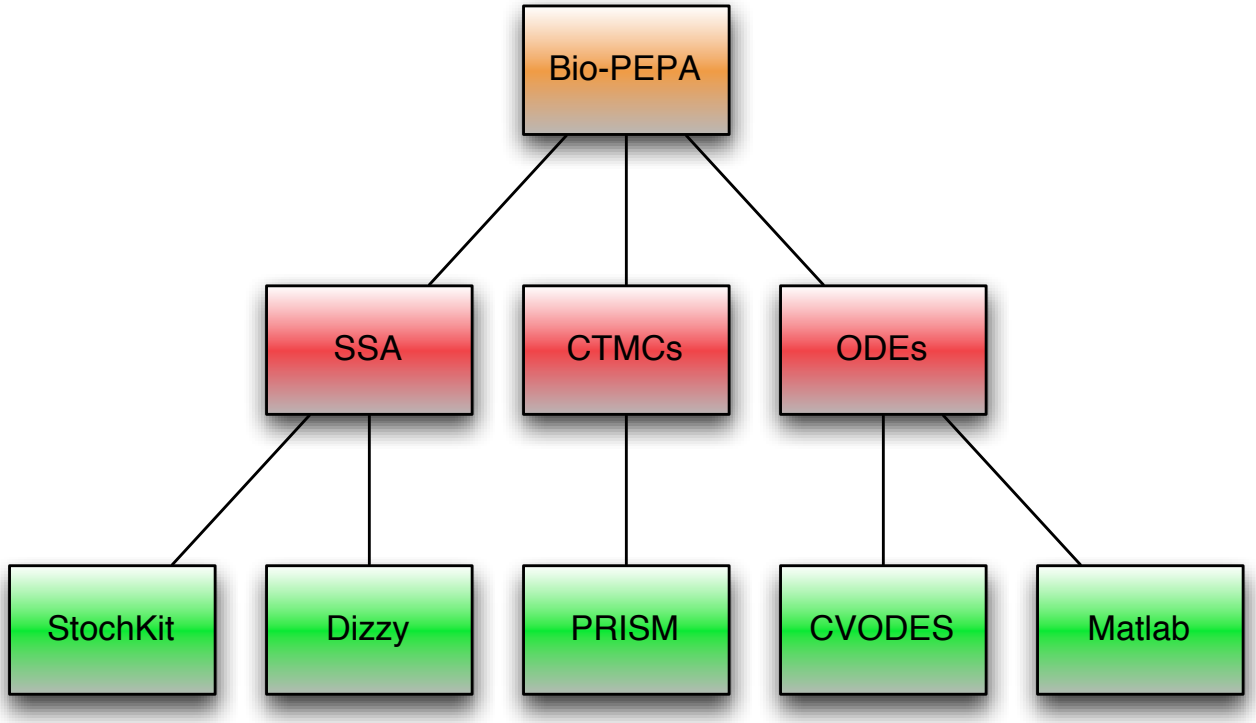
r_{α_j} represents the parameter of an exponential distribution and the dynamic behaviour is determined by a race condition.

The rate r_{α_j} is defined as $f_{\alpha_j}(\mathcal{V}, \mathcal{N}, \mathcal{K})/h$.

Analysis



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.

Examples from the literature

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- Goldbeter's model describing the oscillation of cyclin in the cell cycle.
- A simple genetic network, with a negative feedback loop.
- The repressilator.
- Edelstein's model for the acethylcholine receptor (with events).
- Model for complex intracellular calcium oscillations (by Goldbeter and co-authors).

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- JAK/STAT pathway in chickens: investigating the differences between chickens susceptible and resistant to Marek's disease. (Roslin Institute)

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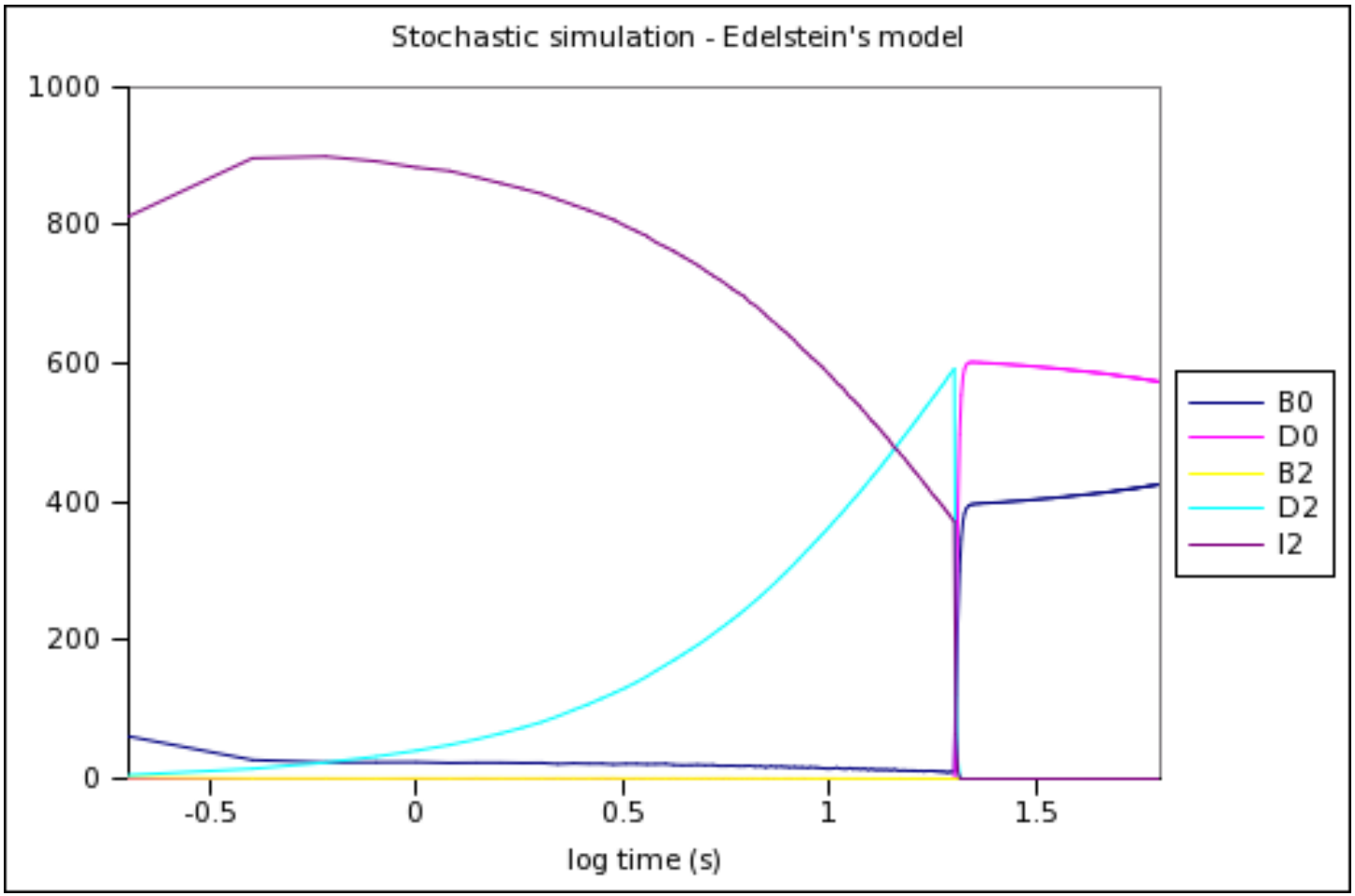
Such an extension of Bio-PEPA has been defined consisting of a separate specification of the events and their effects, and mappings to hybrid automata and stochastic simulation models.

Example with Events



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Recent work by Ciocchetta and Guerriero has extended this view of compartments, allowing the relative positioning of compartments and membranes to be captured.

Additionally species and reactions may be specified to have a particular location relative to this structure, for example on a membrane or within a compartment.

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In particular we are investigating the situations in which biologists regard models or elements of models to be equivalent, especially when this is employed for model simplification.

Biologically-inspired equivalences

After studying models from the literature and talking to biological collaborators we are investigating the following possibilities:

- Lumping
  - two species are viewed as one
- Fast versus slow reactions
  - Michaelis-Menten abstraction using QSSA
- Unobservable species
  - species that cannot be observed/measured in experiments
  - example: $A \rightarrow A_1 \rightarrow A_2 \rightarrow A_3 \rightarrow A_4 \rightarrow B$ and $A \rightarrow B$

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Currently, we are studying these at the qualitative level, but ultimately relationships based on the stochastic relation will be important.

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The SBGN standard lacks quantitative information such as kinetic rates and initial concentrations/molecule counts, so our translation is based on the version of SBGN supported by the Edinburgh Pathway Editor, which has these values defined as attributes.

Narrative Language input to Bio-PEPA models

We are also using the narrative language developed in Guerriero's PhD thesis (joint work with Heath and Priami) as a means to help biologists capture details of the system to be modelled.

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Previously these tables were used to automatically generate a Beta-binders model, and we will soon be implementing a translation into Bio-PEPA.

More Information?

http://homepages.inf.ed.ac.uk/jeh/biopepa

Acknowledgements

This work has been/is being developed under the auspices of the following projects:

- *The Centre for Systems Biology at Edinburgh (CSBE)*, funded by BBSRC and EPSRC (one of six Centres for Integrative Systems Biology).
- *Process Algebra Approaches for Collective Dynamics*, Advanced Research Fellowship and associated project (EP/c543696/01 and EP/c54370x/01), funded by EPSRC and BBSRC.
- *SIGNAL: Stochastic Process Algebra for Biochemical Signalling Pathways Analysis* with Prof Muffy Calder and Prof Walter Kolch (University of Glasgow) (EP/EO31439/1), funded by EPSRC.

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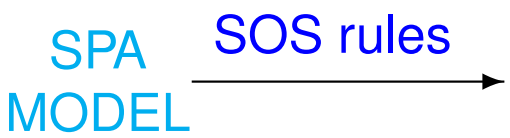

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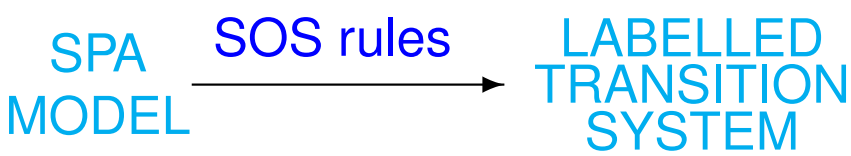

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As the granularity tends to zero the behaviour of this CTMC with levels tends to the behaviour of the ODEs [CDHC FBTC08].

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- Building a reward structure over the model it is possible to express complex analysis questions.

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- As with SSA, in practice it is more straightforward to directly map to the input language of the tool, as interacting reactive modules.
- From a Bio-PEPA description one module is generated for each species component with an additional module to capture the functional rate information.

Integrated analyses
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- Moreover, the finite nature of the state representation used means that *a priori* bounds must be set (whether numbers of molecules or discrete levels for each species are used).
- We can use stochastic simulation to establish appropriate bounds to use for defining the PRISM state space.