The Bio-PEPA project

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

System

Mathematical Model
e.g ODE or SSA
Integrated Analysis

System

Stochastic Process Algebra Model

ODE
SSA
Model Checking
Integrated Analysis

- Stochastic Process Algebra Model
- ODE
- SSA
- Model Checking
- Analysis
Bio-PEPA: motivations

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Abstract models are more amenable to integrated analysis.

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.
Motivations for Abstraction

Our motivations for seeking more abstraction:

- Process algebra-based analyses such as comparing models (e.g. for equivalence or simulation) and model checking are only possible if the state space is not prohibitively large.
- The data that we have available to parameterise models is sometimes speculative rather than precise.

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

- ODEs
- Abstract SPA model
  - Stochastic Simulation

The Bio-PEPA project
Alternative Representations

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

- ODEs
- CTMC with $M$ levels
- Stochastic Simulation

Abstract SPA model
Alternative Representations

Abstract SPA model

- ODEs
  - population view

- CTMC with $M$ levels
  - abstract view

- Stochastic Simulation
  - individual view
Modelling biological features

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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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Bio-PEPA

In Bio-PEPA:

- Unique rates are associated with each reaction (action) type, separately from the specification of the logical behaviour.
- 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.
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- 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)

\[ S ::= (\alpha, \kappa) \text{ op } S | S + S | C \quad \text{where op} = \downarrow \mid \uparrow \mid \oplus \mid \ominus \mid \odot \]
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\[ P ::= P \text{ \textasciicircum} P \mid S(l) \]


The Bio-PEPA project
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Model component

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Model component

\[ P ::= P \uplus P \mid S(l) \]

The parameter \( l \) is abstract, recording quantitative information about the species.
The syntax

Sequential component (species component)

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

Model component

\[ P ::= P \; \text{T} \; P \mid S(l) \]

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 $P$ is a 6-tuple $\langle V, N, K, F_R, \text{Comp}, P \rangle$, where:

- $V$ is the set of compartments;
- $N$ is the set of quantities describing each species (step size, number of levels, location, ...);
- $K$ is the set of parameter definitions;
- $F_R$ is the set of functional rate definitions;
- $\text{Comp}$ 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:

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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

\[ \text{prefixReac } ((\alpha, \kappa)\downarrow S)(l) \xrightarrow{(\alpha, [S: \downarrow (l, \kappa)])} cS(l - \kappa) \]
\[ \kappa \leq l \leq N \]
Semantics: prefix rules

\[
\text{prefixReac} \quad ((\alpha, \kappa) \downarrow S)(l) \xrightarrow{\alpha,[S:\downarrow(l,\kappa)]} cS(l - \kappa) \\
\kappa \leq l \leq N
\]

\[
\text{prefixProd} \quad ((\alpha, \kappa) \uparrow S)(l) \xrightarrow{\alpha,[S:\uparrow(l,\kappa)]} cS(l + \kappa) \\
0 \leq l \leq (N - \kappa)
\]
Semantics: prefix rules

\[
\text{prefixReac} \quad ((\alpha, \kappa) \downarrow S)(l) \xrightarrow{(\alpha, [S: \downarrow (l, \kappa)])} cS(l - \kappa) \\
\quad \kappa \leq l \leq N
\]

\[
\text{prefixProd} \quad ((\alpha, \kappa) \uparrow S)(l) \xrightarrow{(\alpha, [S: \uparrow (l, \kappa)])} cS(l + \kappa) \\
\quad 0 \leq l \leq (N - \kappa)
\]

\[
\text{prefixMod} \quad ((\alpha, \kappa) \text{ op } S)(l) \xrightarrow{(\alpha, [S: \text{op}(l, \kappa)])} cS(l) \\
\quad 0 \leq l \leq N
\]

with \( \text{op} = \ominus, \oplus, \text{ or } \ominus \)
Semantics: constant and choice rules

\[
\text{Choice1} \quad \frac{S_1(l) \xrightarrow{(\alpha, \nu)} c S'_1(l')}{(S_1 + S_2)(l) \xrightarrow{(\alpha, \nu)} c S'_1(l')}
\]


The Bio-PEPA project
Semantics: constant and choice rules

Choice 1

\[
S_1(I) \xrightarrow{(\alpha, \nu)} c S_1'(I')
\]

\[
(S_1 + S_2)(I) \xrightarrow{(\alpha, \nu)} c S_1'(I')
\]

Choice 2

\[
S_2(I) \xrightarrow{(\alpha, \nu)} c S_2'(I')
\]

\[
(S_1 + S_2)(I) \xrightarrow{(\alpha, \nu)} c S_2'(I')
\]
Semantics: constant and choice rules

Choice 1
\[
S_1(l)^{(\alpha,v)} \xrightarrow{c} S'_1(l')
\]
\[
(S_1 + S_2)(l)^{(\alpha,v)} \xrightarrow{c} S'_1(l')
\]

Choice 2
\[
S_2(l)^{(\alpha,v)} \xrightarrow{c} S'_2(l')
\]
\[
(S_1 + S_2)(l)^{(\alpha,v)} \xrightarrow{c} S'_2(l')
\]

Constant
\[
S(l)^{(\alpha,S:\{op(l,\kappa)\})} \xrightarrow{c} S'(l')
\]
\[
C(l)^{(\alpha,C:\{op(l,\kappa)\})} \xrightarrow{c} S'(l')
\]

with \( C \stackrel{\text{def}}{=} S \)
Semantics: cooperation rules

coop1

\[
\frac{P_1 \xrightarrow{(\alpha, v)} cP'_1}{P_1 \Join P_2 \xrightarrow{(\alpha, v)} cP'_1 \Join P_2}
\]

with \( \alpha \notin \mathcal{L} \)
Semantics: cooperation rules

coop1

\[
P_1 \xrightarrow{(\alpha, \nu)} cP'_1 \quad \text{with } \alpha \notin \mathcal{L}
\]

\[
P_1 \sqcap P_2 \xrightarrow{(\alpha, \nu)} cP'_1 \sqcap P_2
\]

coop2

\[
P_2 \xrightarrow{(\alpha, \nu)} cP'_2 \quad \text{with } \alpha \notin \mathcal{L}
\]

\[
P_1 \sqcap P_2 \xrightarrow{(\alpha, \nu)} cP_1 \sqcap P'_2
\]
Semantics: cooperation rules

coop1

\[
P_1 \xrightarrow{(\alpha,v)} cP'_1
\]

with \(\alpha \notin \mathcal{L}\)

\[
P_1 \otimes P_2 \xrightarrow{(\alpha,v)} cP'_1 \otimes P_2
\]

coop2

\[
P_2 \xrightarrow{(\alpha,v)} cP'_2
\]

with \(\alpha \notin \mathcal{L}\)

\[
P_1 \otimes P_2 \xrightarrow{(\alpha,v)} cP'_1 \otimes P'_2
\]

coopFinal

\[
P_1 \xrightarrow{(\alpha,v_1)} cP'_1 \quad P_2 \xrightarrow{(\alpha,v_2)} cP'_2
\]

with \(\alpha \in \mathcal{L}\)

\[
P_1 \otimes P_2 \xrightarrow{(\alpha,v_1::v_2)} cP'_1 \otimes P'_2
\]
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 $r \in \mathbb{R}^+$. The rate $r_{\alpha_j}$ represents the parameter of an exponential distribution and the dynamic behaviour is determined by a race condition. The rate $r_{\alpha_j}$ is defined as $f_{\alpha_j}(V, N, K) / h$. 
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The relation is defined in terms of the previous one:

\[
P^{(\alpha_j, \nu)} \xrightarrow{c} P'
\]

\[
\langle V, N, K, F_R, \text{Comp}, P \rangle \xrightarrow{(\alpha_j, r_{\alpha_j})} s \langle V, N, K, F_R, \text{Comp}, P' \rangle
\]
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The relation is defined in terms of the previous one:

\[ P^{(\alpha, v)} \xrightarrow{c} P' \]

\[ \langle V, N, K, F_R, Comp, P \rangle^{(\alpha, r_{\alpha_j})} \xrightarrow{s} \langle V, N, K, F_R, Comp, P' \rangle \]

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The relation is defined in terms of the previous one:

$$P \xrightarrow{(\alpha_j, \nu)} c P'$$

$$\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P \rangle \xrightarrow{(\alpha_j, r_{\alpha_j})} s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P' \rangle$$

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

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The Bio-PEPA project
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

We have used Bio-PEPA for a number of examples, originally taken from the literature, but increasingly in collaboration with biologists.
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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 acetylcholine receptor (with events).
- Model for complex intracellular calcium oscillations (by Goldbeter and co-authors).
Examples undertaken with biologists

- **rRNA synthesis pathway** in the formation of ribosomes: the model was used to investigate the relative frequency of co-transcriptional cleavage. (Tollervey Laboratory, CSBE)
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- **JAK/STAT pathway in chickens**: investigating the differences between chickens susceptible and resistant to Marek’s disease. (Roslin Institute)
Bio-PEPA with Events [Cioc ProcMod08]

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- When modelling *in vitro* systems it can be the case that the system is deliberately perturbed in a controlled way at a specific time.
- There may be discrete changes in systems, such as gene activation and deactivation.
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- There may be discrete changes in systems, such as gene activation and deactivation.

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
Improved Compartments [CG MeCBiC08]

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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.
Equivalence relations

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We are now seeking to define equivalence and simulation relations for Bio-PEPA which might be more useful from the biological perspective.

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: $A \to A_1 \to A_2 \to A_3 \to A_4 \to B$ and $A \to B$
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Currently, we are studying these at the qualitative level, but ultimately relationships based on the stochastic relation will be important.
Mapping from SBGN to Bio-PEPA

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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
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- *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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- A transient analysis provides statistics relating to the evolution of the model over a fixed period. This will be dependent on the starting state.
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SPA
MODEL
CTMC with levels

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- A steady state analysis provides statistics for average behaviour over a long run of the system, when the bias introduced by the initial state has been lost.
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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].
PRISM model and model checking

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- Building a reward structure over the model it is possible to express complex analysis questions.
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- Formally the mapping from Bio-PEPA is based on the structured operational semantics, generating the underlying CTMC in the usual way.
- 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
[CHDC FBTC08] and [CGGH PASM08]

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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).
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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.