Modelling Biochemical Pathways with Stochastic Process Algebra

Jane Hillston.
LFCS, University of Edinburgh

9th May 2007
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- Process algebras offered a compositional description technique supported by apparatus for formal reasoning.
- Performance Evaluation Process Algebra (PEPA) sought to address these problems by the introduction of a suitable process algebra.
- The project has sought to investigate and exploit the interplay between the process algebra and the continuous time Markov chain (CTMC).
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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- Robotic workcells (Holton, Gilmore and Hillston, Bradford and Edinburgh)
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- Automotive diagnostic expert systems (Console, Picardi and Ribaudo, Turin)
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Alternative Representations

Summary
Systems Biology

- Biological advances mean that much more is now known about the components of cells and the interactions between them.
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- **Systems biology** aims to develop a better understanding of the processes involved.
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- It involves taking a **systems theoretic** view of biological processes — analysing inputs and outputs and the relationships between them.
Motivation

Systems Biology

- Biological advances mean that much more is now known about the components of cells and the interactions between them.
- Systems biology aims to develop a better understanding of the processes involved.
- It involves taking a systems theoretic view of biological processes — analysing inputs and outputs and the relationships between them.
- A radical shift from earlier reductionist approaches, systems biology aims to provide a conceptual basis and a methodology for reasoning about biological phenomena.
Systems Biology Methodology

Natural System \[\xrightarrow{Measurement} \xrightarrow{Observation} \] Biological Phenomena

Explanation
Interpretation

Systems Analysis \[\xrightarrow{Deduction} \xrightarrow{Inference} \] Formal System

Induction
Modelling

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Measurement Observation

Deduction Inference
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↑ Explanation
↑ Observation

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↓ Interpretation
↓ Inference

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Modelling Biochemical Pathways with Stochastic Process Algebra
Biochemical Pathways

At the intra-cellular level we can distinguish three distinct types of pathways or networks
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Biochemical Pathways

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**Metabolic pathways:** The survival of the cell depends on its ability to transform nutrients into energy.
Biochemical Pathways

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**Gene networks:** Genes control the production of proteins but are themselves regulated by the same or different proteins.

**Signal transduction networks:** External stimuli initiate messages that are carried through a cell via a cascade of biochemical reactions.

**Metabolic pathways:** The survival of the cell depends on its ability to transform nutrients into energy.

But these distinctions are to some extent arbitrary as models may include elements of more than one pathway type.
Signal transduction pathways

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Signal transduction pathways

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> Increasing protein concentration broadcasts the information about an event.

> The message is “received” by a concentration dependent response at the protein signal’s site of action.

> This stimulates a response at the signalling protein’s site of action.

> Signals propagate through a series of protein accumulations.
Formal Systems

There are two alternative approaches to constructing dynamic models of biochemical pathways commonly used by biologists:

- **Ordinary Differential Equations**
  - continuous time,
  - continuous behaviour (concentrations),
  - deterministic.

- **Stochastic Simulation**
  - continuous time,
  - discrete behaviour (no. of molecules),
  - stochastic.
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Modelling Biochemical Pathways with Stochastic Process Algebra
Ordinary Differential Equations

- This deterministic approach has at its core the law of mass action. This states that for a reaction in a homogeneous, free medium, the reaction rate will be proportional to the concentrations of the individual reactants involved.
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For example, for a reaction $A + B \xrightarrow{k} C$:

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k[A][B]$$

$$\frac{d[C]}{dt} = k[A][B]$$
Limitations of Ordinary Differential Equations

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- This is based on the assumption that chemical reactions to be macroscopic under convective or diffusive stirring, continuous and deterministic.
- This is a simplification, because in reality chemical reactions involve discrete, random collisions between individual molecules.
- As we consider smaller and smaller systems, the validity of a continuous approach becomes ever more tenuous.
As explicitly derived by Gillespie, the stochastic model uses basic Newtonian physics and thermodynamics to arrive at a form often termed the propensity function that gives the probability $a_\mu$ of reaction $\mu$ occurring in time interval $(t, t + dt)$.

$$a_\mu dt = h_\mu c_\mu dt$$

where the $M$ reaction mechanisms are given an arbitrary index $\mu$ ($1 \leq \mu \leq M$), $h_\mu$ denotes the number of possible combinations of reactant molecules involved in reaction $\mu$, and $c_\mu$ is a stochastic rate constant.
Stochastic: Chemical Master Equation

Applying this leads us to an important *partial differential equation* (PDE) known as the Chemical Master Equation (CME).

\[
\frac{\partial \Pr(X; t)}{\partial t} = \sum_{\mu=1}^{M} a_\mu (X - v_\mu) \Pr(X - v_\mu; t) - a_\mu(X) \Pr(X; t)
\]

Does not lend itself to either analytic nor numerical solutions.
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Modelling Biochemical Pathways with Stochastic Process Algebra
Stochastic simulation algorithms

Gillespie’s Stochastic Simulation Algorithm (SSA) is essentially an exact procedure for numerically simulating the time evolution of a well-stirred chemically reacting system by taking proper account of the randomness inherent in such a system.
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As with the chemical master equation, the SSA converges, in the limit of large numbers of reactants, to the same solution as the law of mass action.
**Systems Analysis**

- In biochemical signalling pathways the events of interests are:
  - when reagent concentrations start to increase;
  - when concentrations pass certain thresholds;
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- These data can be collected from wet lab experiments.
- The accumulation of protein is a stochastic process affected by several factors in the cell (temperature, pH, etc.).
- Thus it is more realistic to talk about a distribution rather than a deterministic time.
Formal Systems Revisited

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- Moreover taking this “high-level programming” style approach offers the possibility of different “compilations” to different mathematical models.
Outline

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Motivation

Stochastic Process Algebra
   Abstract Modelling
   Case Study
   Alternative Representations

Summary
Using Stochastic Process Algebras

Process algebras have several attractive features which could be useful for modelling and understanding biological systems:
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- Process algebraic formulations are compositional and make interactions/constraints explicit.
- Structure can also be apparent.
- 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

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[Regev et al 2000]
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Mapping biological systems to process algebra

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Abstract Modelling

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In our mapping we focus on species (c.f. a type rather than an instance, or a class rather than an object).

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

Our motivations for seeking more abstraction in process algebra models for systems biology are:
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- 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 semiquantitative models rather than quantitative ones.
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Alternative Representations

- Abstract SPA model
- Stochastic Simulation
- ODEs
Alternative Representations

Abstract SPA model

- ODEs (population view)
- Stochastic Simulation (individual 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 PEPA model

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

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Alternative Representations

Abstract PEPA model

CTMC with $M$ levels

ODEs population view

Stochastic Simulation individual view

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Model checking and Markovian analysis

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Modelling Biochemical Pathways with Stochastic Process Algebra
Abstract Modelling

PEPA: Performance Evaluation Process Algebra

\[ S ::= (\alpha, r).S \mid S + S \mid A \]
\[ P ::= S \mid P \otimes P \mid P/L \]
Abstract Modelling

**PEPA**: Performance Evaluation Process Algebra

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\[
P ::= S | P \triangledown S | P / L
\]

Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.
Abstract Modelling

**PEPA**: Performance Evaluation Process Algebra

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The language may be used to generate a Markov Process (CTMC).

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SPA MODEL \xrightarrow{\text{SOS rules}} \text{LABELLED TRANSITION SYSTEM} \xrightarrow{\text{state transition diagram}}
**PEPA: Performance Evaluation Process Algebra**

\[
S ::= (\alpha, r).S | S + S | A \\
P ::= S | P \oplus P | P/L
\]

The language may be used to generate a Markov Process (CTMC).

\[Q\] is the infinitesimal generator matrix characterising the CTMC.
PEPA: Performance Evaluation Process Algebra

\[
S ::= (\alpha, r).S | S + S | A
\]

\[
P ::= S | P \bowtie P | P/L
\]

The language may be used to generate a system of ordinary differential equations (ODEs).
Abstract Modelling

**PEPA: Performance Evaluation Process Algebra**

\[ S ::= (\alpha, r) \cdot S \mid S + S \mid A \]
\[ P ::= S \mid P \boxtimes_l P \mid P/L \]

The language may be used to generate a system of ordinary differential equations (ODEs).

SPA

MODEL
Abstract Modelling

PEPA: Performance Evaluation Process Algebra

\[ S ::= (\alpha, r).S \mid S + S \mid A \]
\[ P ::= S \mid P \otimes P \mid P/L \]

The language may be used to generate a system of ordinary differential equations (ODEs).
Abstract Modelling

PEPA: Performance Evaluation Process Algebra

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S \ ::= \ (\alpha, r).S \mid S + S \mid A \\
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The language may be used to generate a system of ordinary differential equations (ODEs).

SPA MODEL \rightarrow \text{syntactic analysis} \rightarrow \text{ACTIVITY MATRIX}
PEPA: Performance Evaluation Process Algebra

\[ S ::= (\alpha, r).S | S + S | A \]

\[ P ::= S | P \otimes L P | P/L \]

The language may be used to generate a system of ordinary differential equations (ODEs).

SPA MODEL \(\xrightarrow{\text{syntactic analysis}}\) ACTIVITY MATRIX \(\xrightarrow{\text{continuous interpretation}}\)
PEPA: Performance Evaluation Process Algebra

\[ S ::= (\alpha, r).S \mid S + S \mid A \]
\[ P ::= S \mid P \parallel P \mid P/L \]

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The language also may be used to generate a stochastic simulation.
Abstract Modelling

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SPA
MODEL
PEPA: Performance Evaluation Process Algebra

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The language also may be used to generate a stochastic simulation.
Abstract Modelling

PEPA: Performance Evaluation Process Algebra

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PEPA: Performance Evaluation Process Algebra

\[
S ::= (\alpha, r).S | S + S | A \\
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The language also may be used to generate a stochastic simulation.
Abstract Modelling

PEPA: Performance Evaluation Process Algebra

\[ S ::= (\alpha, r).S \mid S + S \mid A \]
\[ P ::= S \mid P \ltimes P \mid P/L \]

The language also may be used to generate a stochastic simulation.
Abstract Modelling

PEPA: Performance Evaluation Process Algebra

\[ S ::= (\alpha, r).S | S + S | A \]
\[ P ::= S | P \parallel P | P/L \]

The language also may be used to generate a stochastic simulation.

Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.

Jane Hillston. LFCS, University of Edinburgh.

Modelling Biochemical Pathways with Stochastic Process Algebra
Markovian analysis

- Analysis of the Markov process can yield quite detailed information about the dynamic behaviour of the model.
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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.
- A transient analysis provides statistics relating to the evolution of the model over a fixed period. This will be dependent on the starting state.
- **Stochastic model checking** is available via the PRISM model checker, assessing the probable validity of properties expressed in CSL (Continuous Stochastic Logic).
Reagent-centric modelling [CGH04]

<table>
<thead>
<tr>
<th>Reagent role</th>
<th>Impact on reagent</th>
<th>Impact on reaction rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Producer</td>
<td>decreases concentration</td>
<td>has a positive impact, i.e. proportional to current concentration</td>
</tr>
<tr>
<td>Product</td>
<td>increases concentration</td>
<td>has no impact on the rate, except at saturation</td>
</tr>
<tr>
<td>Enzyme</td>
<td>concentration unchanged</td>
<td>has a positive impact, i.e. proportional to current concentration</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>concentration unchanged</td>
<td>has a negative impact, i.e. inversely proportional to current concentration</td>
</tr>
</tbody>
</table>
PEPA reagent-centric example

\[
\begin{align*}
A_H & \equiv (ab_c, \alpha).A_L \\
A_L & \equiv (b_a, \beta).A_H + (c_a, \gamma).A_H \\
B_H & \equiv (ab_c, \alpha).B_L + (b_a, \beta).B_L \\
B_L & \equiv (c_b, \delta).B_H \\
C_H & \equiv (c_a, \gamma).C_L + (c_b, \delta).C_L \\
C_L & \equiv (ab_c, \alpha).C_H
\end{align*}
\]
Abstract Modelling

**PEPA reagent-centric example**

Jane Hillston. LFCS, University of Edinburgh.

Modelling Biochemical Pathways with Stochastic Process Algebra
Abstract Modelling

PEPA reagent-centric example

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Modelling Biochemical Pathways with Stochastic Process Algebra
PEPA reagent-centric example

\[
\begin{align*}
\text{AH} & \overset{\text{def}}{=} \ (ab\_c, \alpha).\text{AL} \\
\text{AL} & \overset{\text{def}}{=} \ (b\_a, \beta).\text{AH} + (c\_a, \gamma).\text{AH} \\
\text{BH} & \overset{\text{def}}{=} \ (ab\_c, \alpha).\text{BL} + (b\_a, \beta).\text{BL} \\
\text{BL} & \overset{\text{def}}{=} \ (c\_b, \delta).\text{BH} \\
\text{CH} & \overset{\text{def}}{=} \ (c\_a, \gamma).\text{CL} + (c\_b, \delta).\text{CL} \\
\text{CL} & \overset{\text{def}}{=} \ (ab\_c, \alpha).\text{CH}
\end{align*}
\]
PEPA reagent-centric example

\[
\begin{align*}
A_H & \overset{\text{def}}{=} (ab_c, \alpha).A_L \\
A_L & \overset{\text{def}}{=} (b_a, \beta).A_H + (c_a, \gamma).A_H \\
B_H & \overset{\text{def}}{=} (ab_c, \alpha).B_L + (b_a, \beta).B_L \\
B_L & \overset{\text{def}}{=} (c_b, \delta).B_H \\
C_H & \overset{\text{def}}{=} (c_a, \gamma).C_L + (c_b, \delta).C_L \\
C_L & \overset{\text{def}}{=} (ab_c, \alpha).C_H
\end{align*}
\]

\[(A_H \{ab_c,b_a\} B_H \{ab_c,c_a,c_b\} C_L)\]
Case Study: Schoeberl et al.’s model of the MAPK Cascade [CDGH06]

- Published in *Nature Biotechnology* 20:370-375 in 2002.
- Influential, cited by more than 150 subsequent published papers.
- Consists of 94 reagent species involved in 125 reactions.
- Substantial ODE model consisting of 94 state variables and 95 parameters.
- Original model constructed “by hand”, with help of a graphical representation.
- Original analysis based on numerical integration platform of the Matlab numerical computing platform.
Case Study

The MAP Kinase Cascade

Jane Hillston. LFCS, University of Edinburgh.

Modelling Biochemical Pathways with Stochastic Process Algebra
The MAP Kinase Cascade

There are many ambiguities in the graphical representation, e.g.:
- An infinite supply of EGF is assumed;
- Reaction $v_7$ is uni-directional whereas all others are reversible.
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The MAP Kinase Cascade

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- An infinite supply of EGF is assumed;
- Reaction $v7$ is uni-directional whereas all others are reversible.
**Extracts from the model of the MAP Kinase Cascade**

\[
\begin{align*}
\text{EGF}_H & \quad \overset{\text{def}}{=} (v_1, k_1).\text{EGF}_H \\
\text{EGFR}_H & \quad \overset{\text{def}}{=} (v_1, k_1).\text{EGFR}_L + (v_6, k_6).\text{EGFR}_L \\
\text{EGFR}_L & \quad \overset{\text{def}}{=} (v_{-1}, k_{-1}).\text{EGFR}_H + (v_{-6}, k_{-6}).\text{EGFR}_H + (v_{13}, k_{13}).\text{EGFR}_H \\
\text{EGF-EGFR}_H & \quad \overset{\text{def}}{=} (v_2, k_2).\text{EGF-EGFR}_L + (v_{-1}, k_{-1}).\text{EGF-EGFR}_L \\
\text{EGF-EGFR}_L & \quad \overset{\text{def}}{=} (v_1, k_1).\text{EGF-EGFR}_H + (v_{-2}, k_{-2}).\text{EGF-EGFR}_H
\end{align*}
\]
The PEPA model

Similar PEPA definitions were constructed for each of the 94 species in the pathway.
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This was tedious, but not difficult, although care was needed to handle the points of ambiguity in the graphical representation.
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In order to complete the model we also needed to capture the interactions (i.e. cooperations) between the reagents. In this case we assumed that whenever reagents participated in reactions with the same name they did so in cooperation.
Validation of the PEPA model

- Once the PEPA model was constructed, we wanted to ensure that it was generating the same mathematical representation of the system.
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Case Study

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Validation of the PEPA model

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- In the first instance we derived a set of ODEs in a format suitable for Matlab.
- These could not be compared directly with Schoeberl et al’s ODEs due to different representations being used, but we compared them empirically in terms of the results.
- Then we used an alternative mapping from the PEPA to generate a stochastic simulation of the system.
Comparing Original Results and PEPA Derived ODEs

The PEPA derived ODEs return the same results as the Schoeberl et al. Matlab model.

Jane Hillston. LFCS, University of Edinburgh.
Modelling Biochemical Pathways with Stochastic Process Algebra
Comparing Original Results and PEPA Derived ODEs

The PEPA derived ODEs return the same results as the Schoeberl et al. Matlab model.
Comparing Original Results and PEPA Derived Stochastic Simulation

Raf*

Original Schoeberl et al. Matlab Model
PEPA derived Tau-leap Simulation
Comparing Original Results and PEPA Derived Stochastic Simulation

![Graph comparing Ras-GTP molecules per cell over time between original results and PEPA derived Tau-leap Simulation]

Original Schoeberl et al. Matlab Model
PEPA derived Tau-leap Simulation
Corrected Time Step in Matlab Model

The original parameters for the Matlab model stepped over the true peak.

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Modelling Biochemical Pathways with Stochastic Process Algebra
The original parameters for the Matlab model stepped over the true peak.
On-going work

On-going work on this case study is working on a Markovian analysis of the system.

This involves developing the model to have multiple levels rather than the simple distinction between high and low which is all that is needed in order to generate the ODE and stochastic simulation models.
Equivalent Representations?

Abstract PEPA model

CTMC with $M$ levels

Stochastic Simulation

ODEs

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Modelling Biochemical Pathways with Stochastic Process Algebra
Equivalent Representations?

- Abstract PEPA model
- CTMC with $M$ levels
- Stochastic Simulation
- ODEs

population view
abstract view
individual view

$\text{equal when } M \rightarrow \infty$

[GH07]

Jane Hillston. LFCS, University of Edinburgh.

Modelling Biochemical Pathways with Stochastic Process Algebra
Equivalent Representations?

- Abstract PEPA model
- ODEs (population view)
- CTMC with $M$ levels
  - $\rightarrow \infty$ (equivalent when $M \rightarrow \infty$)
  - $M = N$ (equivalent when $M = N$)
  - ?
- Stochastic Simulation (individual view)
  - ?

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Modelling Biochemical Pathways with Stochastic Process Algebra
Equivalent Representations?

- Abstract PEPA model
- CTMC with $M$ levels
- Stochastic Simulation

$\text{ODEs}$

? equal when $M = N$

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Modelling Biochemical Pathways with Stochastic Process Algebra
Equivalent Representations?

Abstract PEPA model \rightarrow CTMC with \( M \) levels \rightarrow Stochastic Simulation

\[ \text{equal when } M \rightarrow \infty \quad \text{[GHS07]} \]

\[ \text{equal when } M = N \]
Relating CTMC and ODE models

- We consider an extension of PEPA, PEPA+, in which both bounded capacity and mass action kinetics are defined.
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- Kurtz’s theorem states that a sequence of pure jump Markov processes converge to a limit which coincides with a set of ODEs [Kurtz 70]. In particular this holds for a class of CTMCs which are density dependent.
- We show that the CTMCs we construct from the PEPA+ models are density dependent and so satisfy Kurtz’s theorem.
Density Dependent CTMC

A family of CTMCs is called density dependent if and only if there exists a continuous function \( f(x, l), x \in \mathbb{R}^h, l \in \mathbb{Z}^h \), such that the infinitesimal generators of \( X_N \) are given by:

\[
q_{k,k+1} = N f\left(\frac{k}{N}, l\right), \quad l \neq 0
\]

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- $q_{k,k+1}$ denotes an entry in the infinitesimal generator matrix;
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- \( k \) is a numerical state vector and
- \( l \) is a transition vector i.e. it records the adjustment to the number of copies of each state of each entity (species) after the transition is taken.
Outline

Introduction to Systems Biology
  Motivation

Stochastic Process Algebra
  Abstract Modelling
  Case Study
  Alternative Representations

Summary
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- Abstract modelling offers a compromise between the individual-based and population-based views of systems which biologists commonly take.
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▶ Moveover we can undertake additional analysis based on the discretised population view.
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- Further work is needed to establish a better relationship between this view and the population view — empirical evidence has shown that 6 or 7 levels are often sufficient to capture exactly the same behaviour as the ODE model.
Summary

- Abstract modelling offers a compromise between the individual-based and population-based views of systems which biologists commonly take.
- Moreover we can undertake additional analysis based on the discretised population view.
- Further work is needed to establish a better relationship between this view and the population view — empirical evidence has shown that 6 or 7 levels are often sufficient to capture exactly the same behaviour as the ODE model.
- In the future we hope to investigate the extent to which the process algebra compositional structure can be exploited during model analysis.
Challenges

▶ The issue of unknown and uncertain data remains to be addressed.

Promising recent work by Girolami et al. on assessing candidate models which attempt to cover both unknown structure and unknown kinetic rates with respect to experimental data, using Bayesian reasoning.
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  - Better models and simulations of living phenomena
  - New models of computations that are biologically inspired.
Thank You!
Thank You!

Collaborators: Muffy Calder, Federica Ciocchetta, Adam Duguid, Nil Geisweiller, Stephen Gilmore and Marco Stenico.
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