Modelling Biochemical Pathways with Stochastic Process Algebra

Jane Hillston.
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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).
Outline

Introduction to Systems Biology
  Motivation
  Case Studies

Challenges
  Individual vs. Population
  Noise vs. Determinism
  Modularity vs. Infinite Regress
  Dealing with the Unknown

Stochastic Process Algebra
  Abstract Modelling
  Case Study
  Alternative Representations

Summary

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Summary
Motivation

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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- It involves taking a systems theoretic view of biological processes — analysing inputs and outputs and the relationships between them.
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- 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 $\xrightarrow{\text{Measurement}}$ Biological Phenomena

Explanation

Interpretation

Measurement

Observation

Systems Analysis $\xleftarrow{\text{Deduction}}$ Formal System

Deduction

Inference

Induction

Modelling
**Systems Biology Methodology**

**Natural System** → **Measurement** → **Biological Phenomena**

**Systems Analysis** ← **Explanation** ← **Deduction** ← **Formal System**

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- As an approach systems biology can be applied to many different biological systems at different scales.
- For example, from gene regulation within the nucleus of a cell, to whole organs, or even complete organisms.
- The biological phenomena to be studied will clearly depend on the type of system being investigated.
- A grand challenge for systems biology is to develop multi-scale models which seek to account for high-level behaviour (at the level of the whole organisms) at all levels down to the intra-cellular processes.
Biochemical Pathways

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**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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- 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

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

- **Stochastic Simulation:**
  - continuous time,
  - discrete behaviour (no. of molecules),
  - stochastic.
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]
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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.
Stochastic: Propensity function

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, and re-arranging the former, leads us to an important *partial differential equation* (PDE) known as the Chemical Master Equation (CME).

\[
\frac{\partial \Pr(\mathbf{X}; t)}{\partial t} = \sum_{\mu=1}^{M} a_{\mu}(\mathbf{X} - \mathbf{v}_\mu) \Pr(\mathbf{X} - \mathbf{v}_\mu; t) - a_{\mu}(\mathbf{X}) \Pr(\mathbf{X}; t)
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Stochastic simulation algorithms

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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.
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- when reagent concentrations start to increase;
- when concentrations pass certain thresholds;
- when a peak of concentration is reached.
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► 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.
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It is held up as an exemplar of what systems biology is trying to achieve, and the breakthroughs that it can bring about when it is successful.
Case Study: Circadian Rhythms – Initial Model

From initial experiments Locke et al. identified a two genes and two proteins which appeared to operate in a simple loop:

An initial mathematical model (ODEs) was constructed to capture this model.
Case Study: Circadian Rhythms – Role of Mathematics

Initial simulations with the mathematical model showed good agreement with the experimental data for some of the observed phenomena but significant discrepancies for others.
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These mathematical experiments conjectured a network with two interacting loops.
Case Study: Circadian Rhythms – Elaborated Model

Two “new” genes were introduced to the model which now has interlocking loops and more complex feedback.
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The simulation results from this model showed much better agreement with the observed data.
Case Study: Circadian Rhythms – Validating the Model

The researchers then sought to identify the “new” genes X and Y.

Searching the literature elicited several candidate genes which previous experimental studies had suggested were implicated in the circadian rhythm.

In particular, “knockout” data for one, GIGANTEA (GI), coincided with the pattern from simulation experiments of the original model with a single loop.

Subsequent wet lab experiments have reinforced this impression that GI is gene Y.
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- Chiarugi et al. carried out in silico experiments to test the viability of this gene set.
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D. Chiarugi, M. Curti, P. Degano and R. Marangoni
VICE: A VIrtual CEll
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- The experiments showed that MGS was not viable: the cell could not survive in simulation.
- 76 genes were found to be functionally duplicated and 7 additional genes were added to form VICE.
Case Study: The VICE project – In silico experimentation

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- Subsequent models were developed in stochastic $pi$-calculus so that comparison with dynamic biological data was possible.
- A bespoke simulator was written to simulate the behaviour of the alternative gene sets and the VICE gene set was chosen as the most promising.
- The steady state distribution of the concentrations of virtual metabolites was similar to that measured for bacteria experimentally.
Formal Systems Revisited

- Currently mathematics is being used directly as the formal system — even the work with the stochastic $\pi$-calculus only uses the $\pi$-calculus to describe a continuous time Markov chain (CTMC) for simulation.
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- Previous experience in the performance arena has shown us that there can be benefits to interposing a formal model between the system and the underlying mathematical model.
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Previous experience in the performance arena has shown us that there can be benefits to interposing a formal model between the system and the underlying mathematical model.

Moreover taking this “high-level programming” style approach offers the possibility of different “compilations” to different mathematical models.
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- These should be regarded as alternatives, each being appropriate for some models. The challenge then becomes when to use which approach.
- Note that given a large enough number of molecules an “individuals” model will (in many circumstances) be indistinguishable from the a “population” level model.
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- When a large number of such reactions occur, the randomness of the individual reactions can cancel each other out and the apparent behaviour exhibits less variability.
- However, in some systems the variability in the stochastic behaviour plays a crucial role in the dynamics of the system.
Comparing stochastic simulation and ODEs

Consider a Michaelis Menten reaction in which a substrate $S$ is transformed to a product $\overline{S}$ via a complex $C$ formed with an enzyme $E$.

It is relatively straightforward to contrast the results of the two methods. We compare the results of 2000 runs of the stochastic algorithm simulating a system with initial molecular populations $S_0 = 100$, $E_0 = 10$, $C_0 = 0$, $\overline{S}_0 = 0$ and a volume of 1000 units.
Results for $S_0 = 100, E_0 = 10, C_0 = 0, \overline{S}_0 = 0$ (vol 1000)
Results for $S_0 = 100, E_0 = 10, C_0 = 0, \bar{S}_0 = 0$ (vol 1000)
**In vivo behaviour compared with model behaviour**

However, it is worth bearing in mind that an actual *in vivo* biochemical reaction would follow just one of the many random curves that average together producing the closely fitting mean. This curve may deviate significantly from that of the deterministic approach, and thus call into question its validity.
**In vivo behaviour compared with model behaviour**

However, it is worth bearing in mind that an actual *in vivo* biochemical reaction would follow just one of the many random curves that average together producing the closely fitting mean. This curve may deviate significantly from that of the deterministic approach, and thus call into question its validity.

But this does not mean that the randomness exhibited by a particular stochastic simulation trajectory will be the same as the randomness of a particular *in vivo* reaction. Indeed, a set of stochastic simulation trajectories (ensemble) is usually averaged before any conclusions are drawn.
Comparing results at lower population sizes

\[ S_0 = 10, E_0 = 1, C_0 = 0, \bar{S}_0 = 0 \text{ (vol 100)} \]
Mean results for 11, 110 and 1100 molecules
Circadian clock

The Vilar-Kueh-Barkai-Leibler (VKBL in short) description of the circadian oscillator incorporates an abstraction of a minimal set of mechanisms for a circadian system.
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- The activator $A$ binds to the $A$ and $R$ promoters and increases their expression rate. Thus, $A$ implements a positive loop acting on its own transcription.
- Conversely, $R$ sequesters $A$ to form a complex $C$, therefore inhibiting it from binding to the gene promoter and acting as a negative feedback loop.
Circadian clock (cartoon)
Circadian clock (deterministically ...)

Jane Hillston. LFCS, University of Edinburgh.
Modelling Biochemical Pathways with Stochastic Process Algebra
Circadian clock (...and stochastically)
Conclusions from the Circadian Clock

- For some parameter values a differential equation model exhibits autonomous oscillations.
- These oscillations disappear from the deterministic model as the degradation rate of the repressor $\delta_R$ is decreased.
- The system of ODEs undergoes a bifurcation at this point and exhibits a unique stable deterministic equilibrium.
- However, if the effects of molecular noise are incorporated the oscillations in the stochastic system pertain.
- This phenomenon is a manifestation of coherence resonance, and illustrates the crucial interplay between noise and dynamics.
Modularity vs. Infinite Regress

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Some biologists (e.g. Leibler) argue that there is modularity, naturally occurring, where they define a module relative to a biological function.

Others such as Cornish-Bowden are much more skeptical and cite the problem of infinite regress as being insurmountable.
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Dealing with the Unknown

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Even when data exists the quality is often very poor.
Outline

Introduction to Systems Biology
  Motivation
  Case Studies

Challenges
  Individual vs. Population
  Noise vs. Determinism
  Modularity vs. Infinite Regress
  Dealing with the Unknown

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.
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 Markov Process (CTMC).
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Modelling Biochemical Pathways with Stochastic Process Algebra
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The PEPA model is transformed into a labelled transition system and then to a CTMC. The infinitesimal generator matrix \( Q \) characterises the CTMC.

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.
- Note, transient Markovian analysis is exact because it takes account of all possible evolutions, unlike a stochastic simulation which considers only one possible evolution in each run.
Molecular processes as concurrent computations

<table>
<thead>
<tr>
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<th>Molecular Biology</th>
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</tr>
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Motivations for Abstraction

Our motivations for seeking more abstraction in process algebra models for systems biology comes from both key aspects of modelling:

- The data that we have available to parameterise models is sometimes speculative rather than precise. This suggests that we should use semiquantitative models rather than quantitative ones.
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Mapping biological systems to process algebra

The work using the stochastic $\pi$-calculus and related calculi, for modelling biochemical signalling within cells maps a molecule in a pathway to a process in the process algebra description.
Abstract Modelling

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In the PEPA modelling we have been doing we have experimented with more abstract mappings between process algebra constructs and elements of signalling pathways.

In our mapping we focus on species (c.f. a type rather than an instance, or a class rather than an object).
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.
Reagent-centric modelling [CGH04]

<table>
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<th>Impact on reagent</th>
<th>Impact on reaction rate</th>
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<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>
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<td>Inhibitor</td>
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Deriving quantitative data

PEPA models can be analysed for quantified dynamic behaviour in a number of different ways.
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SPA
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SPA → syntactic analysis
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Modelling Biochemical Pathways with Stochastic Process Algebra
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Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.
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
Case Study

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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Modelling Biochemical Pathways with Stochastic Process Algebra
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Extracts from the model of the MAP Kinase Cascade

\[ \text{EGF}_H \overset{\text{def}}{=} (v_1, k_1).\text{EGF}_H \]

\[ \text{EGFR}_H \overset{\text{def}}{=} (v_1, k_1).\text{EGF}_R + (v_6, k_6).\text{EGF}_R \]

\[ \text{EGFR}_L \overset{\text{def}}{=} (v_1, k_1).\text{EGF}_H + (v_6, k_6).\text{EGF}_H + (v_{13}, k_{13}).\text{EGF}_H \]

\[ \text{EGF-EGFR}_H \overset{\text{def}}{=} (v_2, k_2).\text{EGF-EGF}_R + (v_1, k_1).\text{EGF-EGF}_R \]

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The PEPA model

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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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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.
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Comparing Original Results and PEPA Derived Stochastic Simulation

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Modelling Biochemical Pathways with Stochastic Process Algebra
Comparing Original Results and PEPA Derived Stochastic Simulation

![Graph comparing original results and PEPA derived simulation for Ras-GTP](image)

Legend:
- Original Schoeberl et al. Matlab Model
- PEPA derived Tau-leap Simulation

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Modelling Biochemical Pathways with Stochastic Process Algebra
Corrected Time Step in Matlab Model

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Modelling Biochemical Pathways with Stochastic Process Algebra
Corrected Time Step in Matlab Model

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

Abstract PEPA model

\[ \text{CTMC with } M \text{ levels} \]

\[ \text{Stochastic Simulation} \]

\[ \text{ODEs} \]
Alternative Representations

Abstract PEPA model

CTMC with $M$ levels

Stochastic Simulation

ODEs

Equal when $M \rightarrow \infty$ [GHS07]

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Modelling Biochemical Pathways with Stochastic Process Algebra
Alternative Representations

Abstract PEPA model

CTMC with $M$ levels

ODEs

Stochastic Simulation

equal when $M = N$
Alternative Representations

Abstract PEPA model

- ODEs
  - equal when $M \rightarrow \infty$
  - [GHS07]

- CTMC with $M$ levels
  - equal when $M = N$

- Stochastic Simulation
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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.
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- In the future we hope to investigate the extent to which the process algebra compositional structure can be exploited during model analysis.
Challenges cont.

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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 shows variability.
- Promising recent work by Girolami et al. on assessing candidates models which attempt to cover both unknown structure and unknown kinetic rates with respect to experimental data, using Bayesian reasoning.
Conclusions

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Thank You!
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