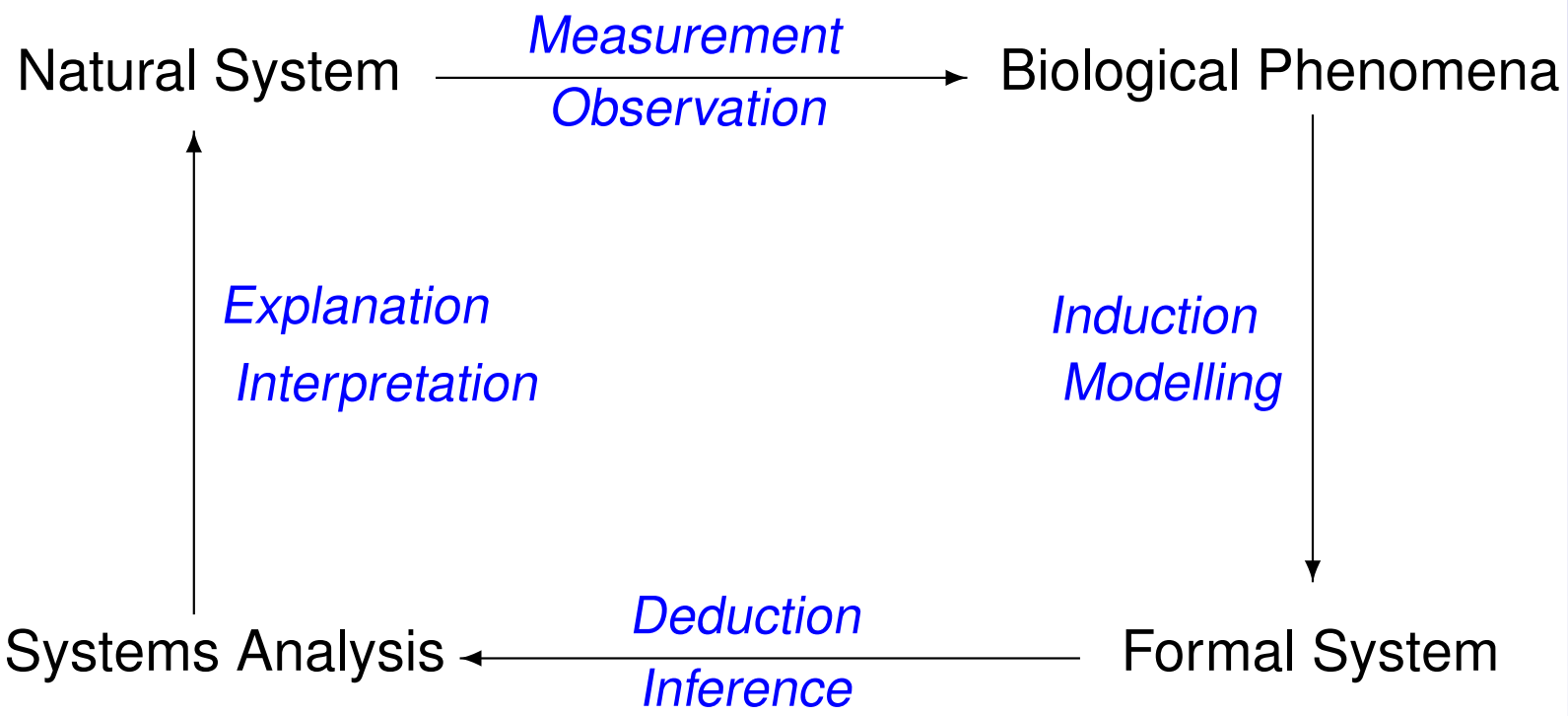
Bio-PEPA: A collective dynamics approach to systems biology

Jane Hillston.
LFCS and CSBE, University of Edinburgh

30th April 2010

Outline

Systems Biology Methodology



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- Ordinary Differential Equations:
  - continuous time,
  - continuous behaviour (concentrations),
  - deterministic.
- Stochastic Simulation:
  - continuous time,
  - discrete behaviour (no. of molecules),
  - stochastic.

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have a key role to play.

Process algebras have mechanisms for each of these, and stochastic extensions which allow dynamic properties to be analysed.

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We also wanted to be able to capture more biological features .

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Ordinary differential equations have been used in the context of biochemistry for decades and for many systems that level of abstraction is appropriate so the collective dynamics view is one which biologists are comfortable with.

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

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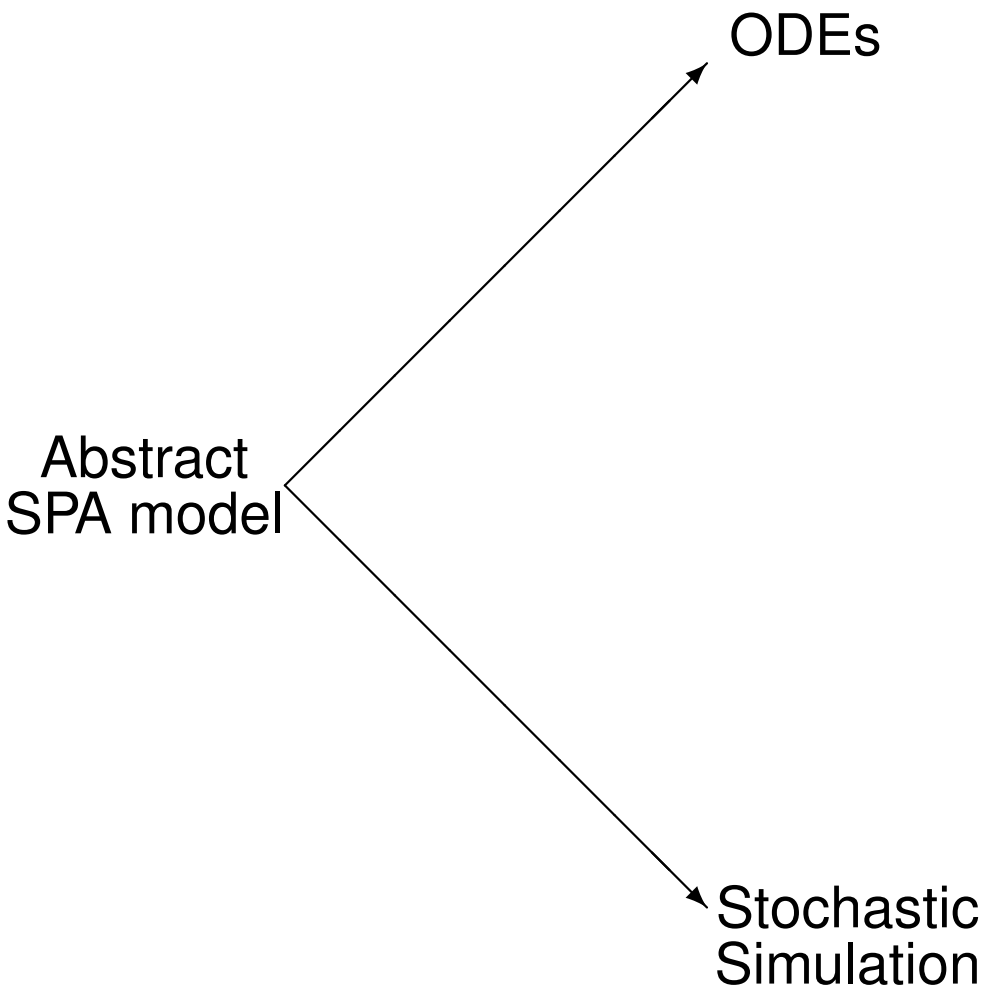

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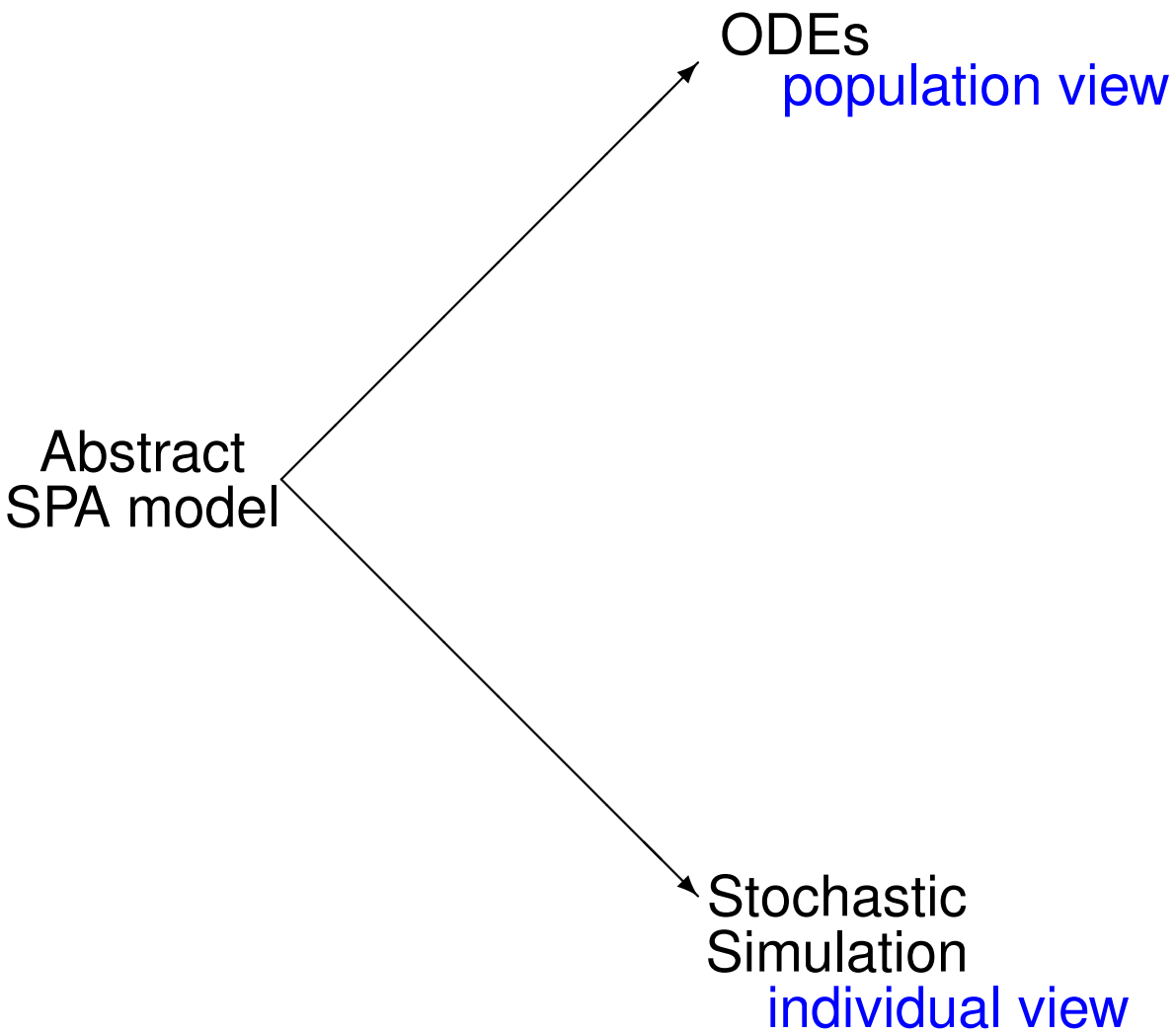

Discretising the population view

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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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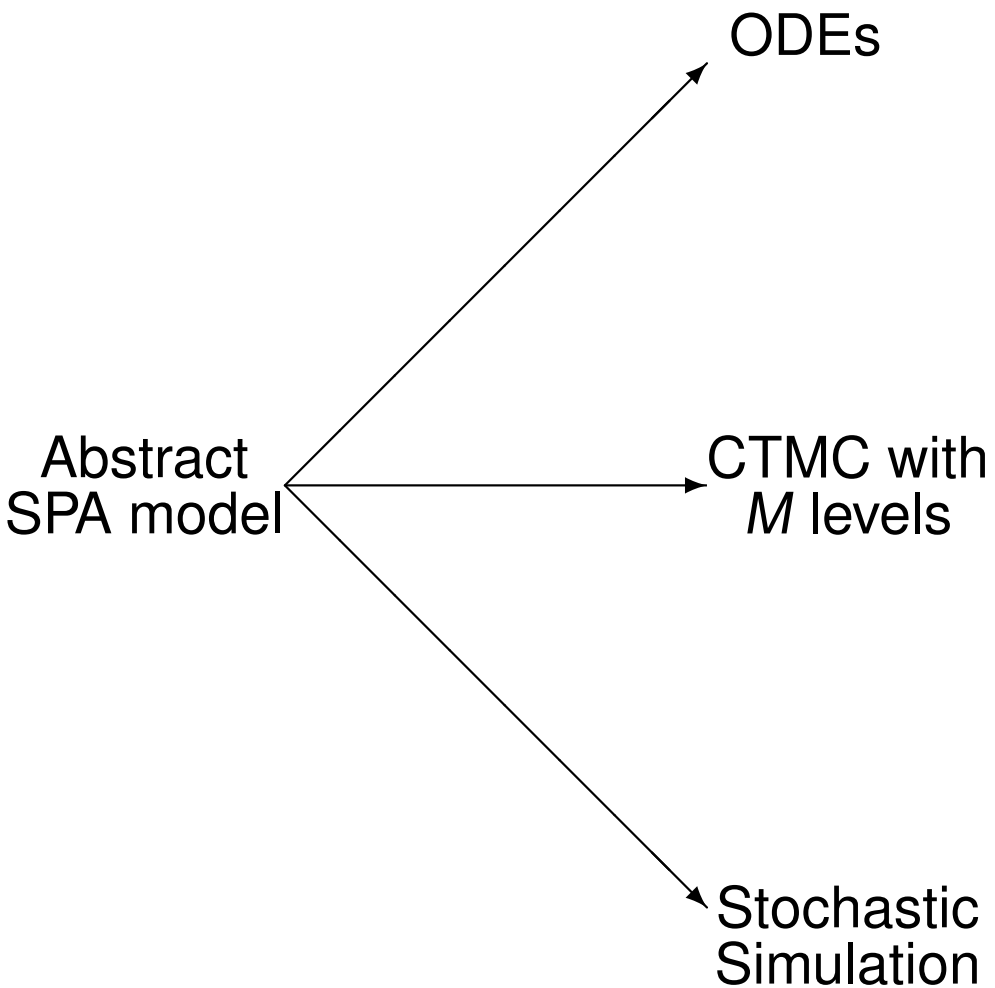

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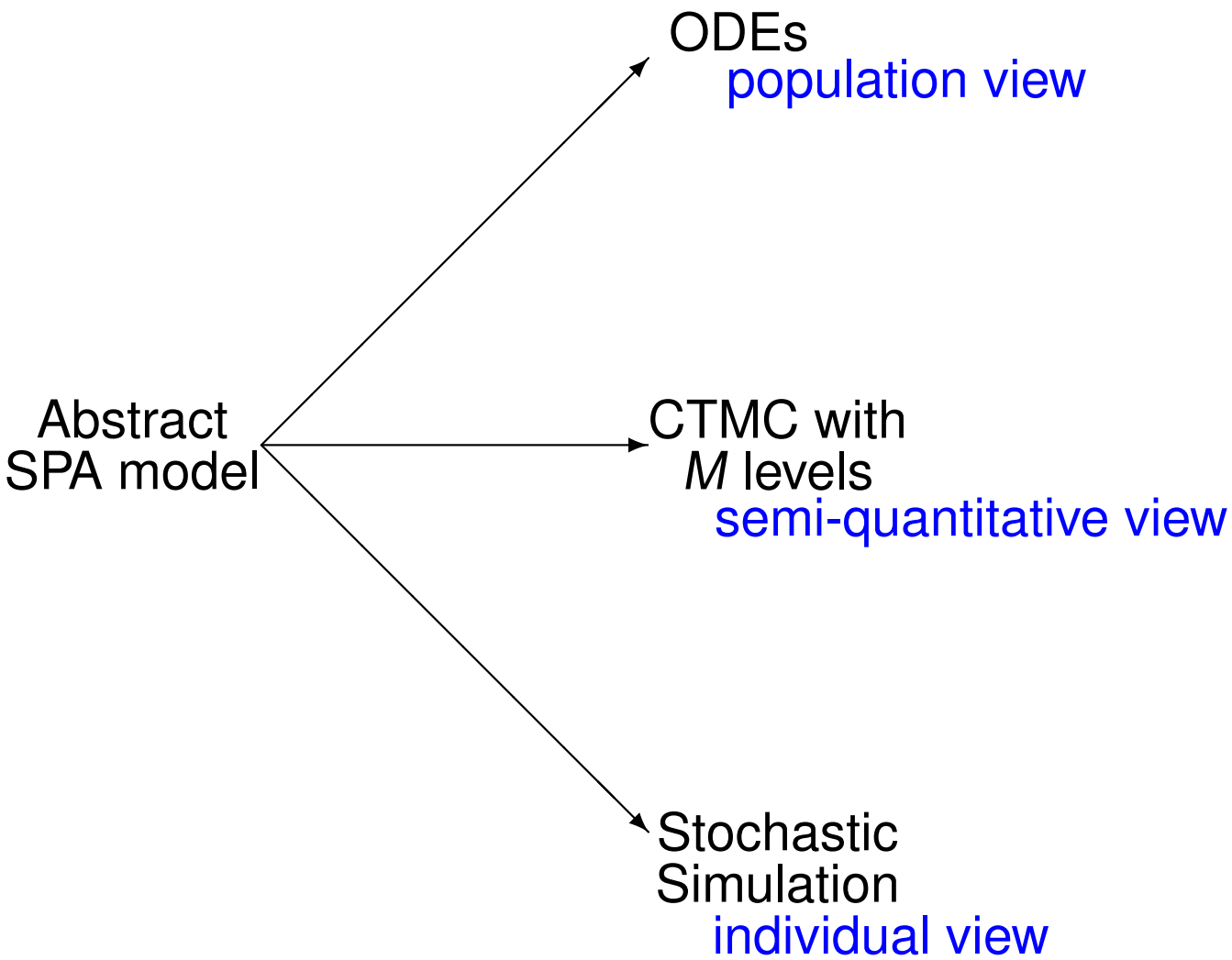

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Particular problems are encountered with:

- 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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- 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.

Outline

The syntax

Sequential component (species component)

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

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

Semantics: prefix rules

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

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

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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$$\text{coop1} \quad \frac{P_1 \xrightarrow{(\alpha,v)}_c P_1'}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha,v)}_c P_1' \underset{\mathcal{L}}{\bowtie} P_2} \quad \text{with } \alpha \notin \mathcal{L}$$

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

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

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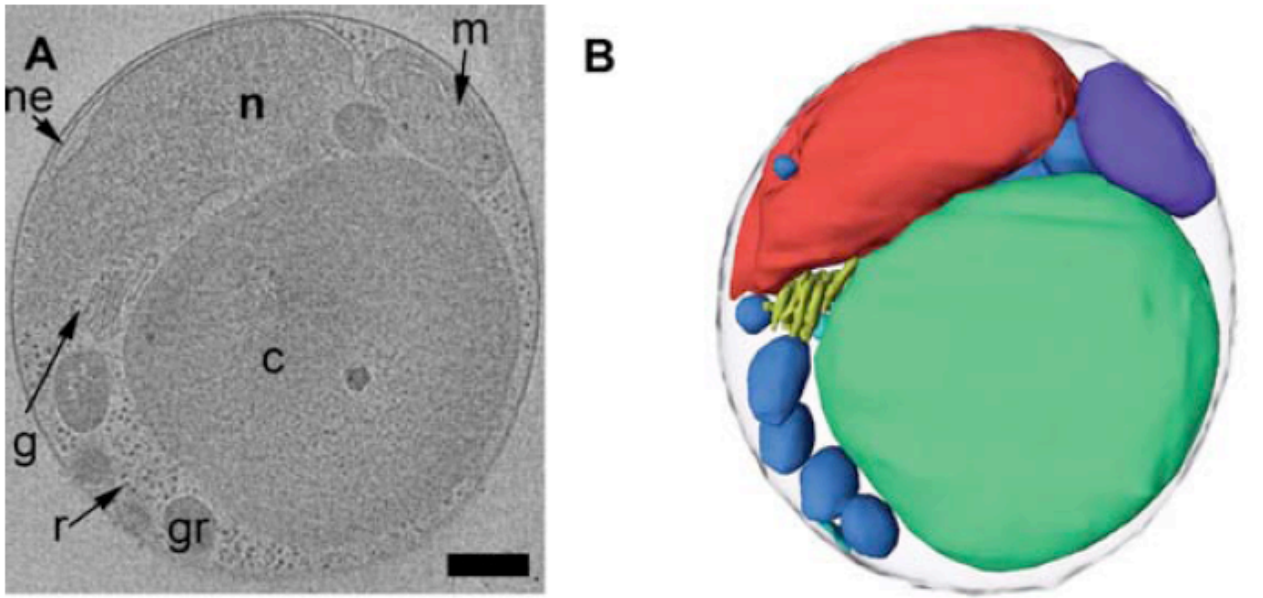
Each of these kinds of analysis can be of help for studying different aspects of the biological model. Moreover we are exploring how they can be used in conjunction.

Outline

Circadian Rhythms in *Ostreococcus Tauri*

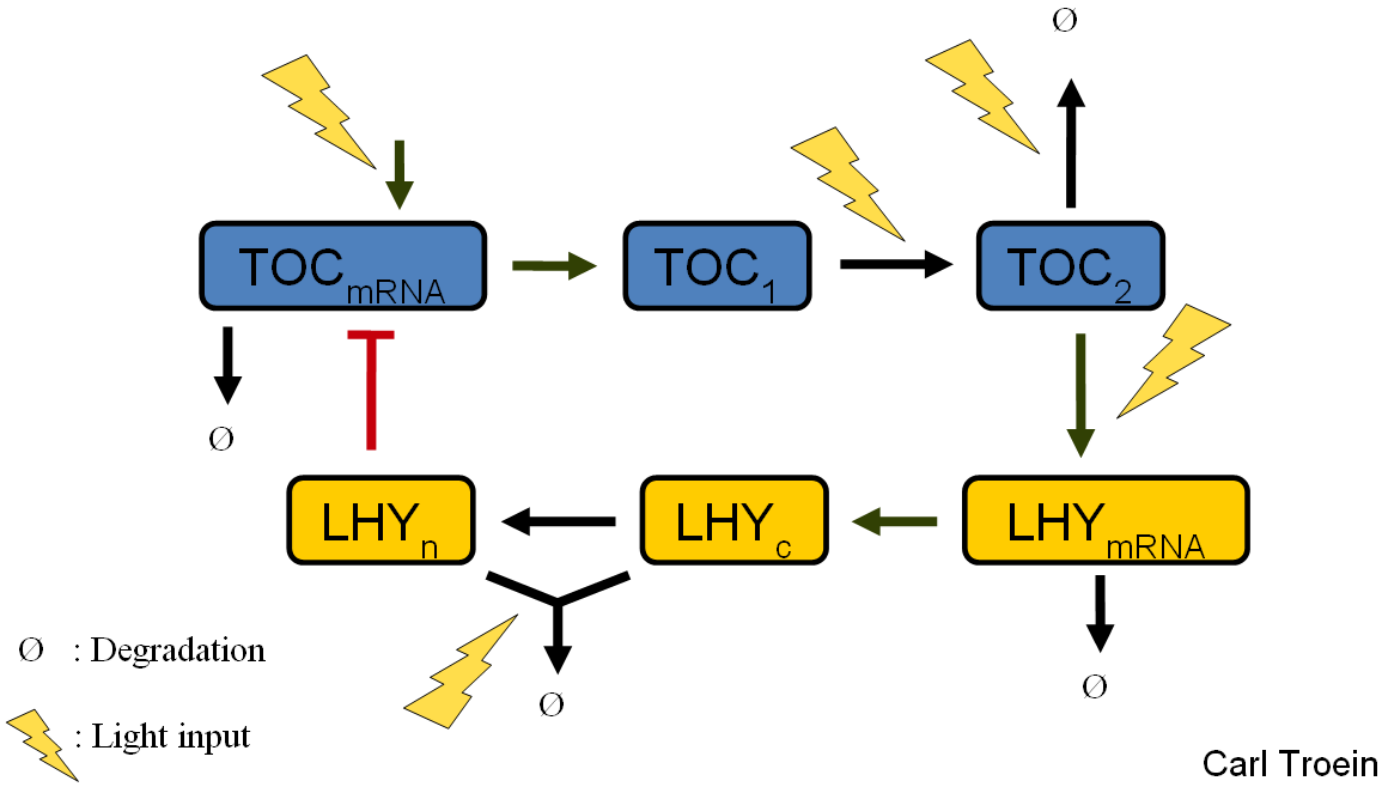
Jane Hillston.
University of Edinburgh.



The green alga *Ostreococcus Tauri* is an ideal model system for understanding the function of plant clocks.

In particular we use a Bio-PEPA model to study the variability and robustness of the clock's functional behaviour with respect to internal stochastic noise and environmental changes.

The biological model



- Feedback loop between the two main genes (TOC1 and LHY).
- Effect of light on several parts of the network.

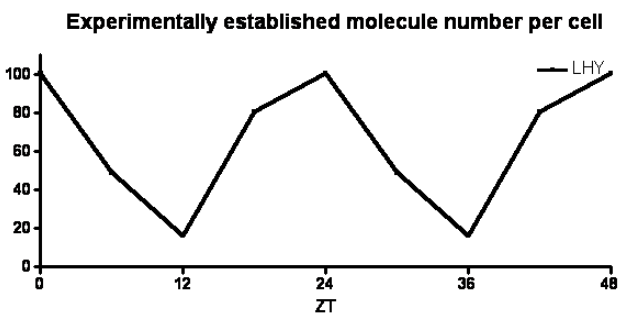
Modelling overview

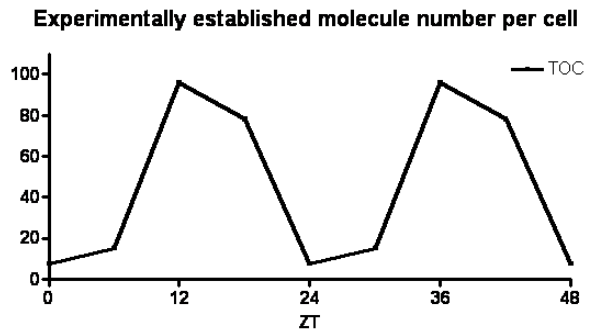
- A previous deterministic (ODE) model of the system had been developed by hand.
- We developed a Bio-PEPA model and validated that its continuous-deterministic interpretation coincided with the original model.
- Stochastic simulation was used with the discrete-stochastic interpretation of the Bio-PEPA model to investigate stochastic fluctuations, focusing on clock phase and sensitivity analysis.
- Model-checking was also used to give more detailed analysis of variability within the system, via specific questions about model behaviour.

Model and experimental settings

- Lab experiments in different light conditions and photoperiods
  - DD (24 hours dark)
  - LL (24 hours light)
  - LD 12:12 (12 hours light / 12 hours dark)
  - LD 6:18 (6 hours light / 18 hours dark)
  - LD 18:6 (18 hours light / 6 hours dark)

- Lab measurements on amounts of proteins





Modelling in Bio-PEPA

- Biological species ⇒ interacting species components
- Reactions ⇒ actions, with functional rates expressing the kinetic rate laws
- Light on/off mechanism for entrainment to day/night cycle ⇒ events switching between day-time and night-time rates

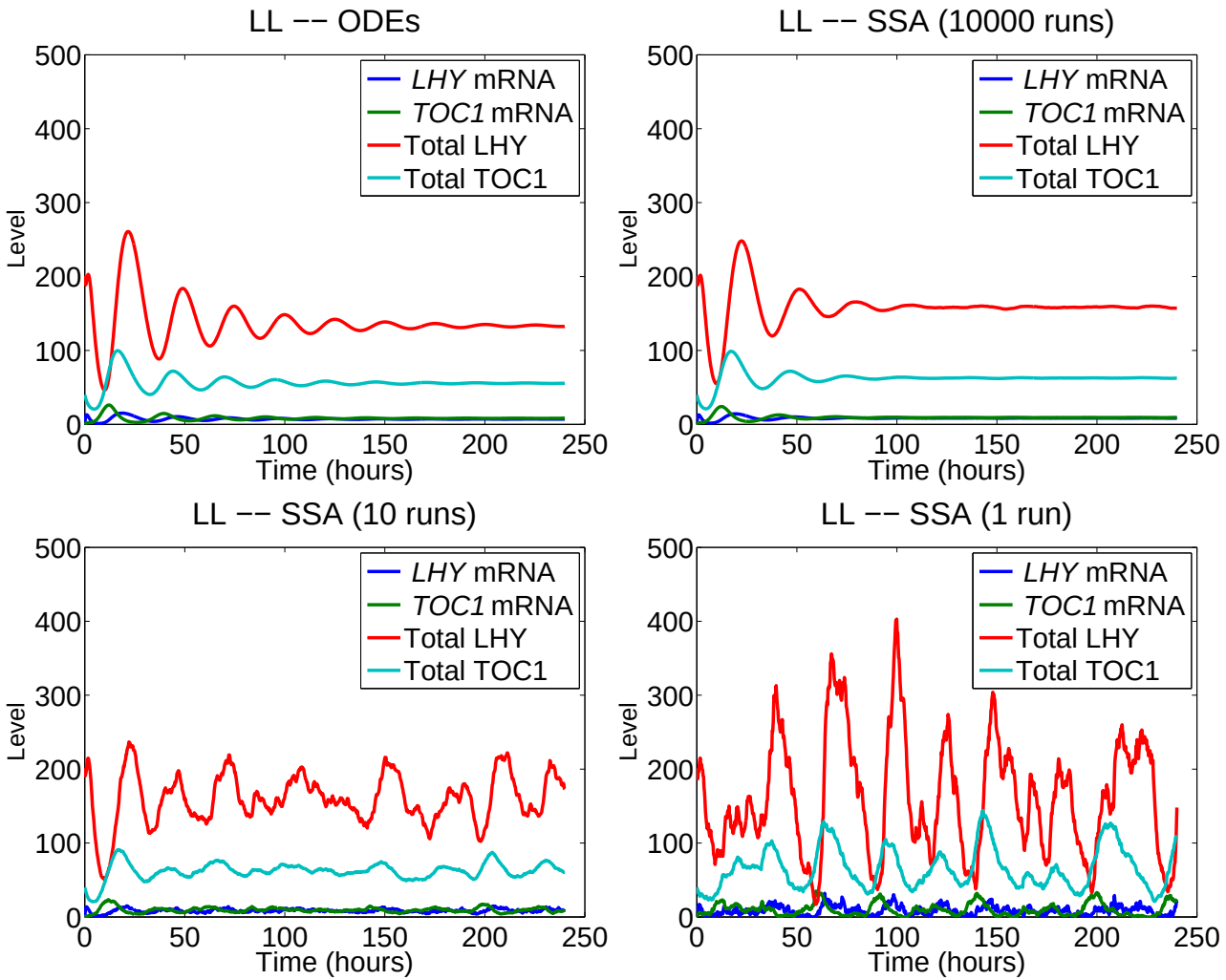
Extracts from the Bio-PEPA model

$$
\begin{aligned}
TOC1\_mRNA &= (transc_3, 1)\uparrow + (transl_5, 1) \oplus + (deg_7, 1)\downarrow \\
TOC1\_a &= (deg_4, 1)\downarrow + (conv_6, 1)\uparrow + (transc_8, 1) \oplus \\
TOC1\_i &= (transl_5, 1)\uparrow + (conv_6, 1)\downarrow \\
\\
LHY\_mRNA &= (transc_8, 1)\uparrow + (deg_9, 1)\downarrow + (transl_{10}, 1) \oplus \\
LHY\_c &= (transl_{10}, 1)\uparrow + (transp_{11}, 1)\downarrow + (deg_{12}, 1)\downarrow \\
LHY\_n &= (transc_3, 1) \ominus + (transp_{11}, 1)\uparrow + (deg_{13}, 1)\downarrow \\
\\
acc &= (prod_1, 1)\uparrow + (deg_2, 1)\downarrow + (transc_3, 1) \oplus
\end{aligned}
$$

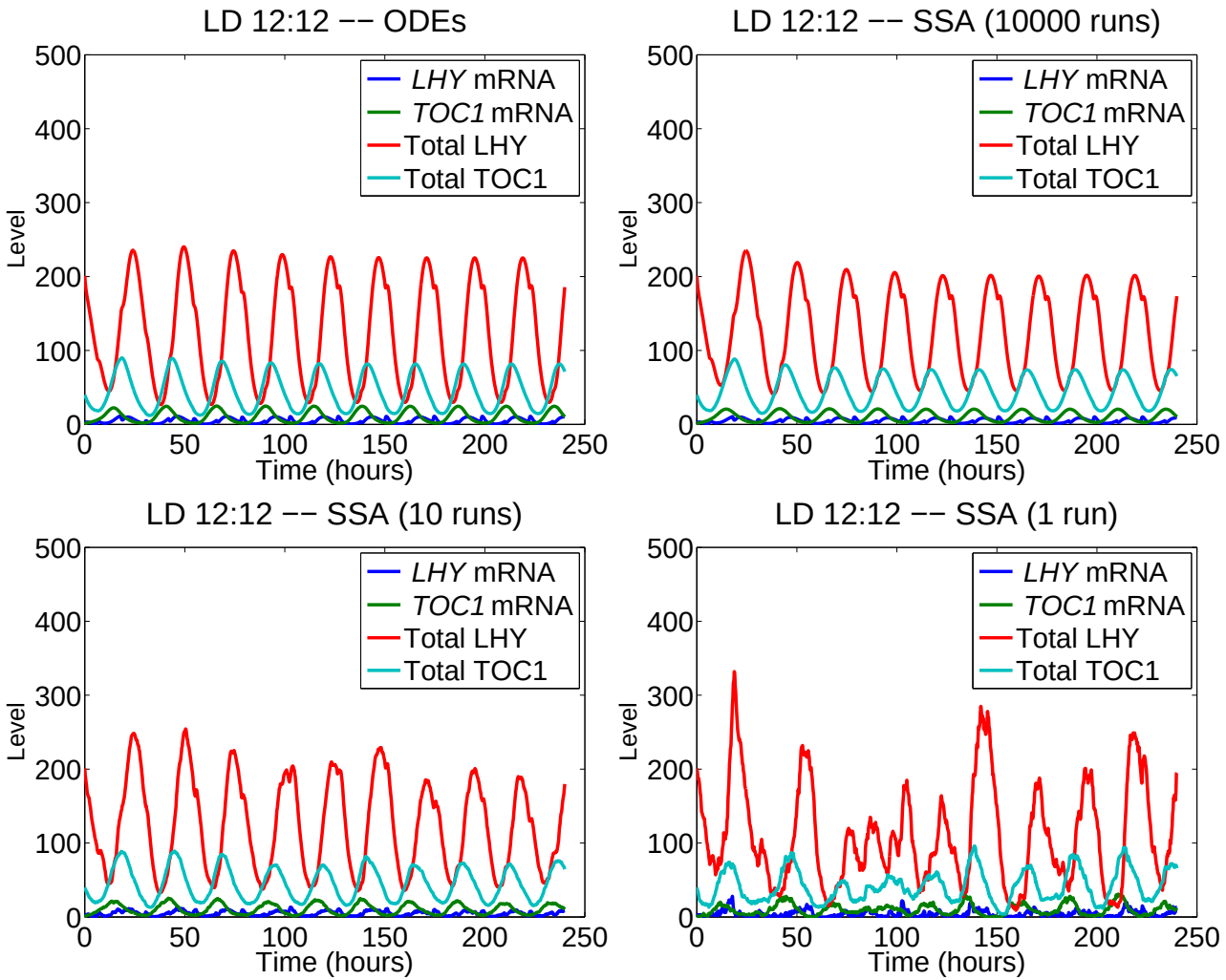
$$
\begin{aligned}
\text{total\_TOC1} &= \text{TOC1\_i} + \text{TOC1\_a} \\
\text{total\_LHY} &= \text{LHY\_c} + \text{LHY\_n}
\end{aligned}
$$

$t\_dawn = 6, \quad t\_dusk = 18$ (e.g. for LD 12:12 system)

Simulations – constant light (LL)



Simulations – light/dark (LD 12:12)



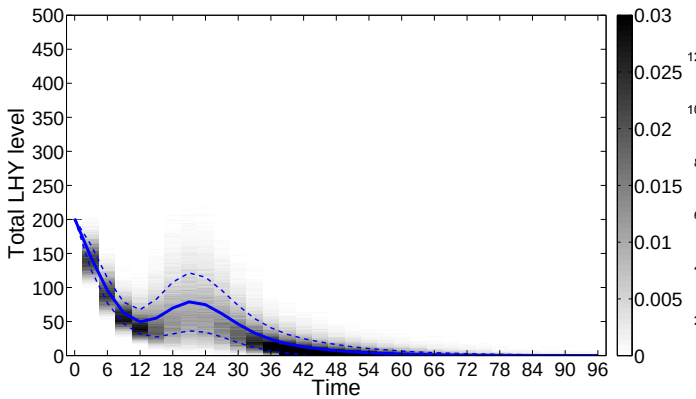
Model-checking

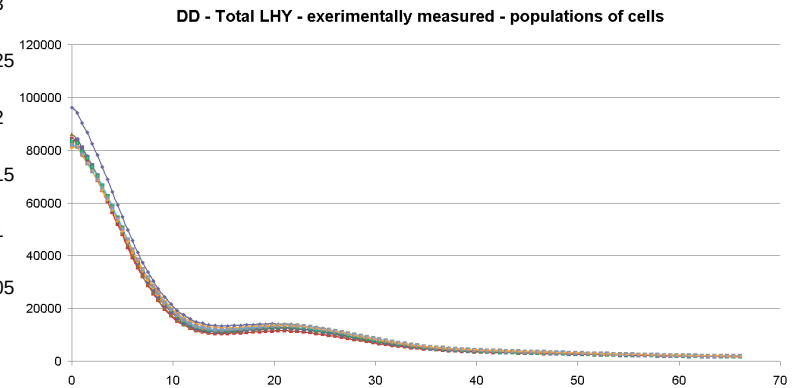
- Here we use statistical model-checking (discrete event simulation and sampling over multiple runs): approximate results.
- The underlying simulation model is enhanced with a representation of time so that rates of reactions can change appropriately at dawn and dusk.
- The model checker can then be used to investigate the probability distribution of the number of molecules of a species over time.

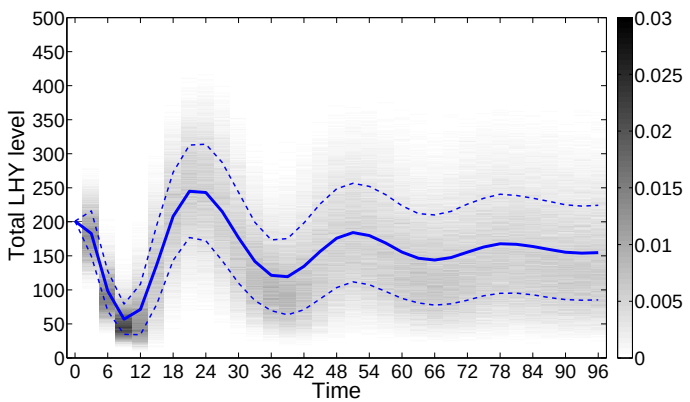
Model-checking – probability distribution of LHY value over 0-96 h

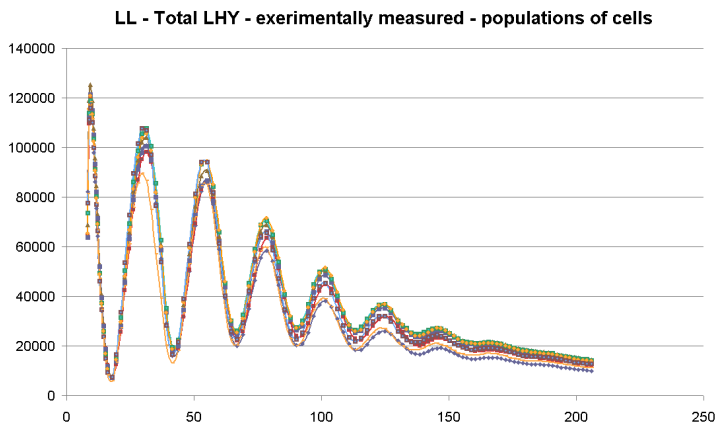
Jane Hillston.
University of Edinburgh.

$$[T, T](\_LHY\_c + \_LHY\_n = level), T = 0 : 3 : 96, level = 0 : 1 : 500$$









Probability that the total LHY stays below some threshold e in the long run

$$[96, 500](LHY\_c + LHY\_n \leq 0 + e)$$

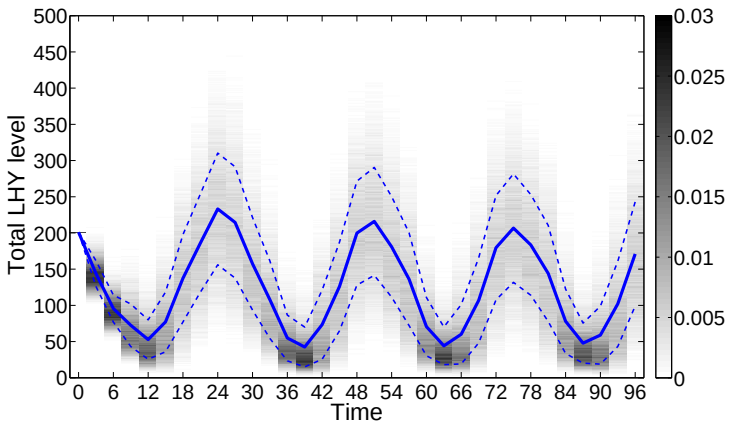
e	0	1	2	3	4
Prob	0.93	0.96	0.96	0.98	0.98

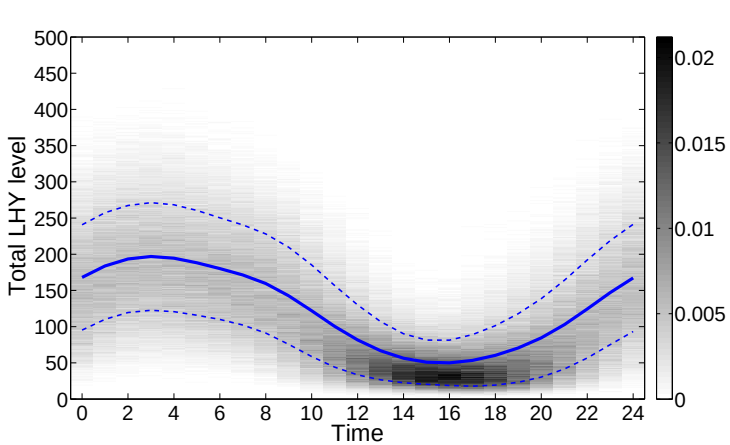
e	5	6	7	8	9	10
Prob	0.99	0.99	0.99	0.99	0.99	1.0

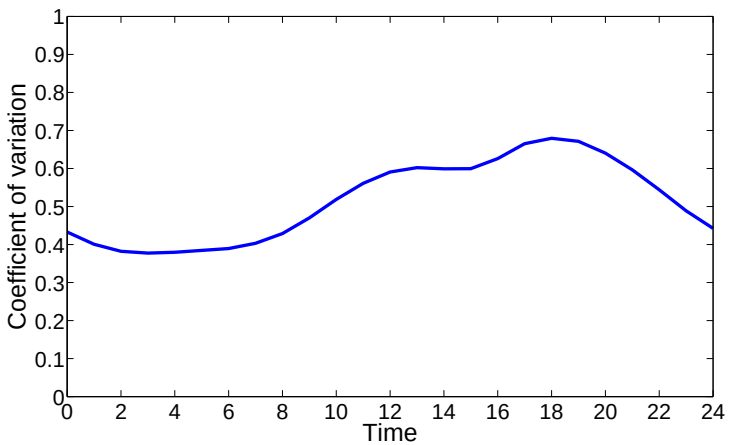
Probability distribution/coefficient of variation of LHY value – LD 12:12

Jane Hillston.
University of Edinburgh.

$$[T, T](\_LHY\_c + \_LHY\_n = level), T = 120 : 1 : 144, level = 0 : 1 : 500$$







Outline

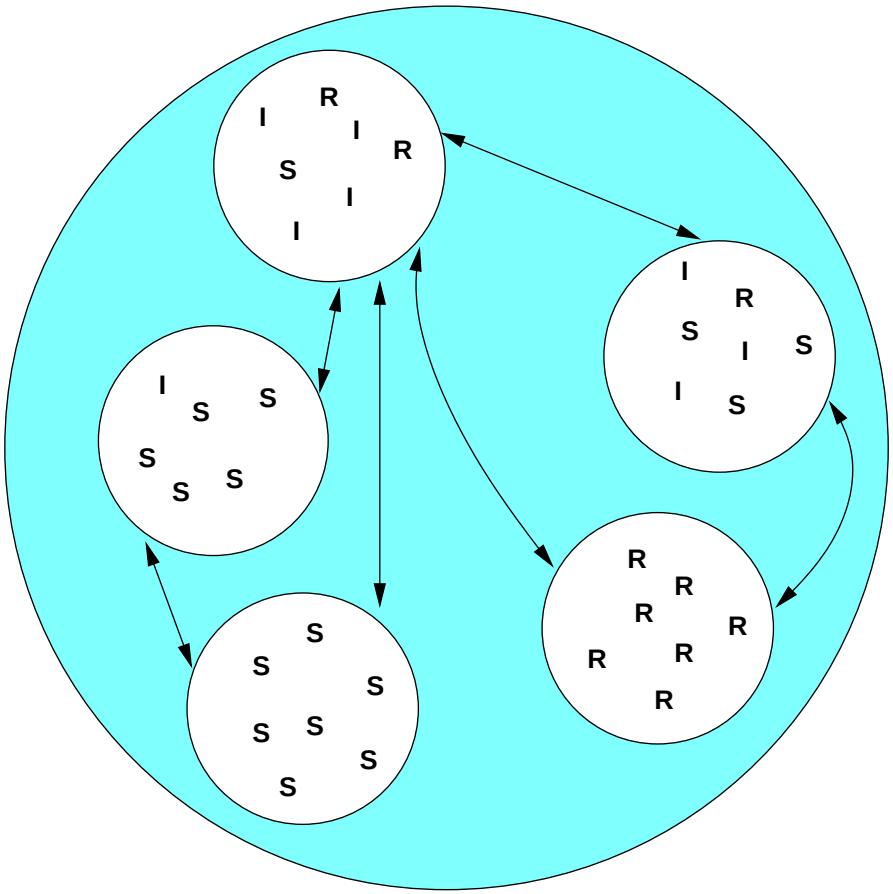
Epidemiological models

Epidemiological models study the spread of disease within a population.

For this purpose the population can be divided into classes: susceptibles (S), those who are infective (I) and those who have recovered (R) and are immune.

Refinements of this might include differentiating those which are symptomatic or asymptomatic, treated or untreated, or suffering from a drug-resistant form of the disease.

Spatial structures also impact infection spread



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University of Edinburgh.

Using Bio-PEPA for epidemiological models

- Each species will correspond to a subset of individuals (e.g. susceptible, infective or recovered individuals), possibly also differentiating locations.
- The role of the individual with respect to an action can be used to indicate that the species decreases, remains invariant or increases in an interaction.
- Interactions such as $I + S \rightarrow 2I$ are possible, where an entity is present on both sides of the interaction with different multiplicity. Note that this cannot be represented in Bio-PEPA.

Modifying Bio-PEPA for epidemiology

The key change is that two multiplicities can be associated with an action in a component, rather than the single stoichiometry used in biochemistry:

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A Bio-PEPA model for epidemiological system is described by the following syntax:

$$S ::= (\alpha, \kappa) \downarrow S \mid (\alpha, \kappa) \uparrow S \mid (\alpha, (\kappa_1, \kappa_2)) \odot S \mid S + S \mid C \mid S@L$$

$$P ::= P \underset{\mathcal{I}}{\bowtie} P \mid S(x)$$

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The abstraction

The translation of epidemiological models into Bio-PEPA is based on the following correspondences:

- Each subpopulation/patch is abstracted by a location.
- Each type of individual is represented by a species component, whose subterms describe its interaction capabilities.
- Each interaction is represented by an action type. The dynamics are described by a functional rate.
- The model component represents how the species interact and contains information about the initial state.

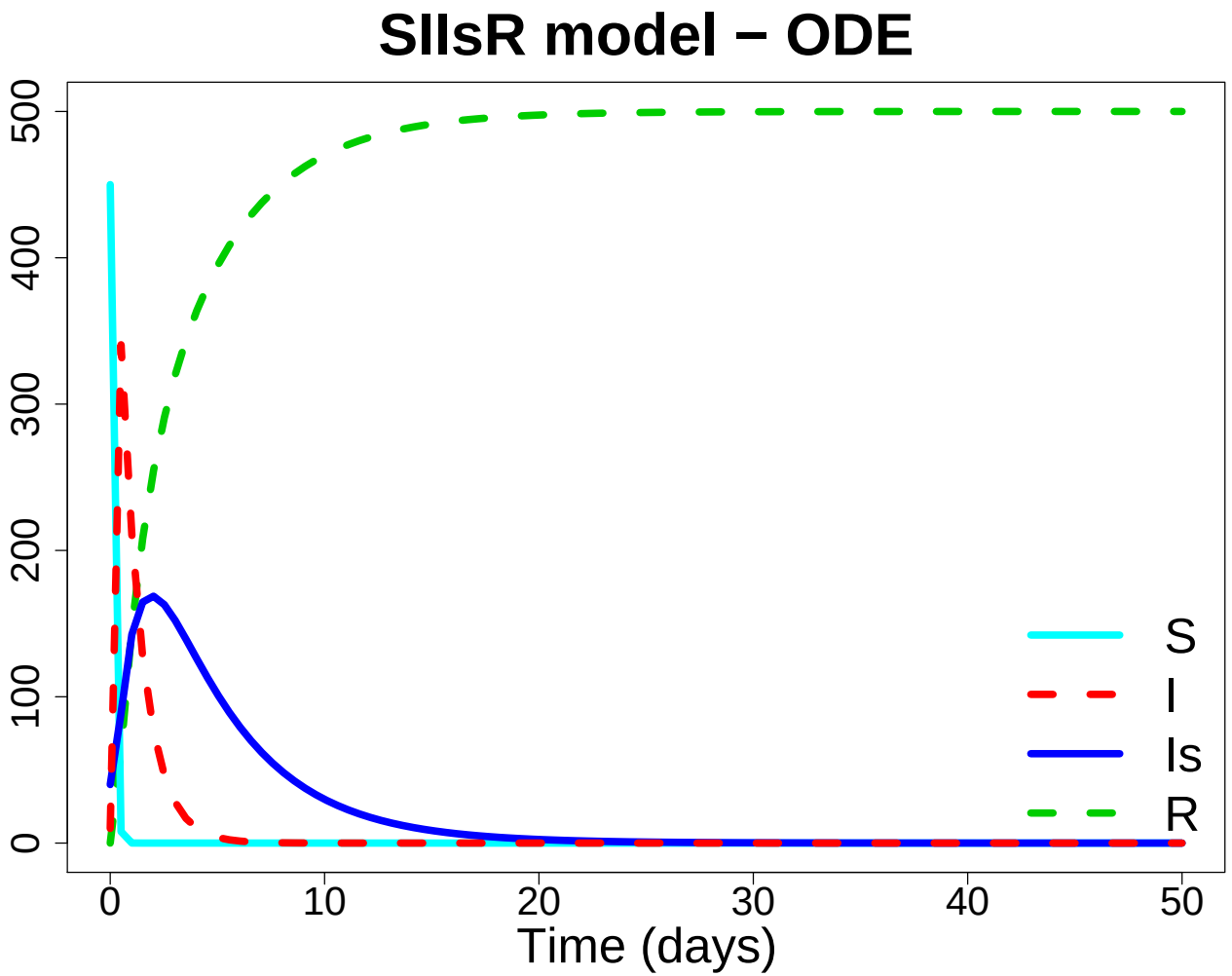
Simple model of H5N1 Avian Influenza: single location, no drug treatment

We distinguish between asymptomatic (I) and symptomatic (I_s) individuals:

$$
\begin{aligned}
S &\stackrel{def}{=} (contact1, 1)\downarrow S + (contact2, 1)\downarrow S \\
I &\stackrel{def}{=} (contact1, (1, 2)) \odot I + (contact2, 1)\uparrow I \\
&\quad + (recovery1, 1)\downarrow I + (symp, 1)\downarrow I \\
I_s &\stackrel{def}{=} (contact2, (1, 1)) \odot I_s + (recovery2, 1)\downarrow I_s \\
&\quad + (symp, 1)\uparrow I_s \\
R &\stackrel{def}{=} (recovery1, 1)\uparrow R + (recovery2, 1)\uparrow R
\end{aligned}
$$

$$S(450) \underset{*}{\bowtie} I(10) \underset{*}{\bowtie} I_s(40) \underset{*}{\bowtie} R(0)$$

Simulation Results



Jane Hillston.
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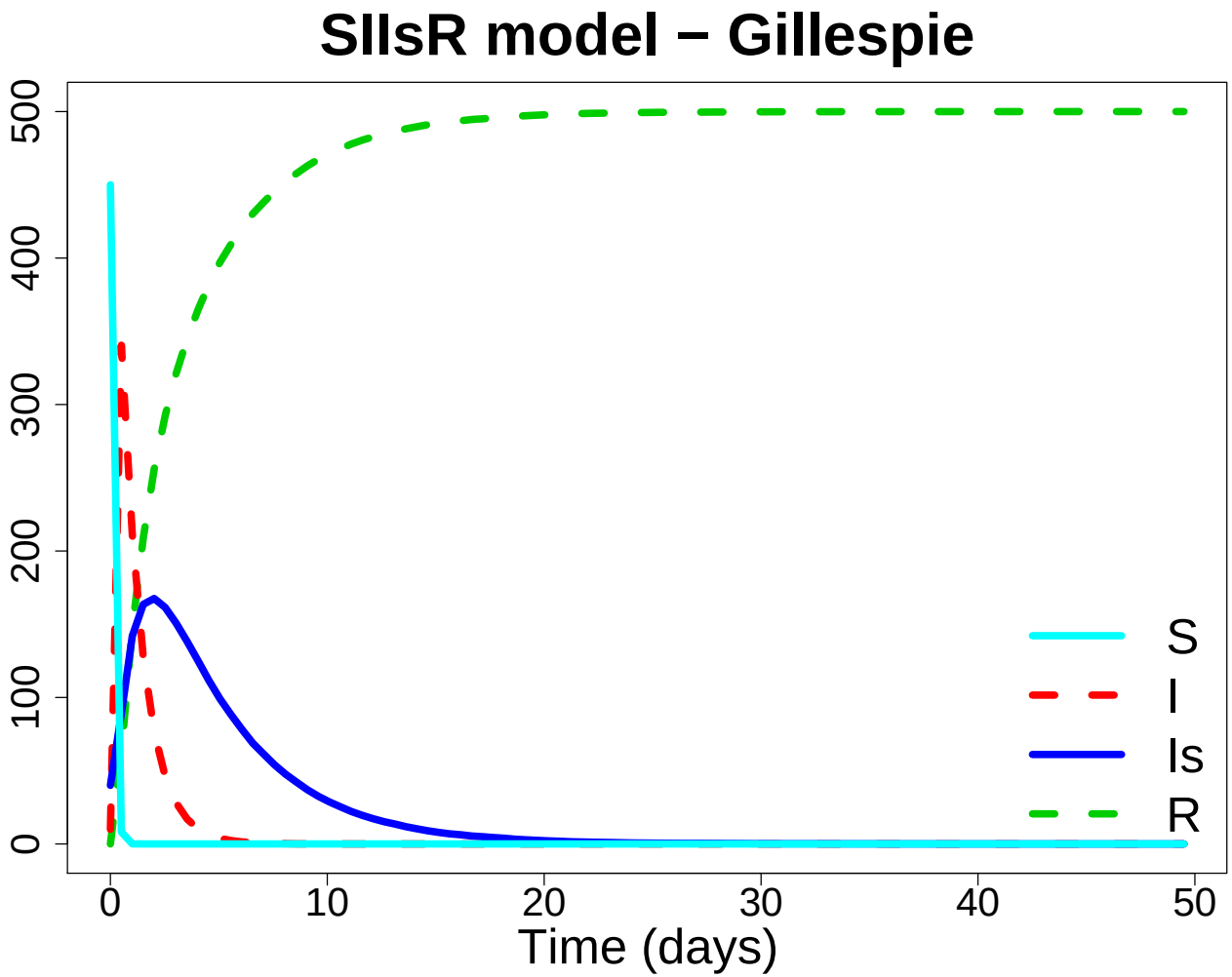

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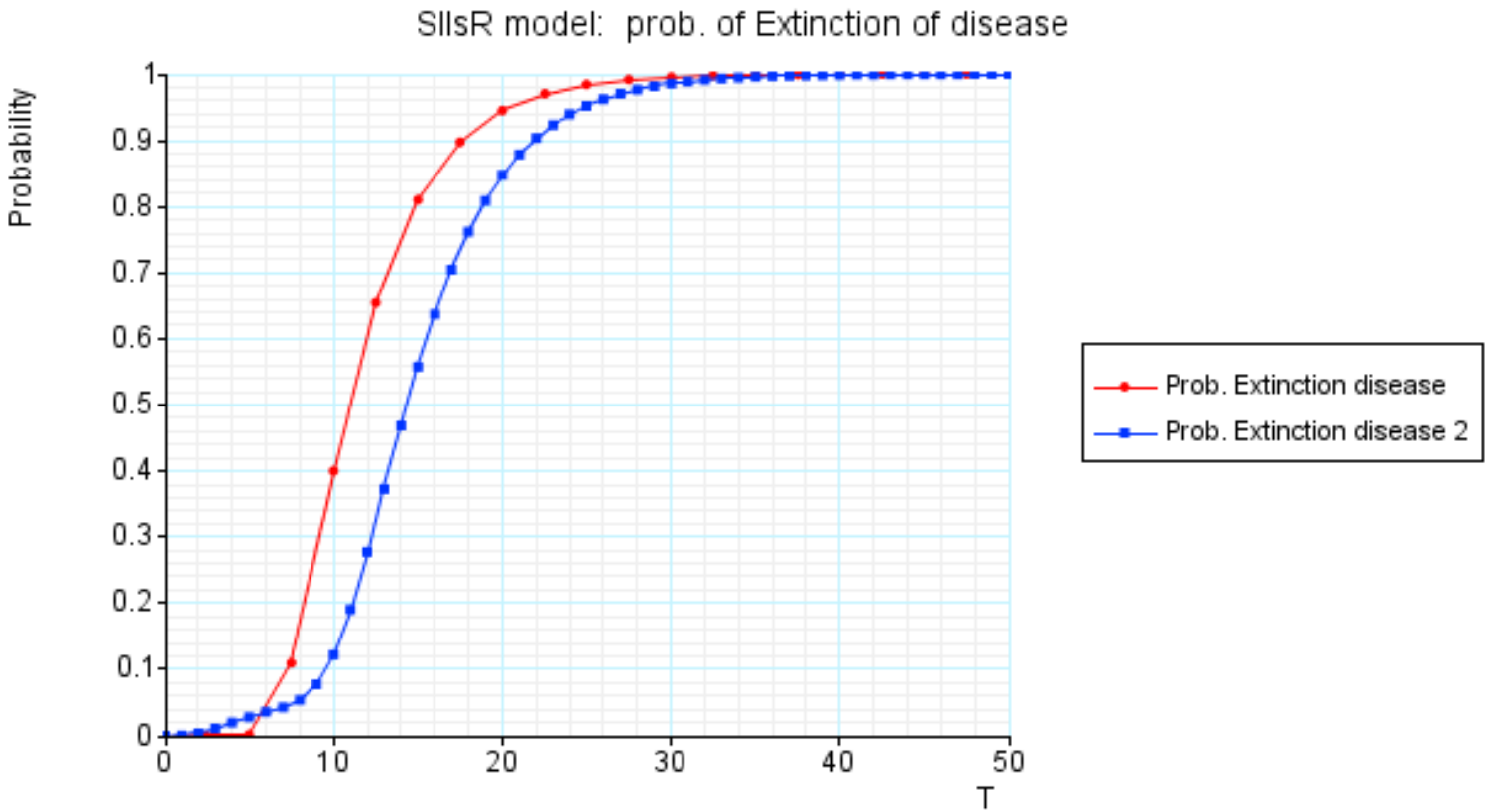
PRISM Results — Varying contact rates



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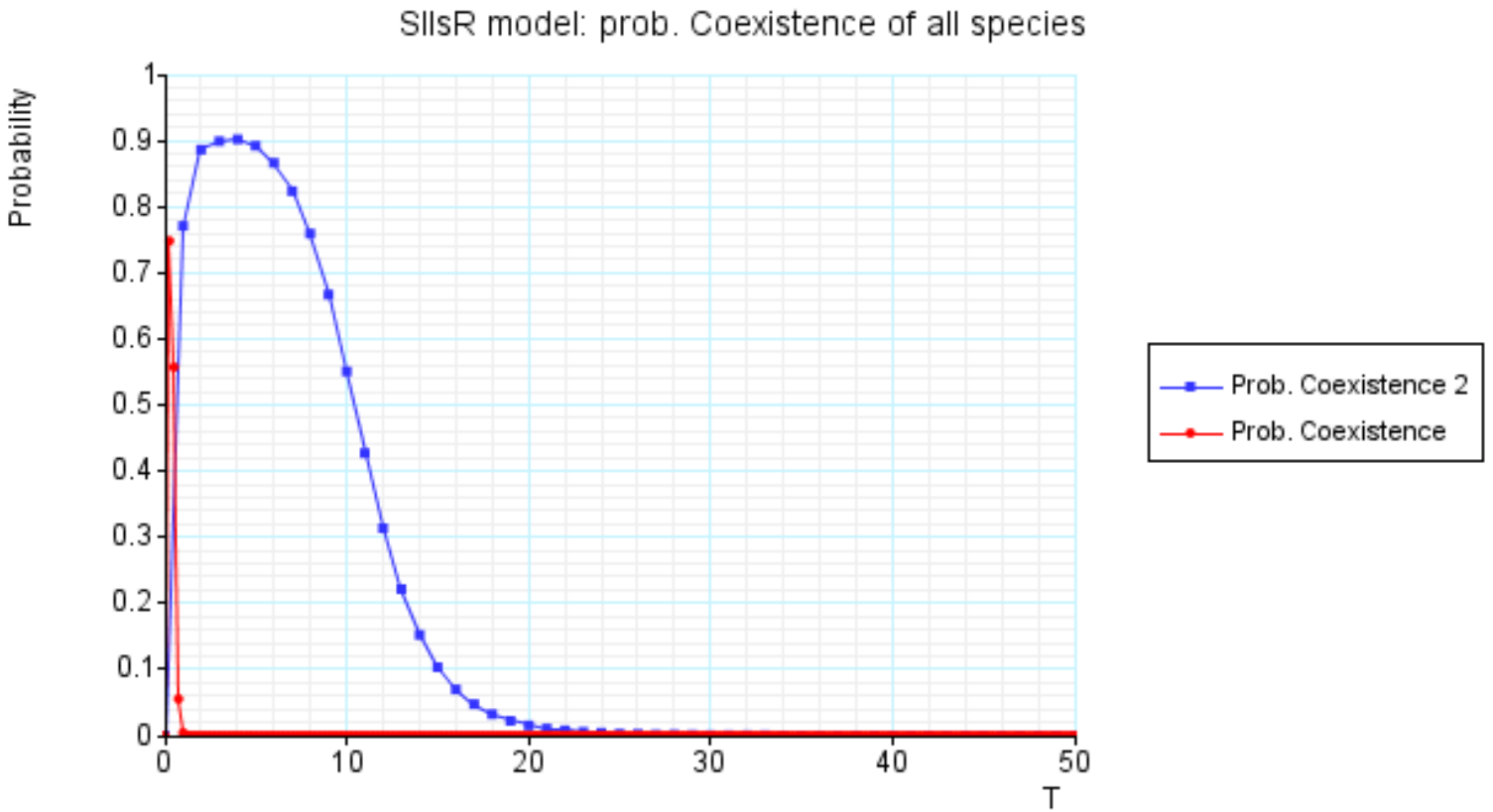

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Models with multiple locations

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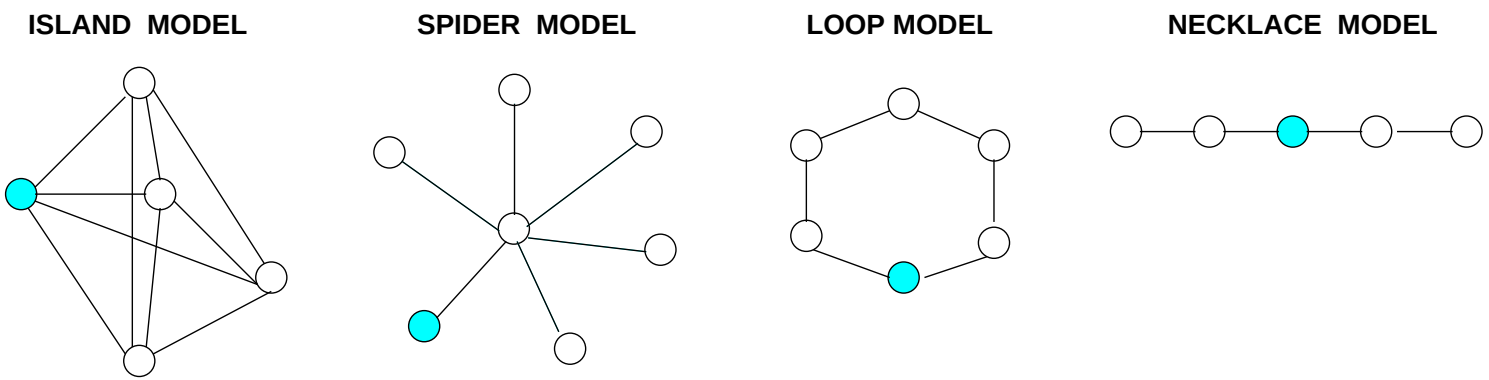
Interactions between individuals are as in the previous model but constrained to only occur when they are in the same location.

Additionally there are migration actions, e.g:

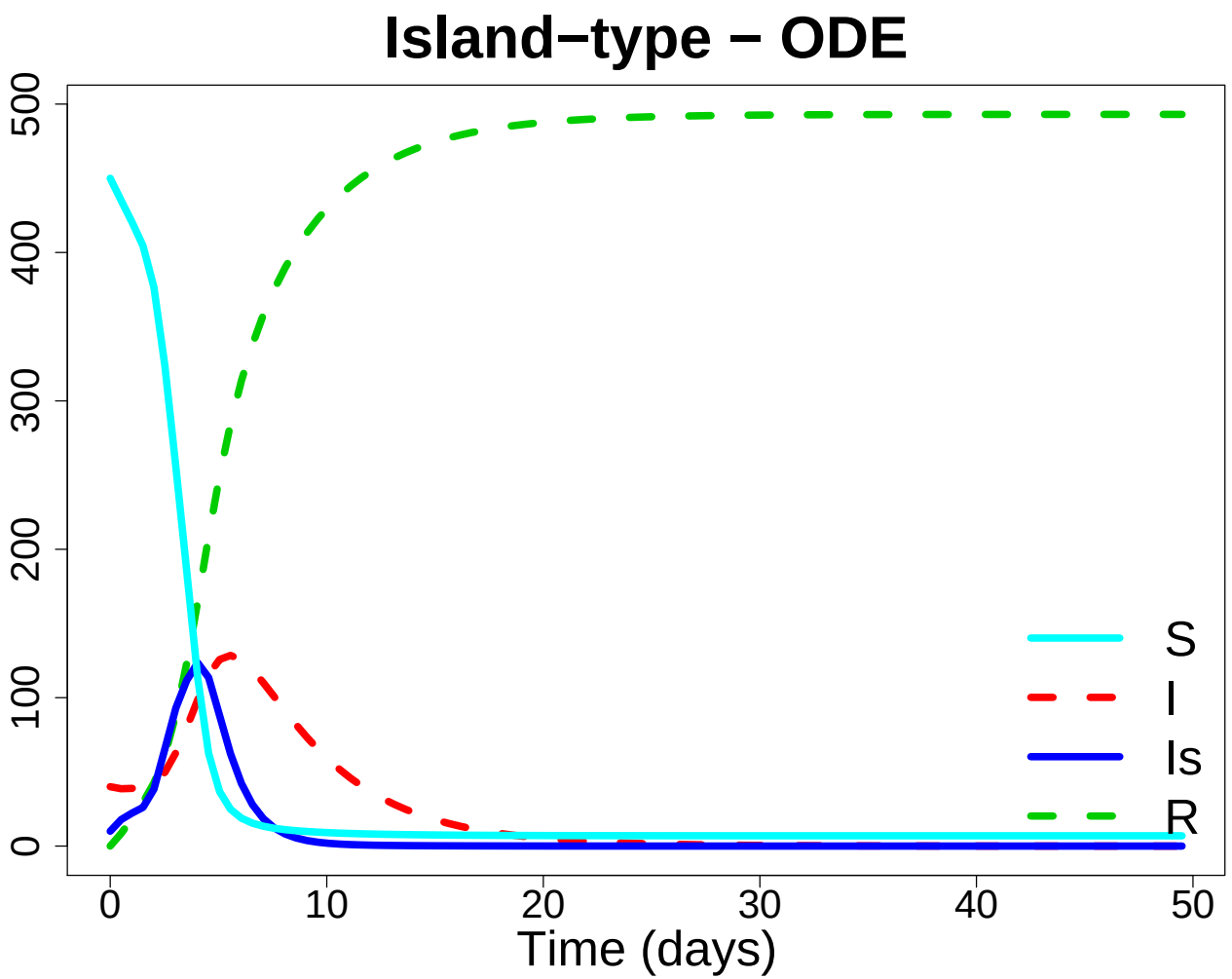
$$S \stackrel{def}{=} (contact1, 1)\downarrow S + (contact2, 1)\downarrow S + \sum_{M(i,j)\neq 0} (m_{ij,S}[location\_i \rightarrow location\_j], (1,1)) \odot S$$

Population structures



The connections between the patches indicate how individuals might move between patches, thus relaying infections through the metapopulation.

Comparing structures



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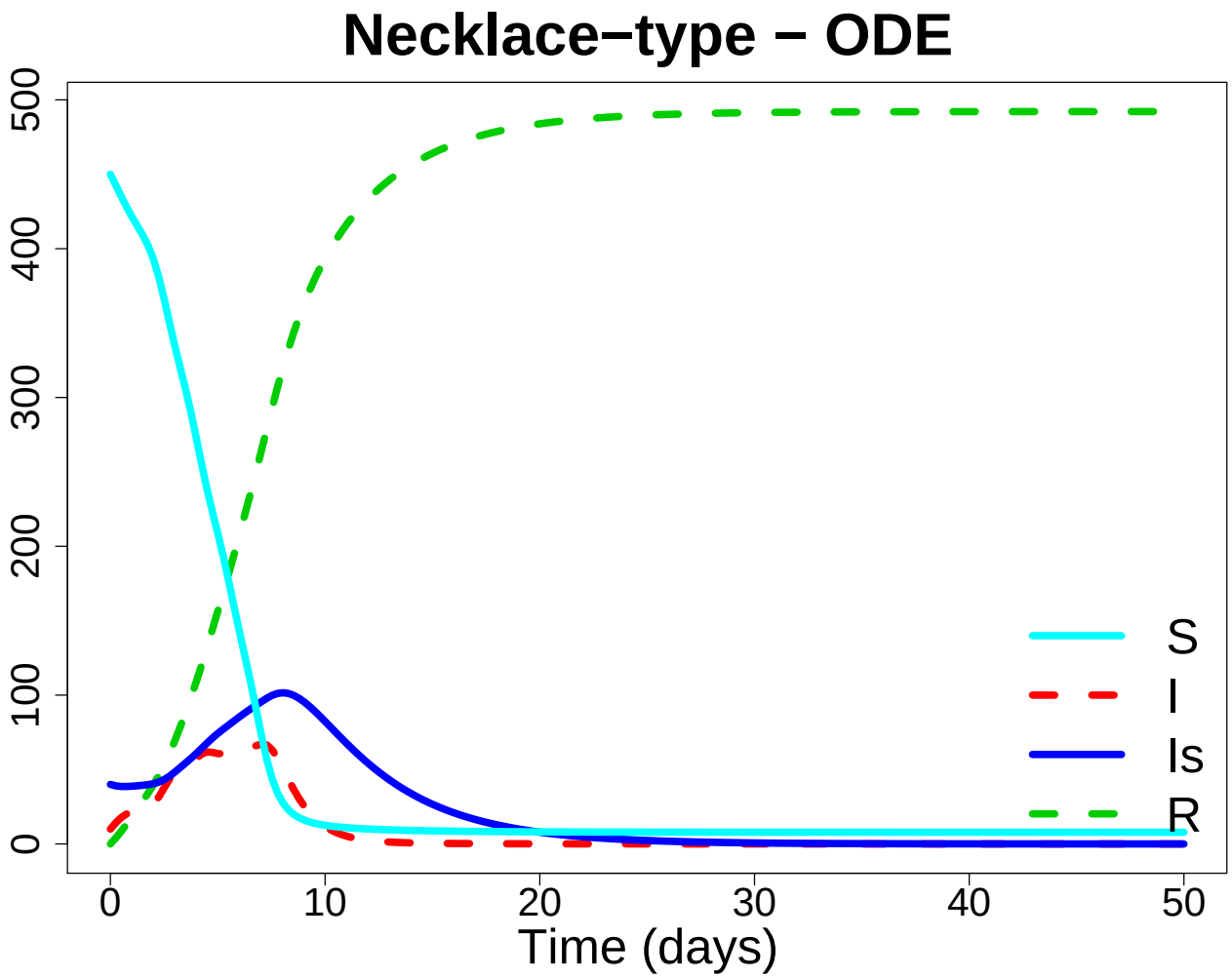

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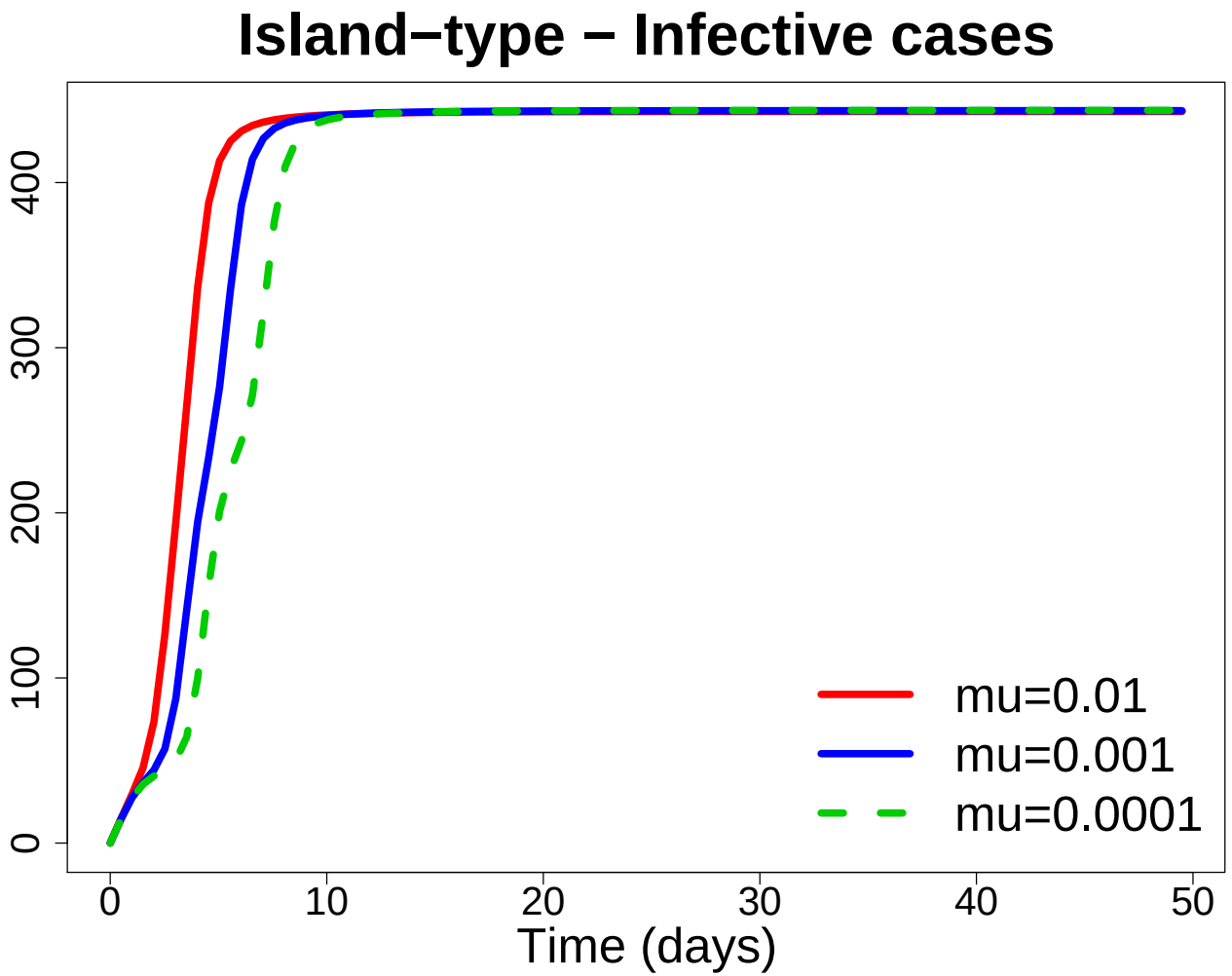
The effect of the migration rate



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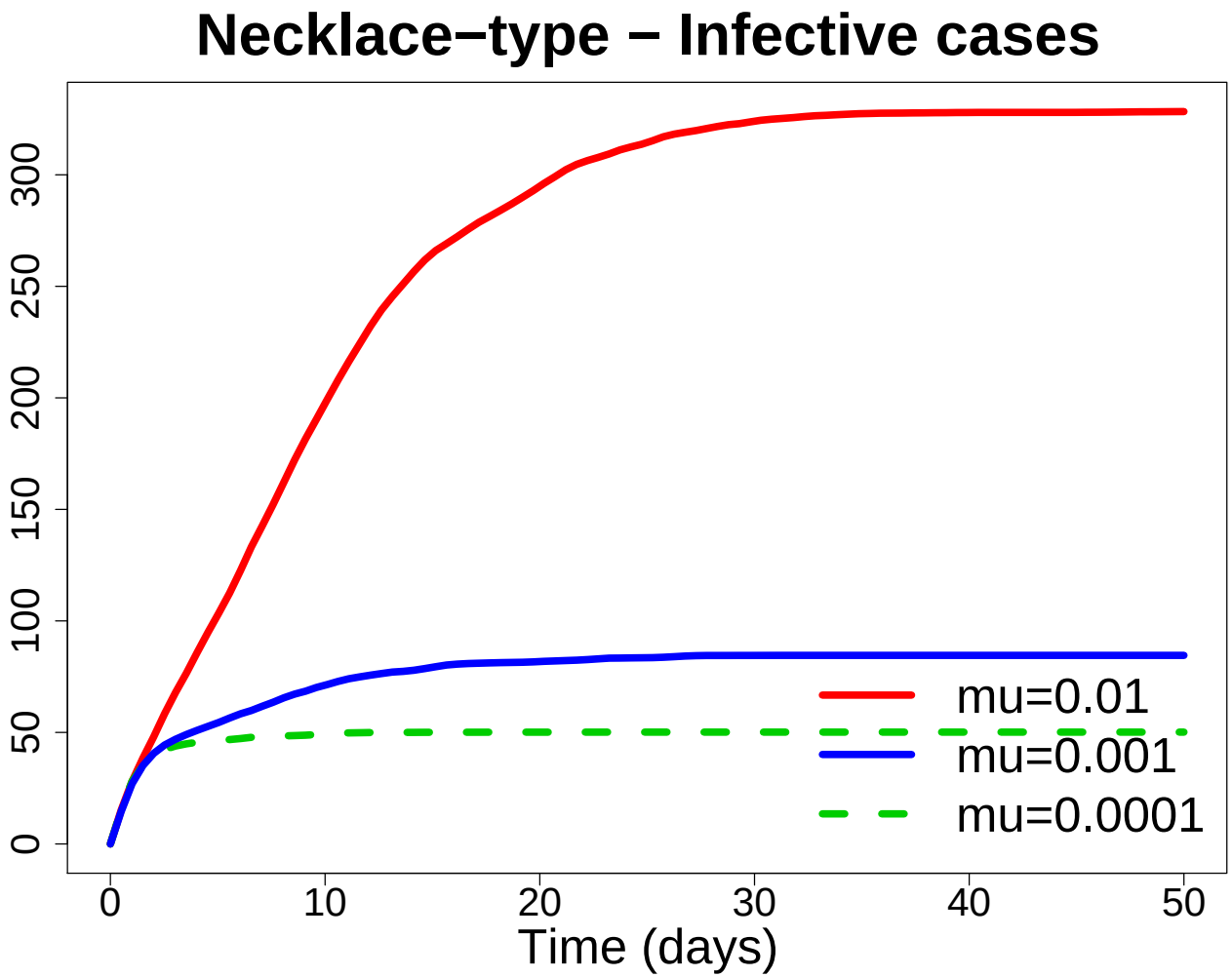

Jane Hillston.
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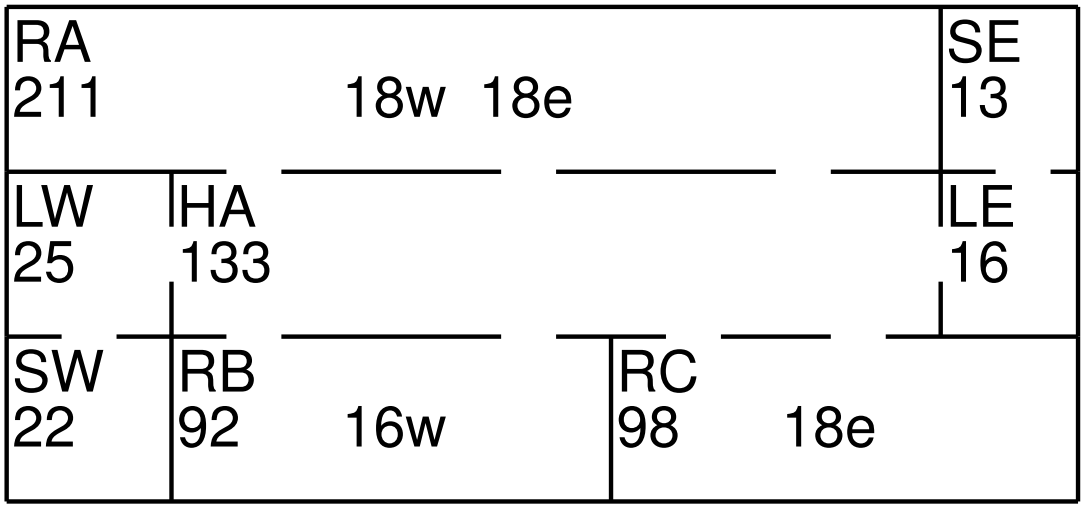
Designing for human crowd dynamics

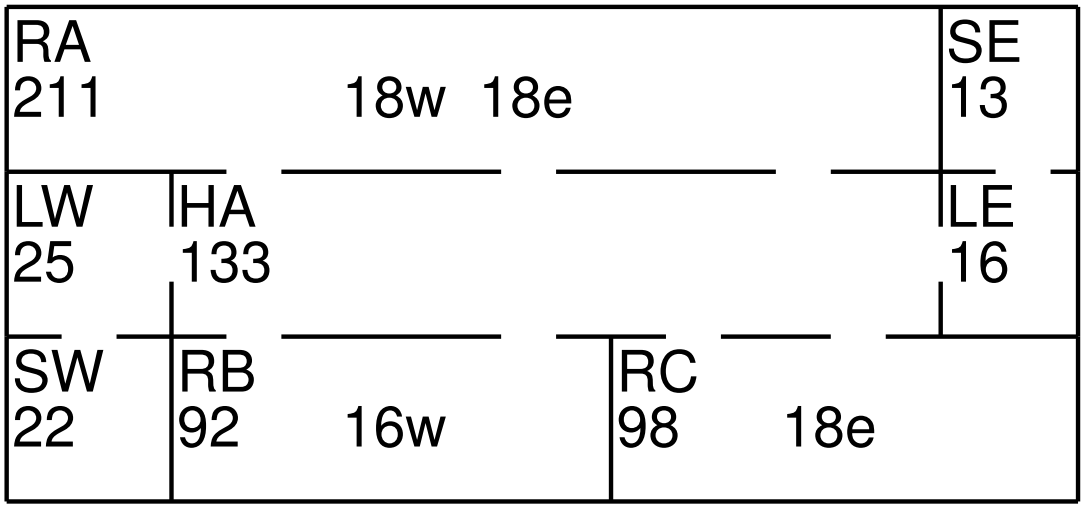
- Widespread take up of mobile and communicating computational devices is making ubiquitous systems a reality and creating new ways for us to interact with our environment.
- One application is to provide routing information to help people navigate through unfamiliar locations.
- In these case the dynamic behaviour of the system as a whole is important to ensure the satisfaction of the users.
- Emergency egress can be regarded as a particular case, when the location may be familiar but circumstances may alter the usual topology and make efficient movement particularly important

Example scenario



The layout of the building is described in terms of the arrangement of the rooms, hallways, landing and stairs. Each has a capacity and may have an initial occupancy.

Example scenario



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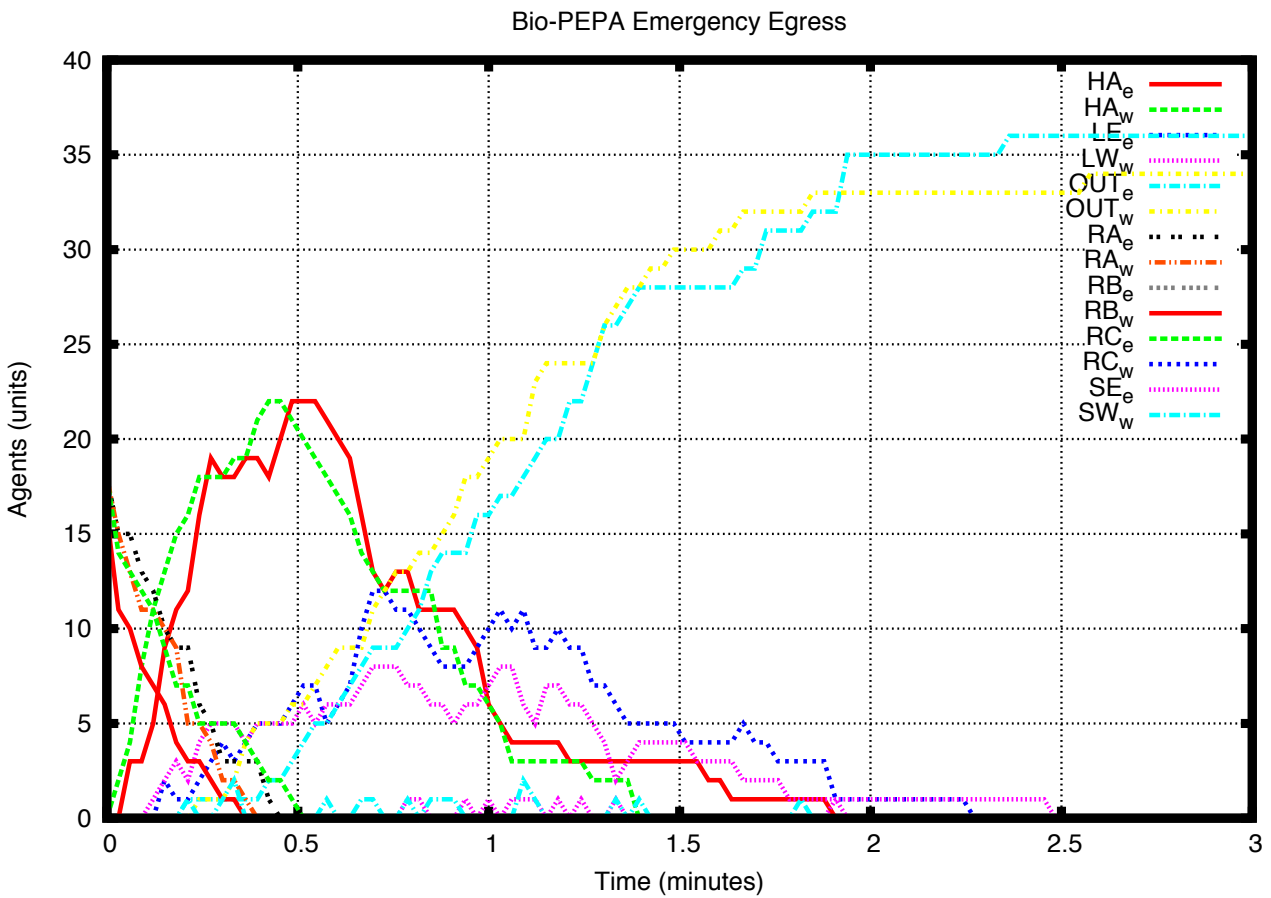
Bio-PEPA species describe the behaviours of individuals, but also rooms and information dissemination.

Model specification

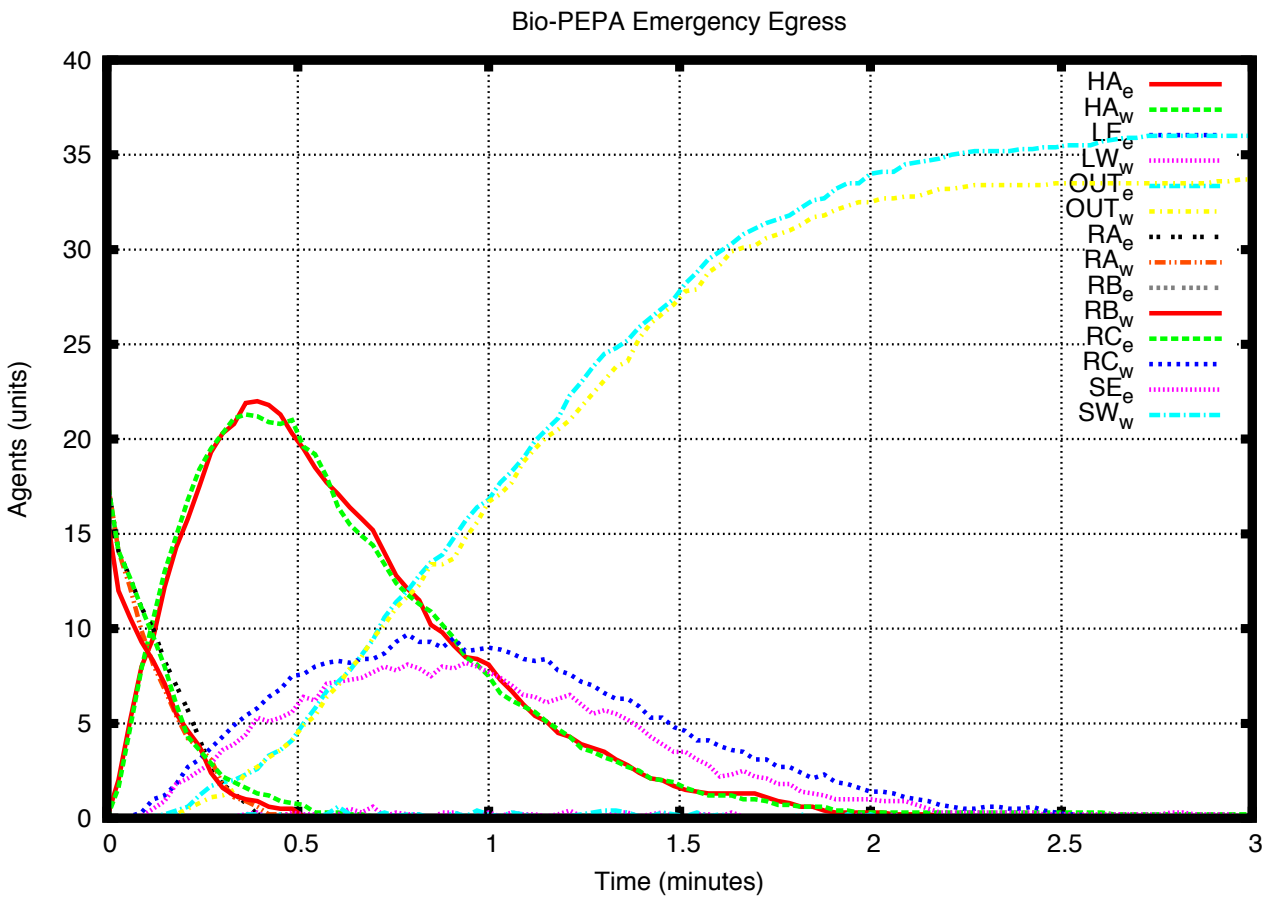
```
// BUILDING LAYOUT   (COMPARTMENTS)

location ra :       size = normal_room,  type= compartment;
location d1_ra_ha : size = normal_door,  type= compartment;
...
// PARAMETERS SET UP

to_ra_d1      =  6;                    // 3 + (60/7);
from_d1       =  door_exit_rate;
...
occupancy_d1 =  D1_ra_e@d1_ra_ha + D1_ra_w@d1_ra_ha + ... :
full_d1       =  H(capacity_d1 - occupancy_d1);
switch_d1     =  open_d1*full_d1;
...
// AGENT DYNAMICS    (FUNCTIONAL RATES)

//   From ra to ha through d1
kineticLawOf ra_e_in__d1_ra_ha  : fMA(to_ra_d1 * switch_d1 * ra_e_in_safe);
kineticLawOf ha_e_out__d1_ra_ha : fMA(from_d1 *  open_d1 * safeD1_ra_e * allowance_ha);
kineticLawOf ra_w_in__d1_ra_ha  : ...
kineticLawOf ha_w_out__d1_ra_ha : ...
//   ... and back
kineticLawOf ha_e_in__d1_ra_ha  : ...
...

// AGENT DEFINITIONS (SEQUENTIAL PROCESSES)

RA_e = (ra_e_in__d1_ra_ha, 1)     << RA_e@ra  +  ...
       (ra_e_out__d1_ra_ha, 1)    >> RA_e@ra  +  ...
RA_w =  ...
HA_e =  ...
...
D1_ra_e = (ra_e_in__d1_ra_ha, 1)  >> D1_ra_e@d1_ra_ha +
          (ha_e_out__d1_ra_ha, 1) << D1_ra_e@d1_ra_ha;
D1_ra_w = ...
D1_ha_e = ...
D1_ha_w = ...
...
// SYSTEM DEFINITION (MODEL COMPONENT)

building ::=     (RA_e@ra[18] <> RA_w@ra[18] <> HA_e@ha[0] <> ...)
```

Example results: room occupancy



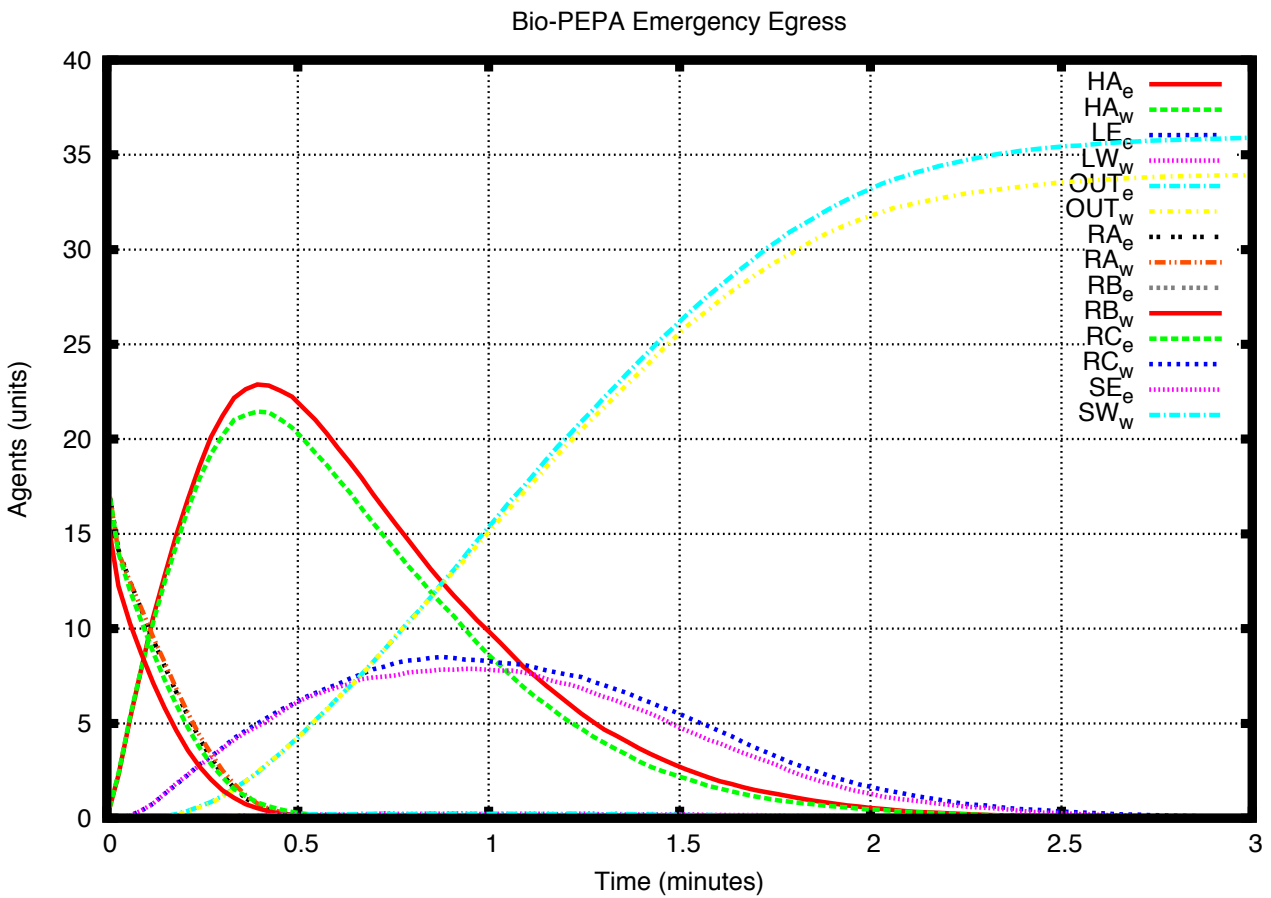
One stochastic simulation run

Example results: room occupancy



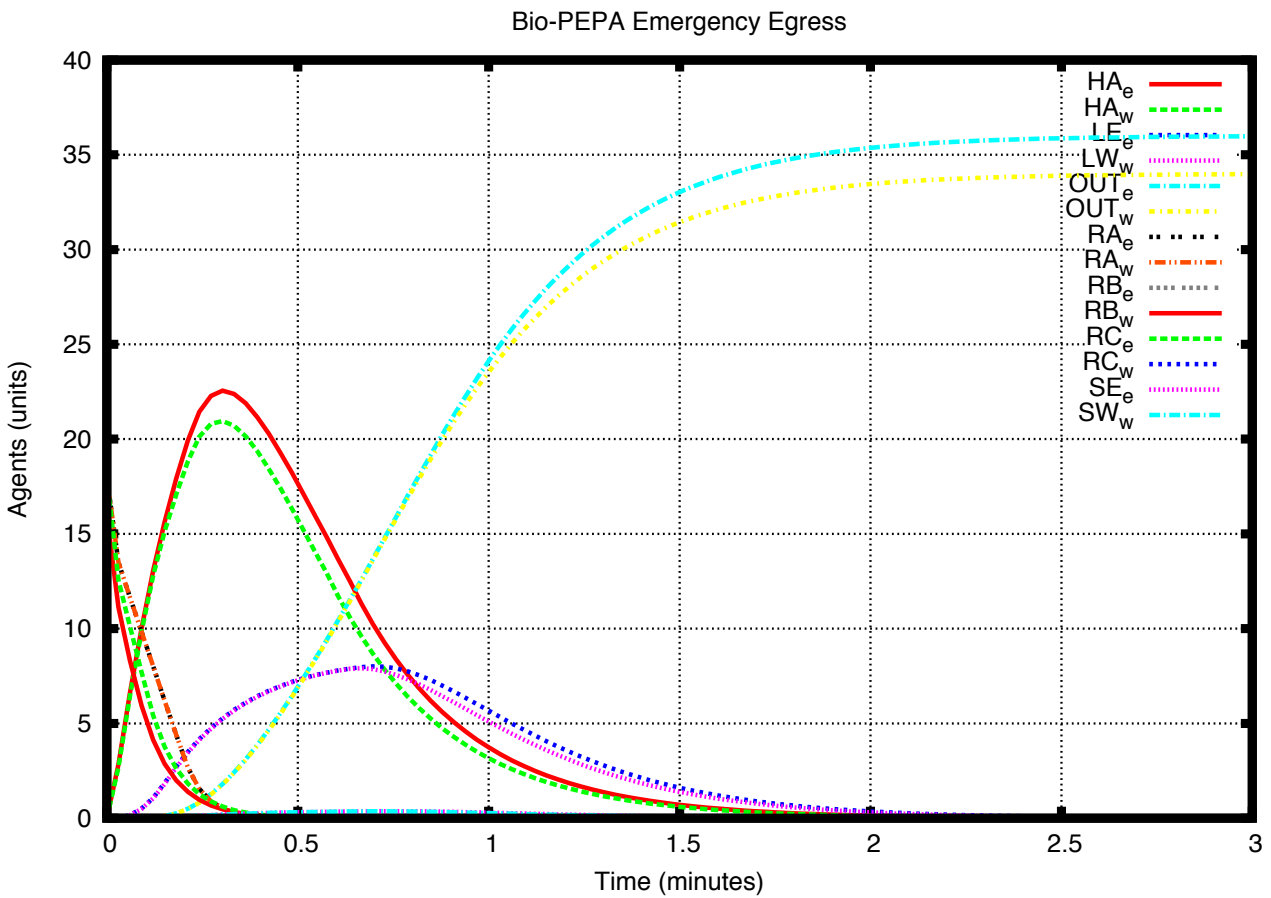
10 stochastic simulation runs

Example results: room occupancy



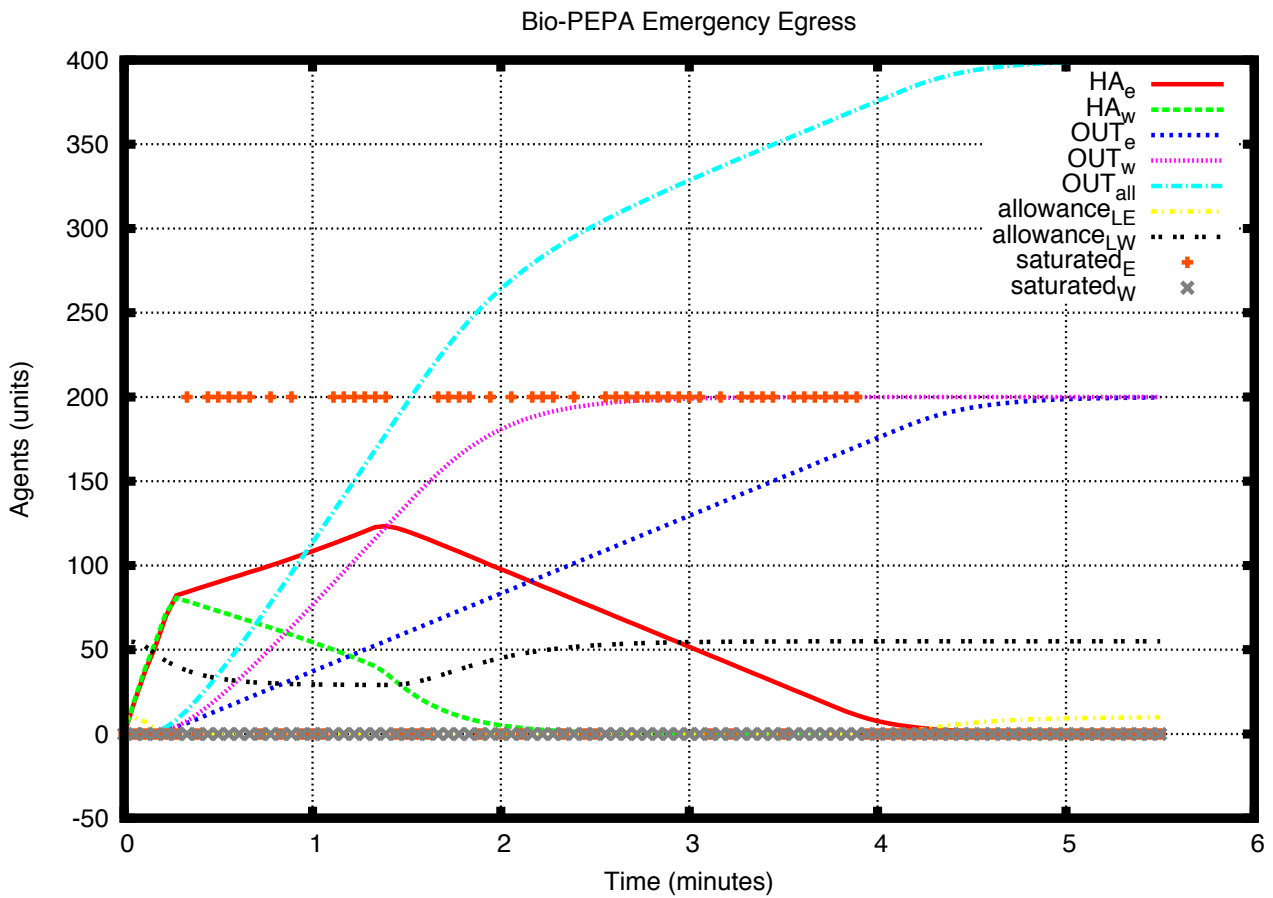
500 stochastic simulation runs

Example results: room occupancy



ODE numerical simulation

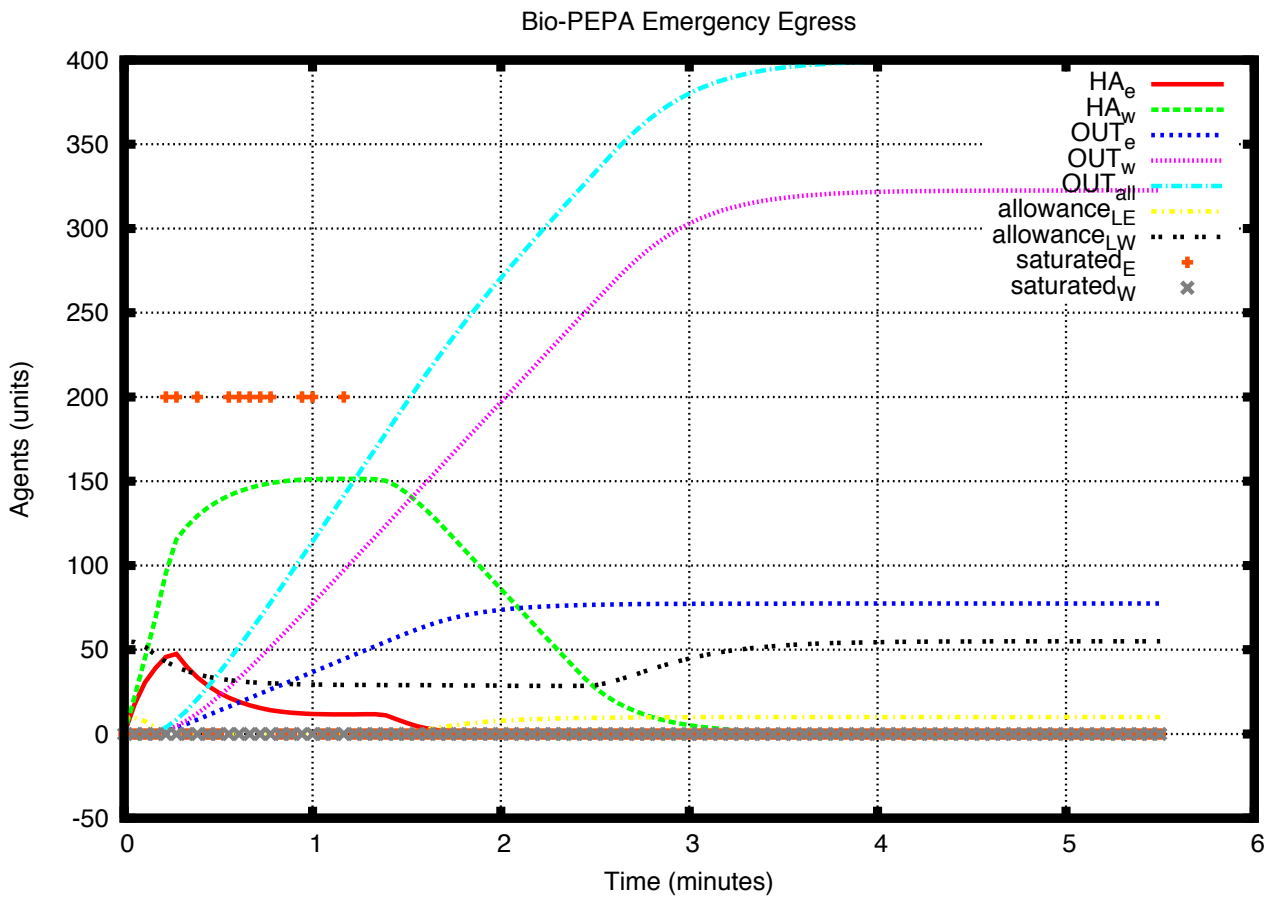
Example results: rerouting through mediation



Room occupancy over time without rerouting capability

Jane Hillston.
University of Edinburgh.

Example results: rerouting through mediation



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Outline

Conclusions

- Having formal representations of biological pathways eases the development of integrated analysis techniques.
- The compositionality of process algebras offers some benefits for model construction...
- ... however there is little work yet exploiting that compositional structure for the benefit of analysis.
- The semi-quantitative approach, based on CTMC with levels, offers a compomise between state space explosion and retaining some stochasticity in the model.
- Analysis based on the collective dynamics allows an efficient alternative to stochastic simulation which in many cases gives a reasonable approximation. Moreover being able to readily compare results of the two approaches can give added insight.

More Information and tool downloads

http://www.biopepa.org

Thank you!

People involved in the work:

- Ozgur Akman
- Andrea Bracciali
- Federica Ciocchetta
- Vashti Galpin
- Stephen Gilmore
- Maria Luisa Guerriero
- Diego Latella
- Mieke Massink
- Andrew Millar
- Carl Troein

Acknowledgements: Engineering and Physical Sciences Research Council (EPSRC) and Biotechnology and Biological Sciences Research Council (BBSRC).

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SPA
MODEL

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SPA MODEL $\xrightarrow{\text{SOS rules}}$

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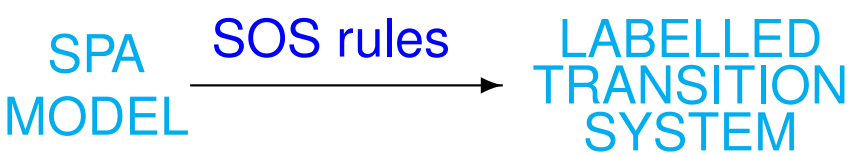

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The structure of the CTMC derived from Bio-PEPA, which we term the CTMC with levels, will depend on the granularity of the model.

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

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- However, in contrast to a simulation run which generates just one trajectory, probabilistic model-checking gives a definitive answer so it is not necessary to re-run the analysis repeatedly and compute ensemble averages of the results.
- 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.

PRISM model and model checking

- Probabilistic model checking in PRISM is based on a CTMC and the logic CSL.
- 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.

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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.