Modelling Biochemical Signalling Pathways with Stochastic Process Algebra

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Outline

- Introduction to Systems Biology
  - Motivation
- Challenges
- Stochastic Process Algebra for Biology
  - Stochastic Process Algebra
  - Abstraction, Modularity and Reasoning
  - Case Study
- Conclusions

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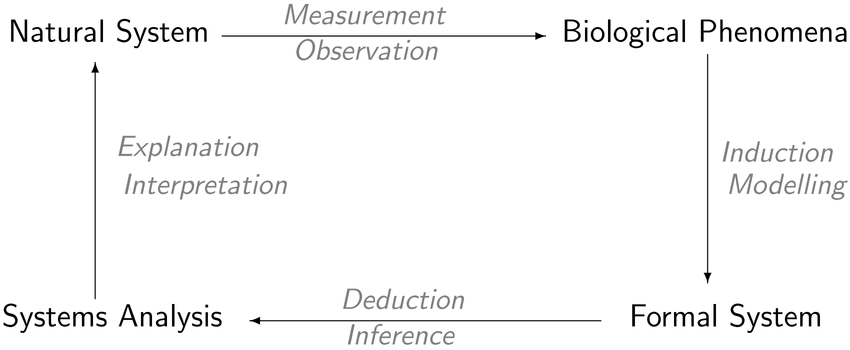
- Systems biology aims to develop a better understanding of the processes involved.
- It involves taking a systems theoretic view of biological processes — analysing inputs and outputs and the relationships between them.
- A radical shift from earlier reductionist approaches, systems biology aims to provide a conceptual basis and a methodology for reasoning about biological phenomena.

Systems Biology Methodology



Natural System

Measurement

Observation

Biological Phenomena

Induction

Modelling

Formal System

Deduction

Inference

Systems Analysis

Explanation

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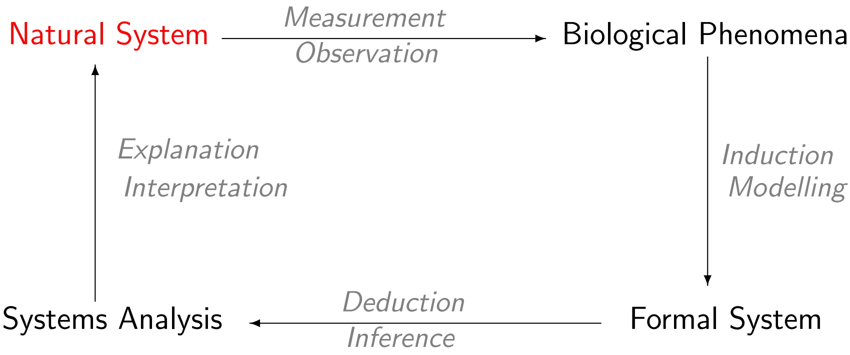

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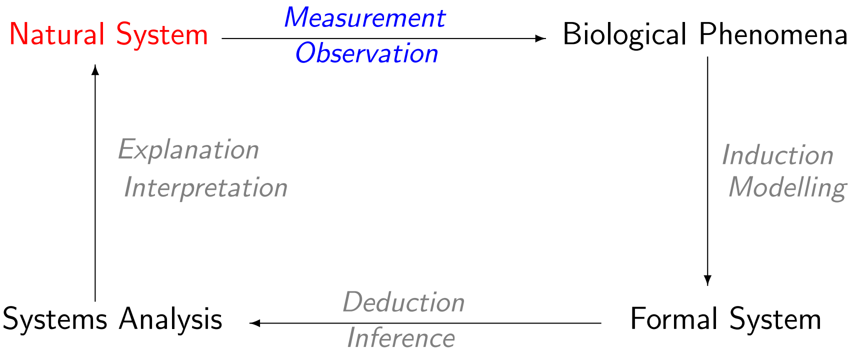

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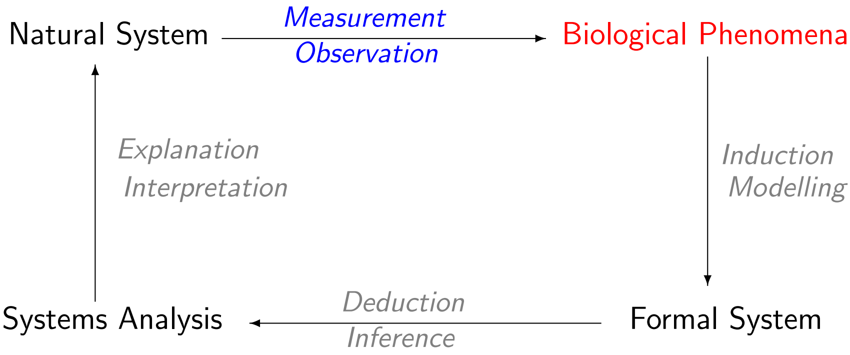

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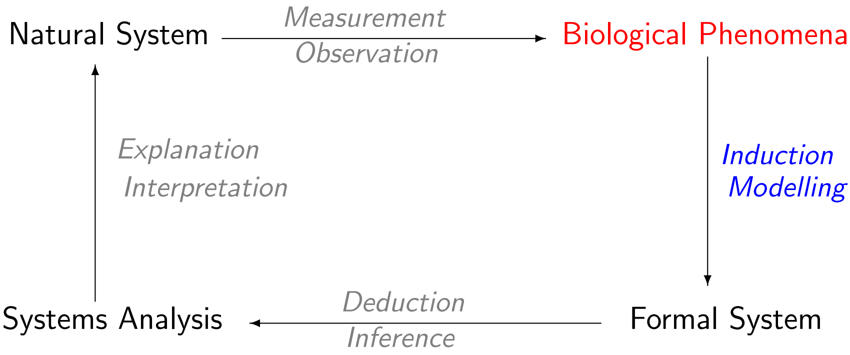

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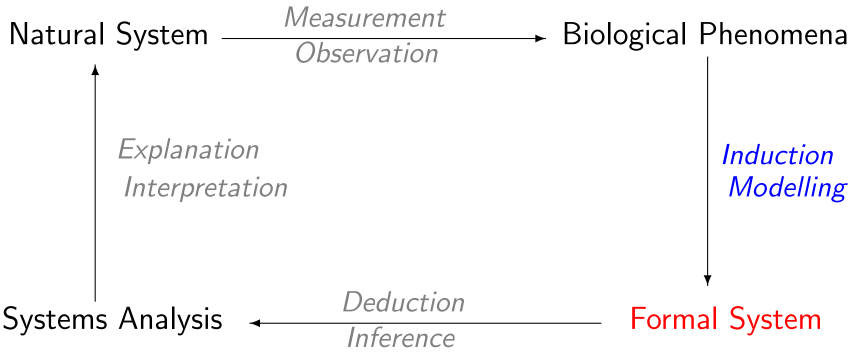

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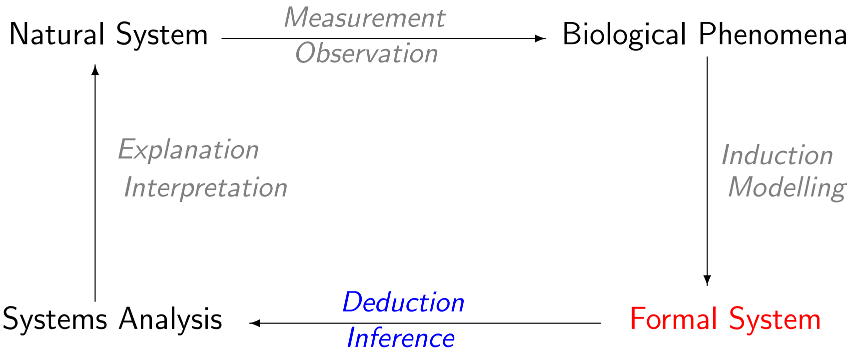

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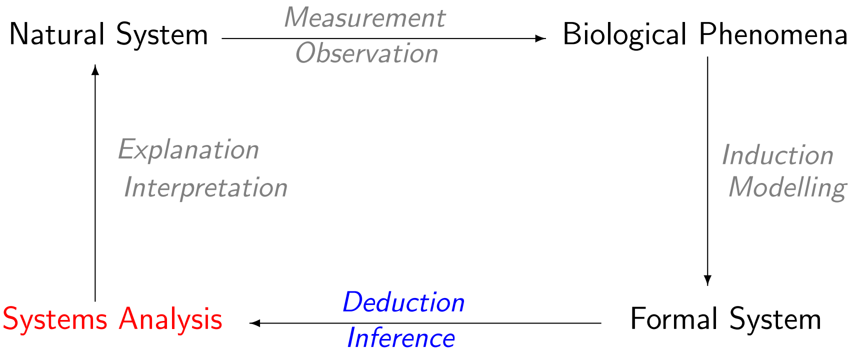

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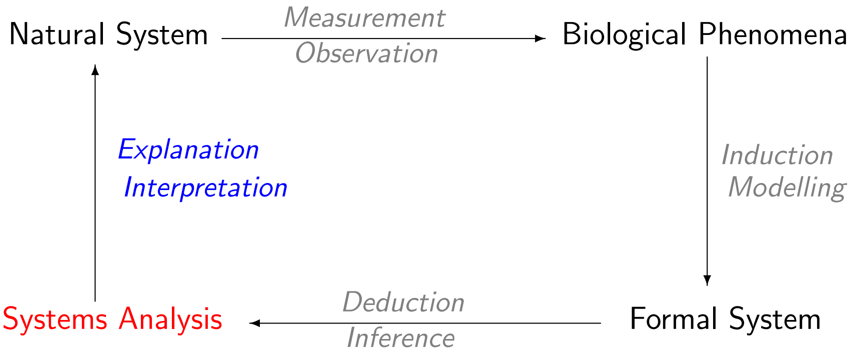

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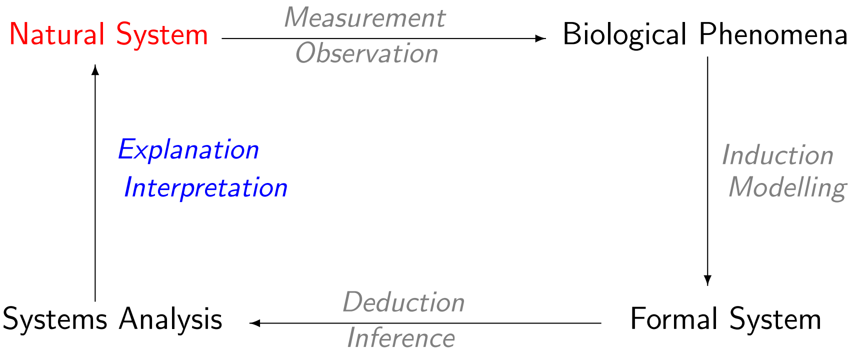

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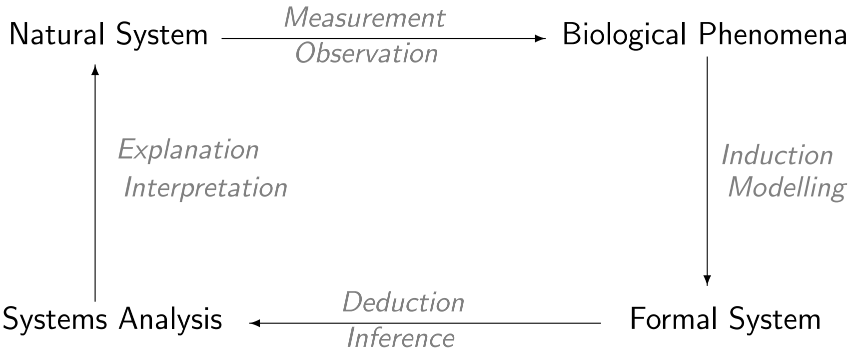

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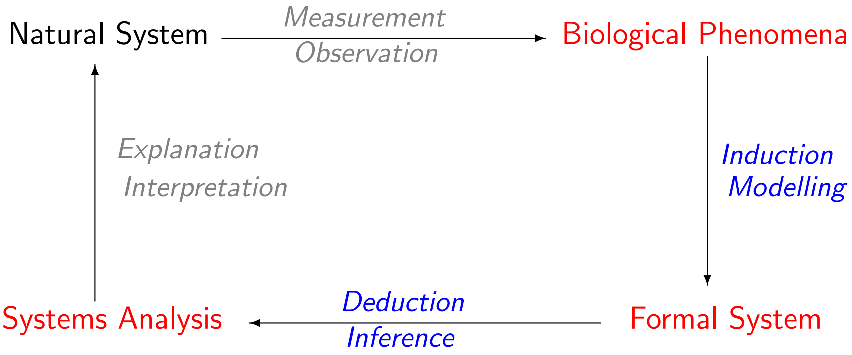
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But these distinctions are to some extent arbitrary as models may include elements of more than one pathway type.

Signal transduction pathways

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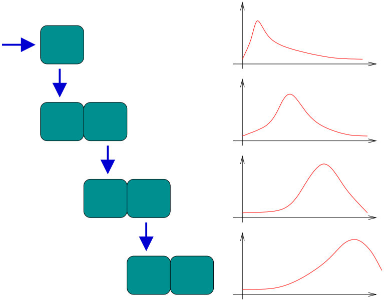

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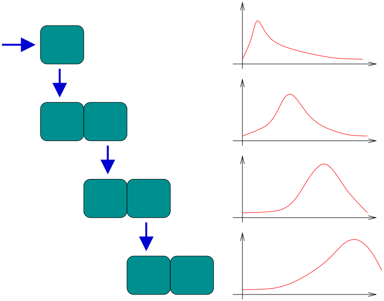

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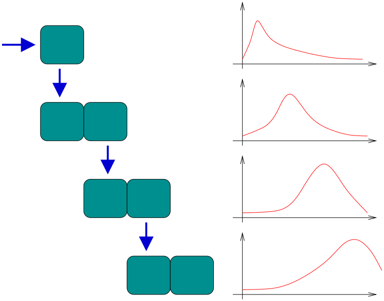

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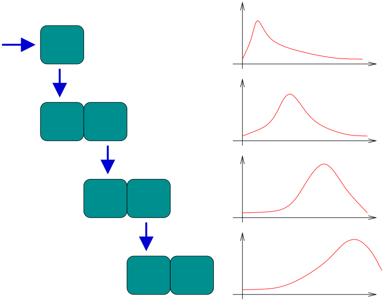

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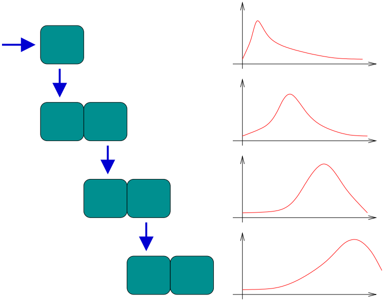
- Signals propagate through a series of protein accumulations.



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

Systems Analysis

- In biochemical signalling pathways the events of interests are
  - when reagent concentrations start to increase;
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- These are the data that 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.

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Individual vs. Population behaviour

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- Note that given a large enough number of molecules, an "individuals" model will (in many circumstances) be indistinguishable from the a "population" level model.

Noise vs. Determinism

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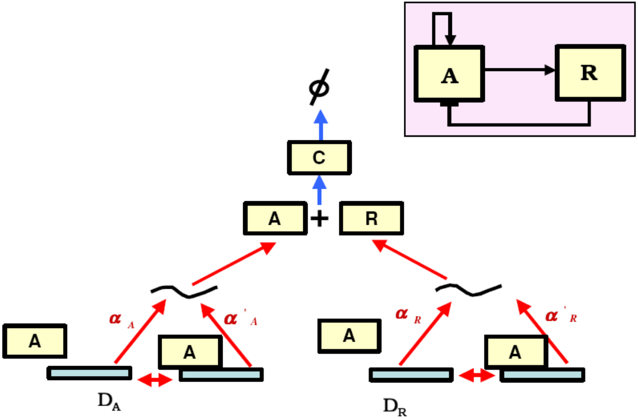
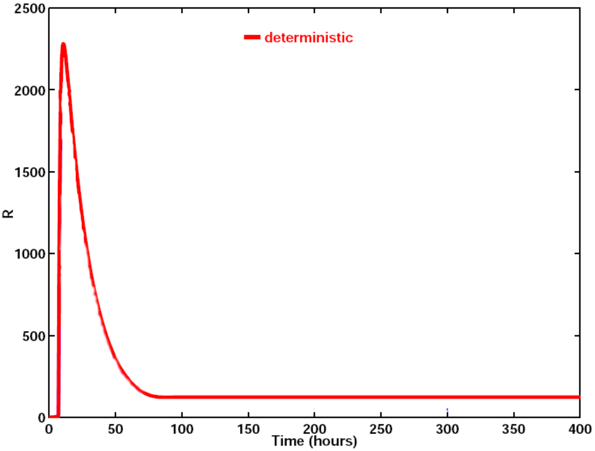
- When a large number of such reactions occur, the randomness of the individual reactions can cancel each other out and the apparent behaviour exhibits less variability.
- However, in some systems the variability in the stochastic behaviour plays a crucial role in the dynamics of the system.

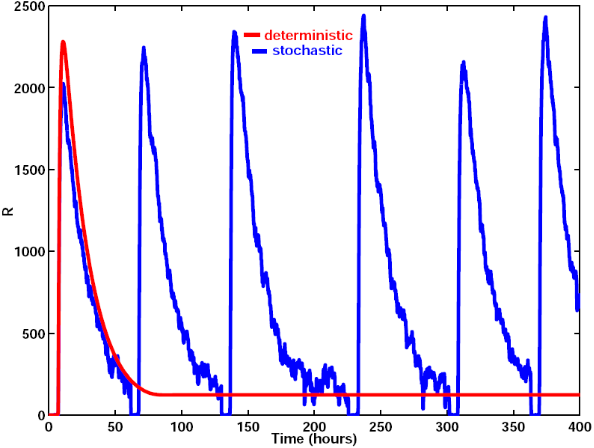
Circadian clock (cartoon)



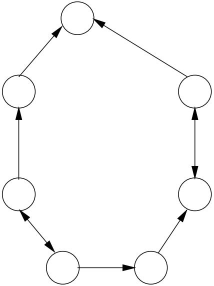
Circadian clock (deterministically . . .)



Circadian clock (. . . and stochastically)



The problem of *Infinite Regress*



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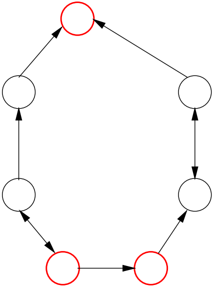

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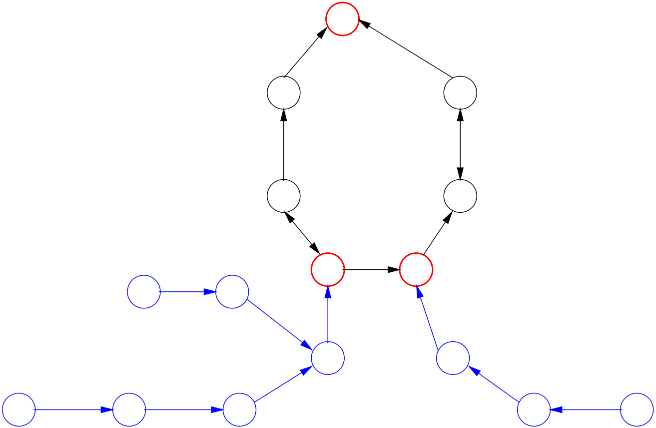

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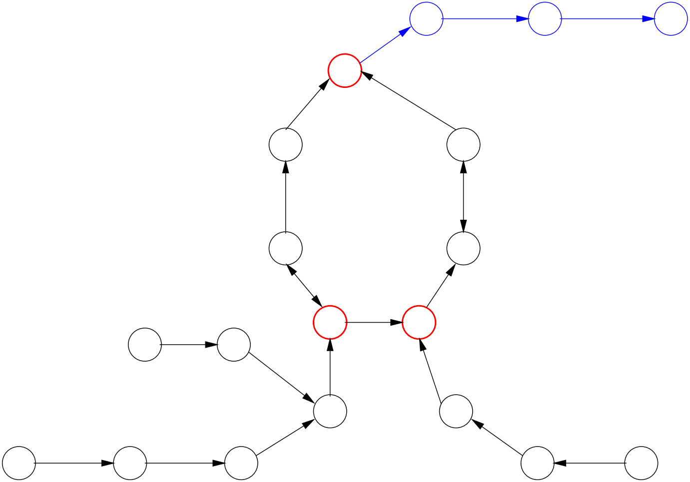

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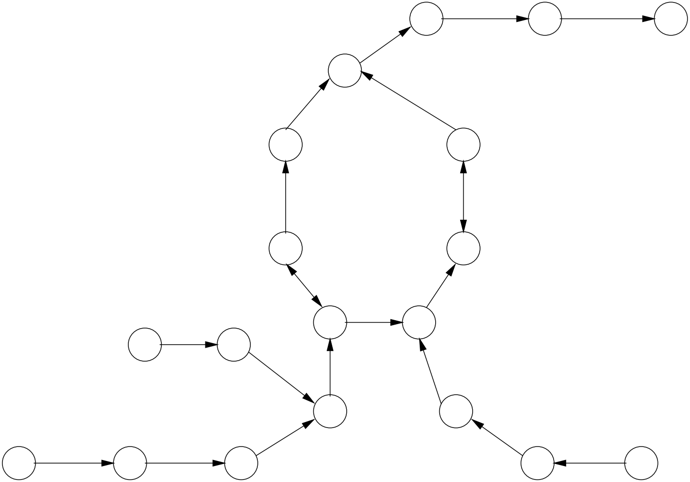

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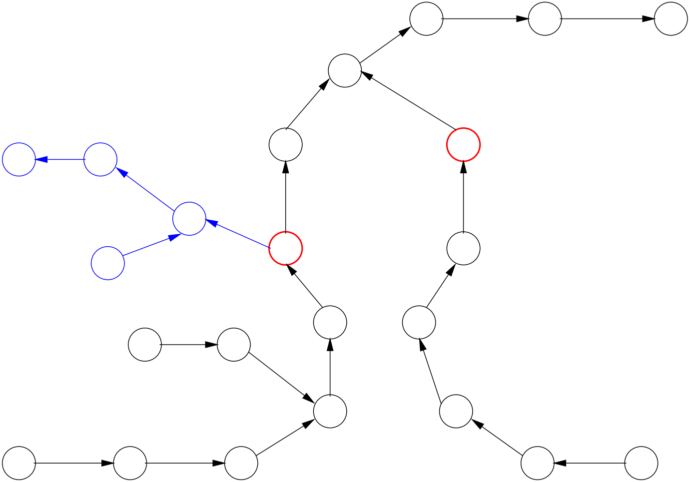

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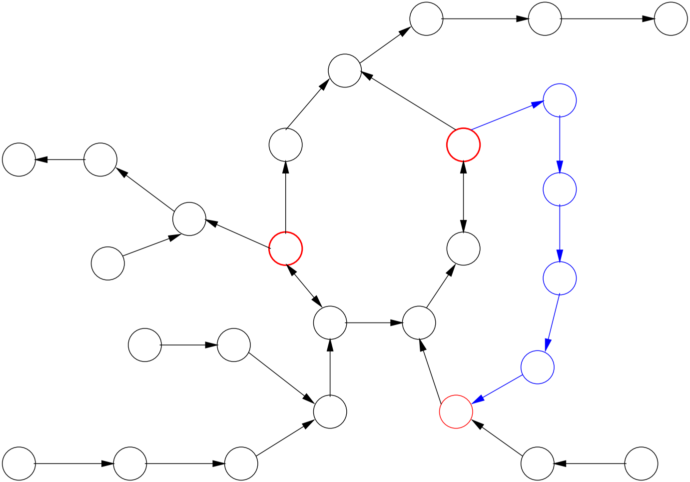

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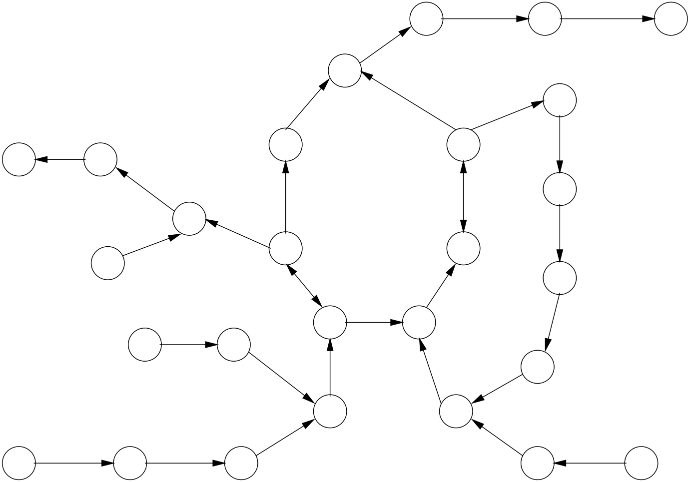

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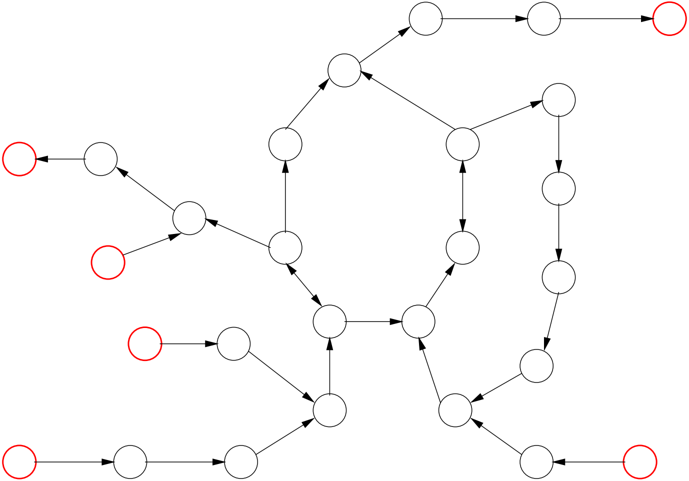

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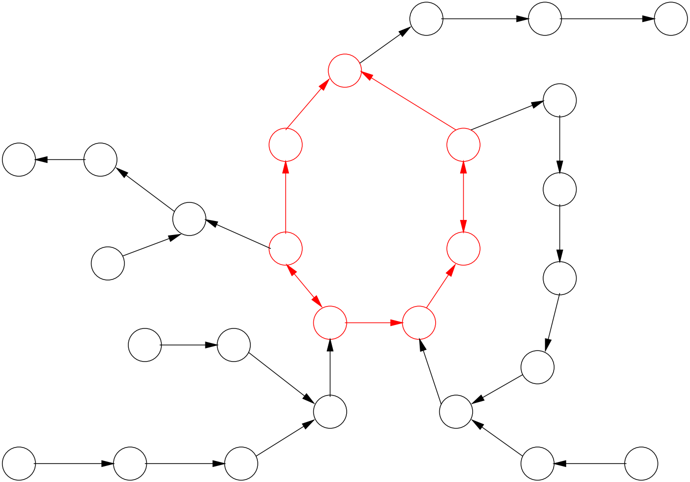

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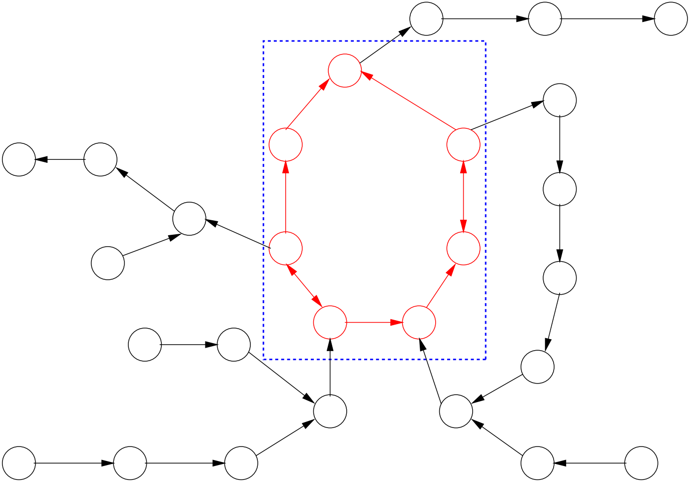

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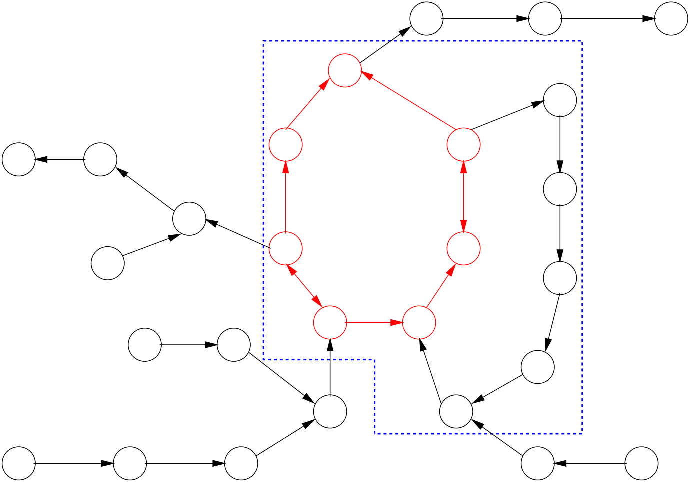

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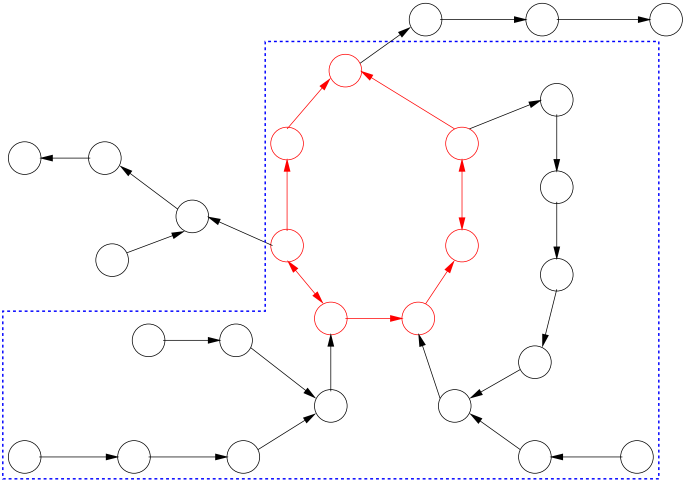

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Others such as Cornish-Bowden are much more skeptical and cite the problem of infinite regress as being insurmountable.

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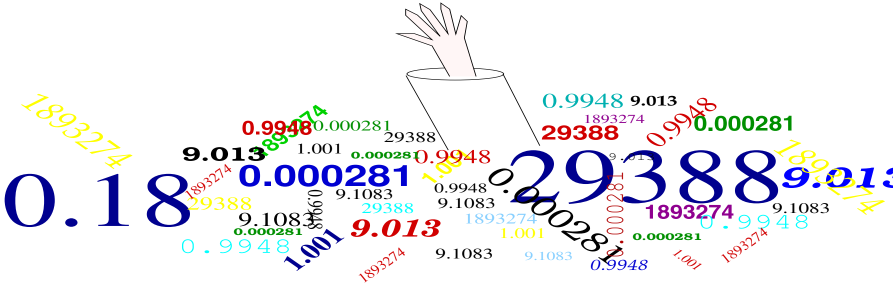
Even when data exists the quality is often poor.

Computational Thinking to the rescue



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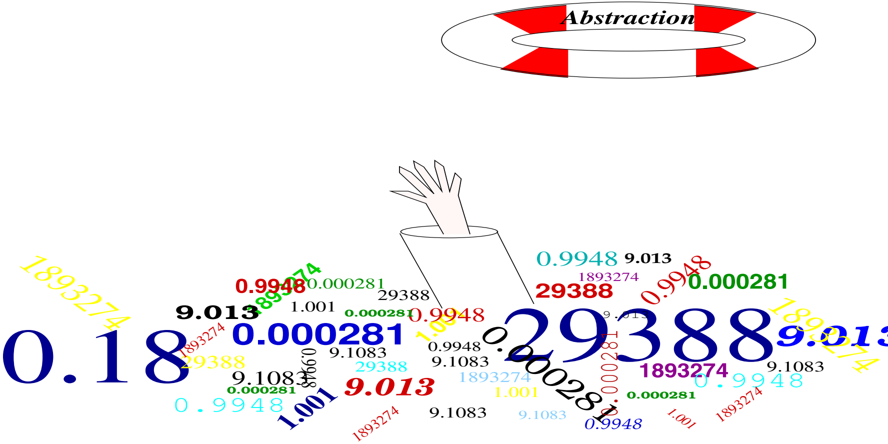

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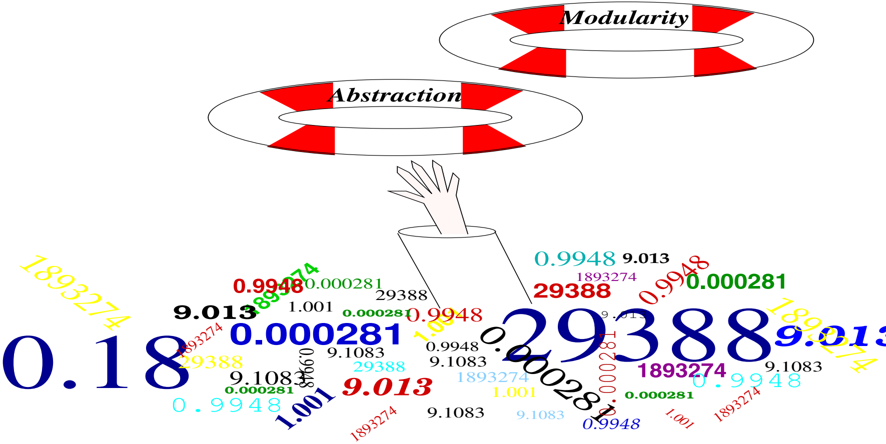

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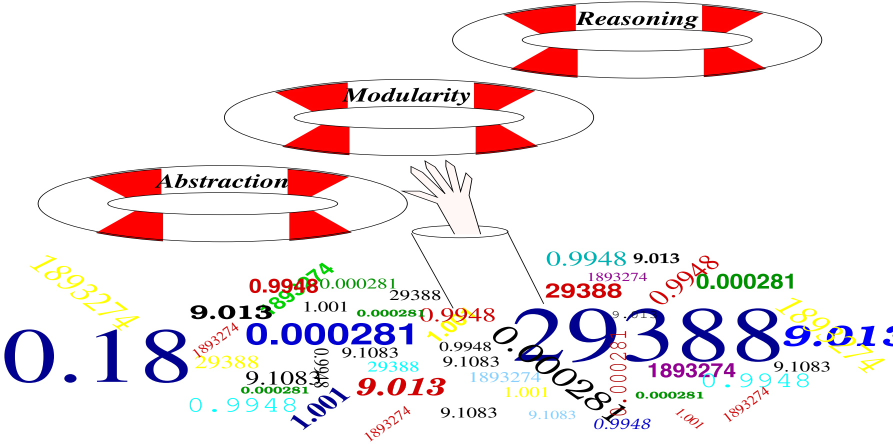

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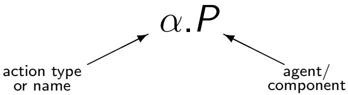
- Process algebraic formulations are compositional and make interactions/constraints explicit.
- Equivalence relations allow formal comparison of high-level descriptions.
- There are well-established techniques for reasoning about the behaviours and properties of models, supported by software. These include qualitative and quantitative analysis, and model checking.

Process Algebra

- Models consist of agents which engage in actions.



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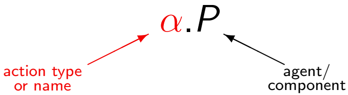

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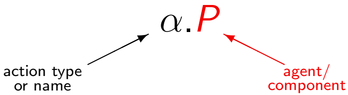

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action type
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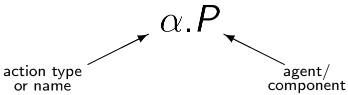

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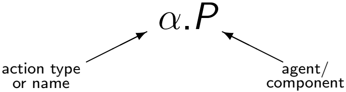

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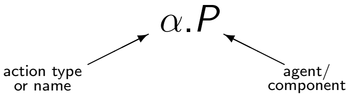

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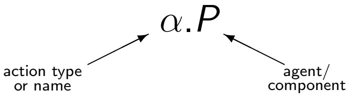

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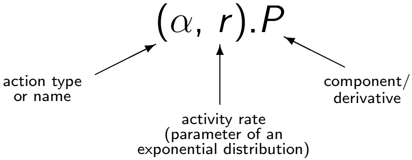

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action type
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activity rate
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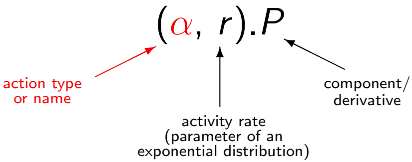

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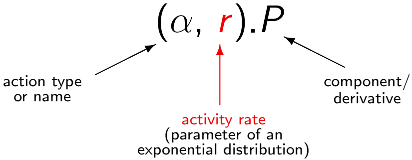

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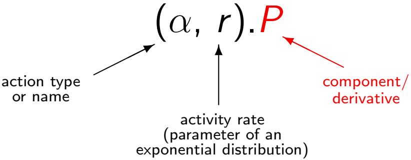

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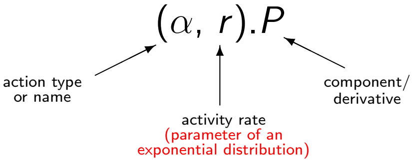

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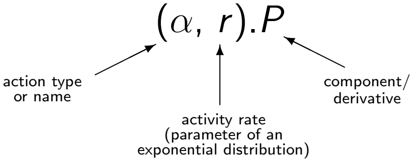

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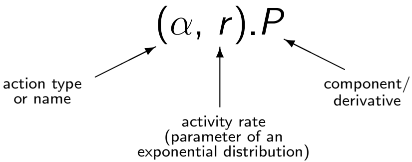

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SPA
MODEL

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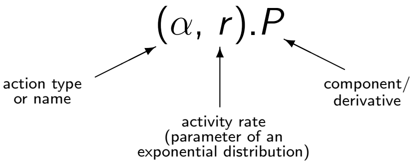

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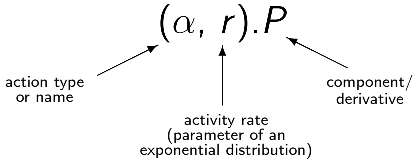

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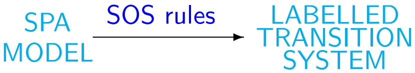

SPA MODEL

SOS rules

LABELLED TRANSITION SYSTEM

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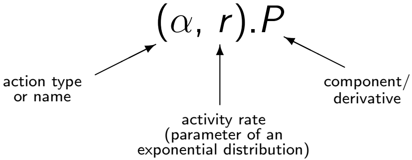

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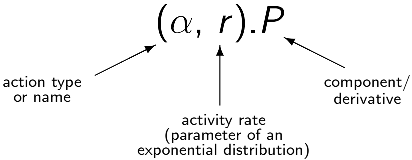

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Molecular processes as concurrent computations

Concurrency	**Molecular Biology**	**Metabolism**	**Signal Transduction**
Concurrent computational processes	Molecules	Enzymes and metabolites	Interacting proteins
Synchronous communication	Molecular interaction	Binding and catalysis	Binding and catalysis
Transition or mobility	Biochemical modification or relocation	Metabolite synthesis	Protein binding, modification or sequestration

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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).

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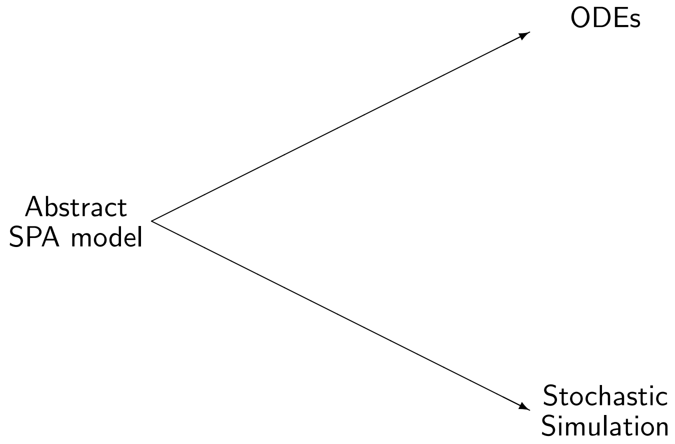
Reagent-centric modelling

Reagent role	*Impact on reagent*	*Impact on reaction rate*
Producer	decreases concentration	has a positive impact, i.e. proportional to current concentration
Product	increases concentration	has no impact on the rate, except at saturation
Enzyme	concentration unchanged	has a positive impact, i.e. proportional to current concentration
Inhibitor	concentration unchanged	has a negative impact, i.e. inversely proportional to current concentration

Alternative Representations

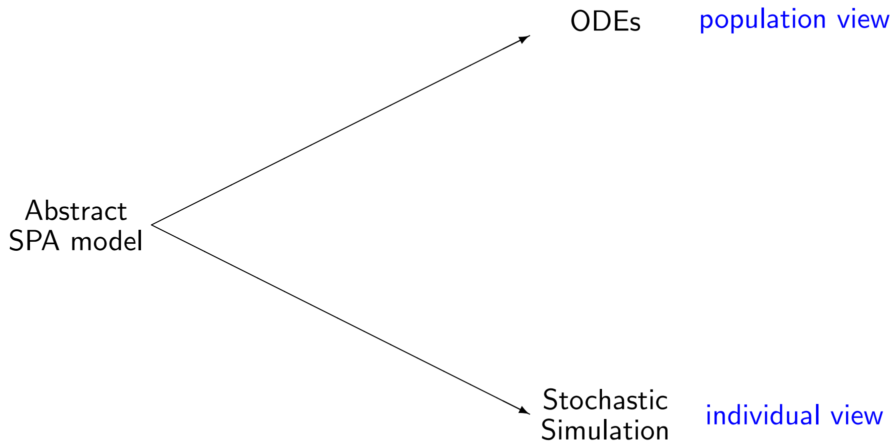


Abstract
SPA model

ODEs

Stochastic
Simulation

Alternative Representations



ODEs population view

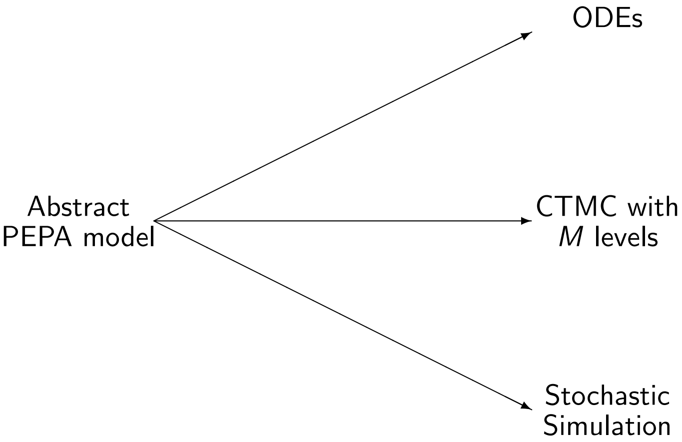
Abstract SPA model

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



Abstract
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CTMC with
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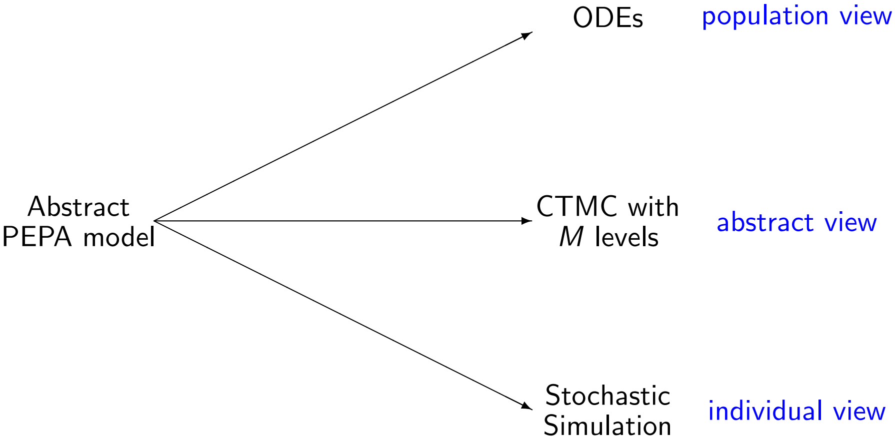


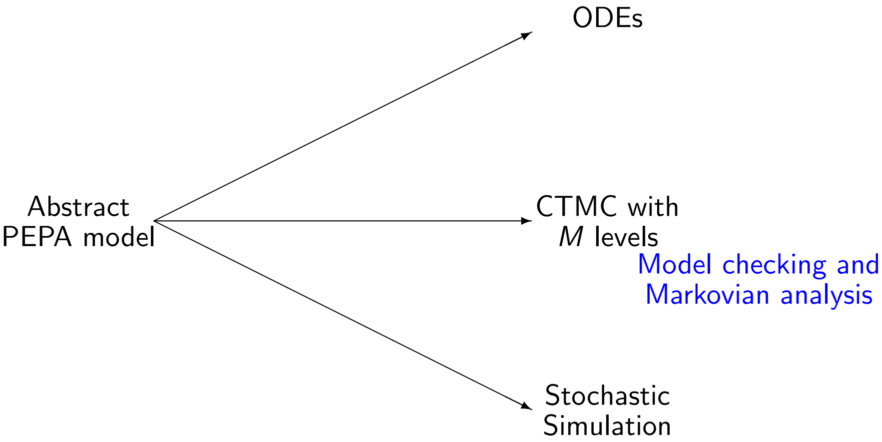
Abstract PEPA model

ODEs — population view

CTMC with M levels — abstract view

Stochastic Simulation — individual view

Alternative Representations



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Model checking and
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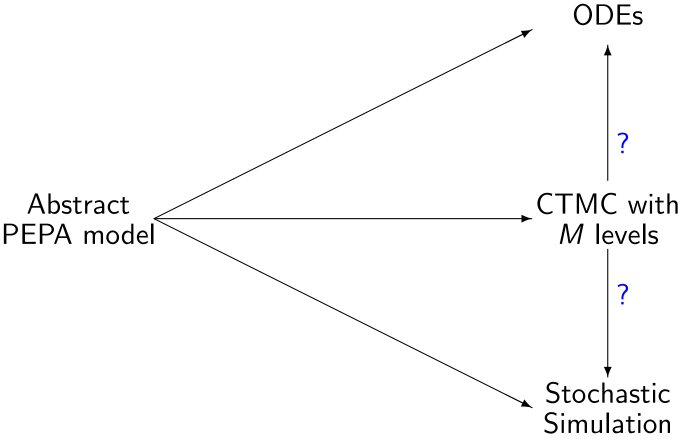

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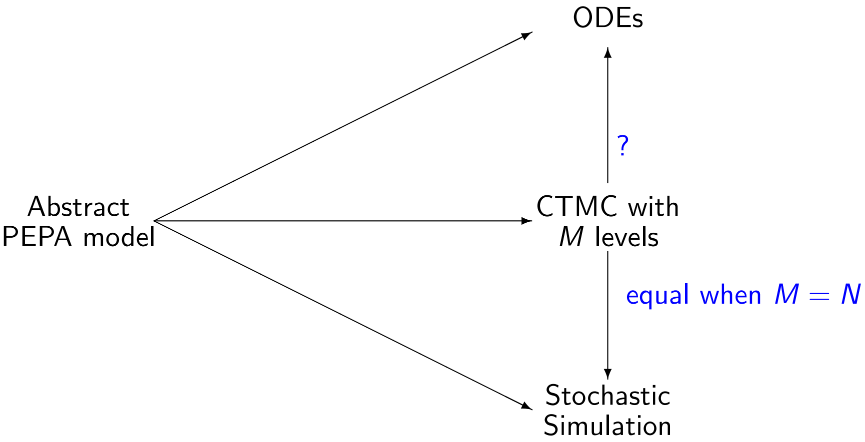

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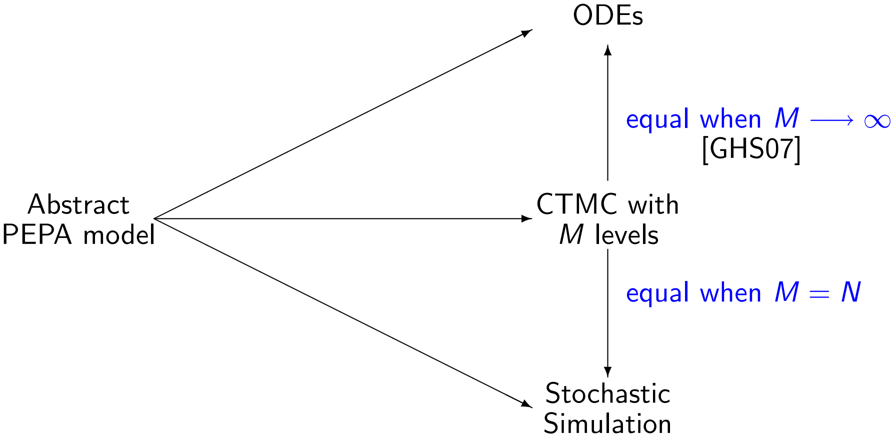


ODEs

equal when $M \longrightarrow \infty$ [GHS07]

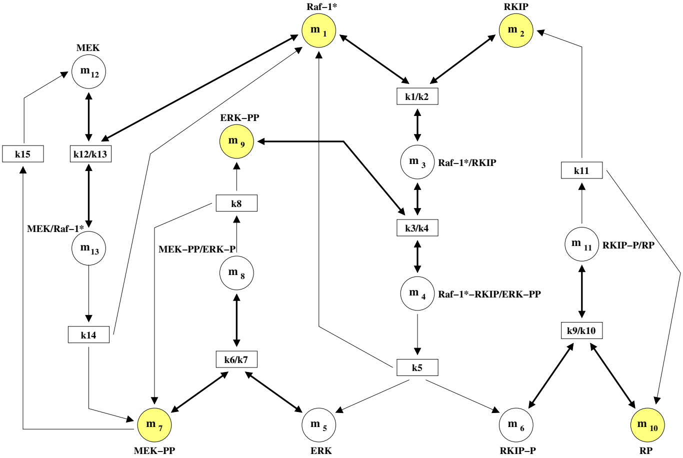
Abstract PEPA model

CTMC with M levels

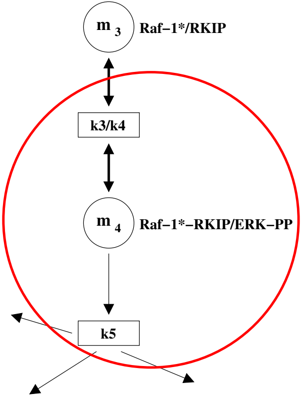
equal when $M = N$

Stochastic Simulation

Example: The Ras/Raf-1/MEK/ERK pathway



PEPA components of the reagent-centric model



$$\begin{aligned}\text{Raf-1}^*/\text{RKIP}/\text{ERK-PP}_\mathrm{H} &\overset{\mathit{def}}{=} (\mathit{k5product}, k_5).\text{Raf-1}^*/\text{RKIP}/\text{ERK-PP}_\mathrm{L} \\ &\quad + (\mathit{k4react}, k_4).\text{Raf-1}^*/\text{RKIP}/\text{ERK-PP}_\mathrm{L}\end{aligned}$$

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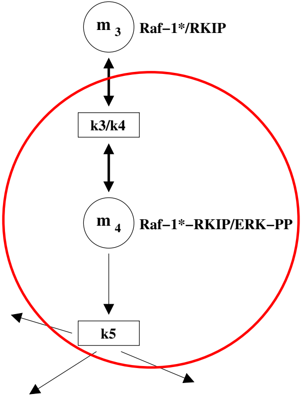

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Each reagent gives rise to a pair of PEPA definitions, one for high concentration and one for low concentration.

Commentary on the model

- I have shown the model with only high and low levels of concentration. In general we would discretise the concentration more coarsely with say 6 or 7 levels. As we add levels we are capturing the concentration at finer levels of granularity.

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- The two levels (high/low) are sufficient to generate the ODEs or stochastic simulation.
- For this model stochastic simulation and ODE analysis coincide.
- We also considered an alternative model of the pathway with subpathways as components, and we were able to use the process algebra equivalence to show that our two models have the same behaviour.

Reasoning and Model Checking

The original published model of the Ras/Raf-1/MEK/ERK pathway had a structure which allowed MEK to grow unboudedly which had not been detected in the ODE model.

Model checking using the PRISM probabilistic model checker allowed us to check properties such as whether one protein will exhibit a peak of concentration before another.

To do this we considered models with 6 levels of concentration, i.e. the range of possible values of concentration are split into 6 discrete levels — this shows good agreement with the ODE solution for transient behaviour.

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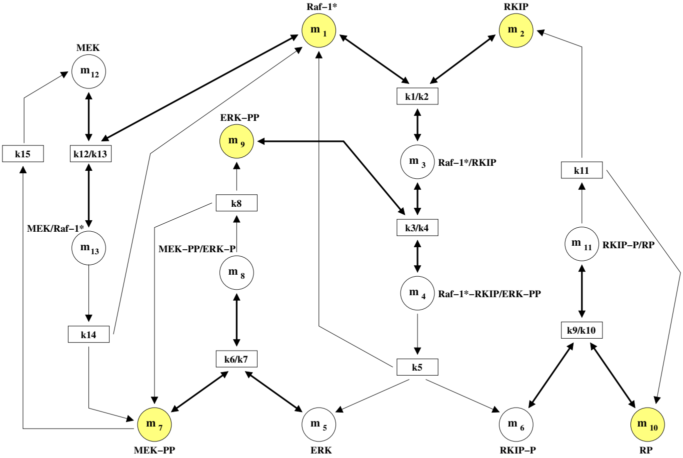

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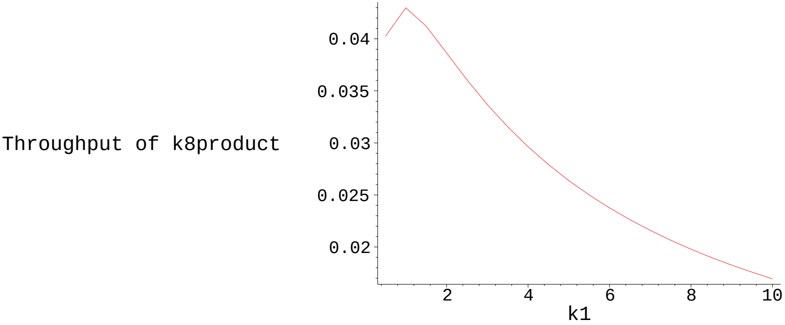
Note, however, that a transient Markovian analysis is exact because it takes account of all possible evolutions, unlike a stochastic simulation which considers only one possible evolution in each run.

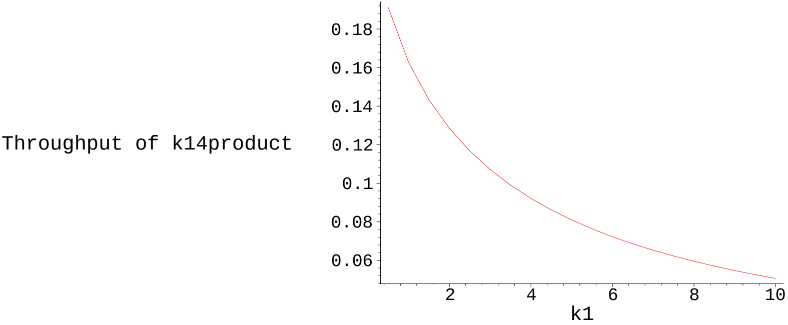
Quantified analysis – *k8product*

Approximating a variation in the initial concentration of RKIP by varying the rate constant k1, we can assess the impact on the production of ERK-PP.



Quantified analysis – *k14product*

Similarly we can assess the impact on the production of MEK-PP.



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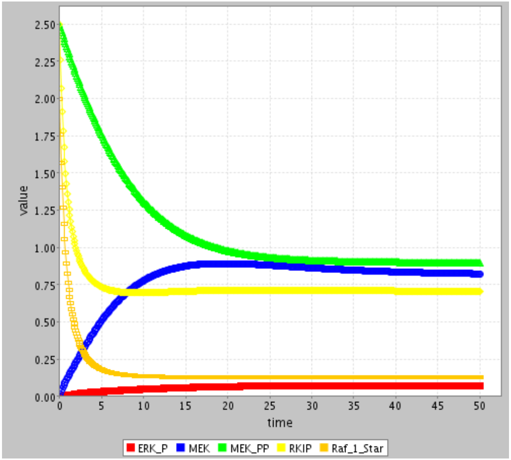
- The algebraic formulation of the model emphasises interactions between the biochemical entities.

ODE Analysis of the MAPK example



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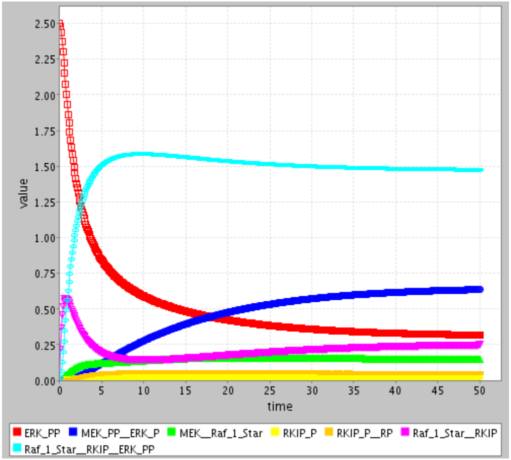

Outline

- Introduction to Systems Biology
  - Motivation
- Challenges
- Stochastic Process Algebra for Biology
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  - Abstraction, Modularity and Reasoning
  - Case Study
- Conclusions

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  - Better models and simulations of living phenomena

Conclusions

- Ultimately we want to understand the functioning of cells as useful levels of abstraction, and to predict unknown behaviour.
- It remains an open and challenging problem to define a set of basic and general primitives for modelling biological systems, inspired by biological processes.
- Achieving this goal is anticipated to have two broad benefits:
  - Better models and simulations of living phenomena
  - New models of computations that are biologically inspired.

Thank You!

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