

Computational Thinking for Life

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LFCS, University of Edinburgh

11th January 2006

(Joint work with Muffy Calder, Adam Duguid, Stephen Gilmore, and
Marco Stenico)

Systems Biology: Will it Work?

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- ▶ Perhaps not surprising for a **new** initiative?

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- ▶ The third in a series of annual symposia: Systems Approach in Biology.
- ▶ Stated objective — “To assess the past development and the future potential of the application of the systems approach in biology.”

Outline

Systems Biology

A Role for Computational Thinking

Models, Formal Systems and Inference

A PEPA example

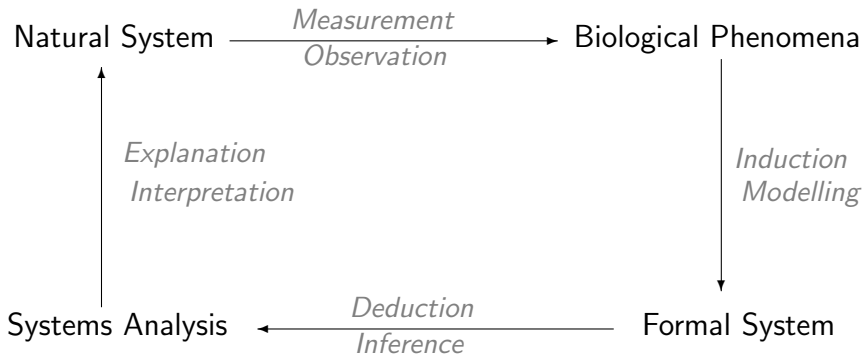
Future Perspectives

What is Systems Biology?

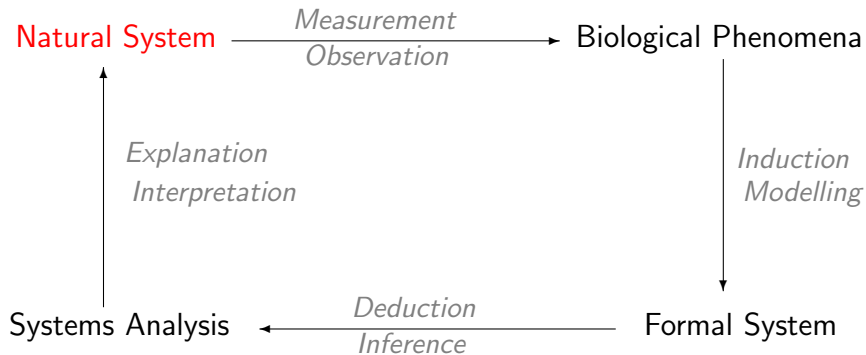
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“The principal aim of systems biology is to provide both a conceptual basis and working methodologies for the scientific explanation of biological phenomena” – Olaf Wolkenhauer

Systems Biology Methodology



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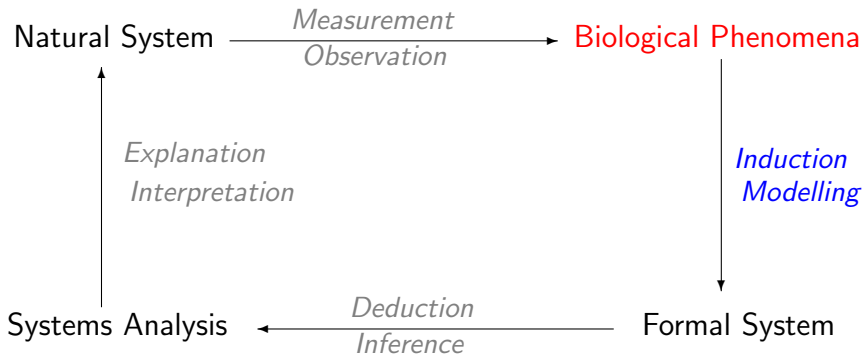


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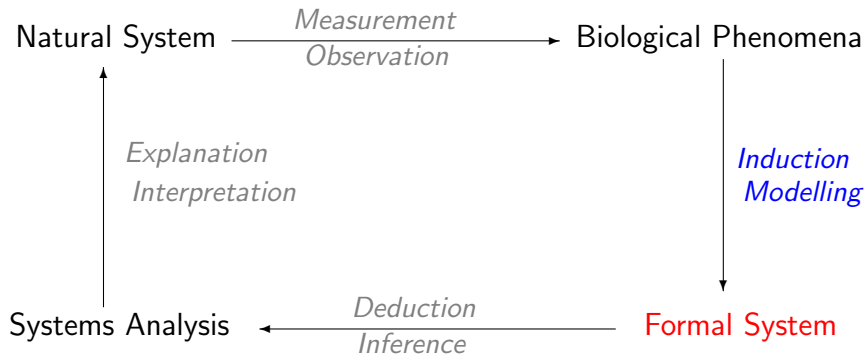




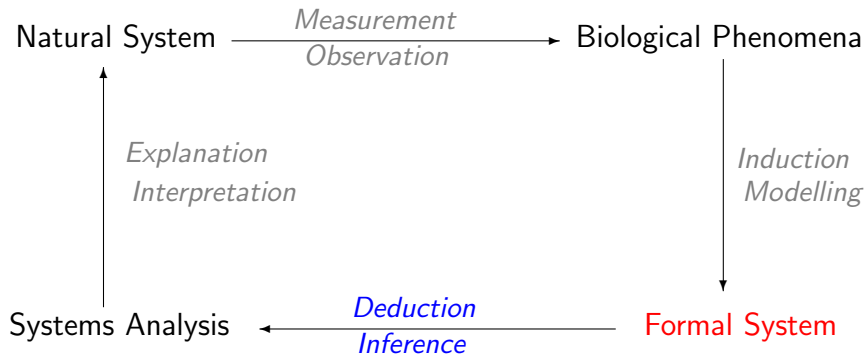
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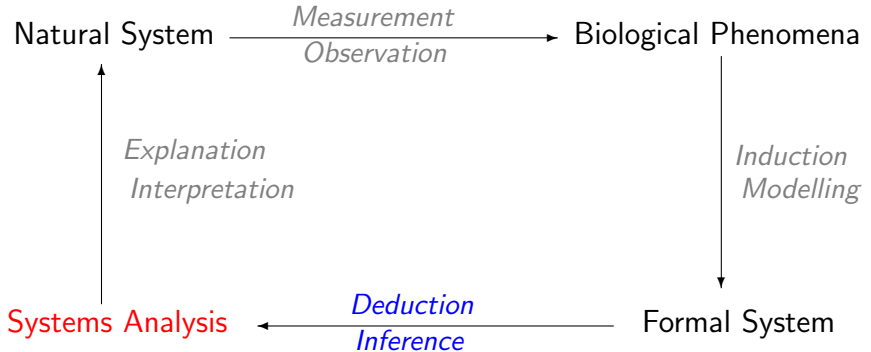
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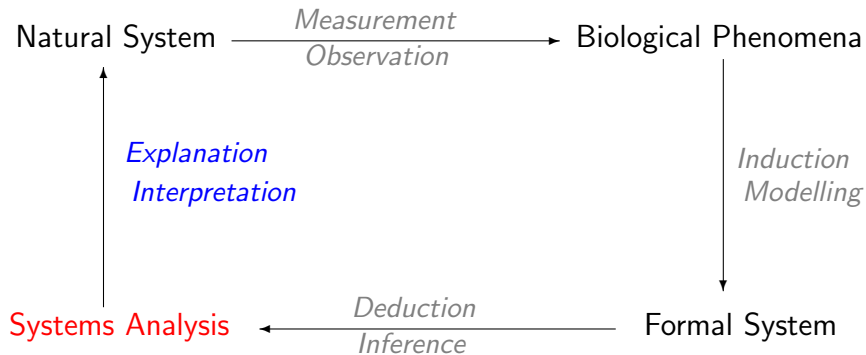
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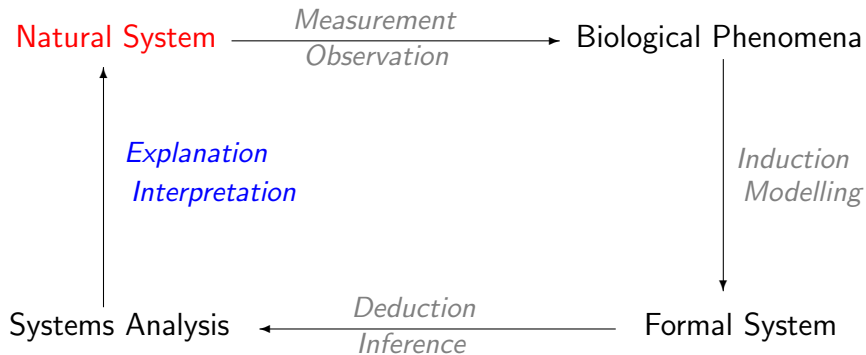
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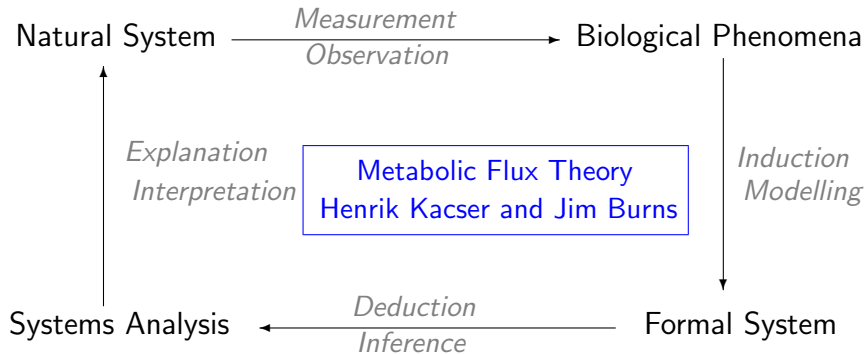
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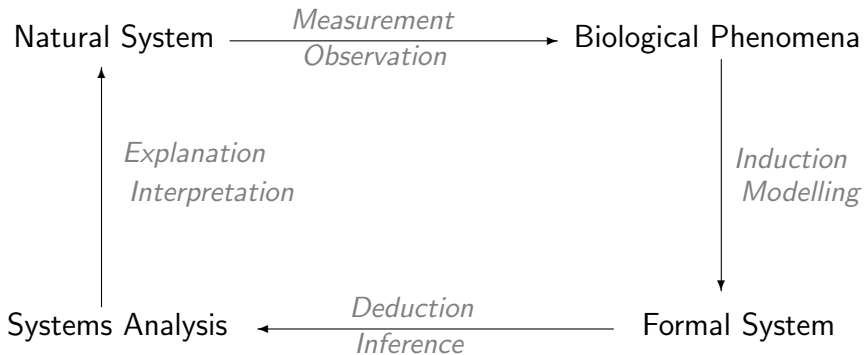
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Measurement, Observation and Induction

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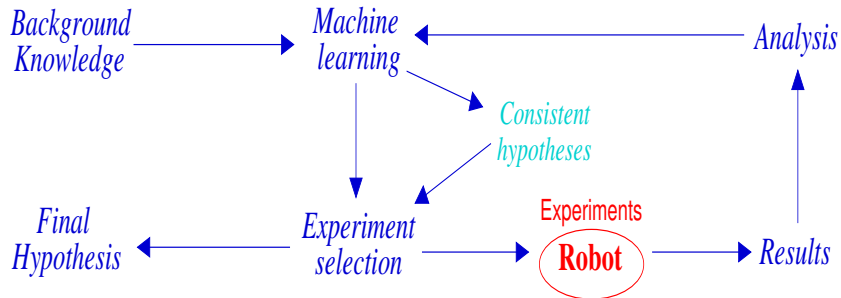
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- ▶ Experiments are carried out by a robot.
- ▶ Data is generated at rates which exceed what is possible when there are humans in the loop.
- ▶ Moreover the intelligent experiment selection strategy is competitive with (good) human strategies, and significantly outperforms *cheapest* and *random* selection strategies.

The Robot Scientist



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The Challenges

Systems biology modelling faces a number of challenges. In particular:

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- ▶ The problem of infinite regress;
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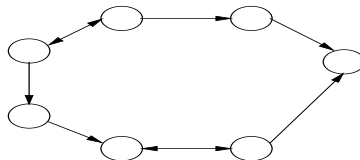
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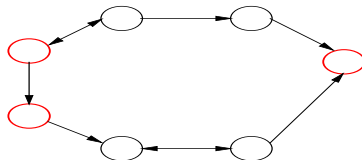
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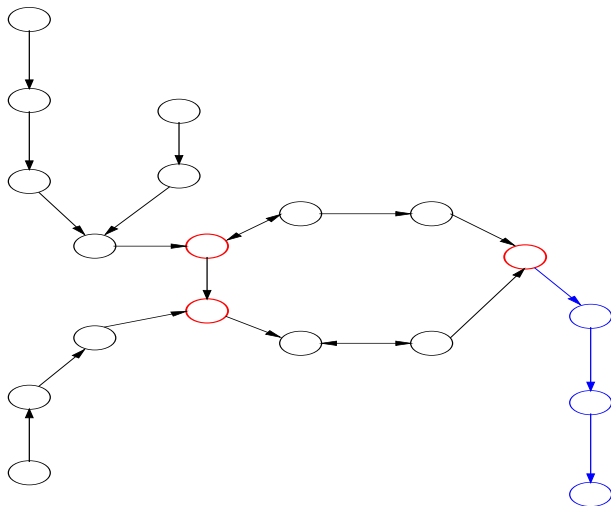
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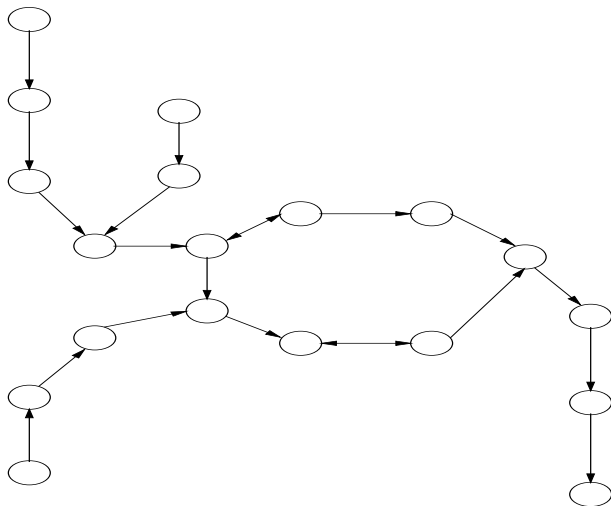


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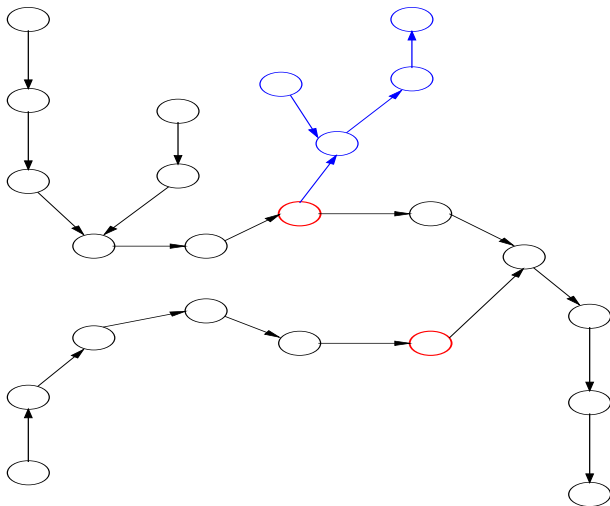




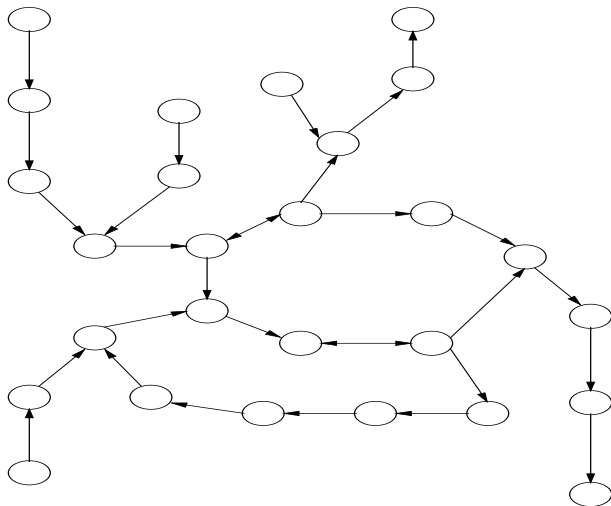
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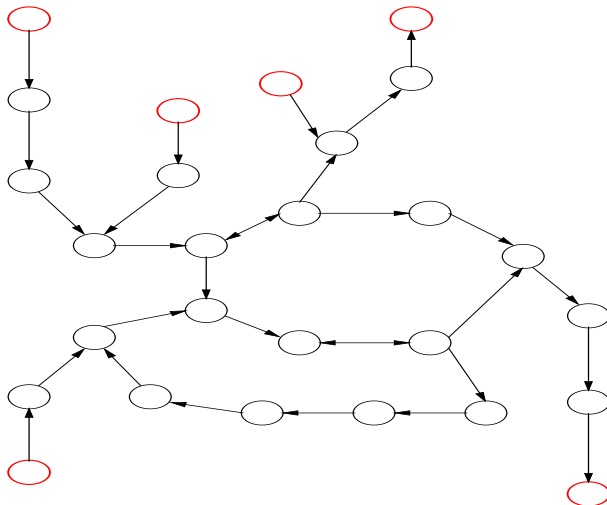
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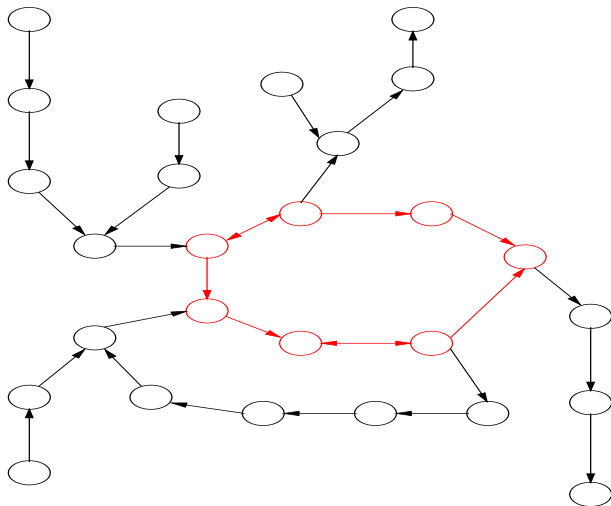


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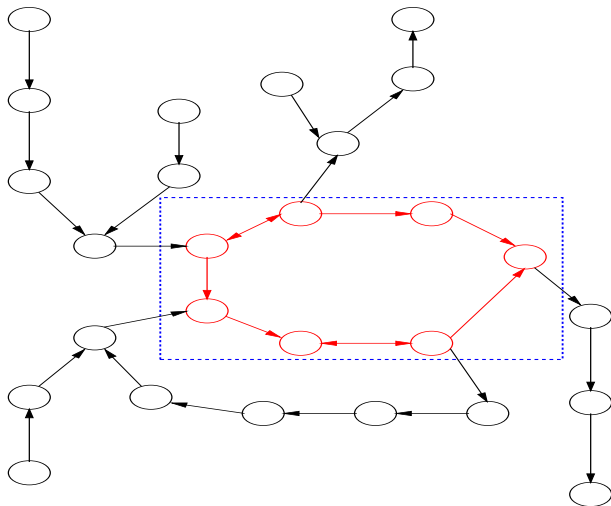


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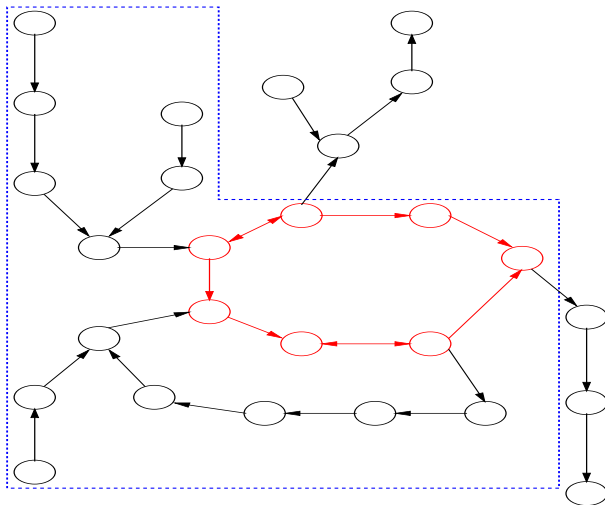




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A proper account of **experimental observations** requires a model which captures **behaviour at all three levels**.

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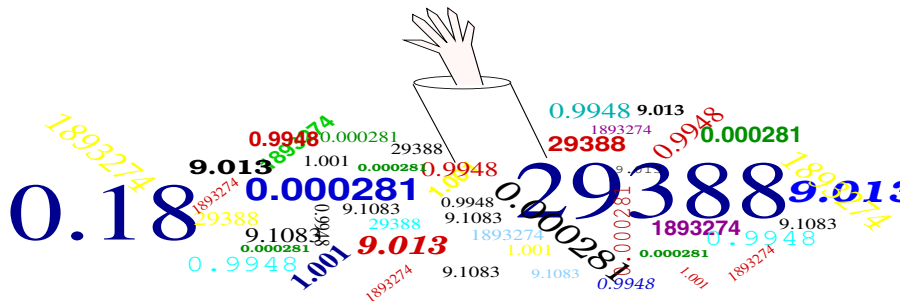
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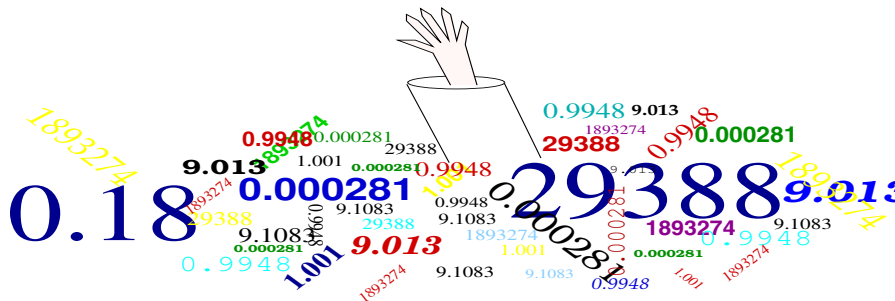
In particular:

- ▶ Abstraction
- ▶ Modularity and
- ▶ Reasoning

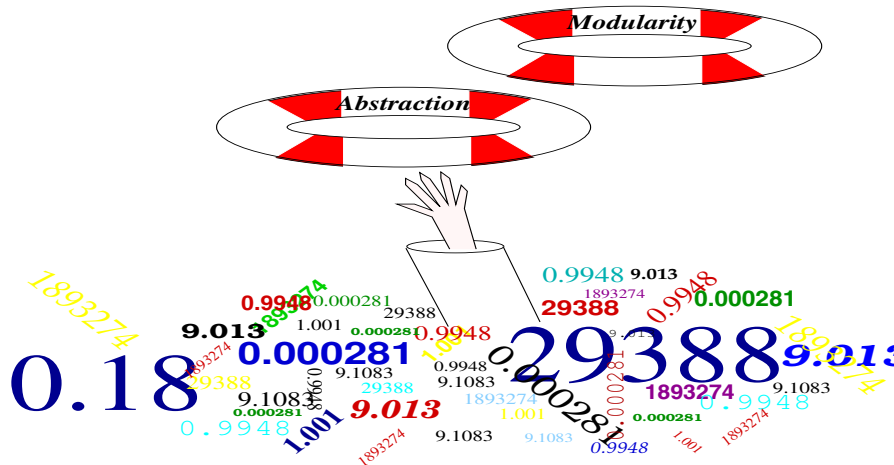
have a key role to play.



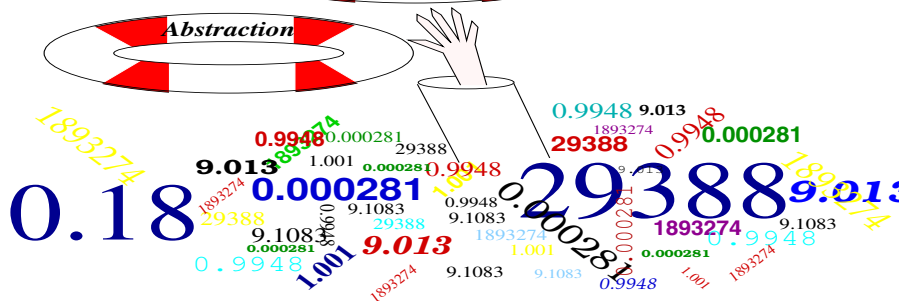
A lifebuoy with the word "Abstraction" written across it.



The Role of Computational Thinking



The diagram illustrates three key concepts in AI: Reasoning, Modularity, and Abstraction, each represented by a lifebuoy. The lifebuoys are arranged in a descending staircase pattern from top-right to bottom-left. A hand is shown reaching up towards the 'Abstraction' lifebuoy, suggesting a progression or a goal.



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I will focus on the use of process algebras for signalling pathways within cells.

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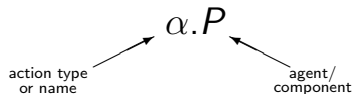
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- ▶ Equivalence relations allow formal comparison of high-level descriptions.
- ▶ There are well-established techniques for **reasoning** about the behaviours and properties of models, supported by software.

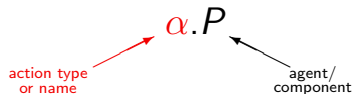
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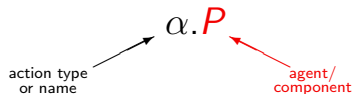
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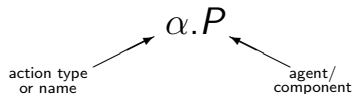
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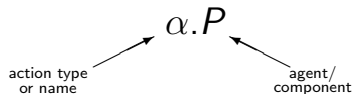
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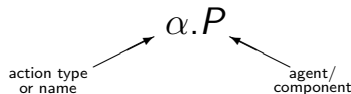


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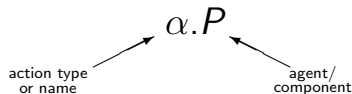


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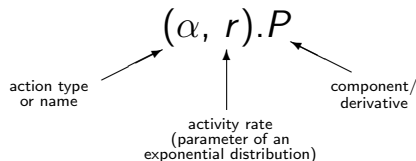


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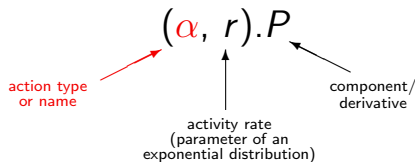
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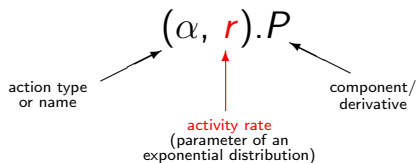
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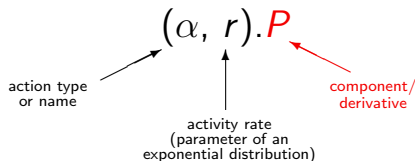
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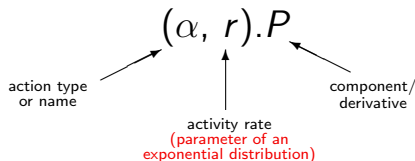
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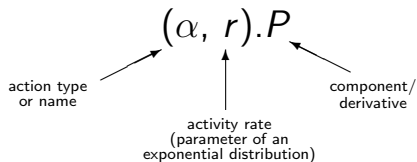
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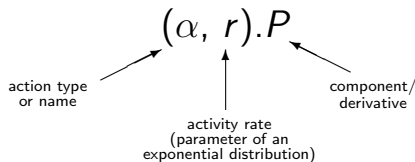
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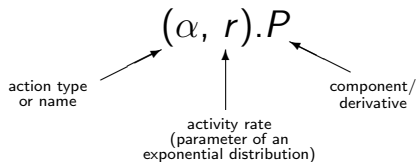


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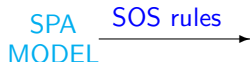
SPA
MODEL

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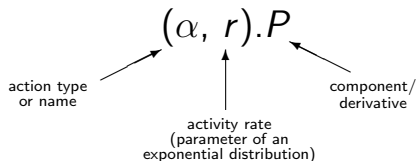


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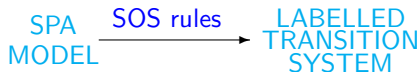


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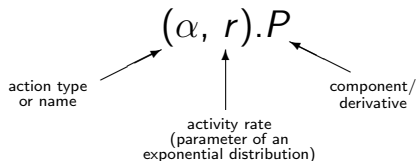


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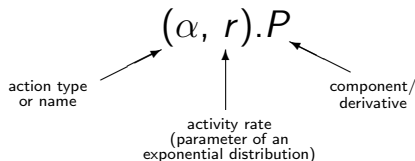


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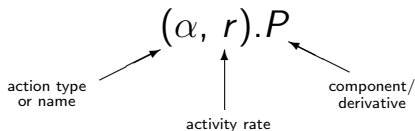


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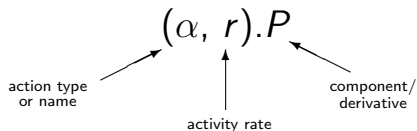
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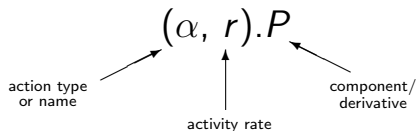


The language may be used to generate a **system of ordinary differential equations (ODEs)**.

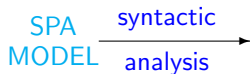
SPA
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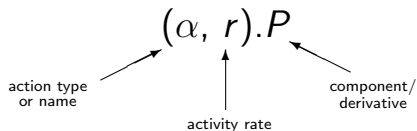


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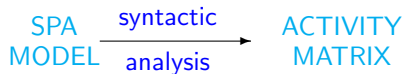


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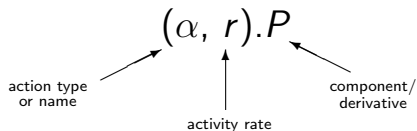


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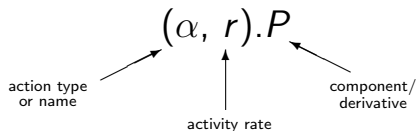


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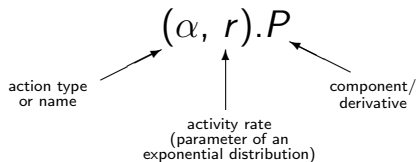


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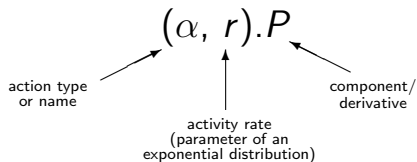
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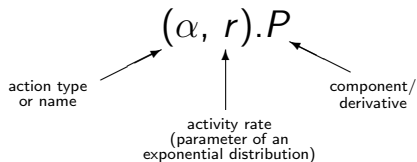


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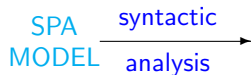
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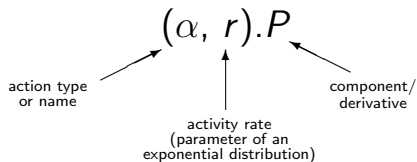


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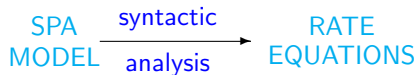


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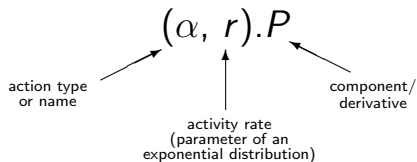


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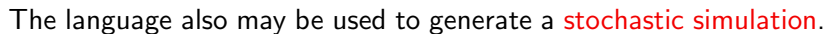
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Molecular processes as concurrent computations

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
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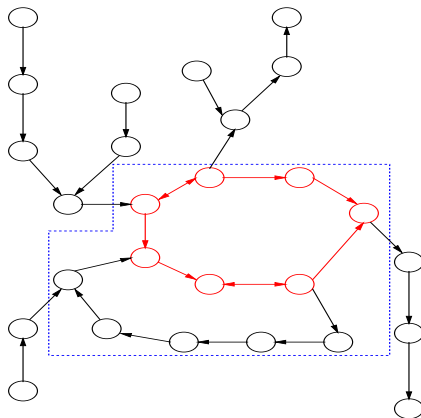
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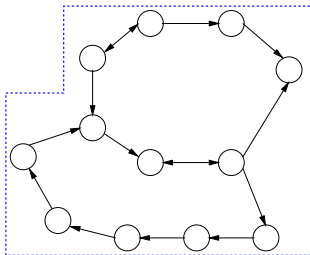
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In our second we focus on **sub-pathways**.

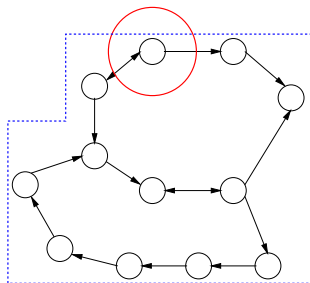
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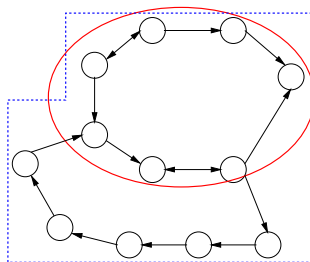


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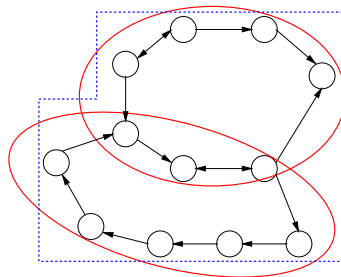
Reagent mapping: Each species is a distinct component in the model with local states to capture differing levels of concentration

Alternative Mappings illustration



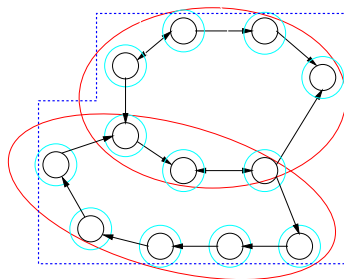
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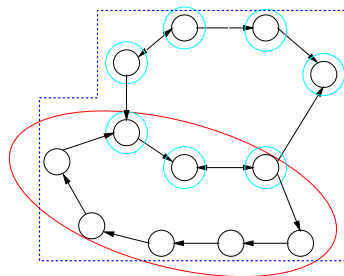
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Alternative Mappings illustration



Reasoning based on bisimulation equivalence is able to prove that the two representation are **equivalent**.

Alternative Mappings illustration



Different parts of the system may use different mappings, reflecting perhaps the level of knowledge (data) available, or the primary interests of the modeller.

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- ▶ Our aim when modelling a system is to capture sufficient information to be able to carry out useful (quantitative) analysis — not necessary to create the most faithful representation of the system possible.
- ▶ Suitable equivalence relations can confirm that our abstraction is valid.

Modularity

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- ▶ As well as the clear advantages that this has for model construction (c.f. software engineering), it also offers potential benefits for multi-level modelling.
- ▶ Moreover, in the Markovian setting, work has already been done to identify forms of interaction in a process algebra which are amenable to decomposed quantitative analysis.

Reasoning

- ▶ Process algebras are equipped with equivalence relations, and partial relations.

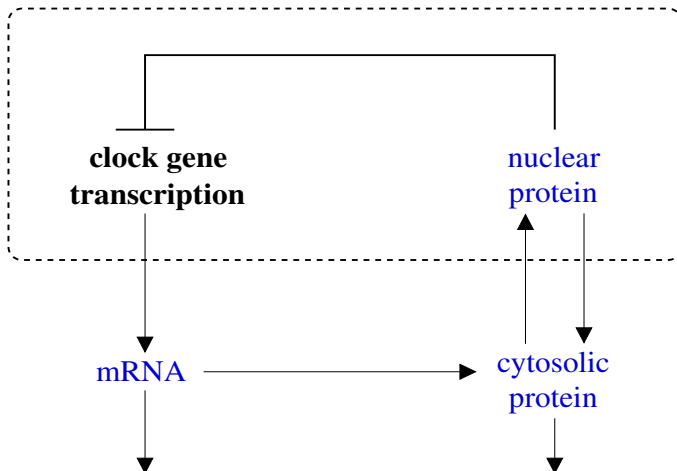
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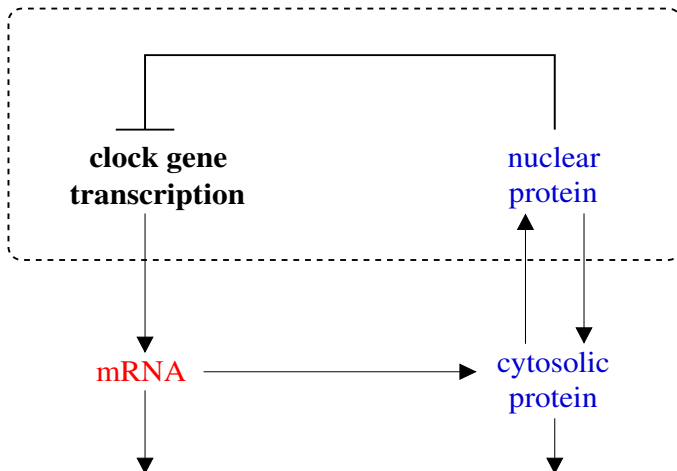
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- ▶ Additionally for some process algebras there are complementary modal logics which allow system properties to be formally expressed and automatically checked.

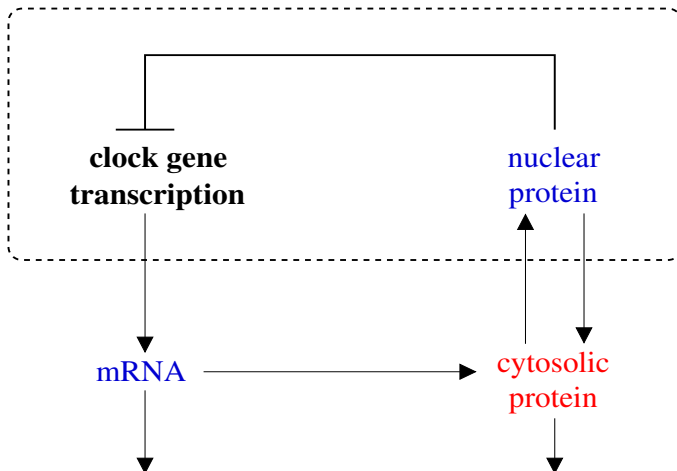
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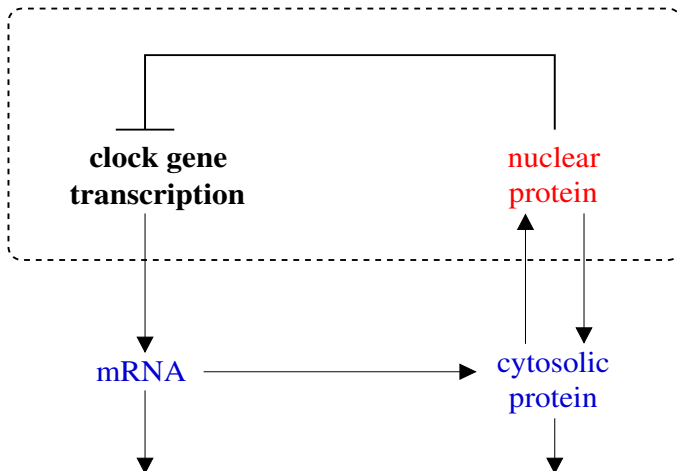
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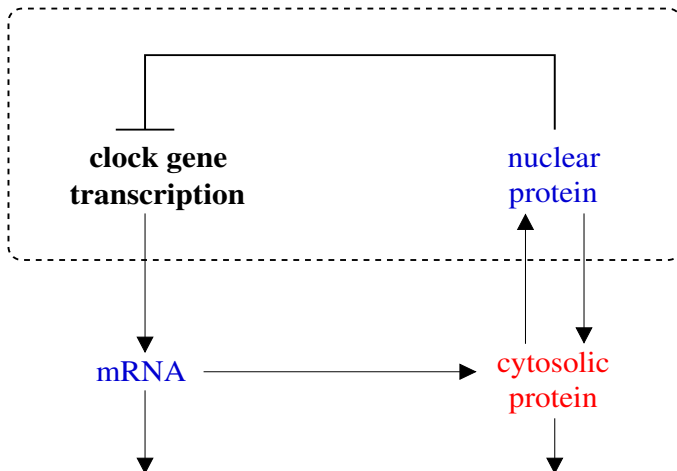
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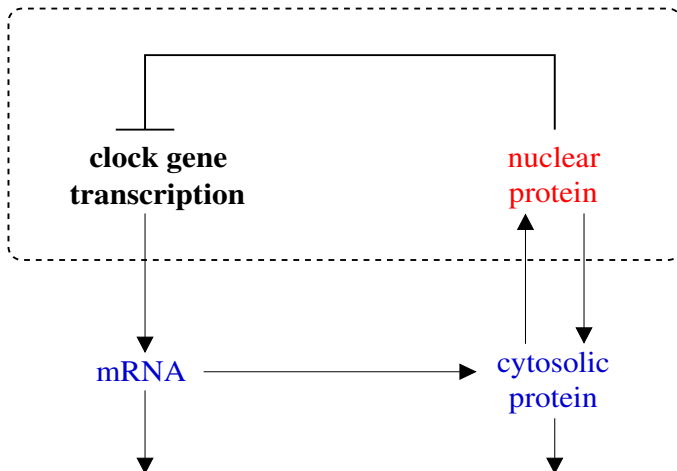
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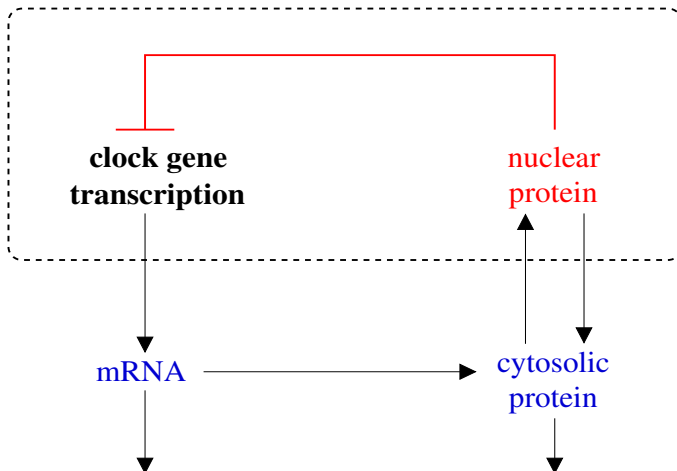
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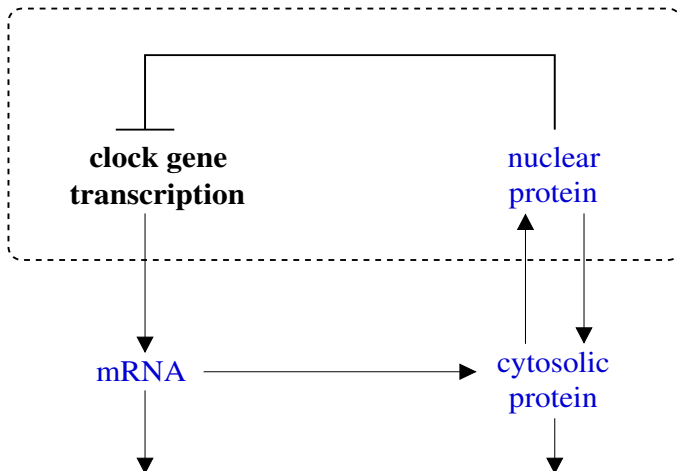
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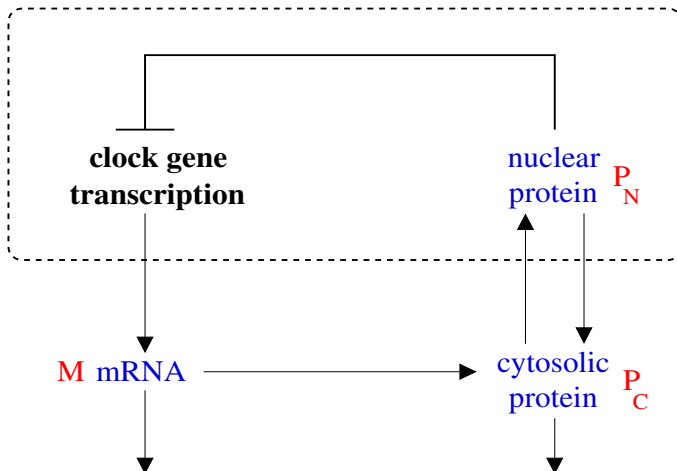
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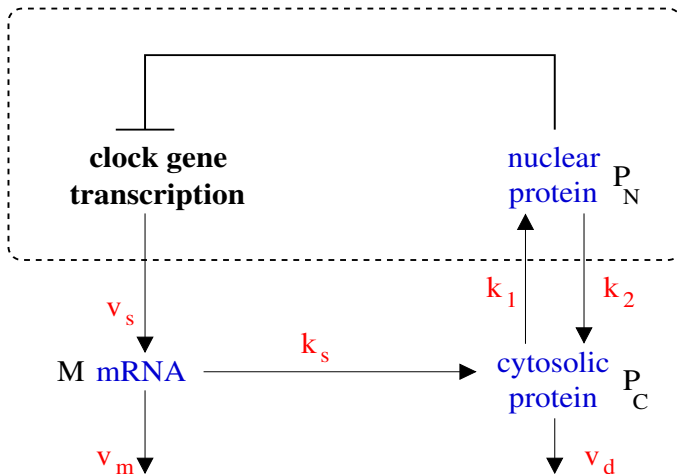
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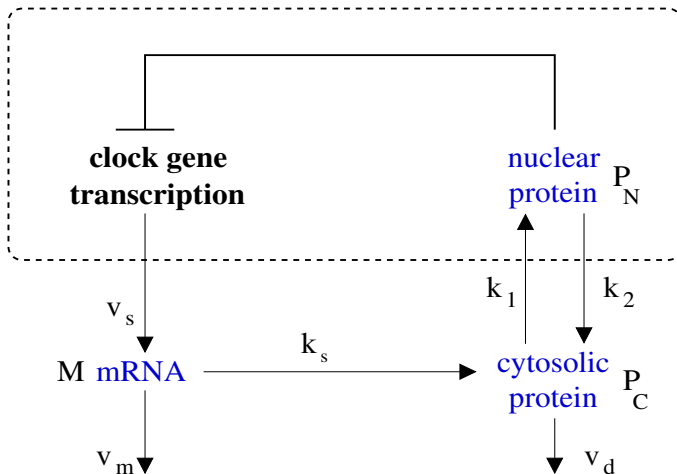
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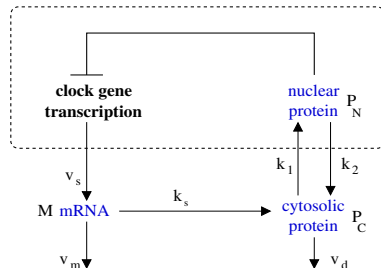
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Handcrafted ODEs

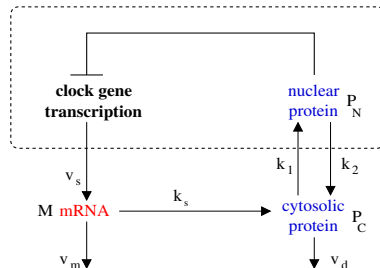


$$\frac{d[M]}{dt} = v_s \frac{k_I^n}{k_I^n + [P_N]^n} - v_m \frac{[M]}{k_m + [M]}$$

$$\frac{d[P_C]}{dt} = k_s[M] - v_d \frac{[P_C]}{k_d + [P_C]} - k_1[P_C] + k_2[P_N]$$

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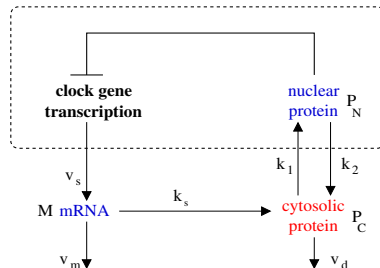


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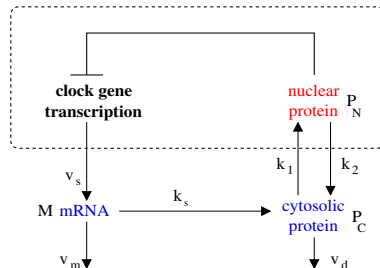


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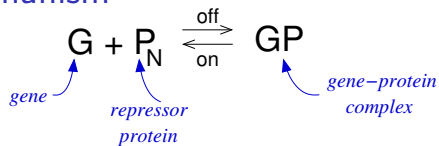
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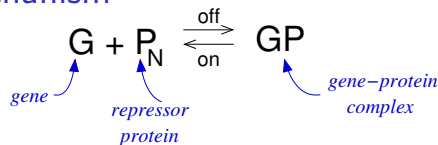
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- ▶ PEPA does not have combinators to express repression or catalysis:
 - ▶ We introduce additional **abstract components** to the PEPA model which do not correspond to species but to **transcription** and **repression**.

Repression mechanism



Repression mechanism

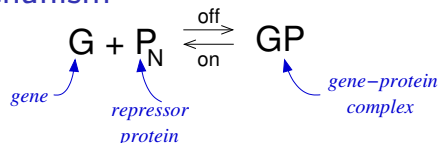


$$\text{Transcription} \begin{cases} T^h \stackrel{\text{def}}{=} (\text{transcribe}, v_s). T^h + (\text{off}, \top). T^l \\ T^l \stackrel{\text{def}}{=} (\text{on}, \top). T^h \end{cases}$$

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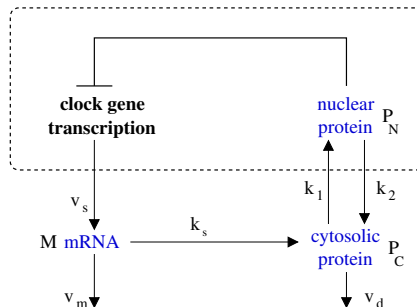
$$P_N^h \stackrel{\text{def}}{=} (\text{off}, v_{\text{off}}).P_N^l + \dots$$

Only P_N is explicitly modelled; T and R are abstract entities.

PEPA model of the circadian clock

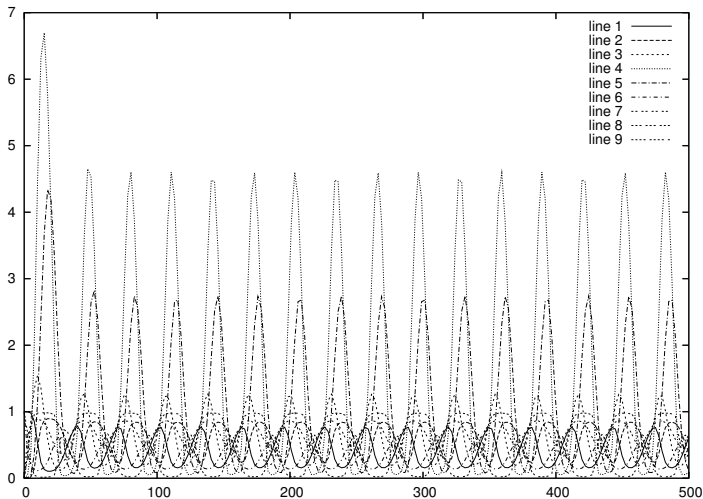
$$T^h \quad \left(R^I \quad \left(M \quad (P_C \quad P_N) \right) \right)$$

$\{transcribe, on, off\}$ $\{off\}$ $\{translate\}$ $\{trans_1, trans_2\}$



A PEPA example

Results of quantitative analysis



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- ▶ PEPA allowed rigorous development of the underlying mathematical models and formalised model manipulations and reductions;
- ▶ Process algebras and other formal modelling techniques became integrated into performance modelling methodology, although sometimes embedded rather than on the surface (UML etc).
- ▶ This work stimulated a lot of other work on formal approaches to performance modelling such as the development of suitably quantified modal logic and model checking.

Outline

Systems Biology

A Role for Computational Thinking

Models, Formal Systems and Inference

A PEPA example

Future Perspectives

Systems Biology: Will it Work?

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The fundamental question for the community of biologists is whether an explanation on the systems theoretic basis is acceptable as a true scientific explanation of the biological inquiry.

What's life got to do with it?

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“Life is a relationship among molecules and not a property of any molecule”

[Linus Pauling]

Thank you!