Computational Thinking for Life

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LFCS, University of Edinburgh

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

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- Perhaps not surprising for a new initiative?

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- Stated objective — "To assess the past development and the future potential of the application of the systems approach in biology."

Outline

What is Systems Biology?

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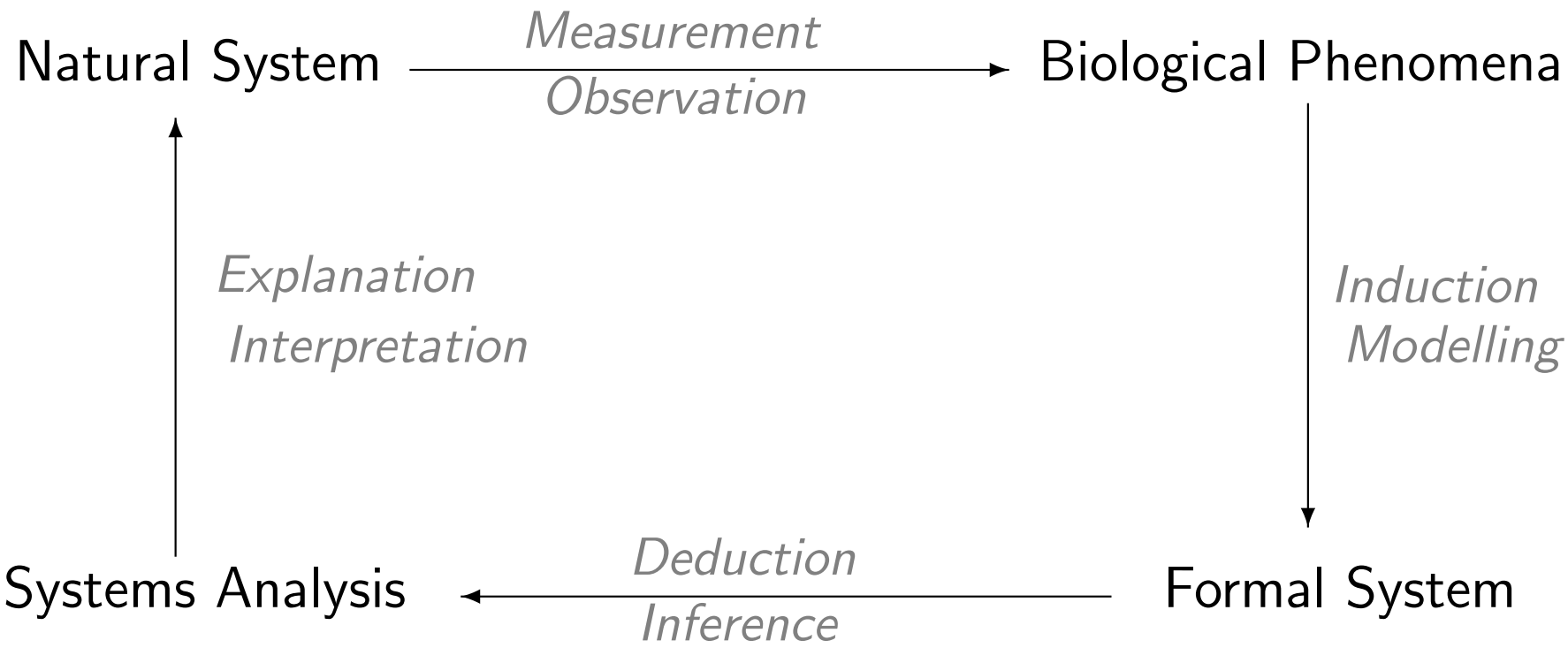
"The principal aim of systems biology is to provide both a conceptual basis and working methodologies for the scientific explanation of biological phenomena" – Olaf Wolkenhauer

Systems Biology Methodology



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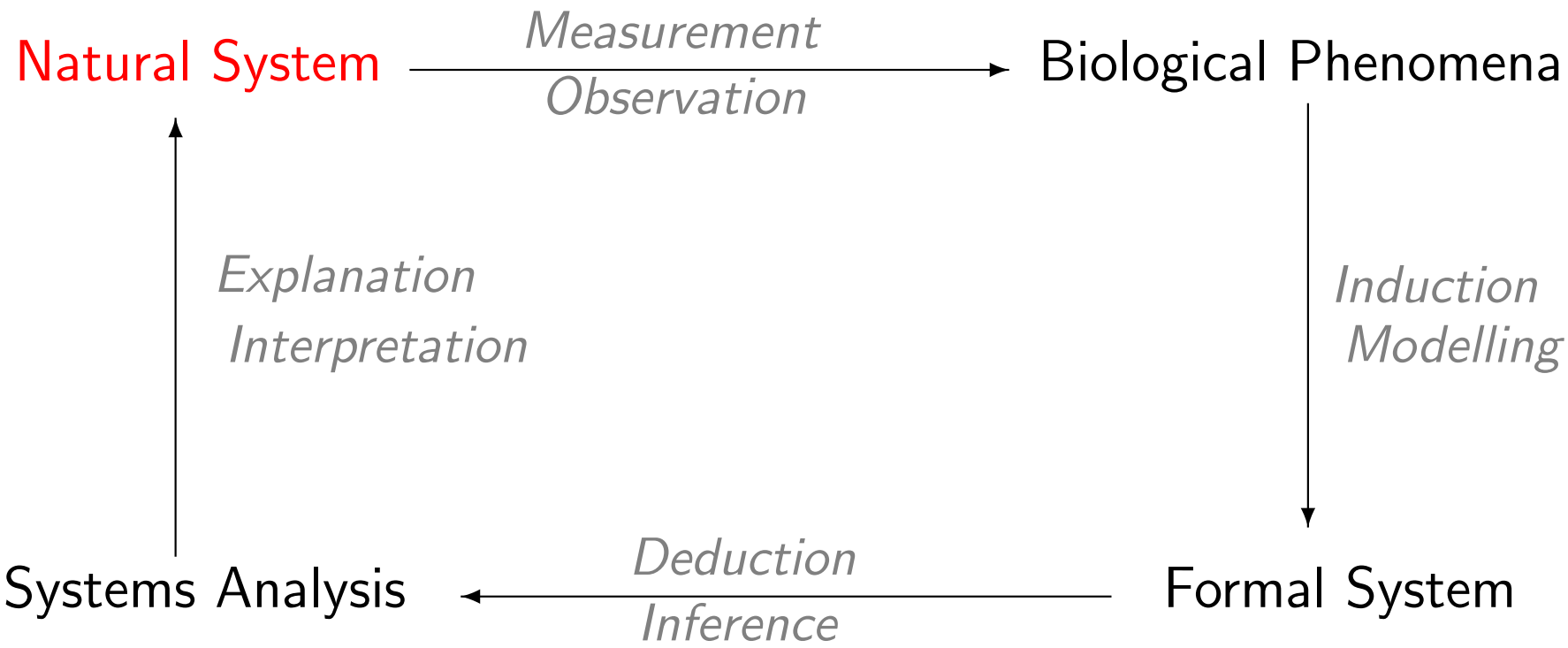

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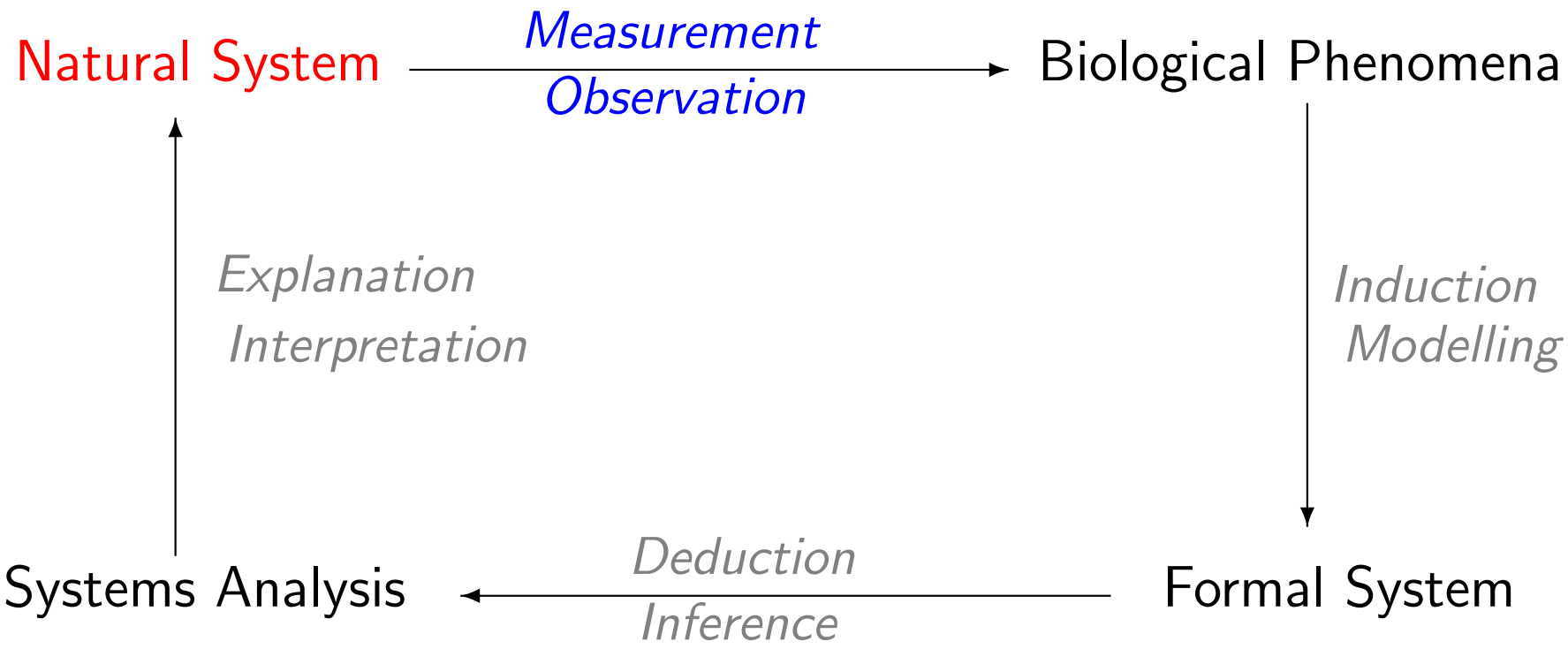

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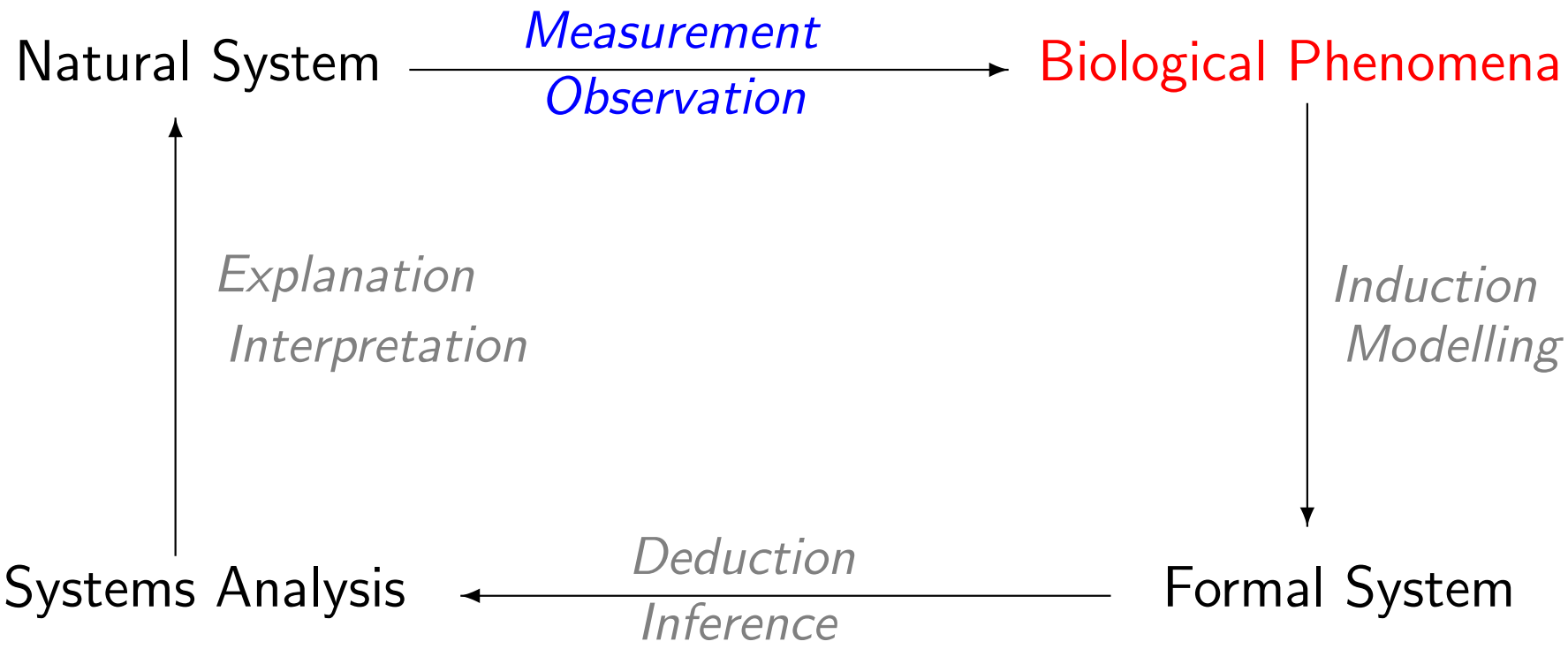

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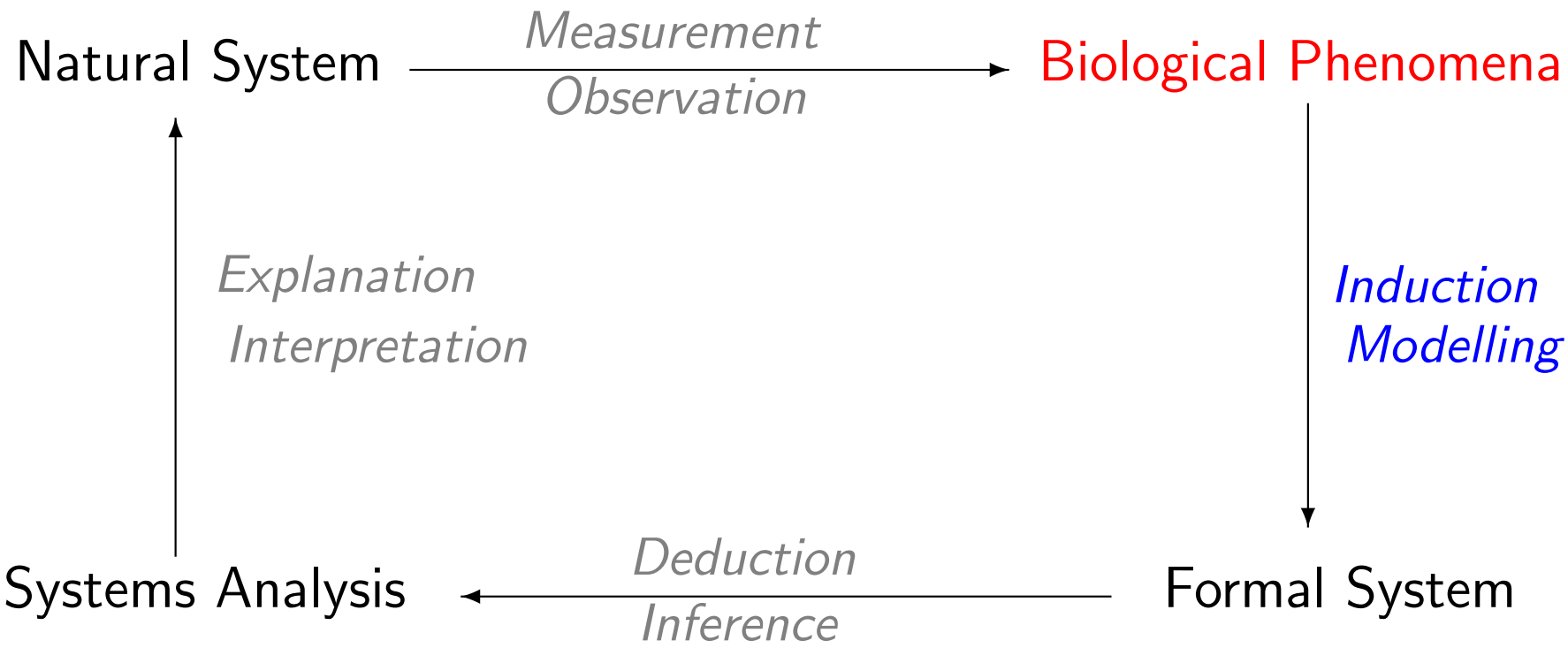

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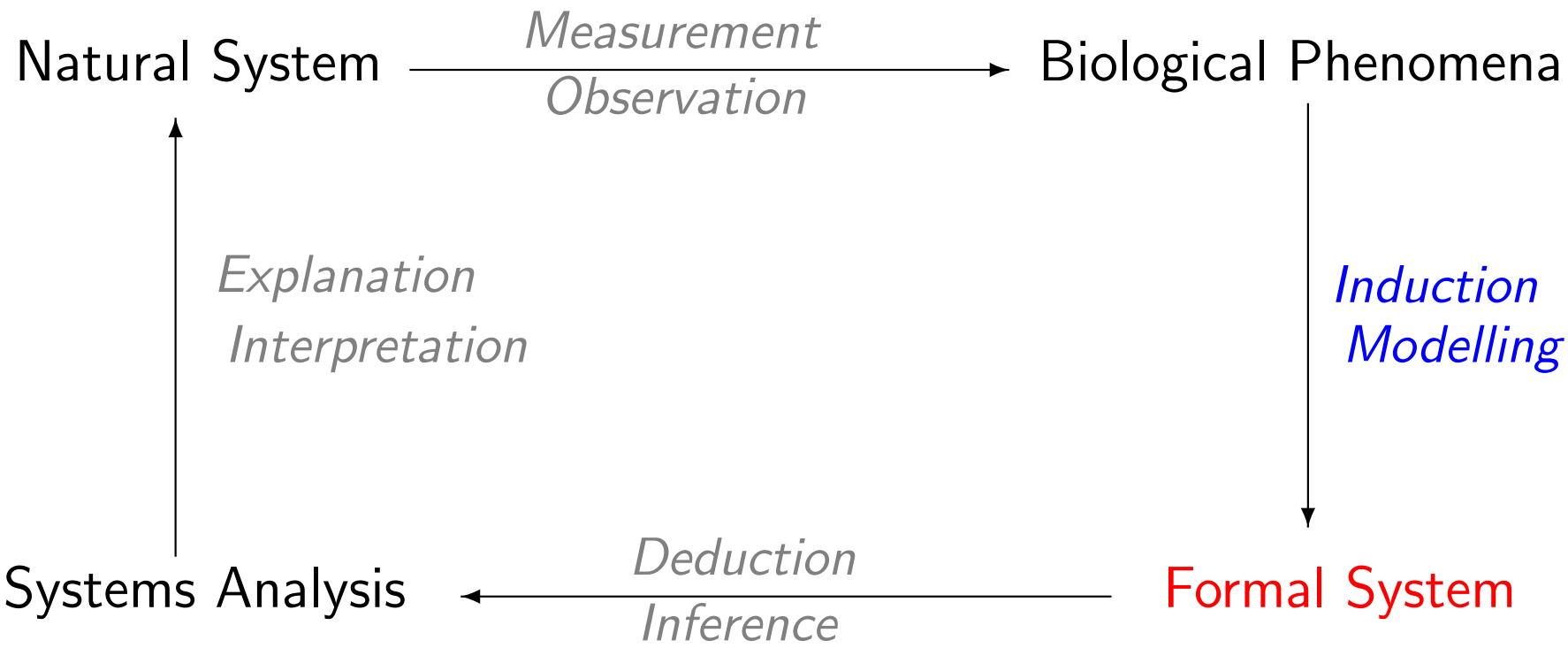

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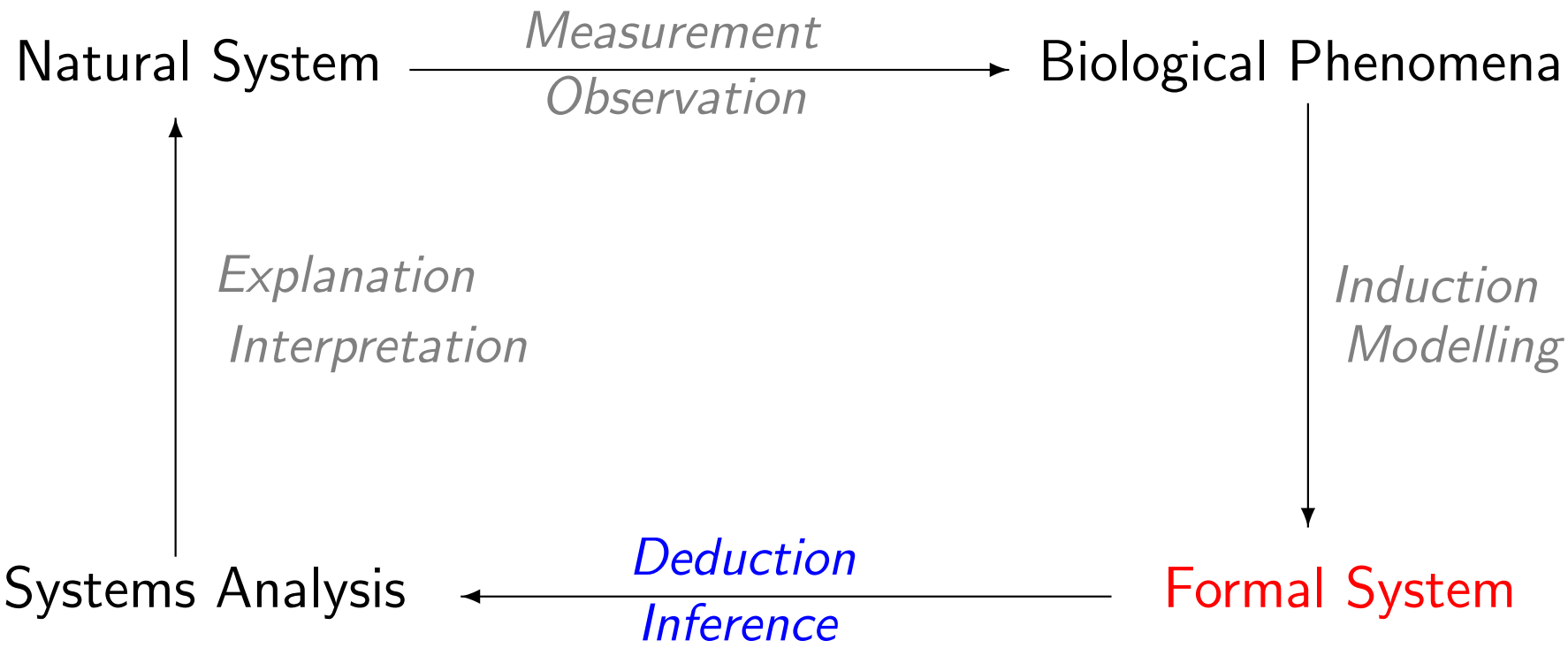

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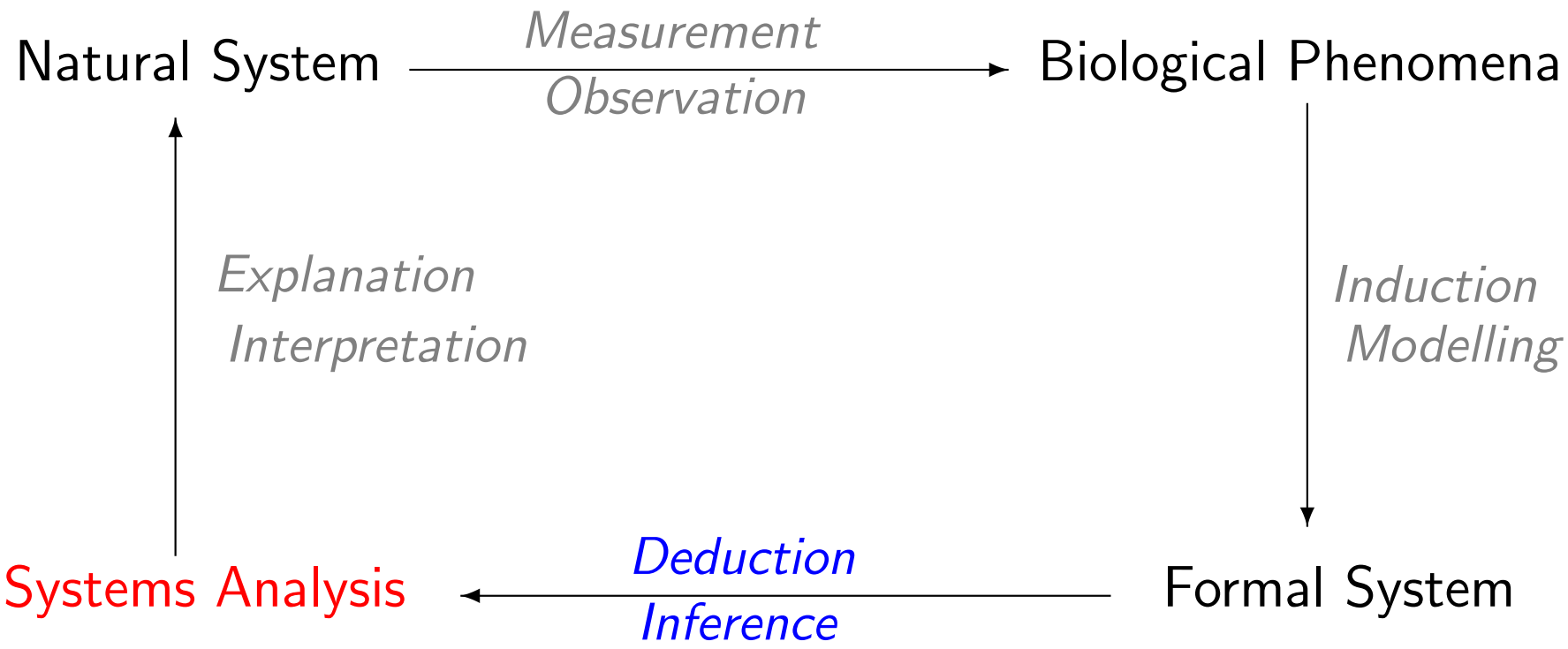

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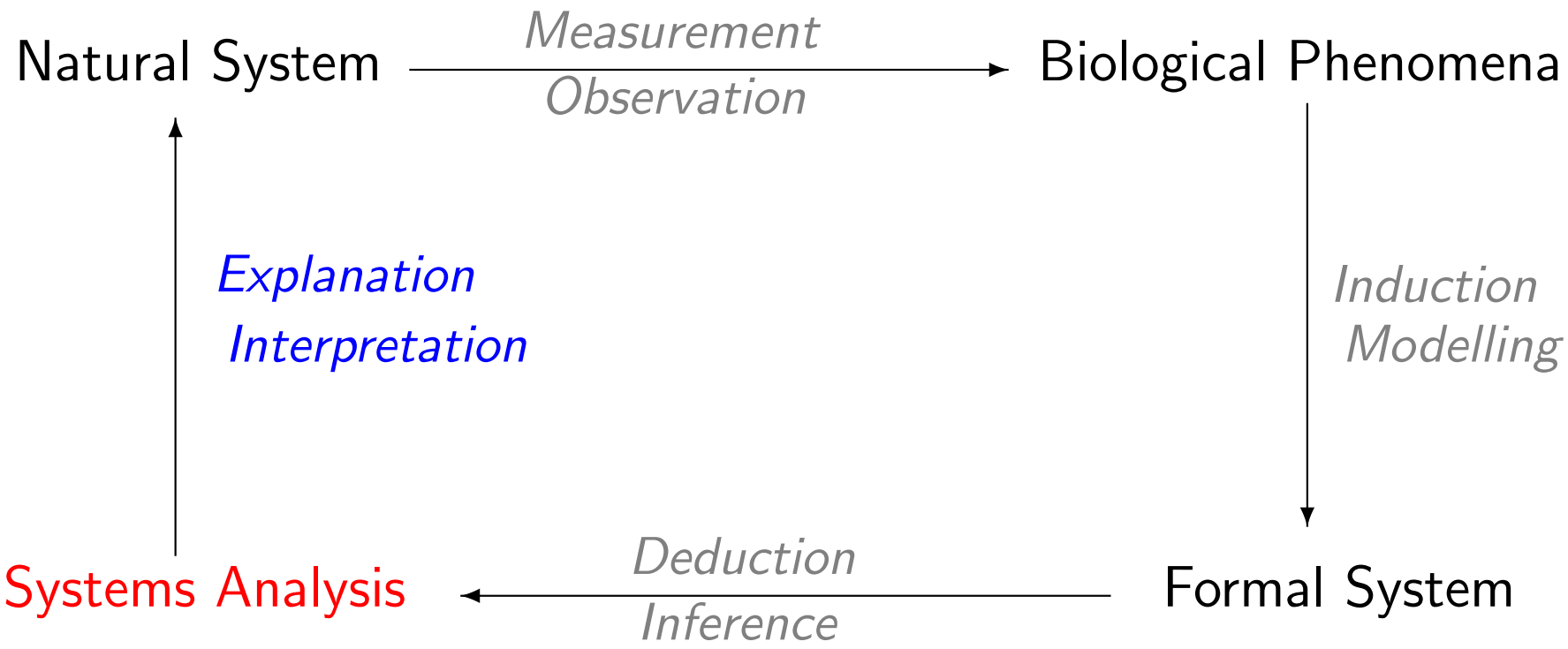

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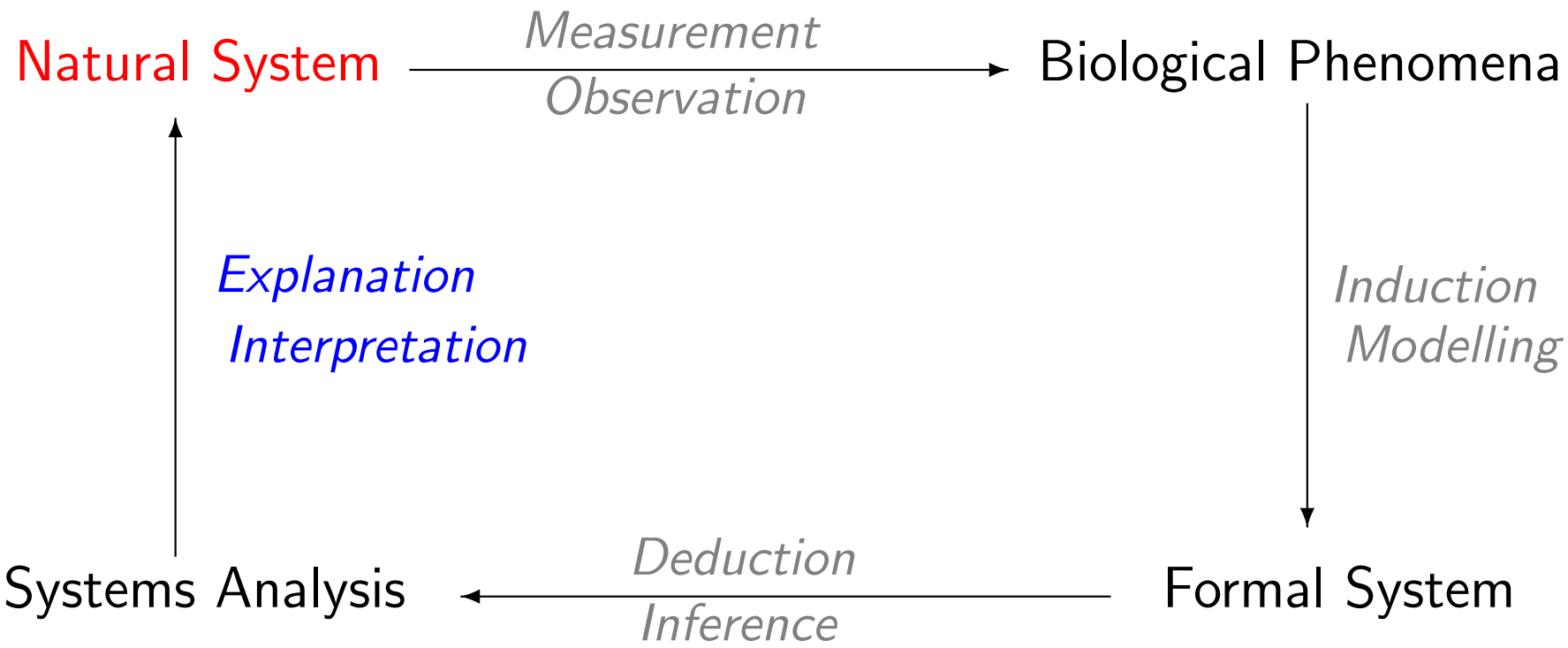

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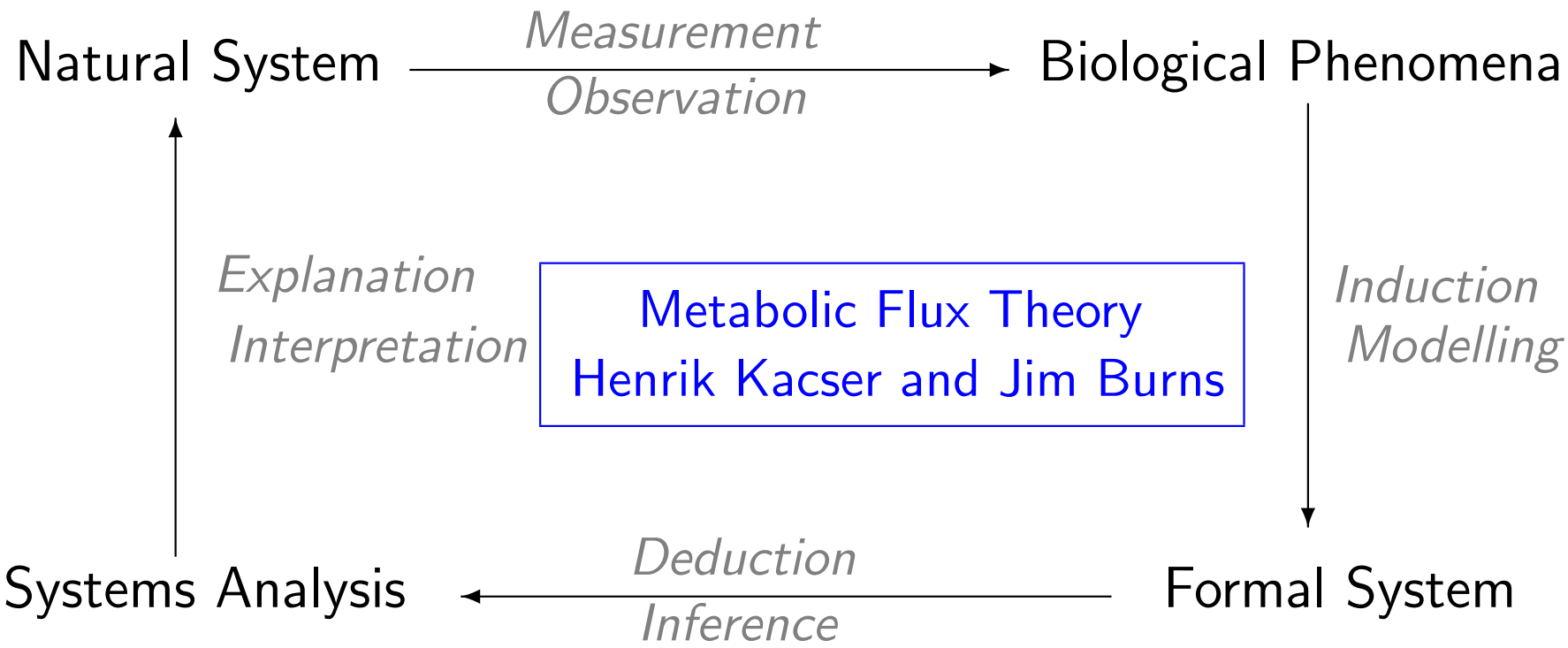

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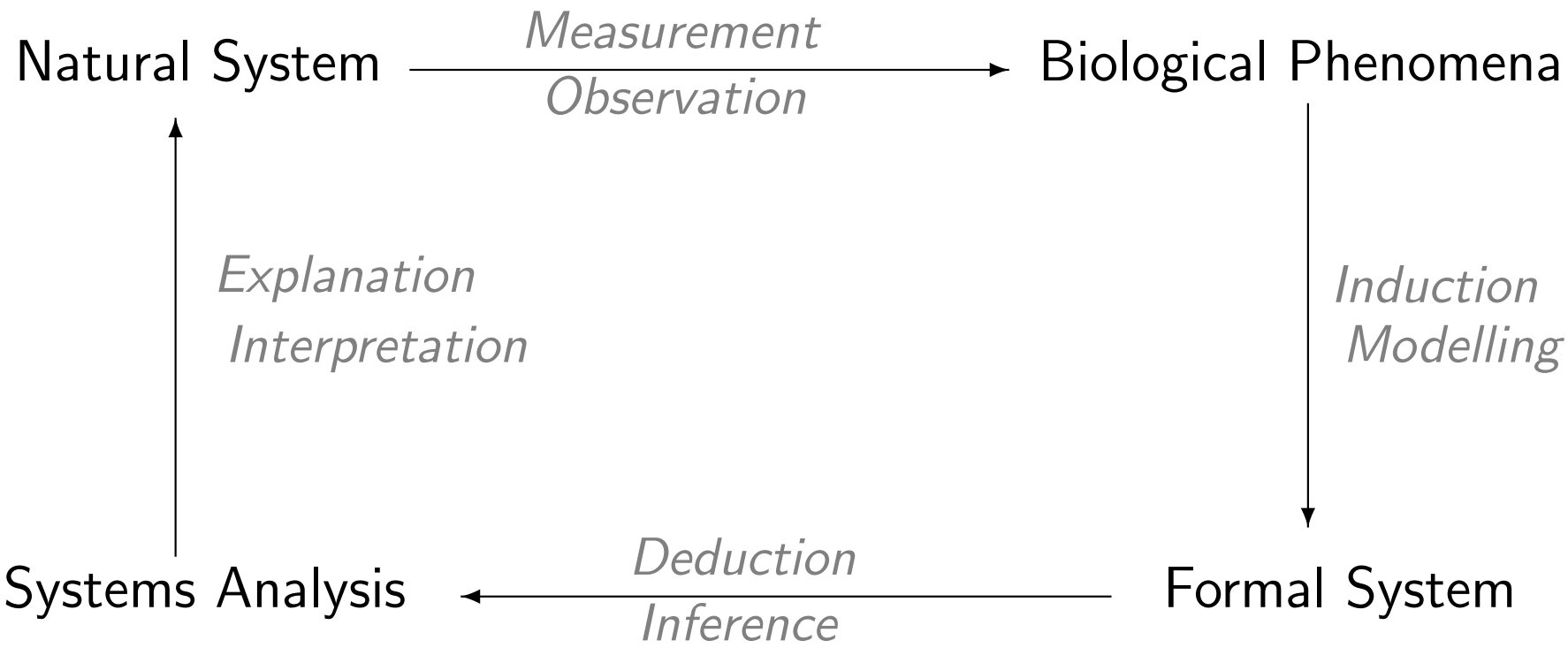

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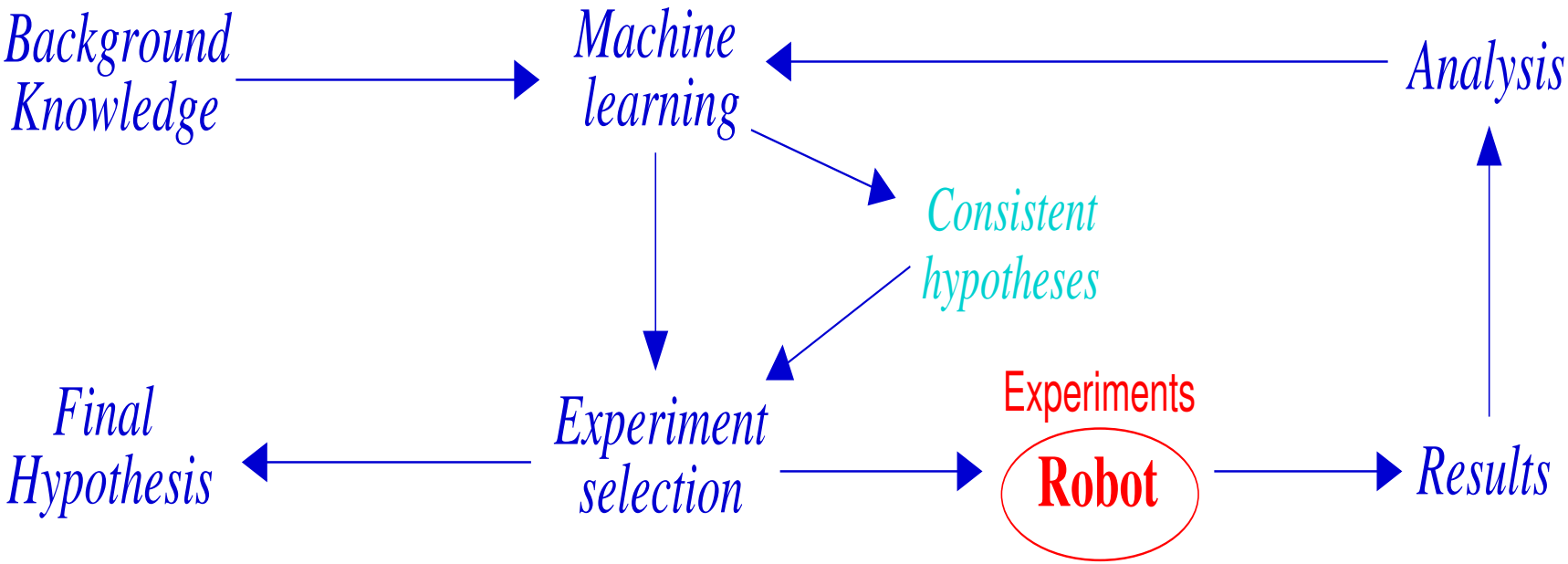
- Experiments are carried out by a robot.
- Data is generated at rates which exceed what is possible when there are humans in the loop.
- Moreover the intelligent experiment selection strategy is competitive with (good) human strategies, and significantly outperforms *cheapest* and *random* selection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

The Robot Scientist



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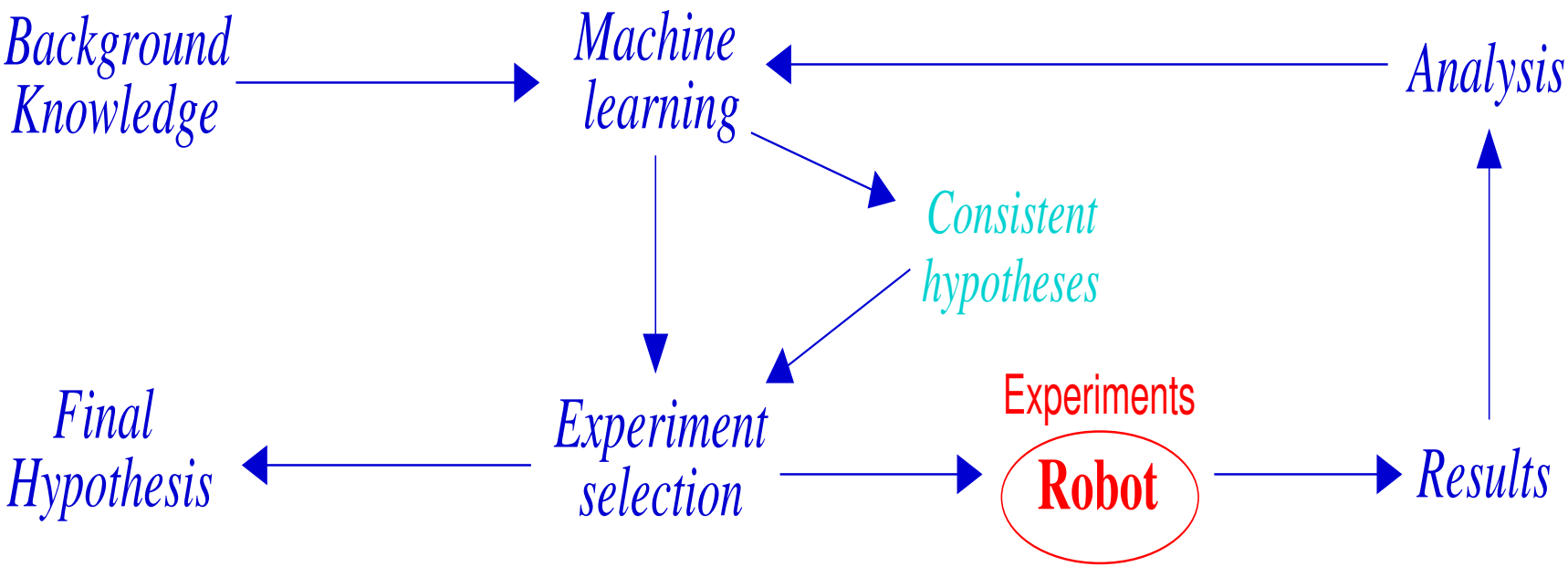

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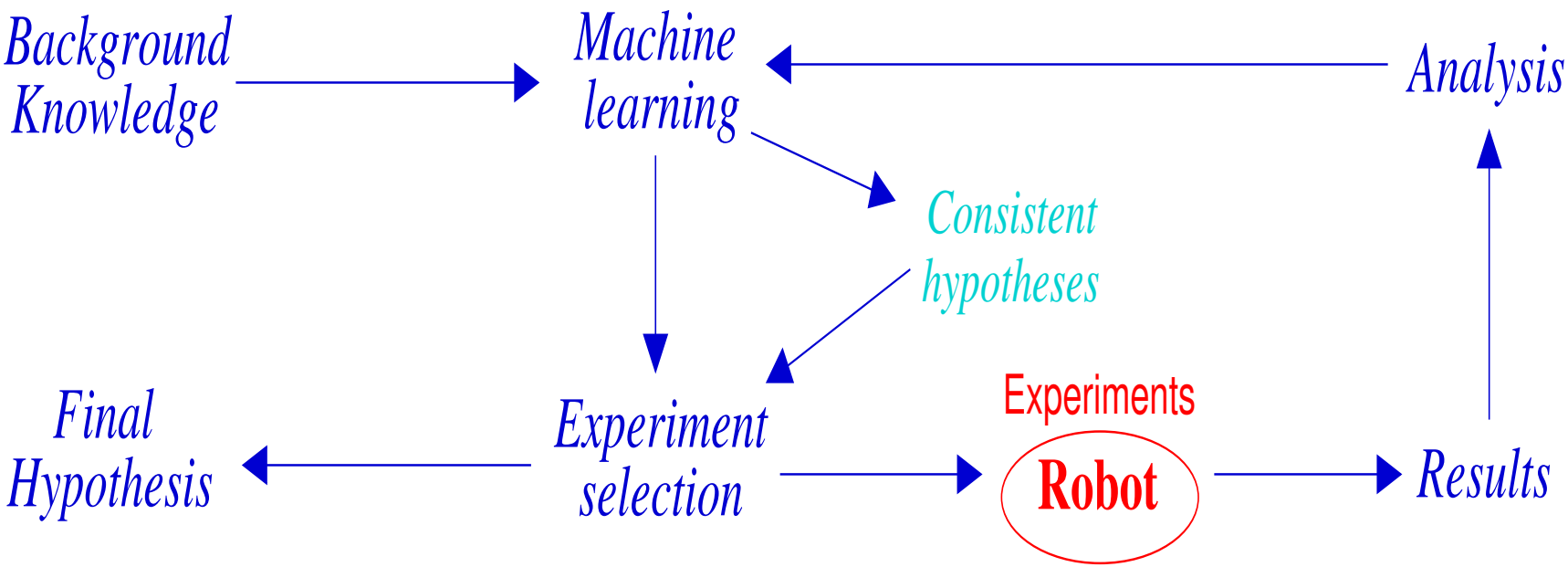

- No human intellectual input in the design of experiments or the interpretation of data.
- Integrates scientific discovery software with laboratory robotics.

Outline

The Challenges

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

- An excess of data, much of which is noisy and/or incomplete;
- The problem of infinite regress;
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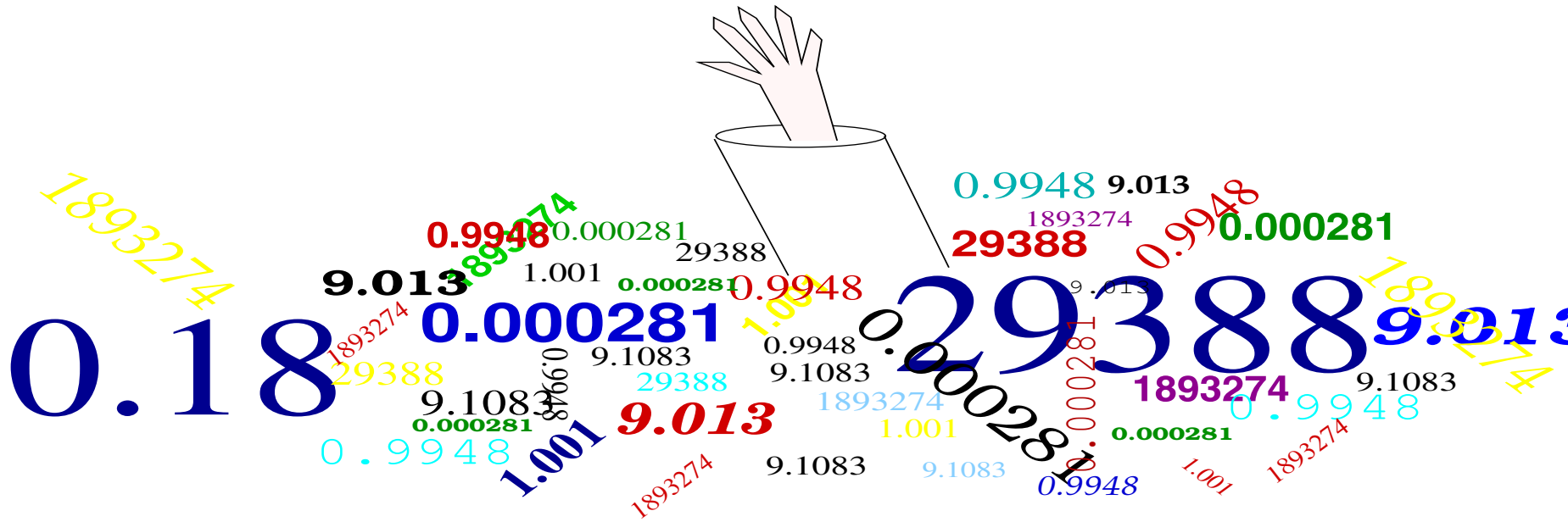

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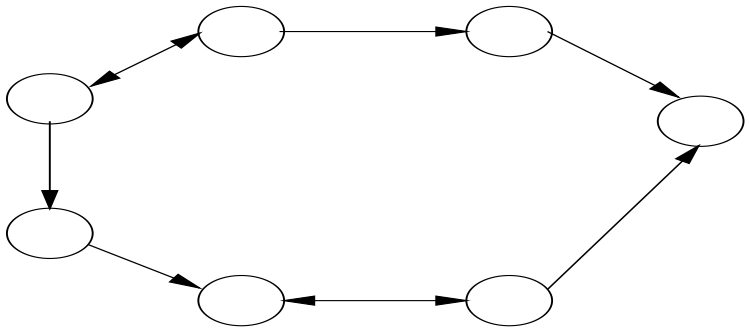

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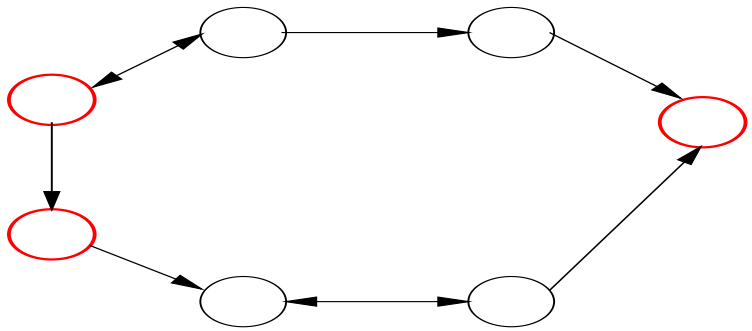

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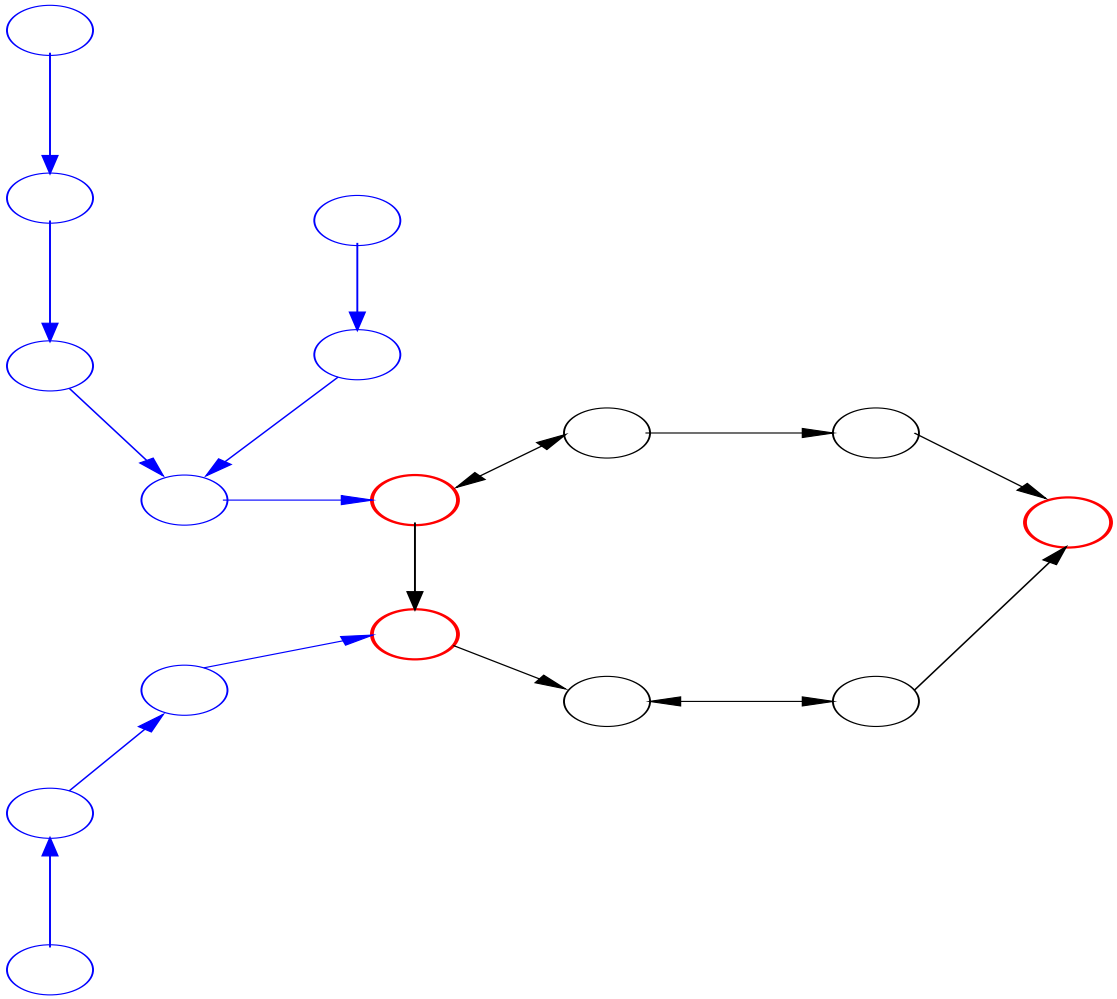

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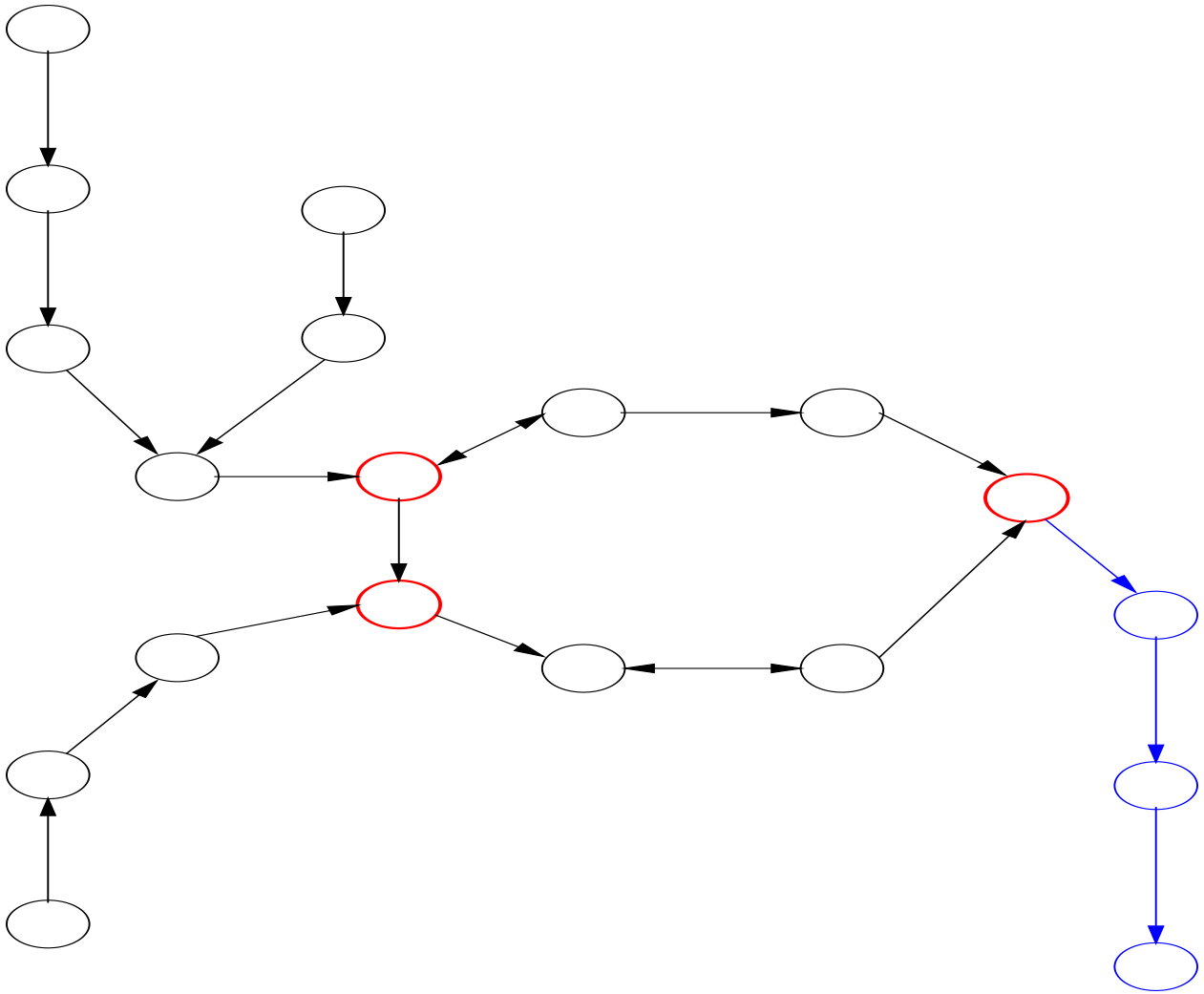

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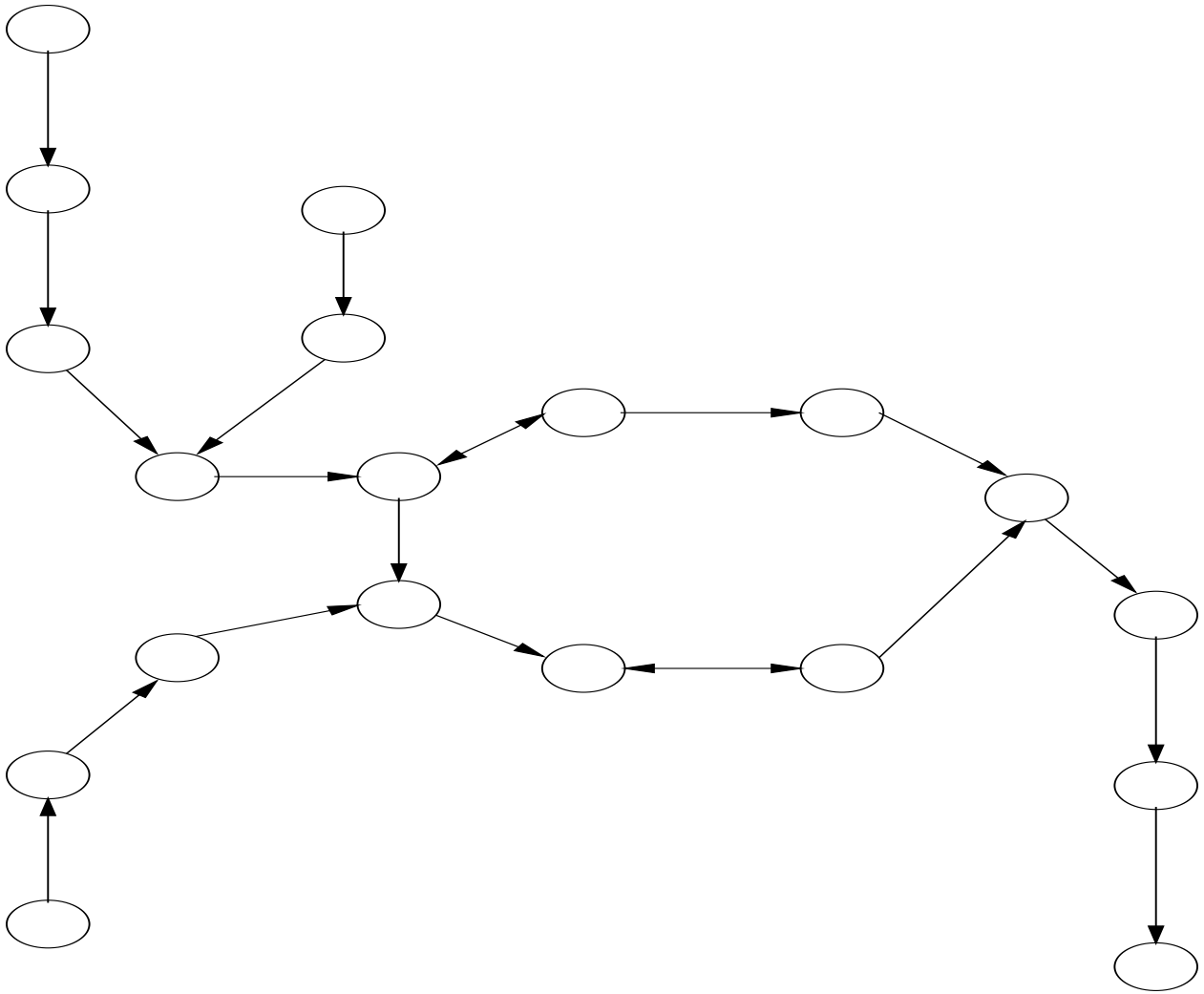

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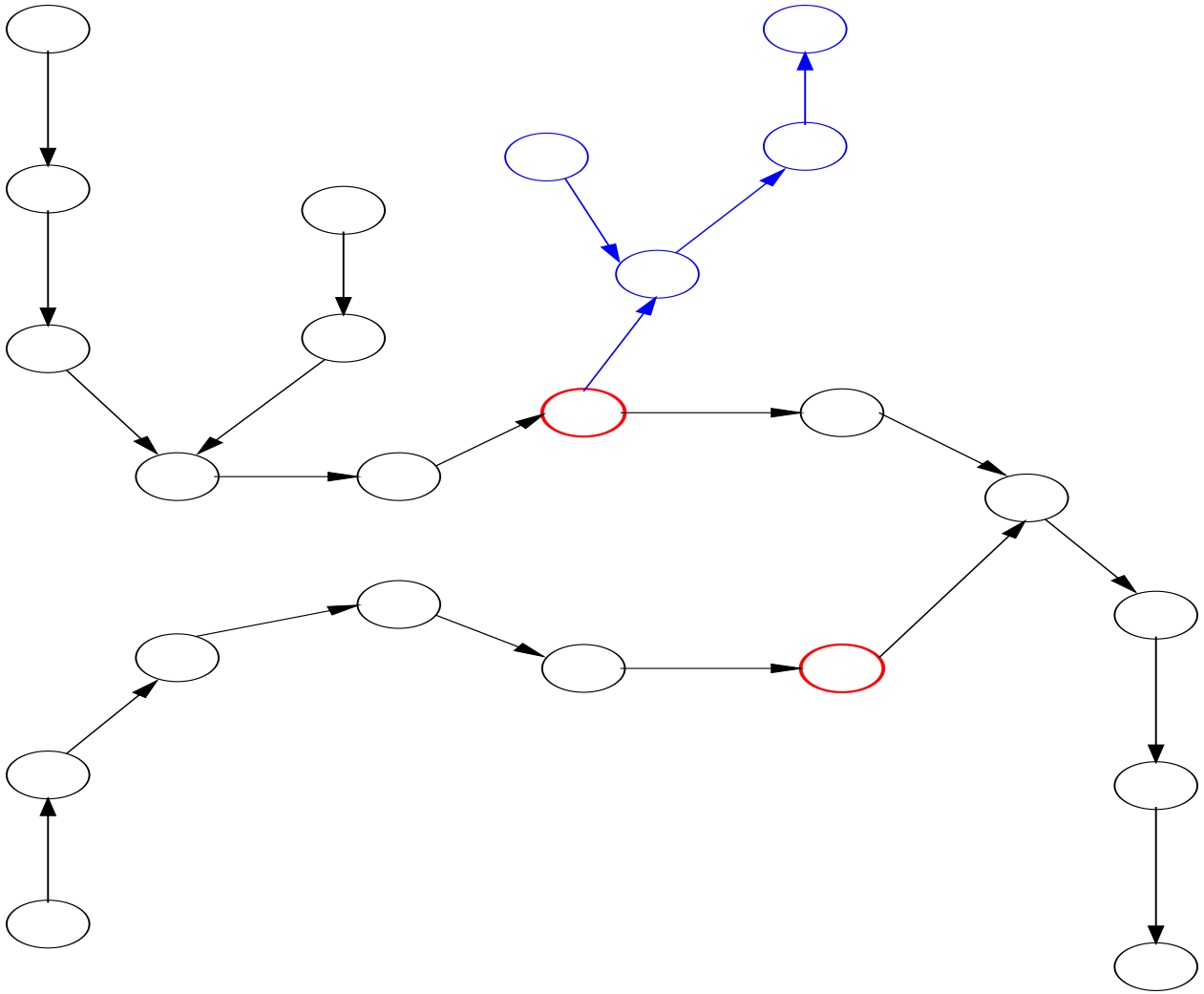

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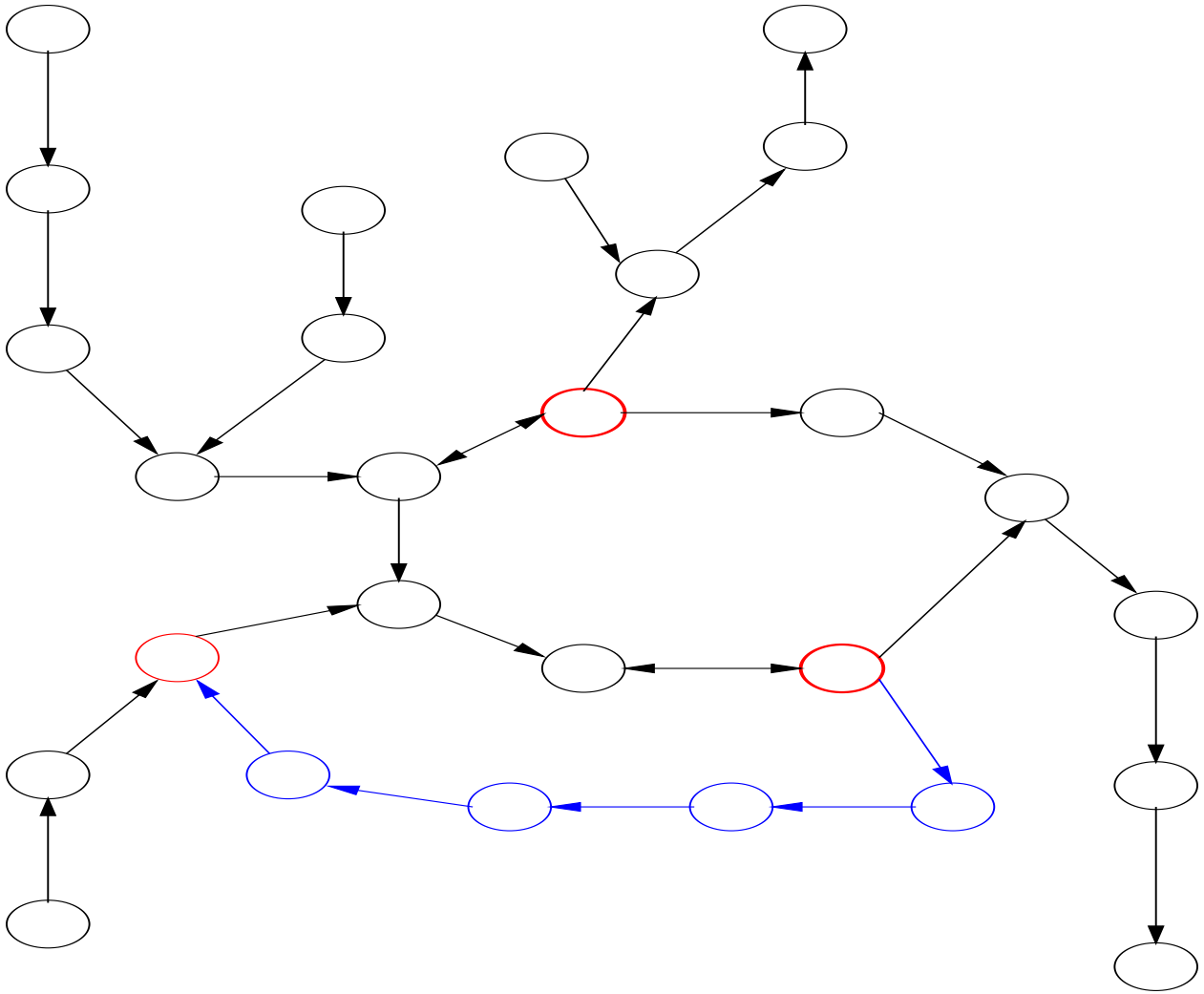

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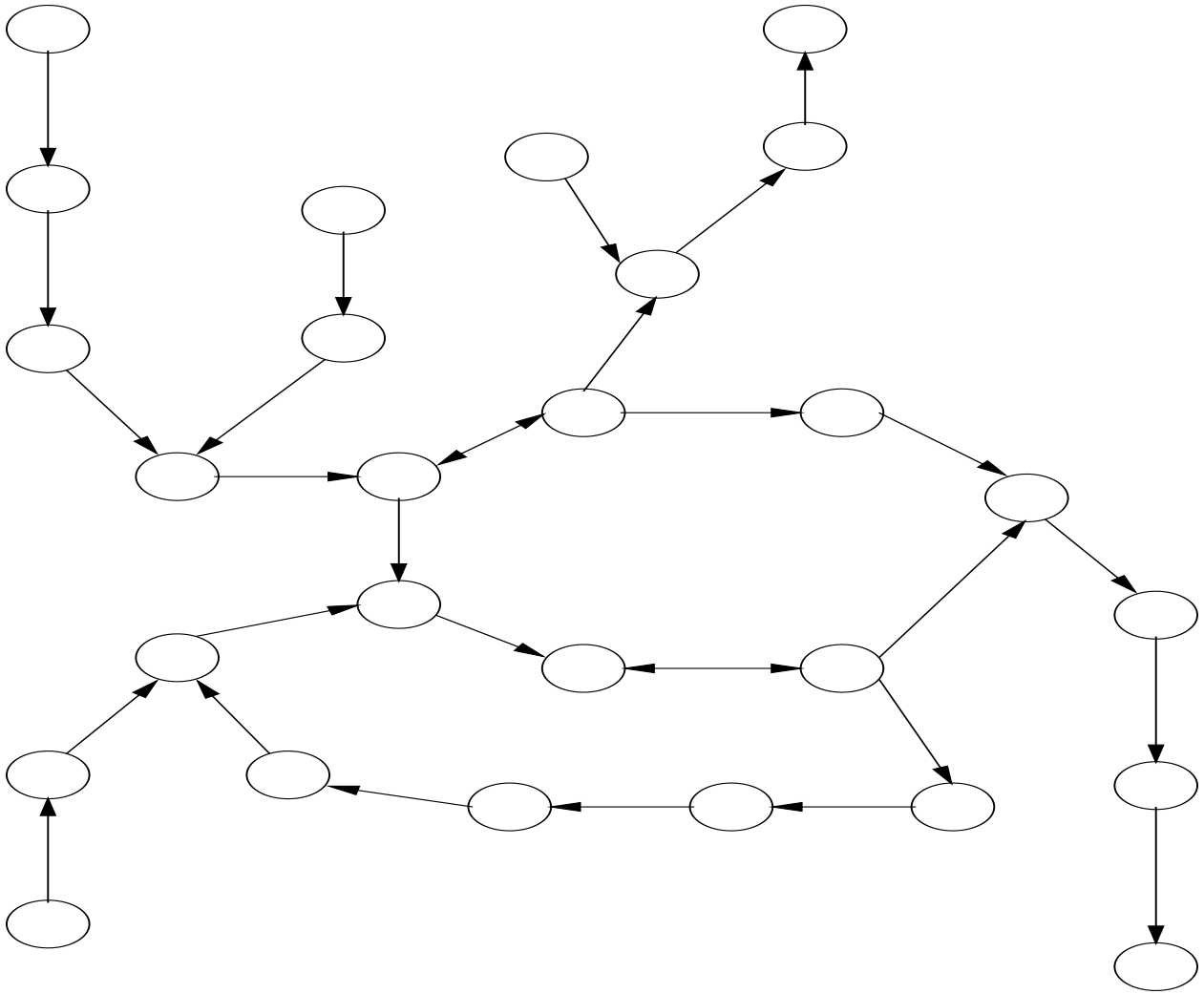

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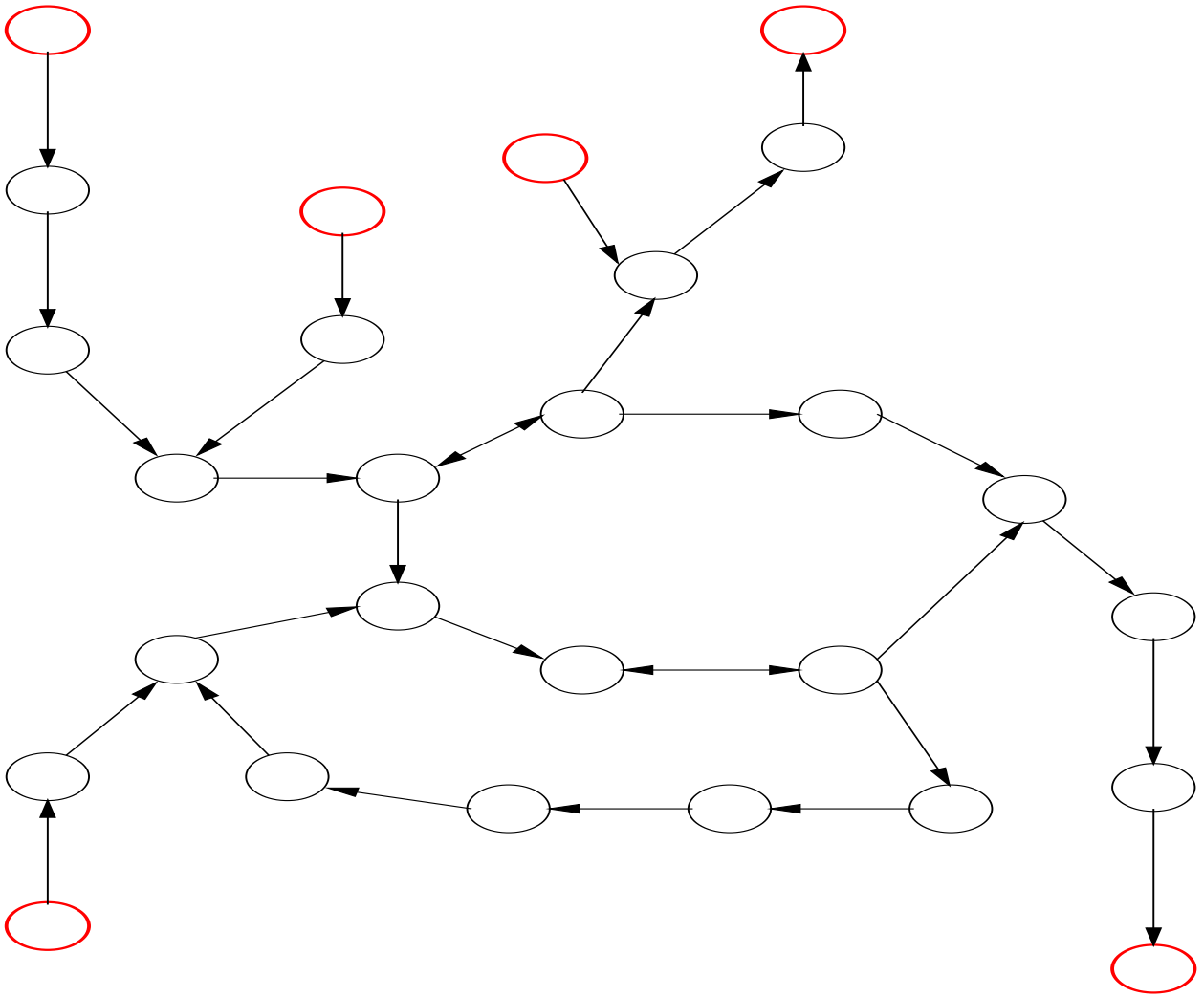

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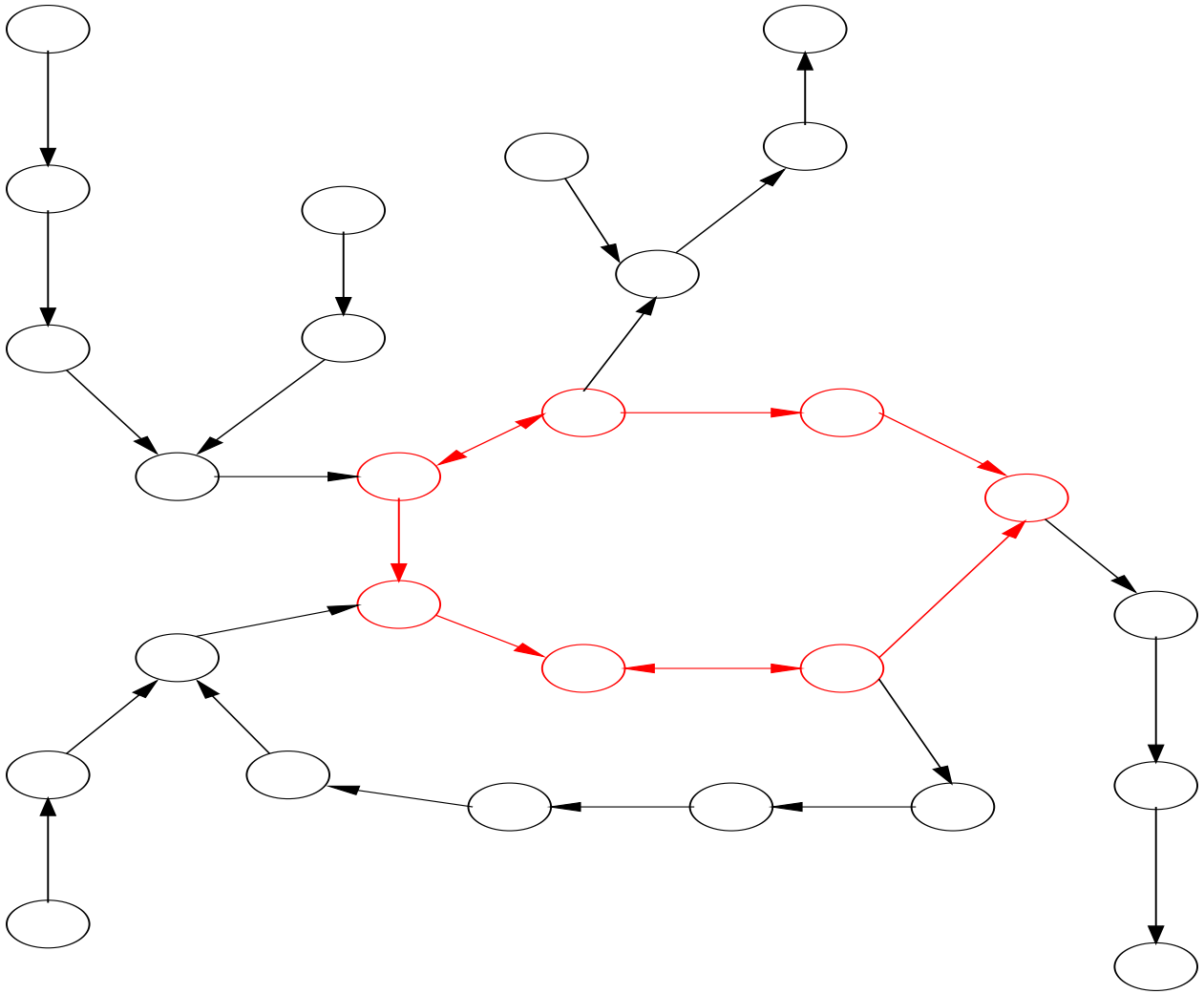

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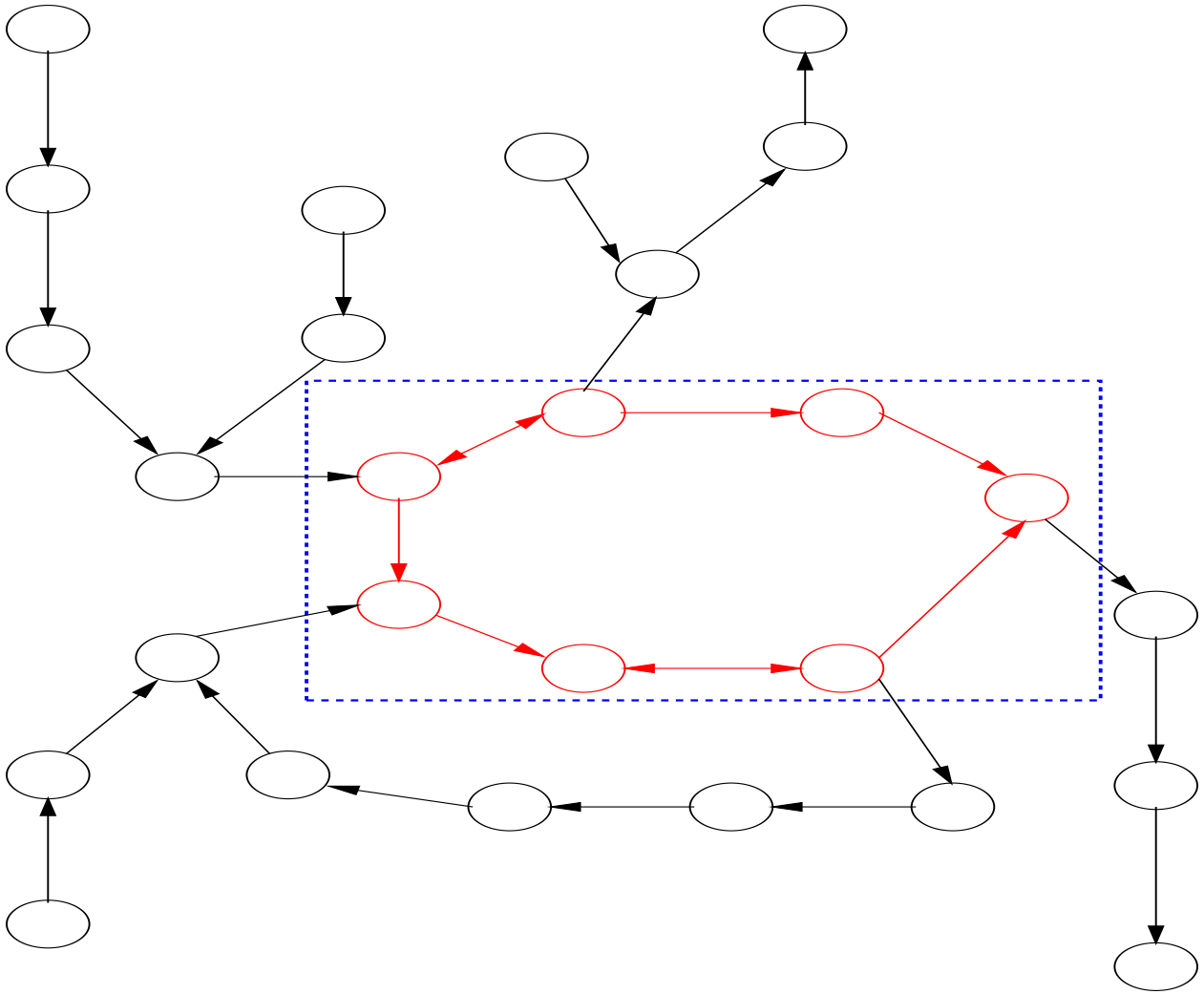

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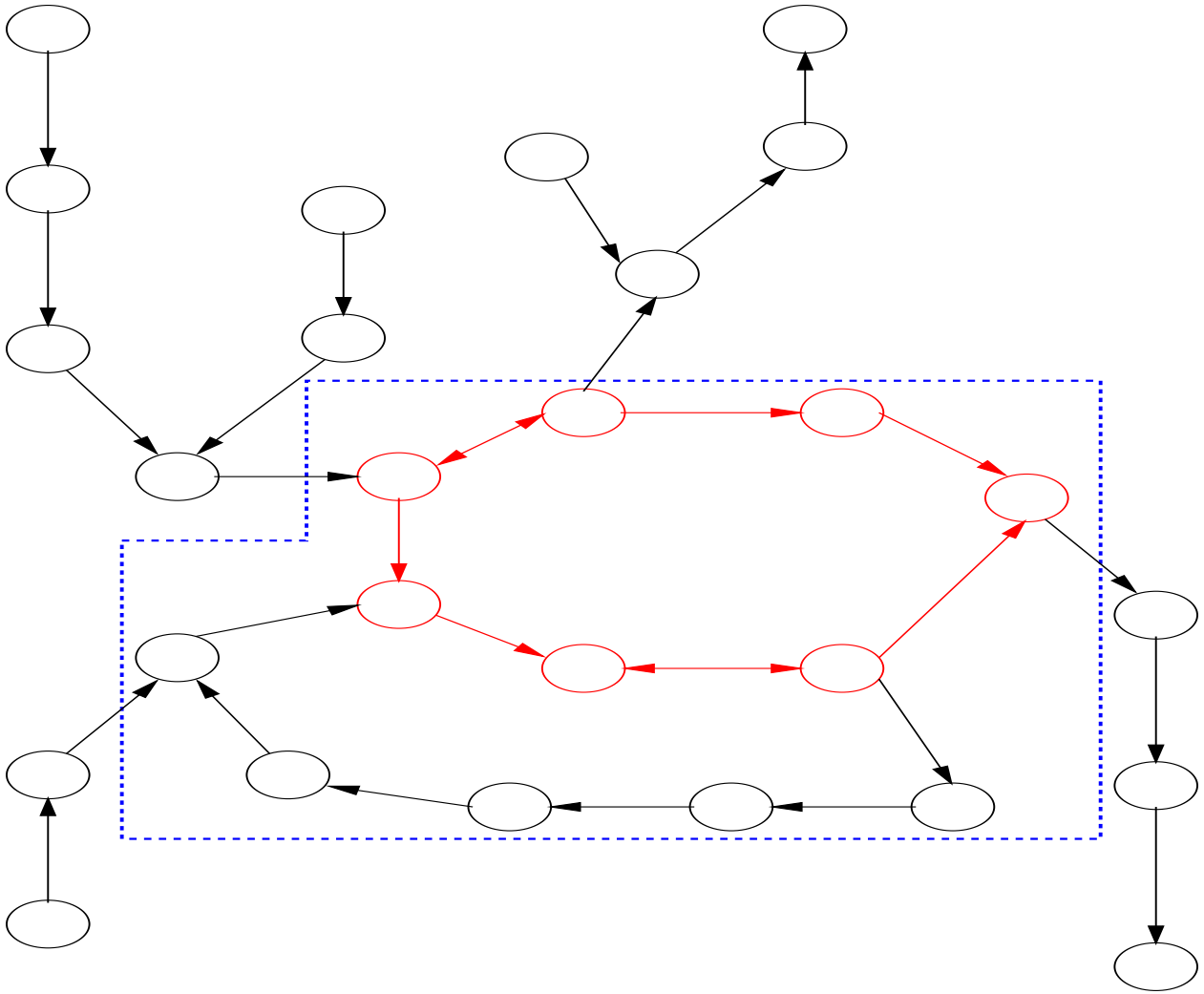

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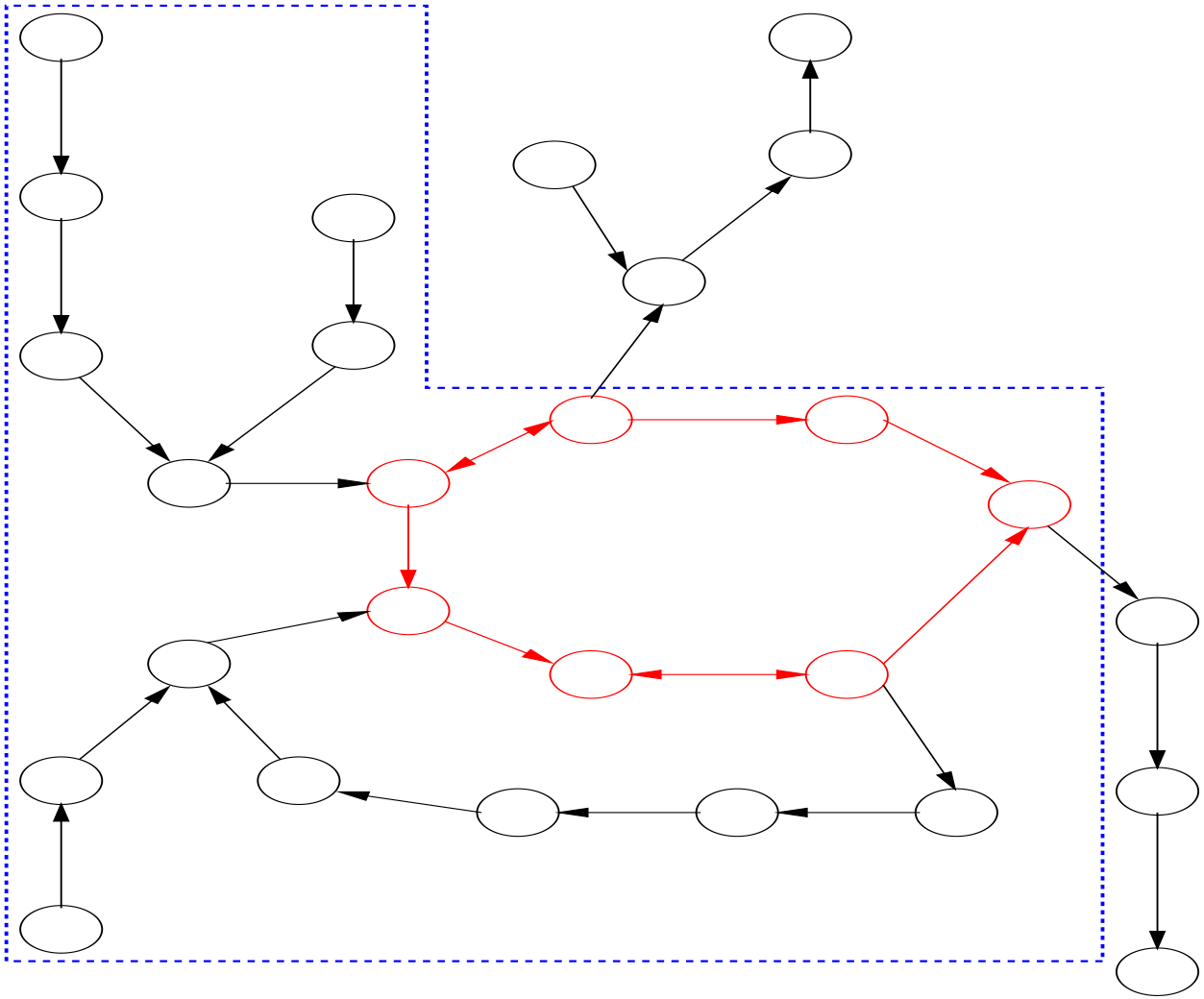

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A proper account of experimental observations requires a model which captures behaviour at all three levels.

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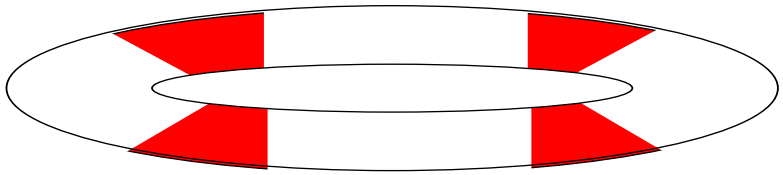
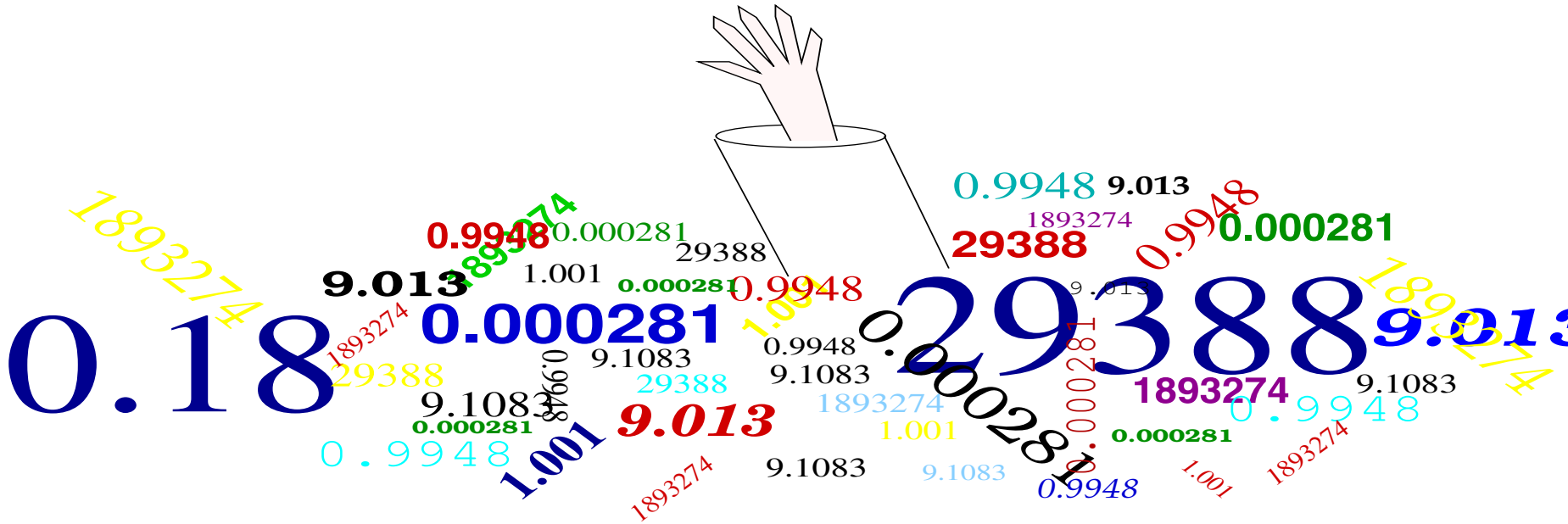
In particular:

- Abstraction
- Modularity and
- Reasoning

have a key role to play.

The Role of Computational Thinking





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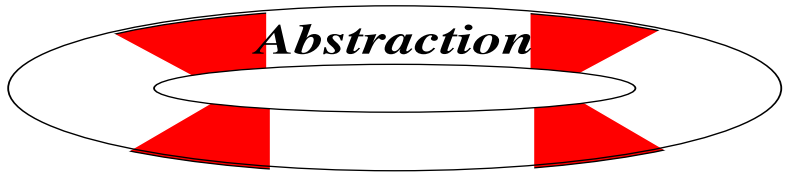

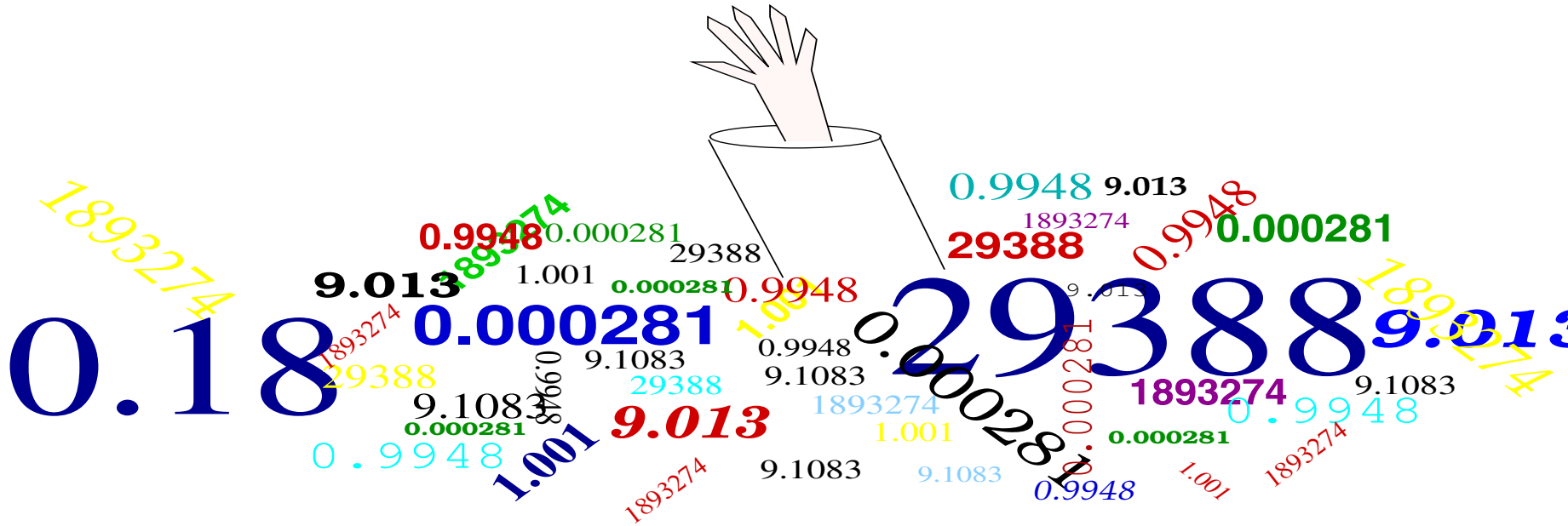

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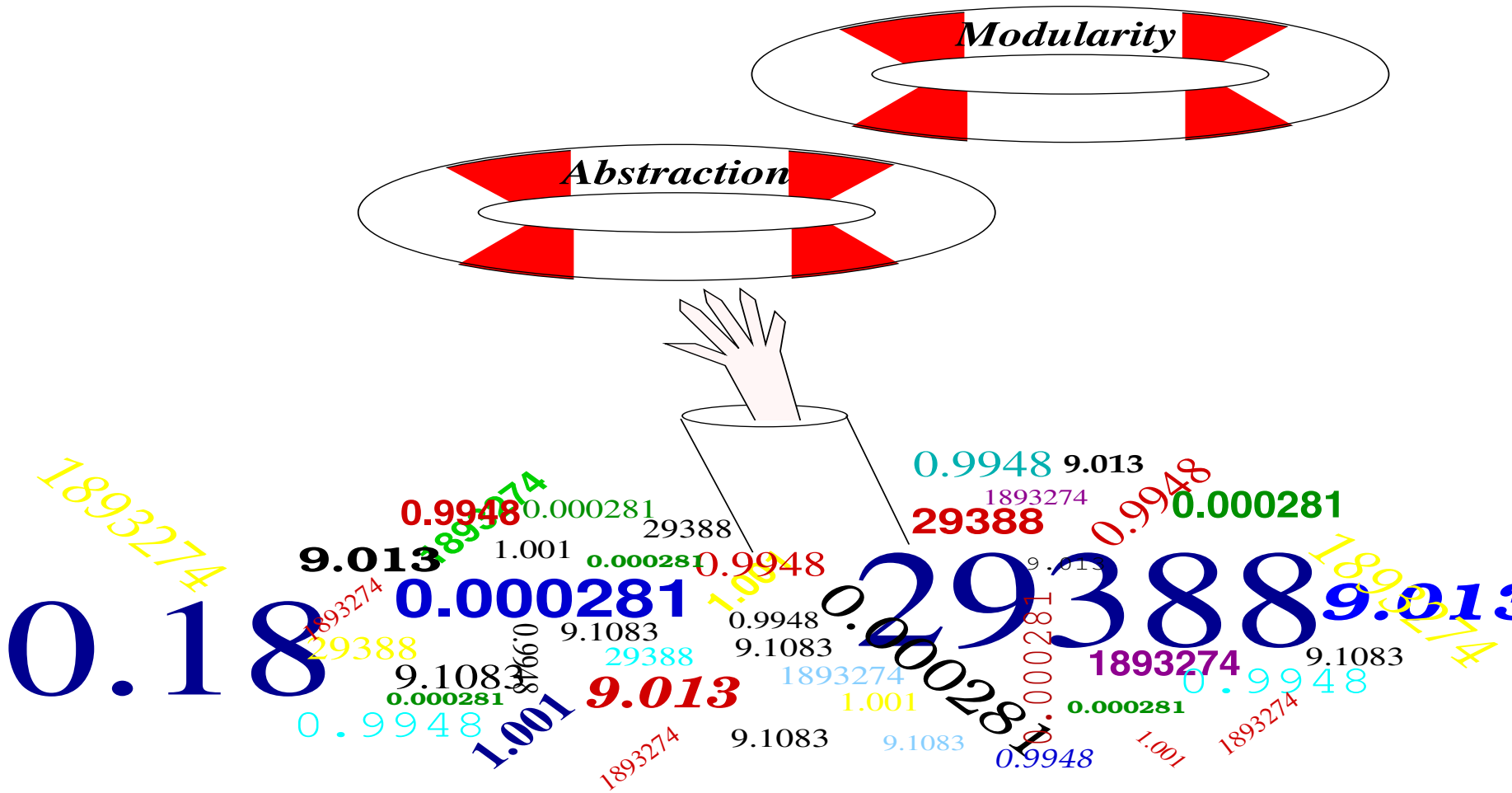

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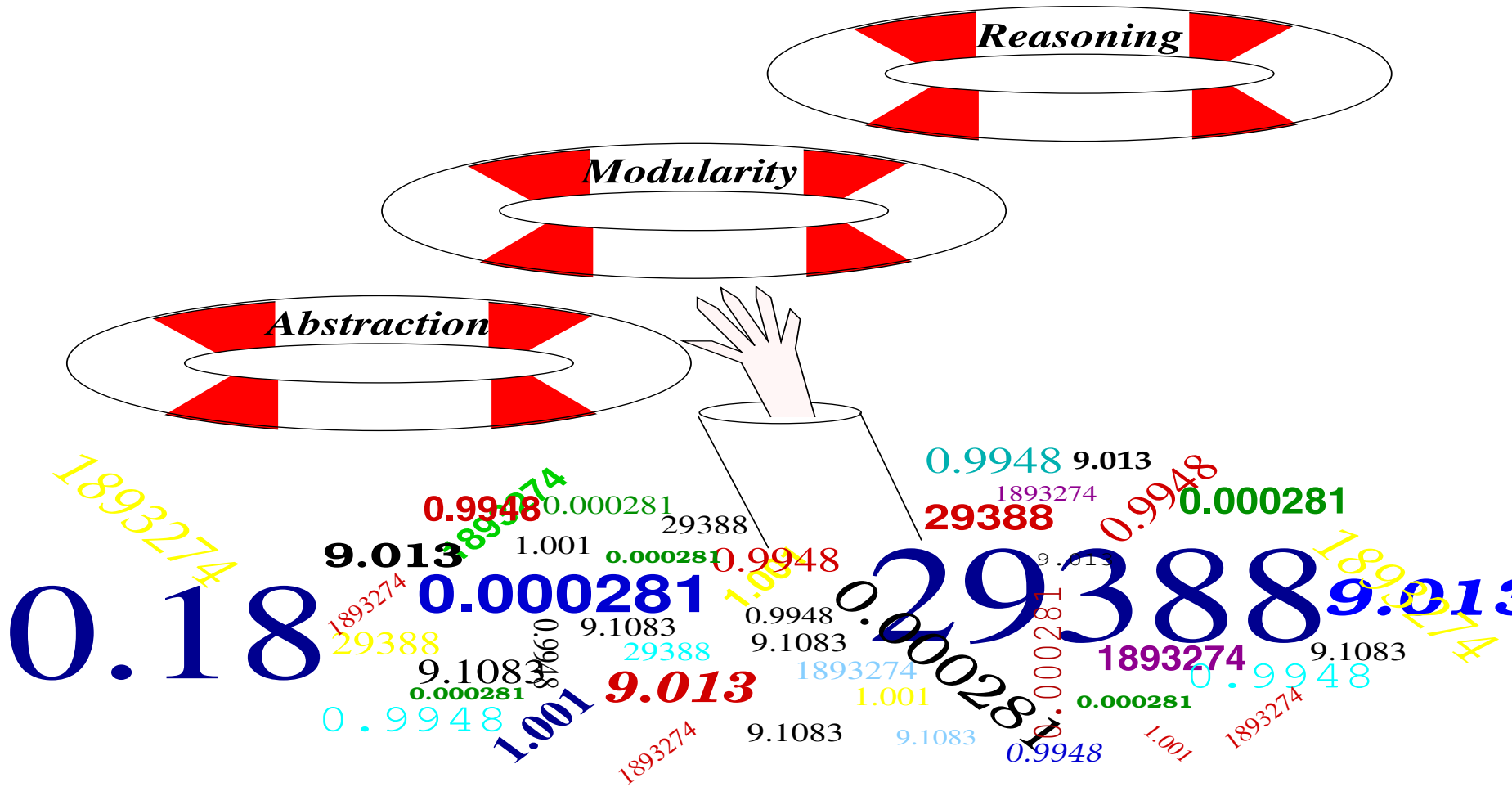

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I will focus on the use of process algebras for signalling pathways within cells.

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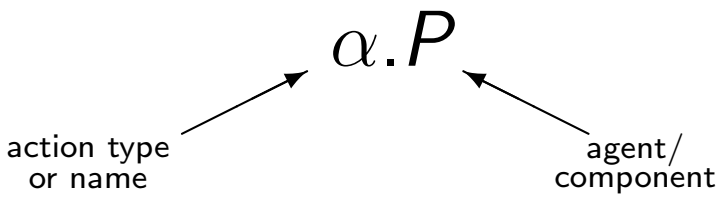
- Equivalence relations allow formal comparison of high-level descriptions.
- There are well-established techniques for reasoning about the behaviours and properties of models, supported by software.

Process Algebra

- Models consist of agents which engage in actions.



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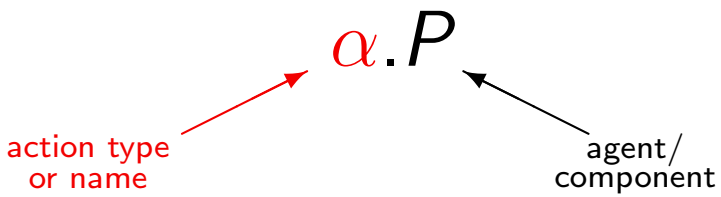

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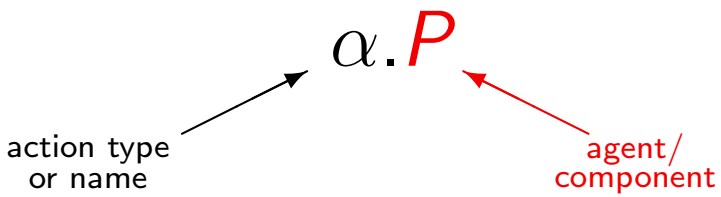

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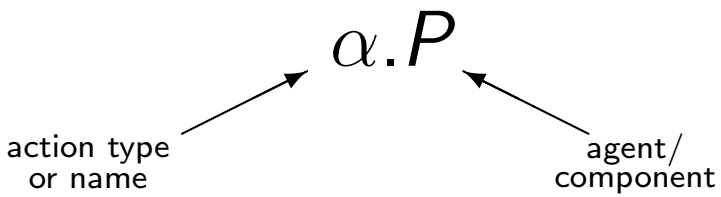

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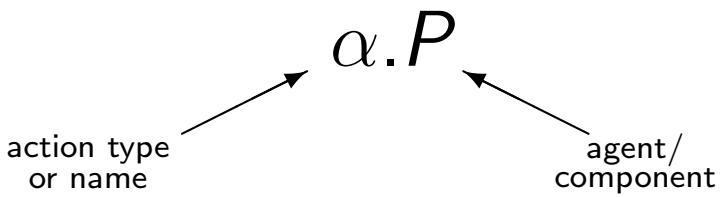

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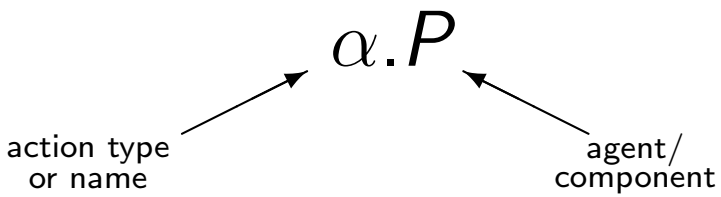

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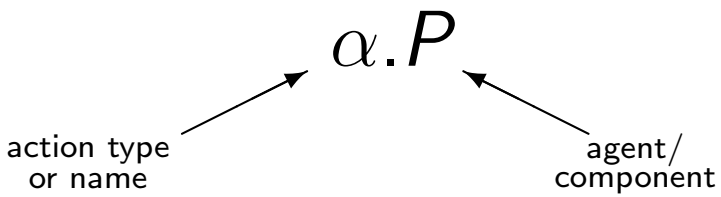

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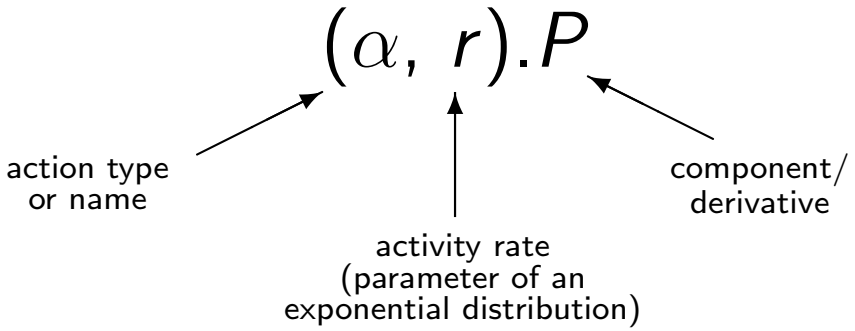

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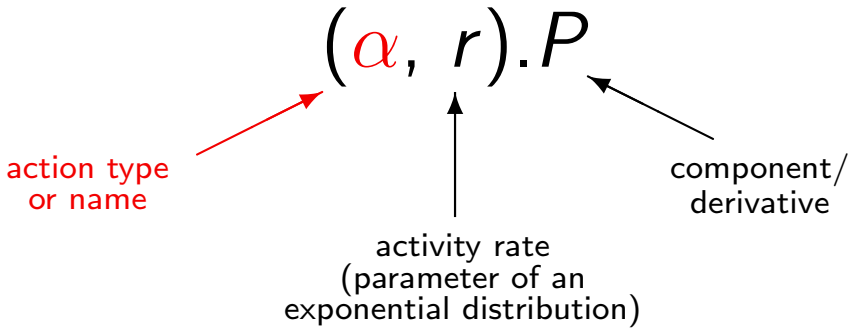

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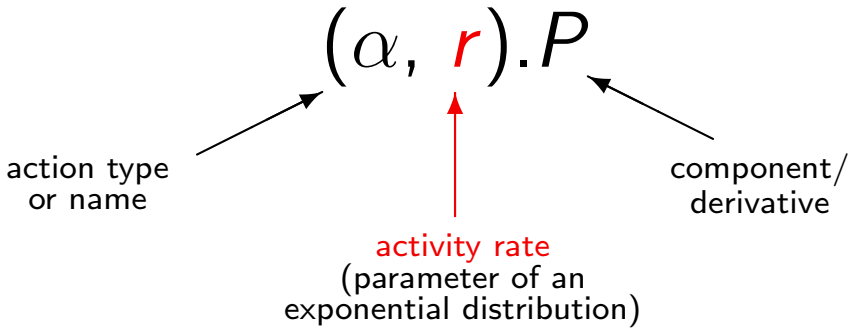

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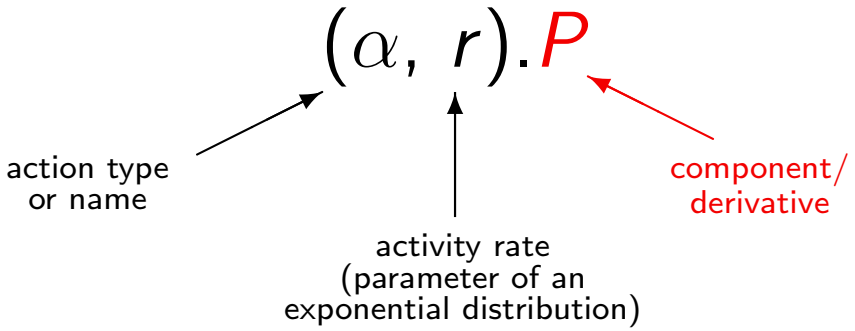

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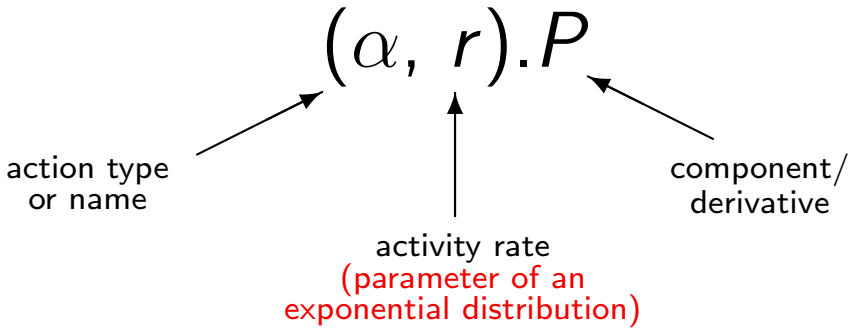

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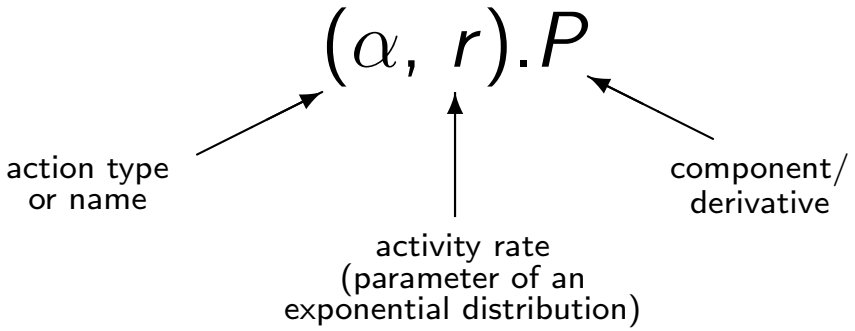

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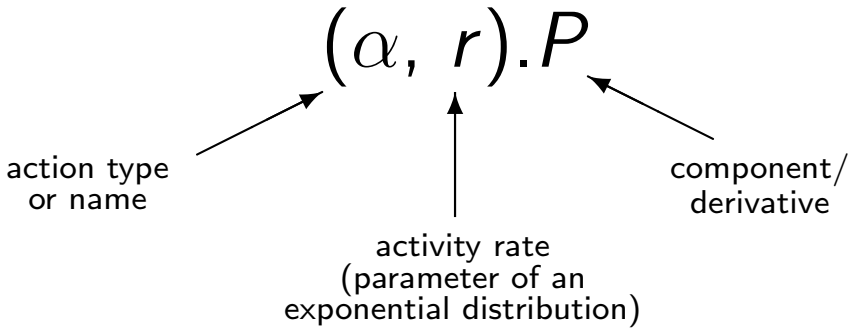

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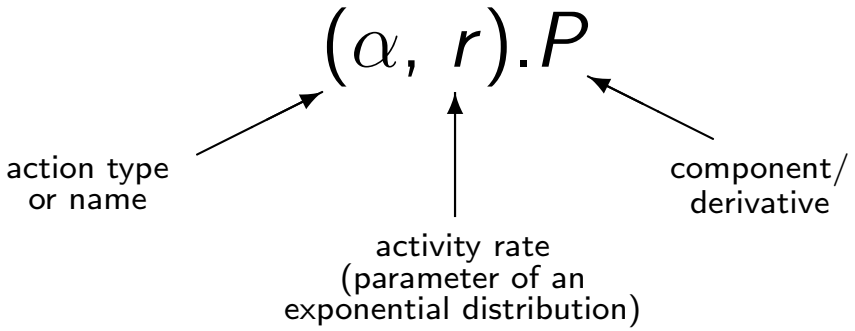

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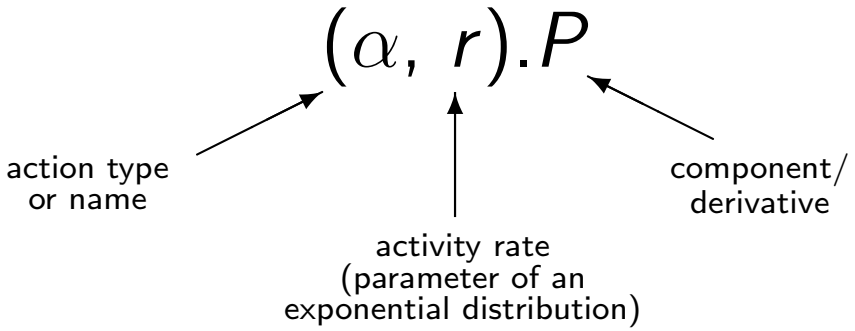

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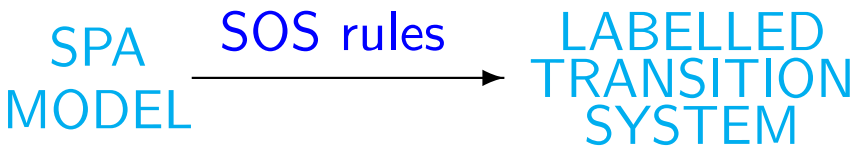

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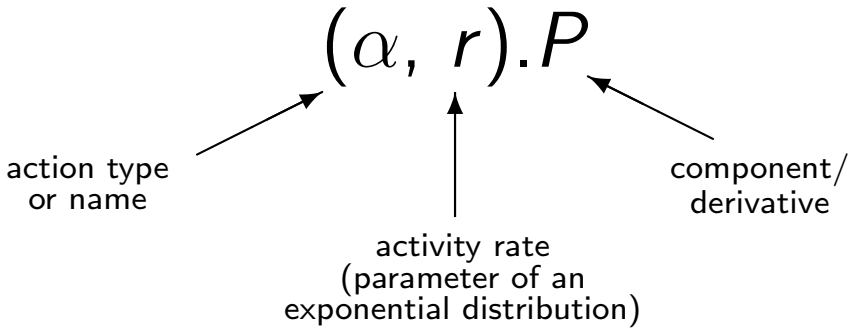

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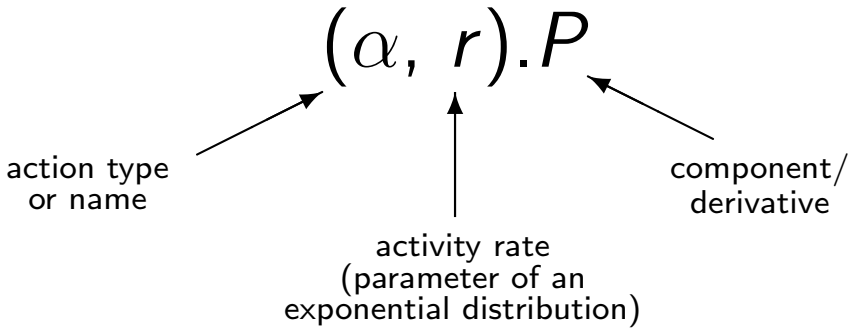

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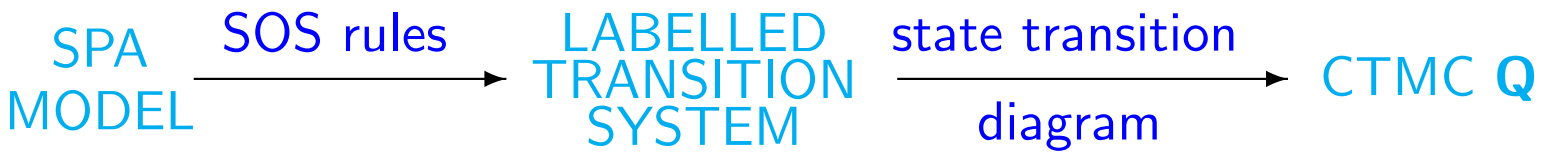

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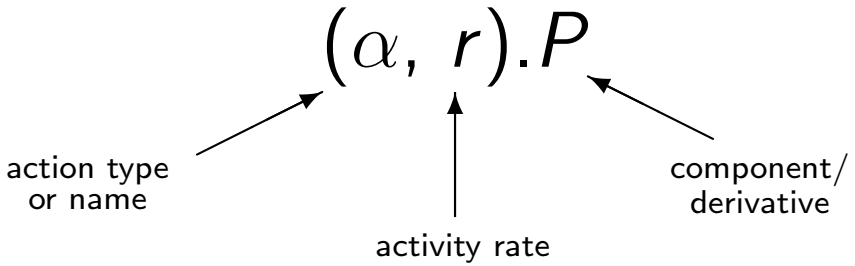

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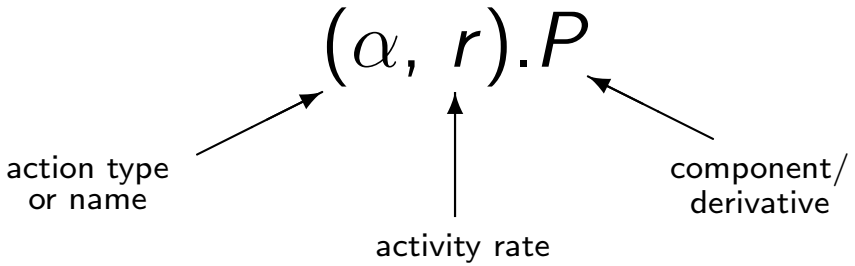

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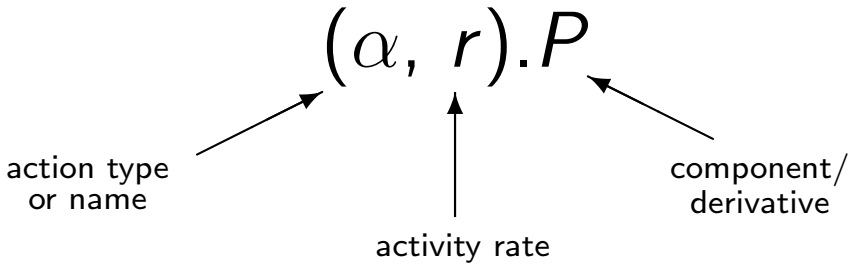

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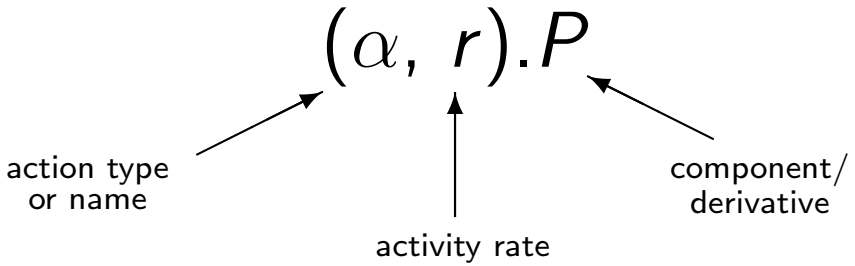

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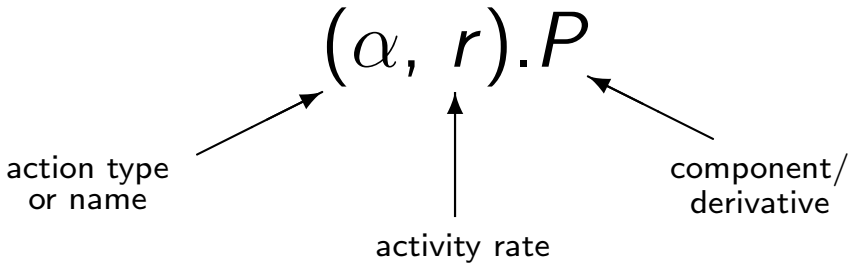

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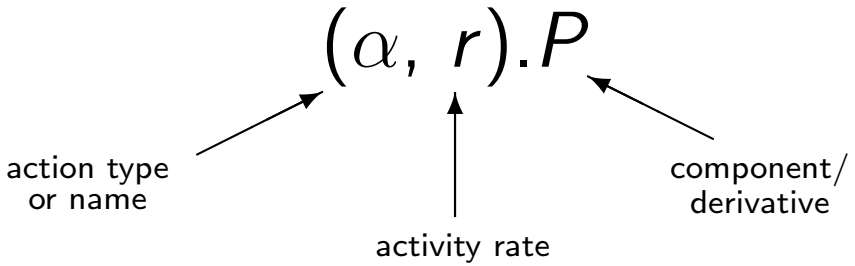

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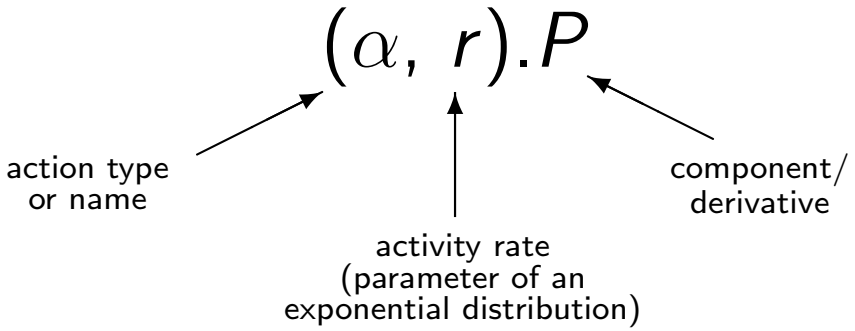

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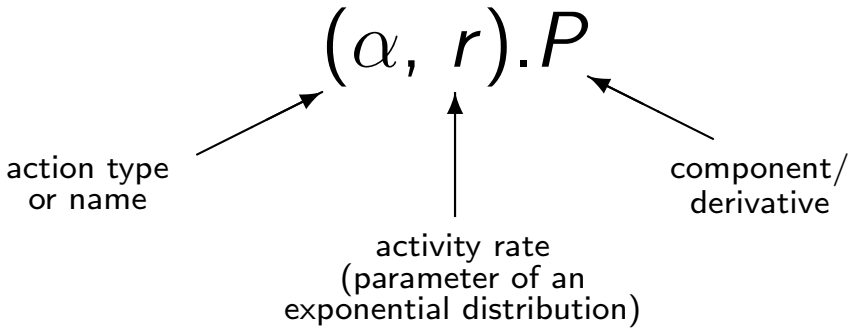

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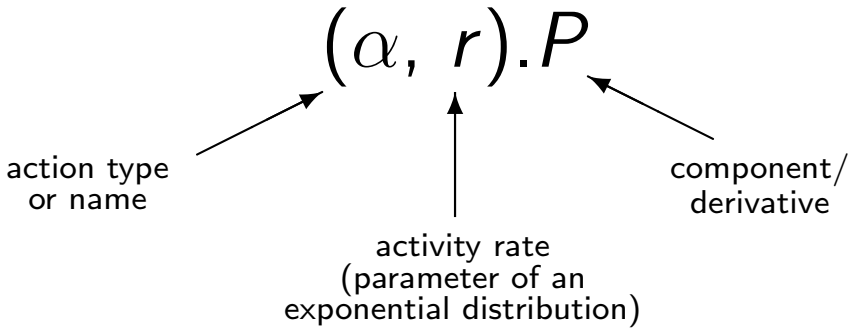

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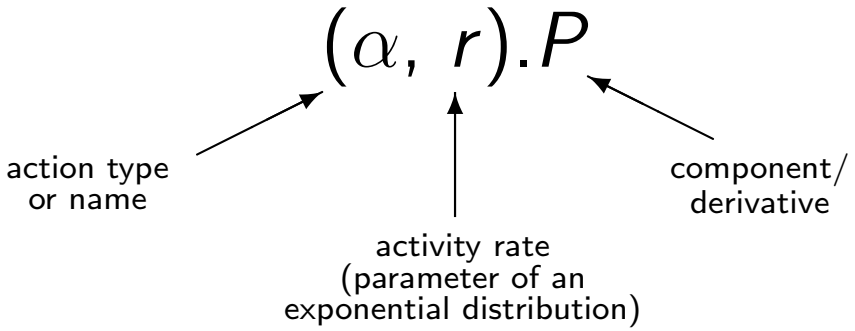

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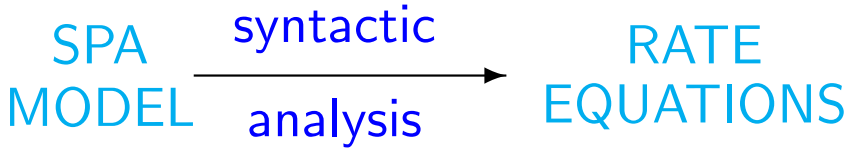

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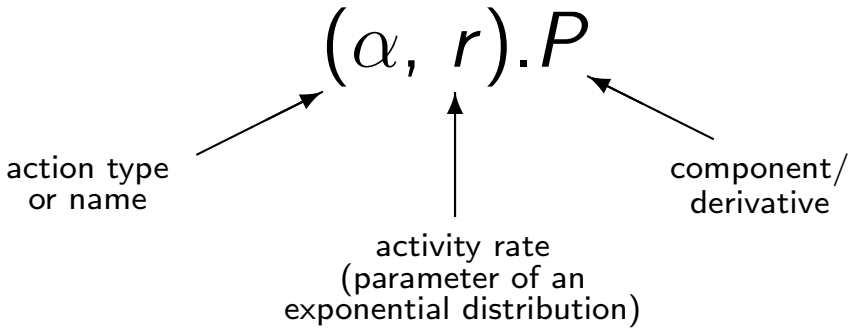

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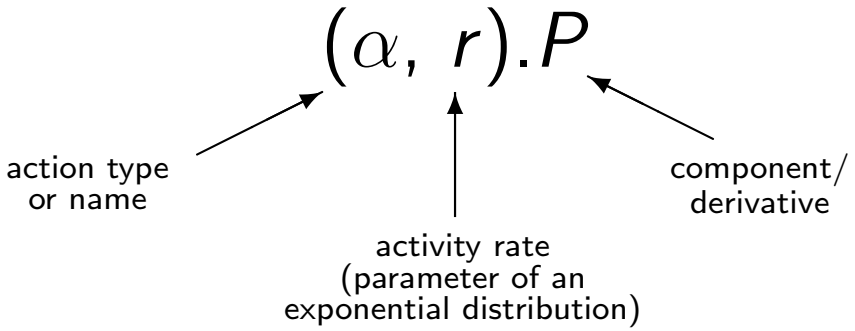

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Molecular processes as concurrent computations

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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[Regev *et al* 2000]

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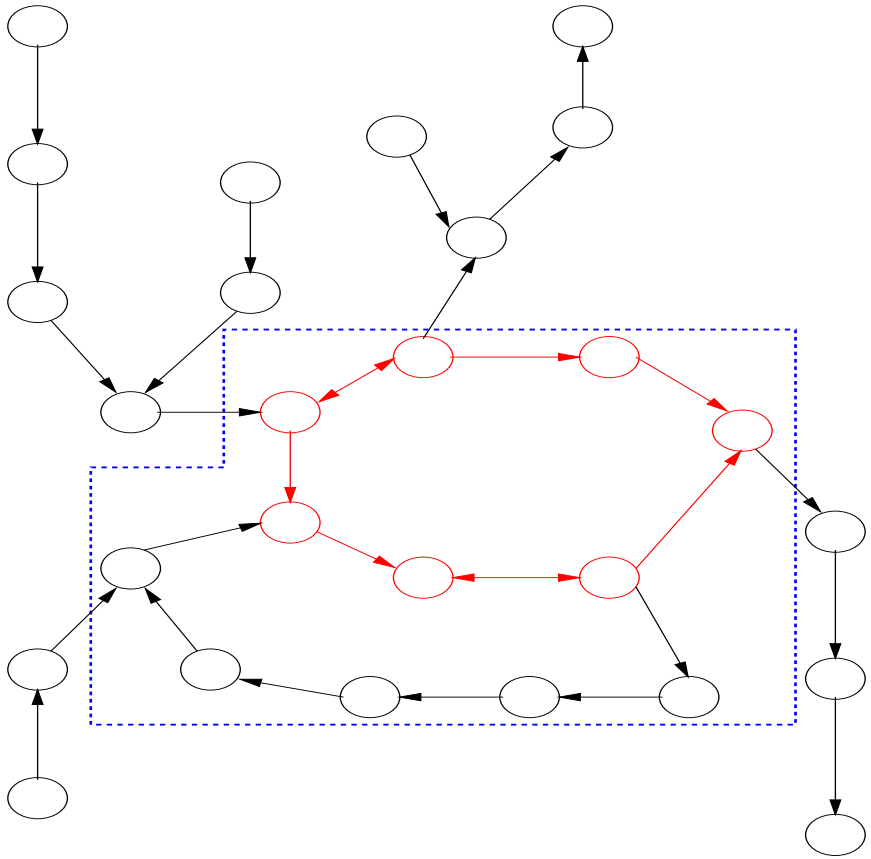
In our second we focus on sub-pathways.

Alternative Mappings illustration



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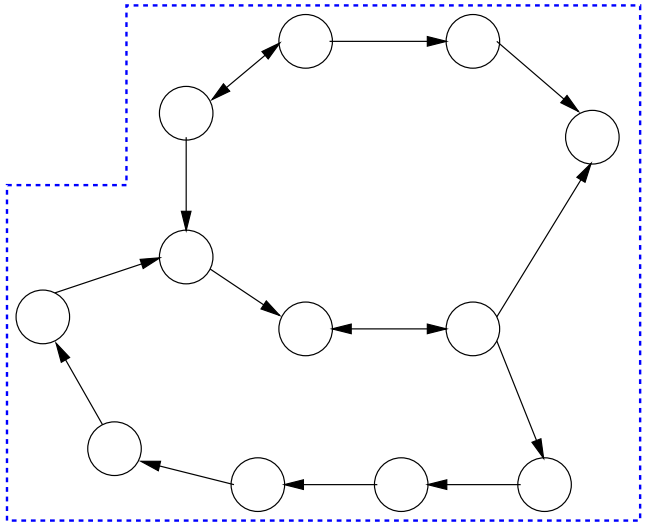

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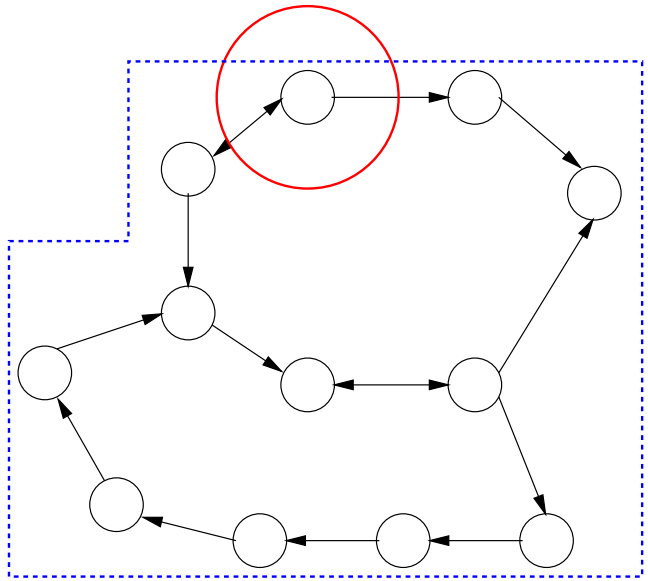

Reagent mapping: Each species is a distinct component in the model with local states to capture differing levels of concentration

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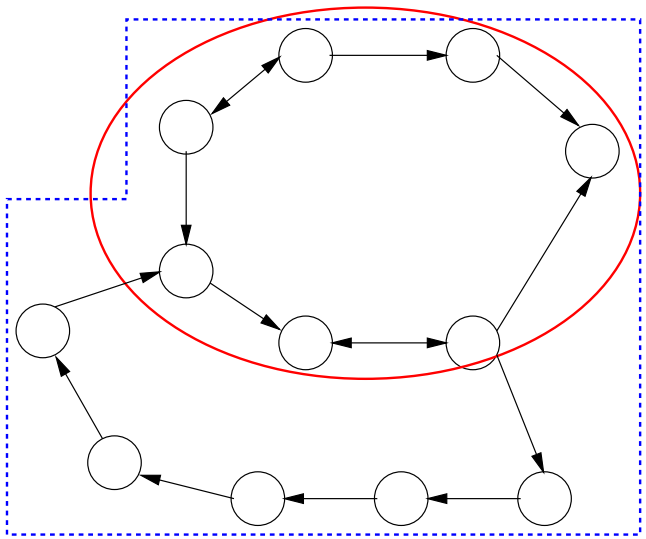

Pathway mapping: Each sub-pathway is a distinct component in the model with local states to capture progress through the pathway

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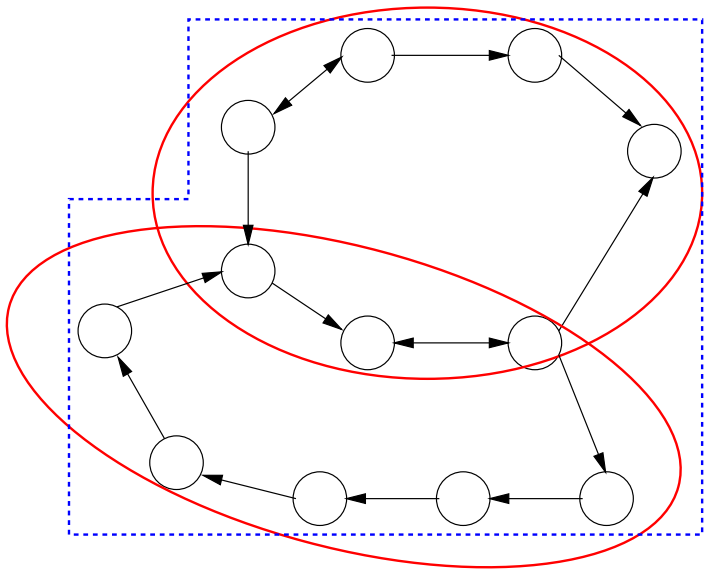

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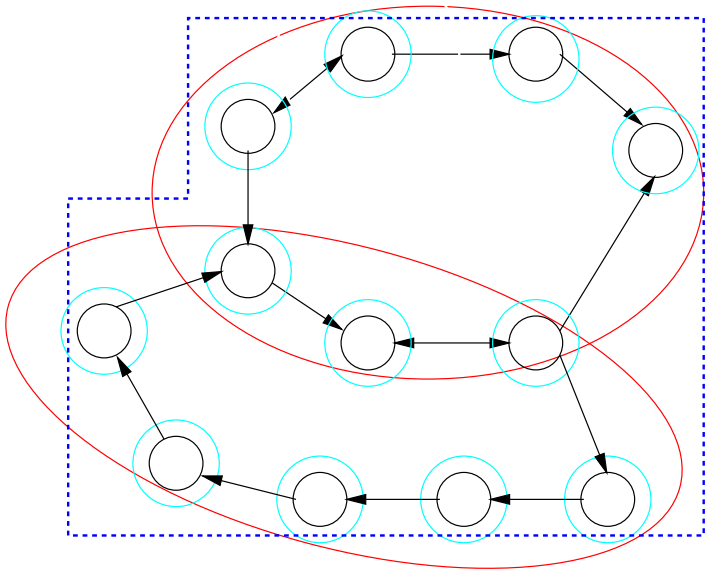

Reasoning based on bisimulation equivalence is able to prove that the two representation are equivalent.

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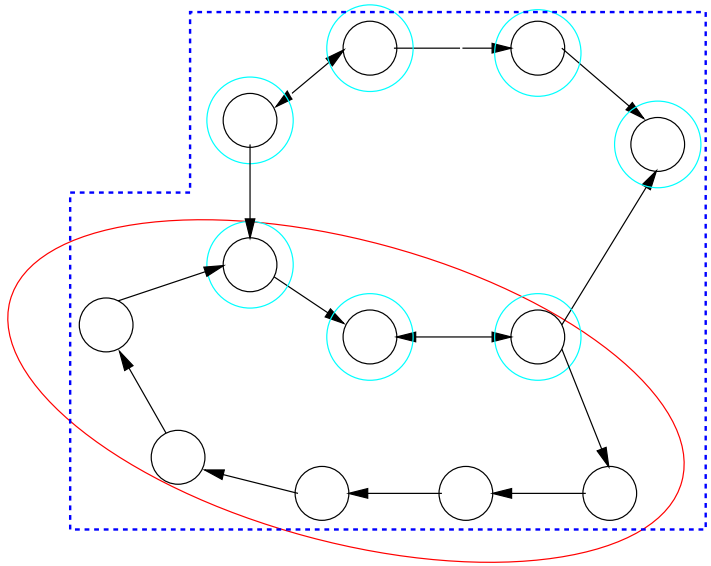

Different parts of the system may use different mappings, reflecting perhaps the level of knowledge (data) available, or the primary interests of the modeller.

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- Suitable equivalence relations can confirm that our abstraction is valid.

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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.

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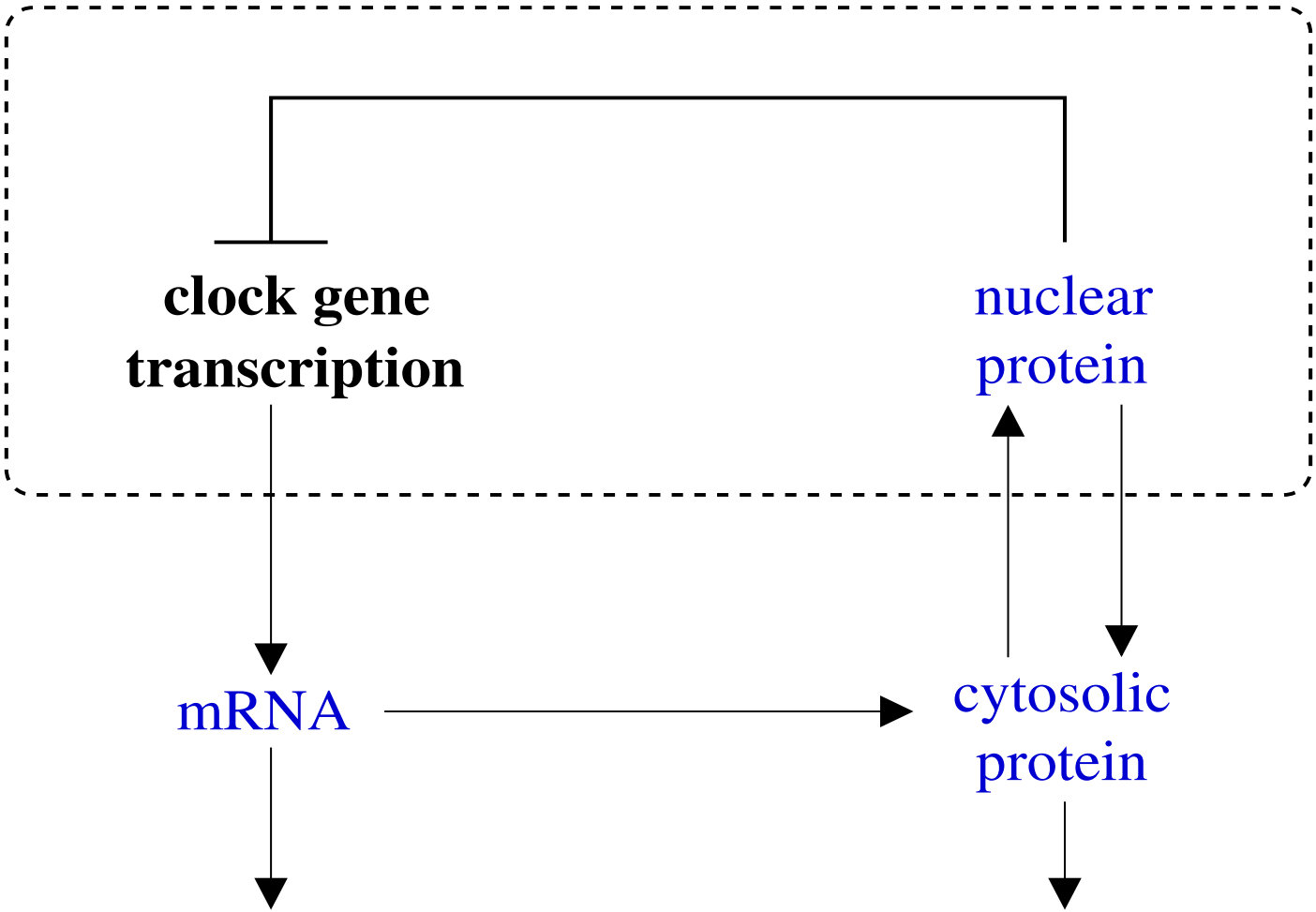
- Additionally for some process algebras there are complementary modal logics which allow system properties to be formally expressed and automatically checked.

A simple circadian clock



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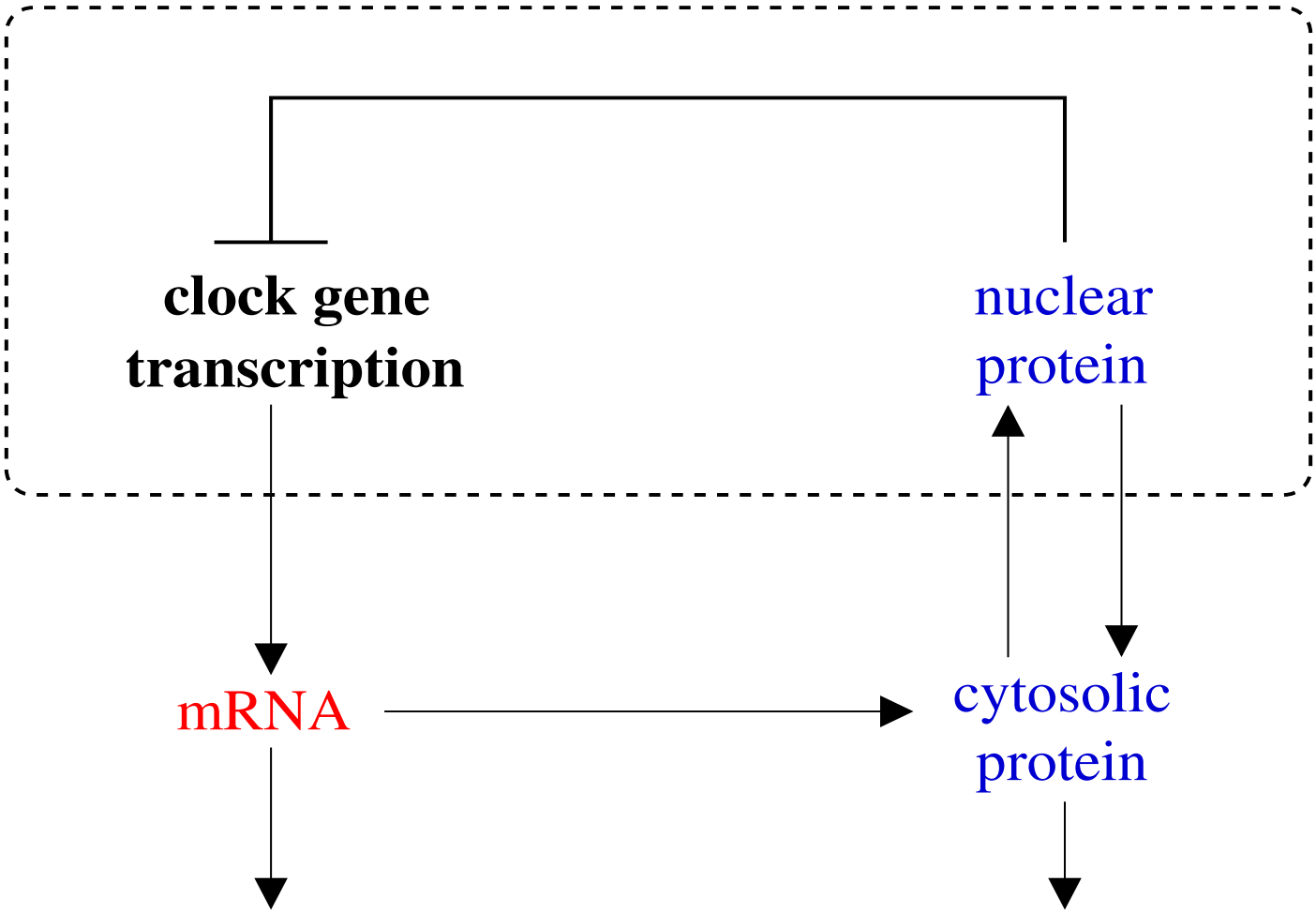

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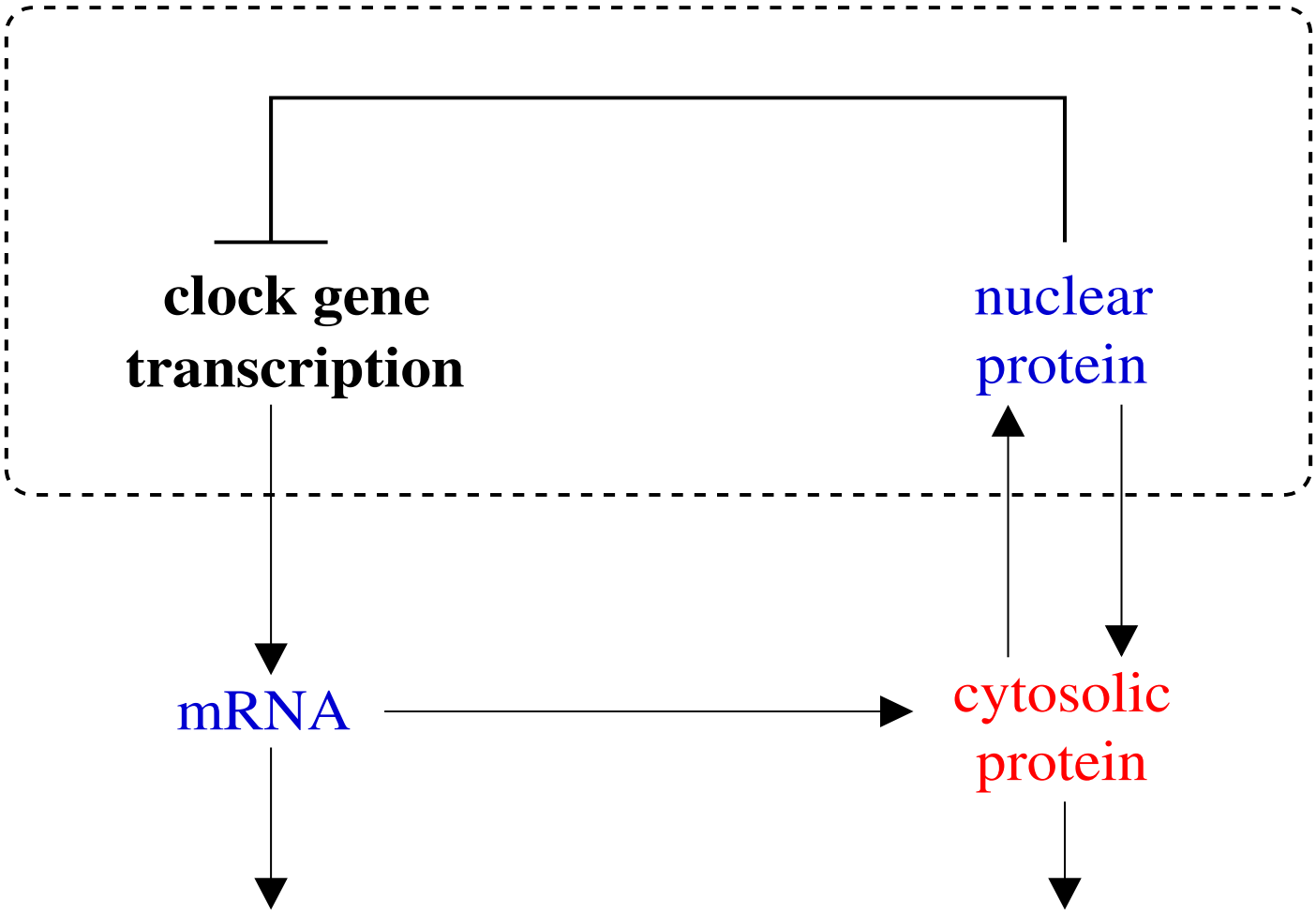

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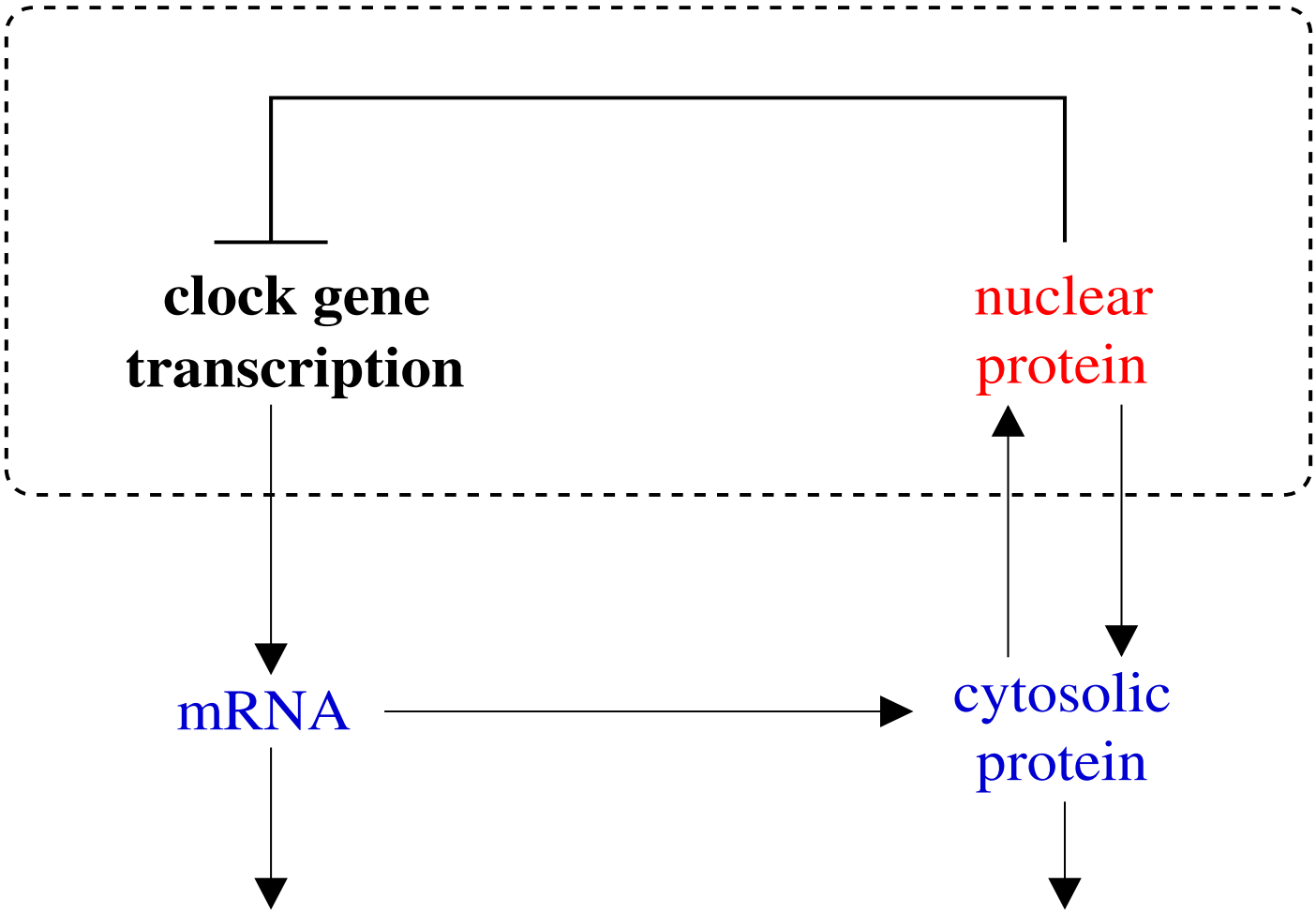

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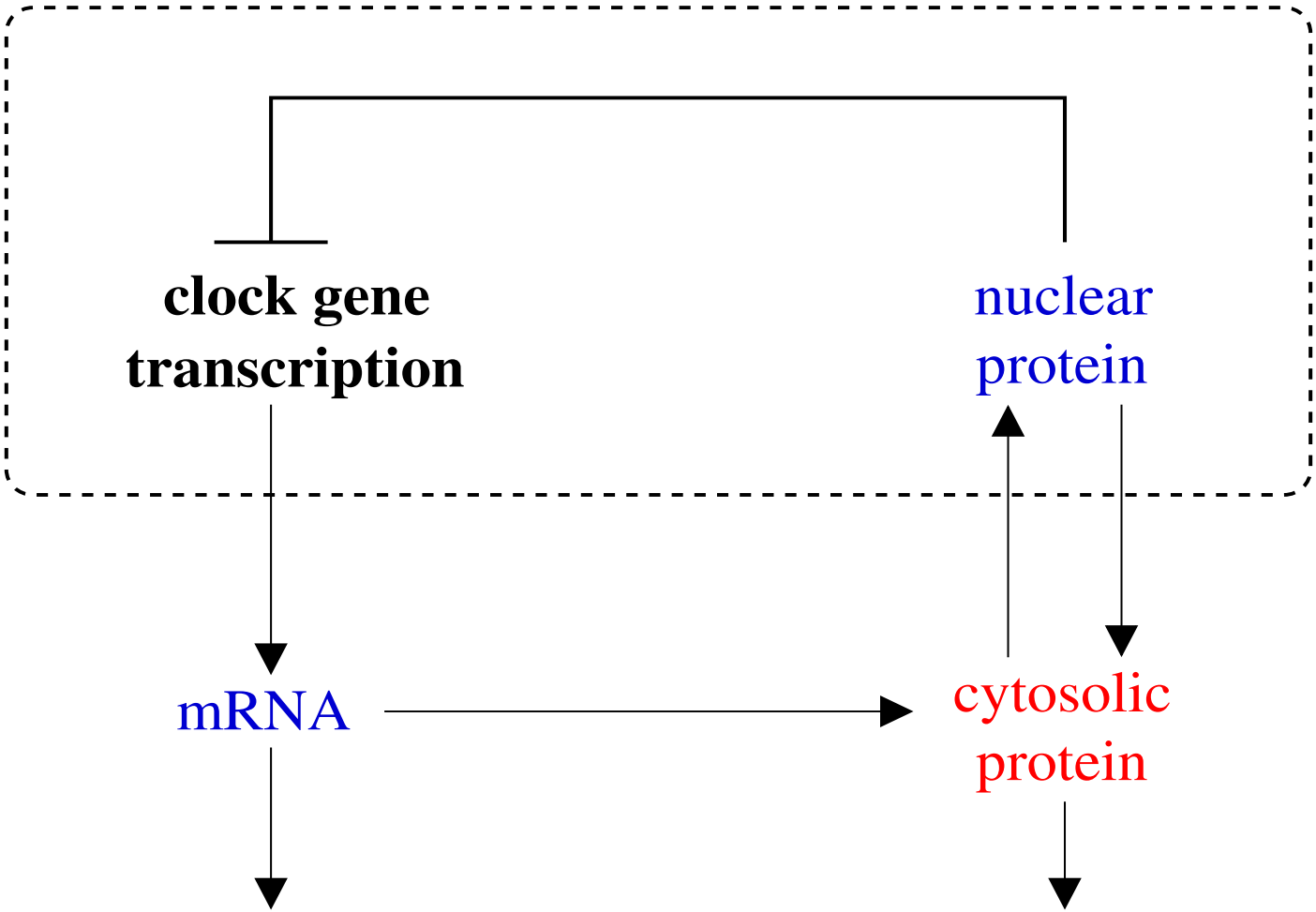

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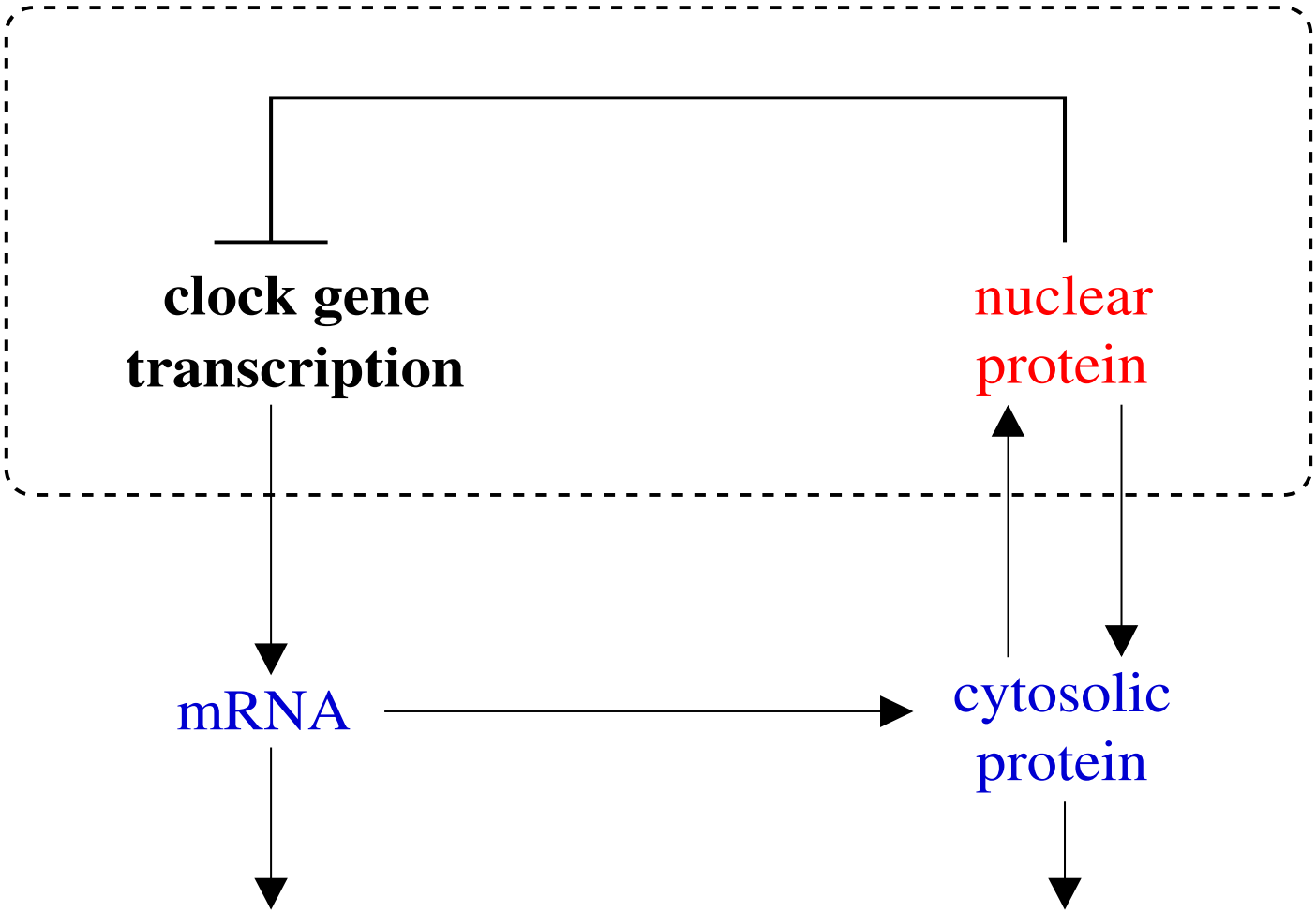

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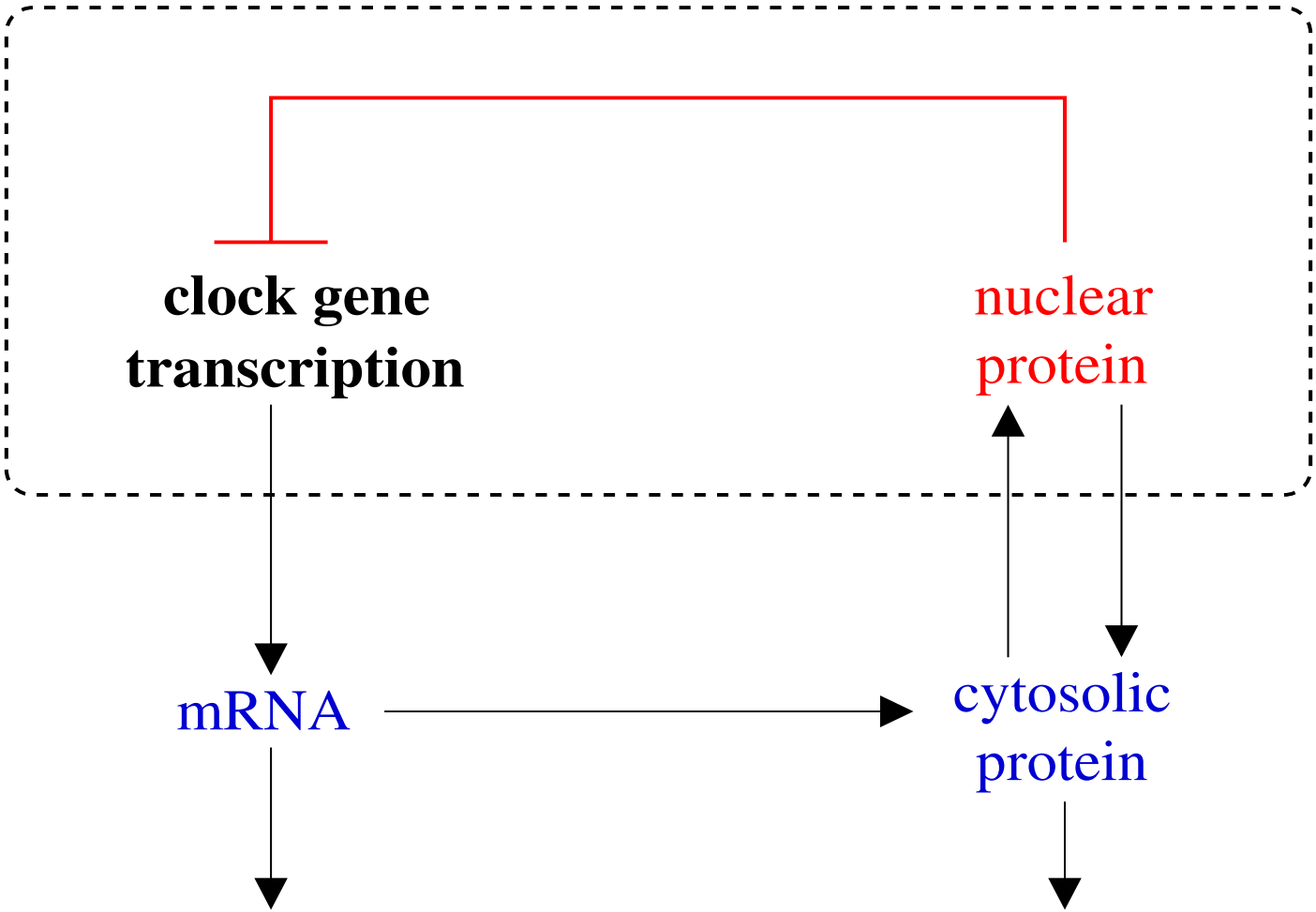

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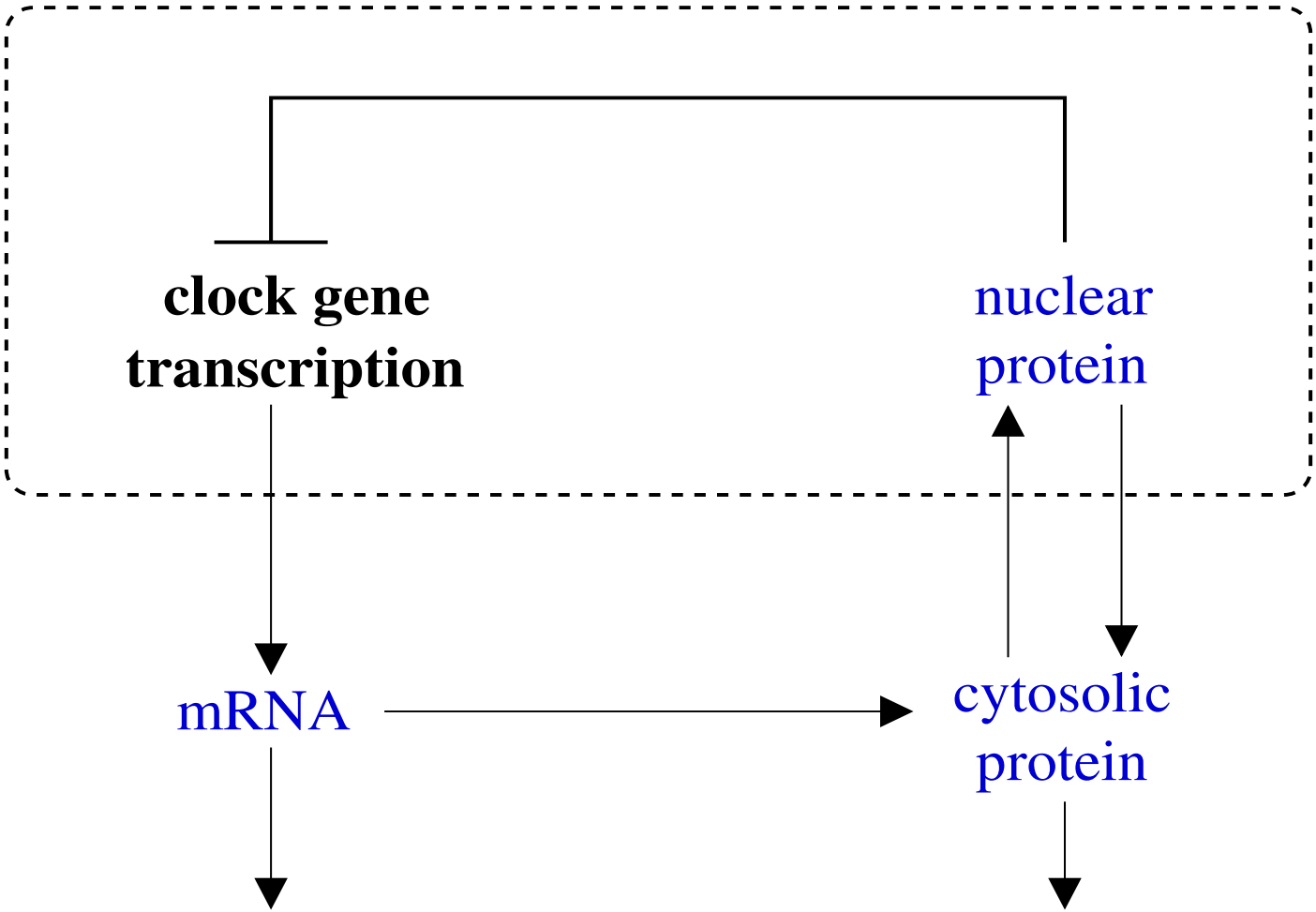

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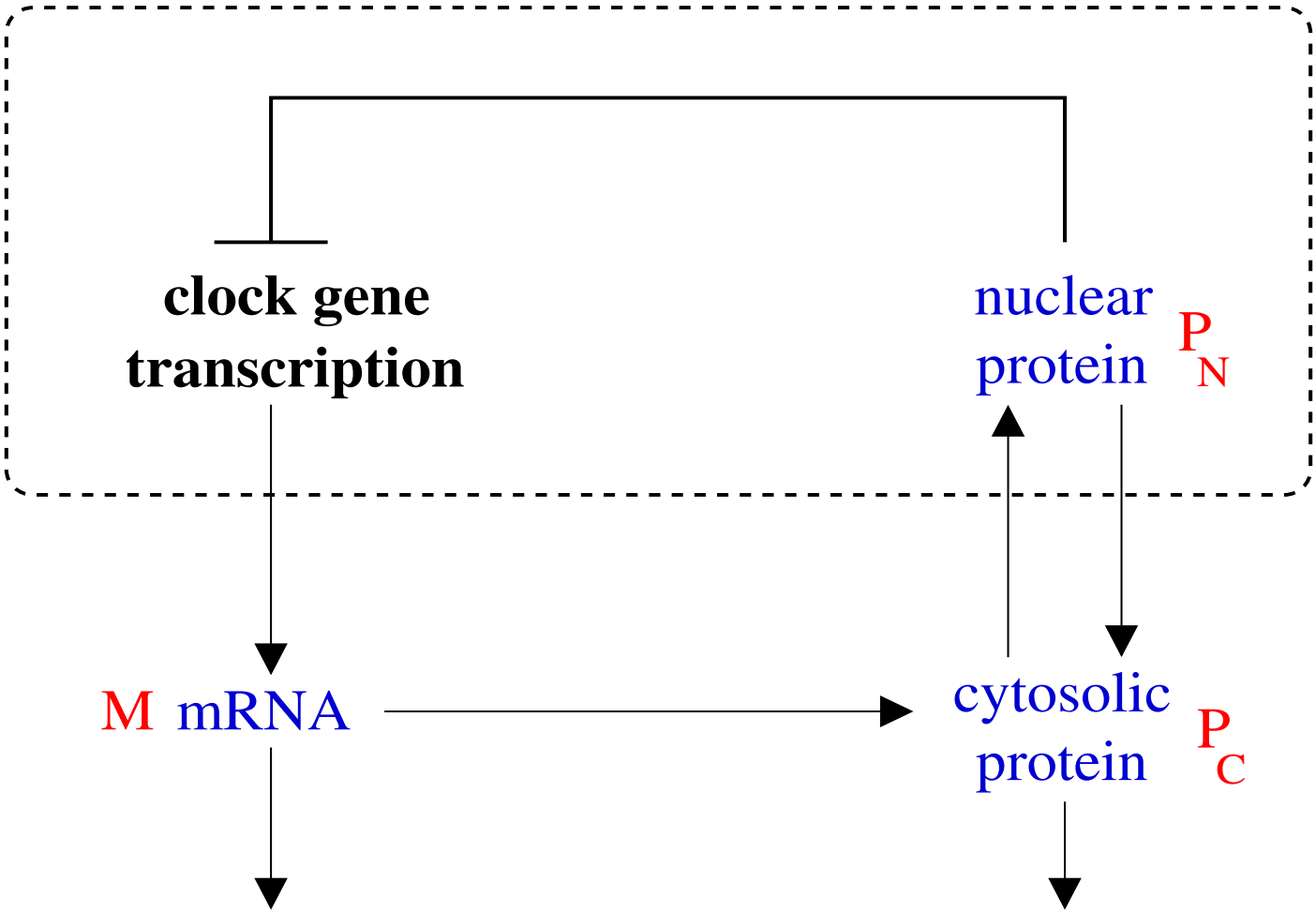

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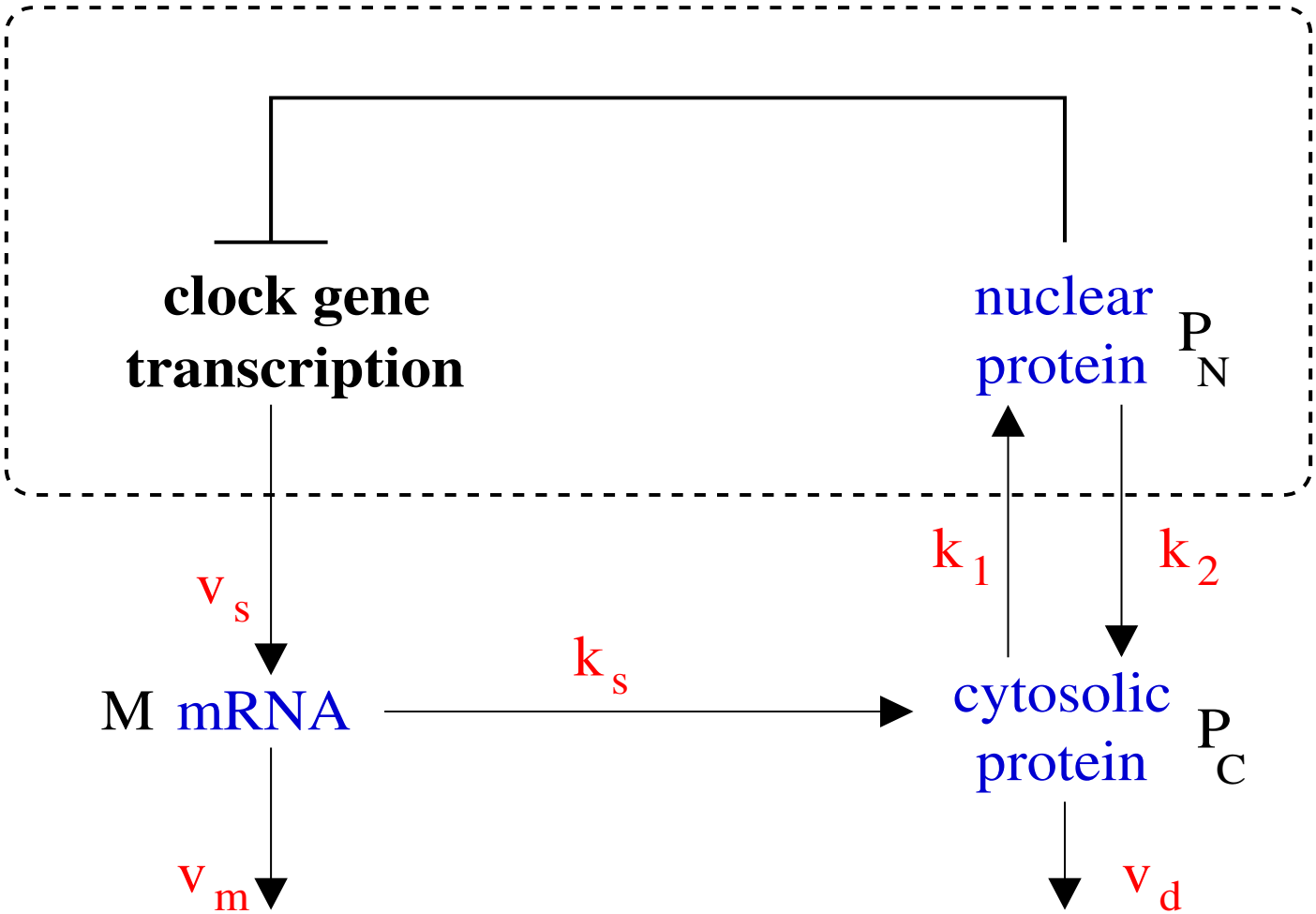

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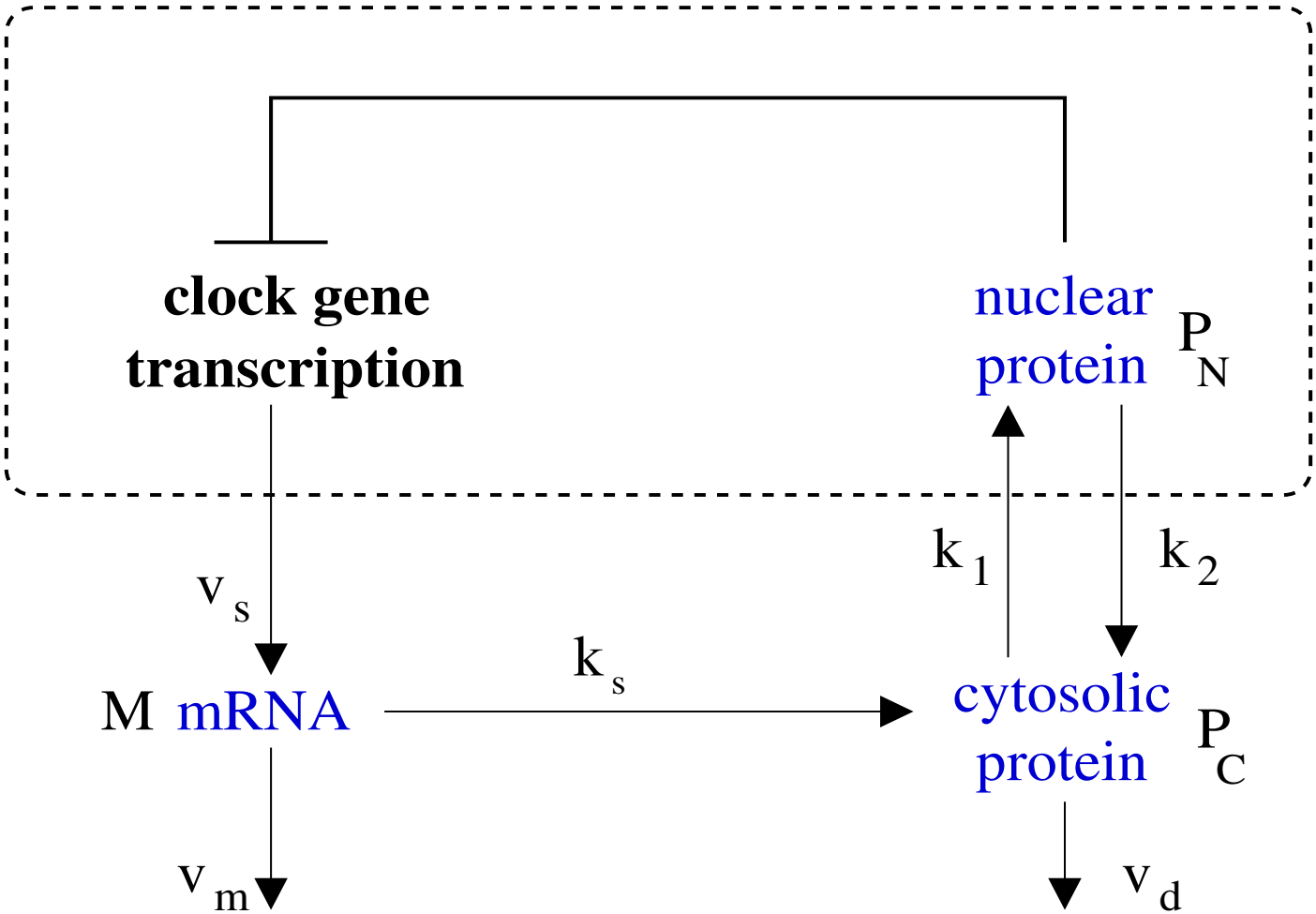
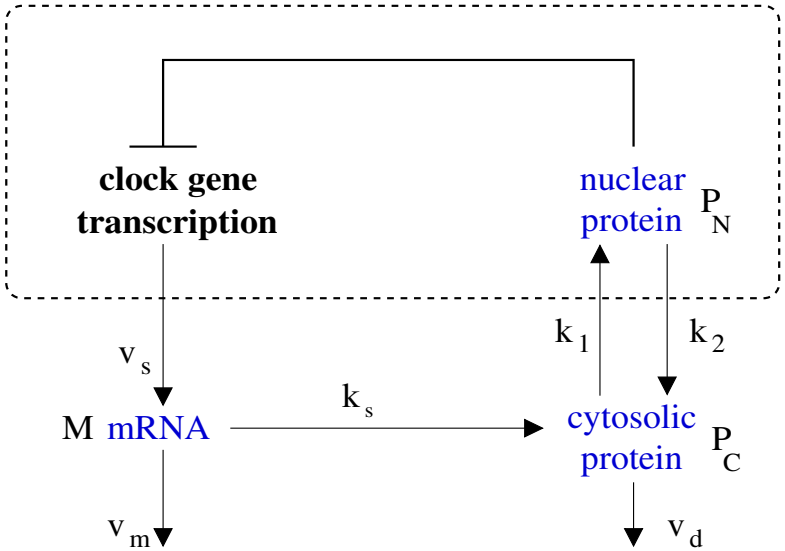


Handcrafted ODEs



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

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

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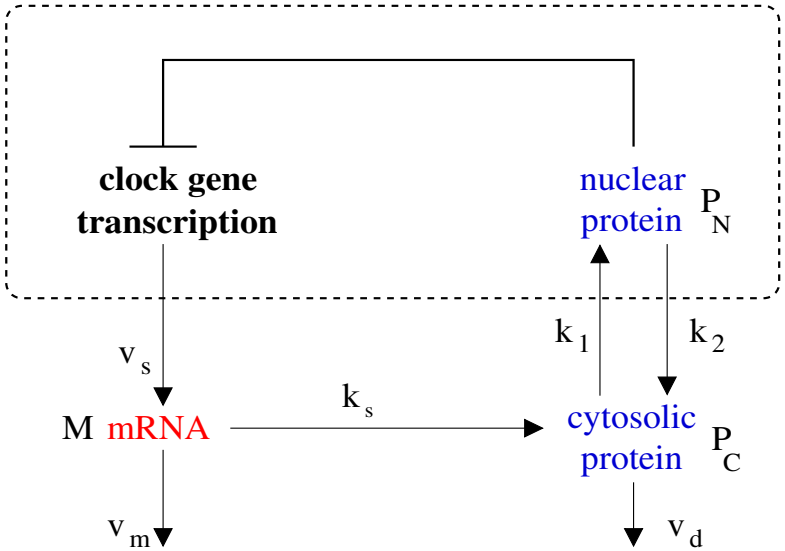

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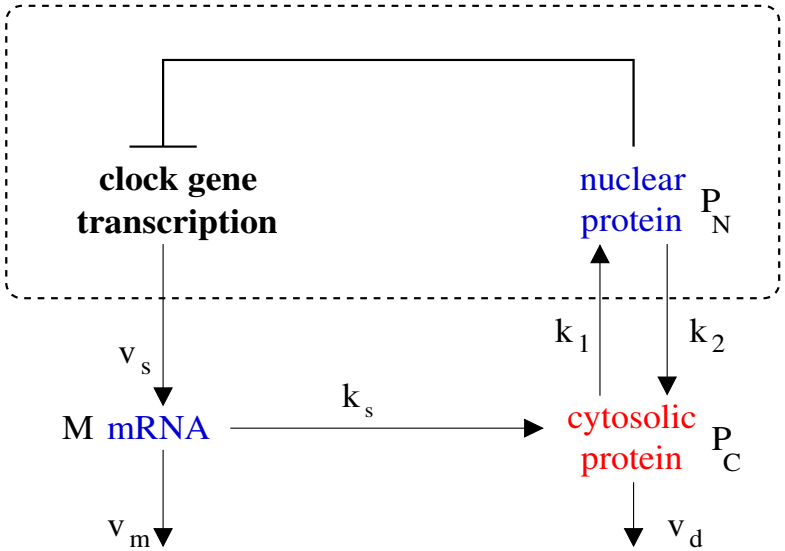

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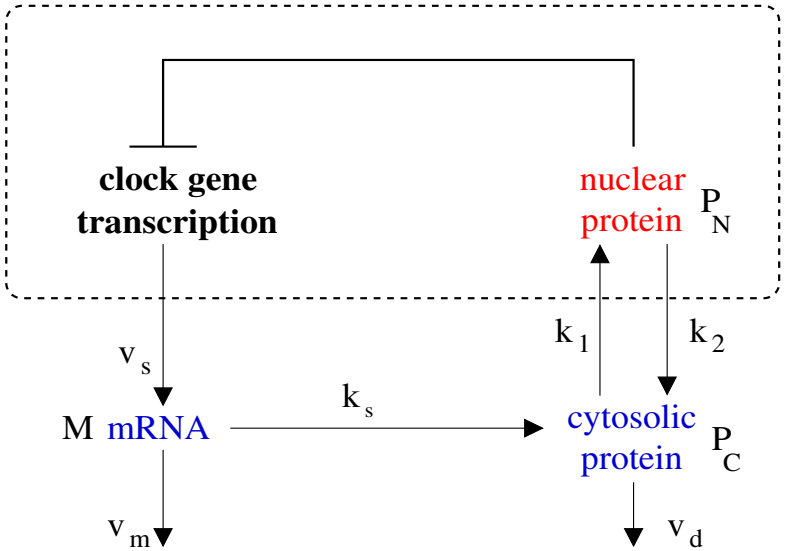

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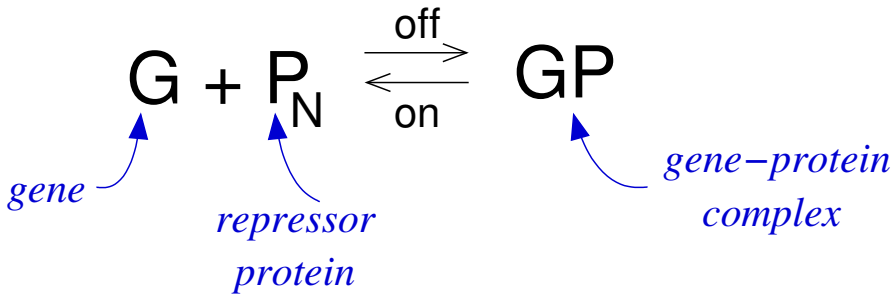
- PEPA does not have combinators to express repression or catalysis:
  - We introduce additional abstract components to the PEPA model which do not correspond to species but to transcription and repression.

Repression mechanism



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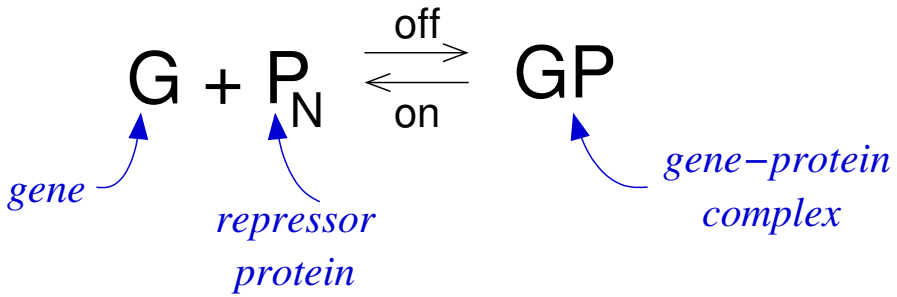

$$\text{Transcription} \begin{cases} T^h \stackrel{def}{=} (transcribe, v_s).T^h + (off, \top).T^l \\ T^l \stackrel{def}{=} (on, \top).T^h \end{cases}$$

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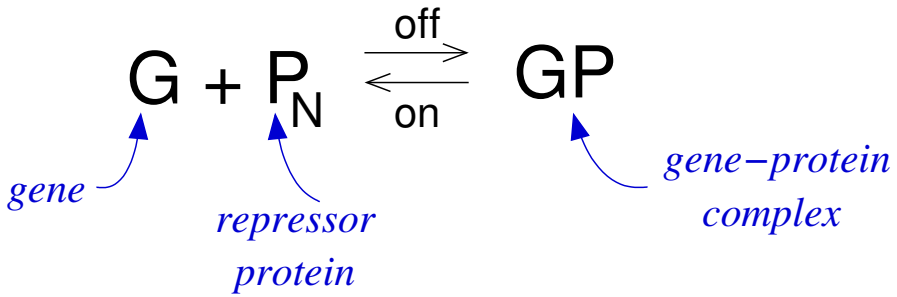

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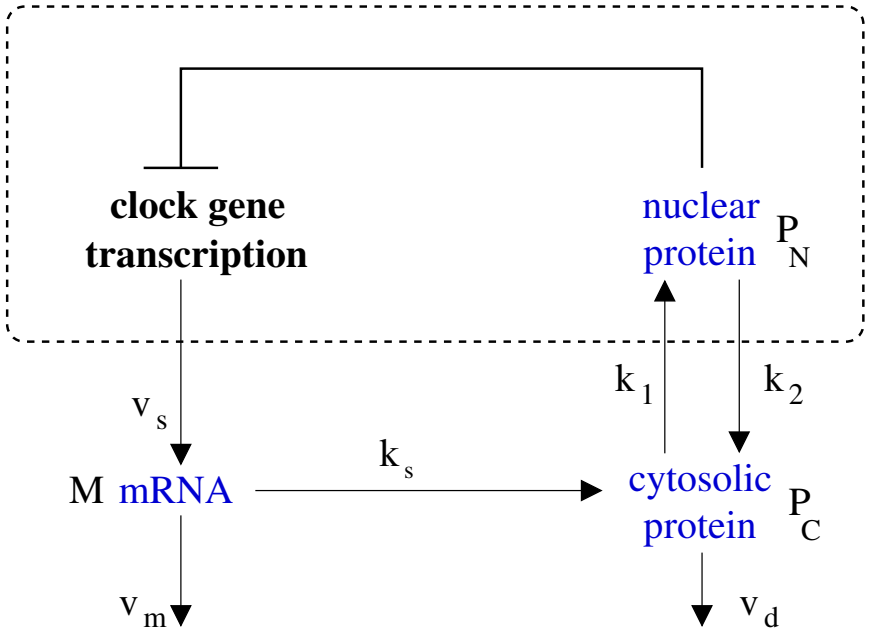
$$P_N^h \stackrel{def}{=} (off, v_{off}).P_N^l + \ldots$$

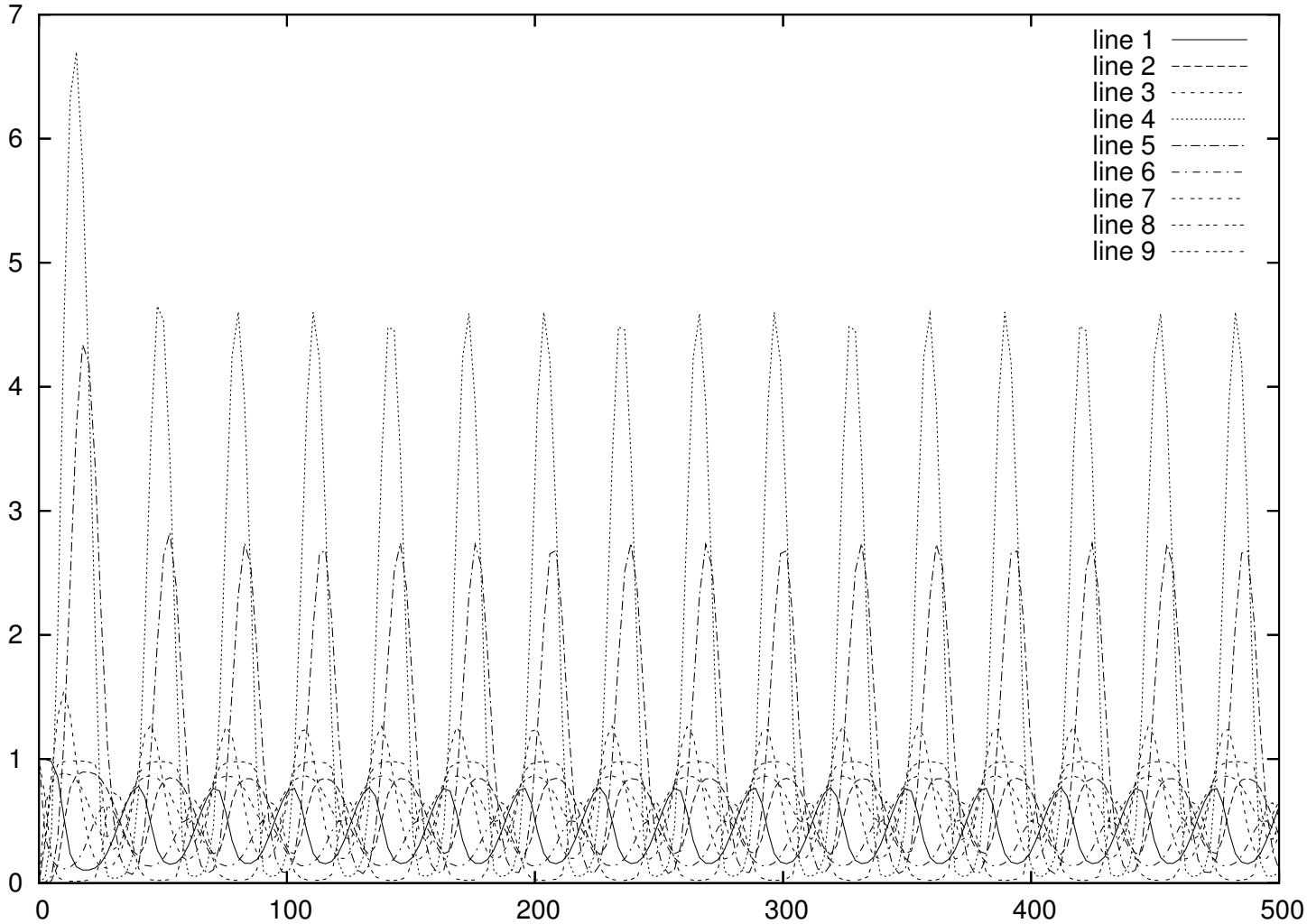
Only P_N is explicitly modelled; T and R are abstract entities.

PEPA model of the circadian clock

$$T^h \underset{\{transcribe,on,off\}}{\bowtie} \left(R^I \underset{\{off\}}{\bowtie} \left(\left(M \underset{\{translate\}}{\bowtie} (P_C \underset{\{trans_1,trans_2\}}{\bowtie} P_N) \right) \right) \right)$$



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

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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!