Quantitative Analysis of Biochemical Signalling Pathways

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LFCS, University of Edinburgh

26th October 2007

Outline

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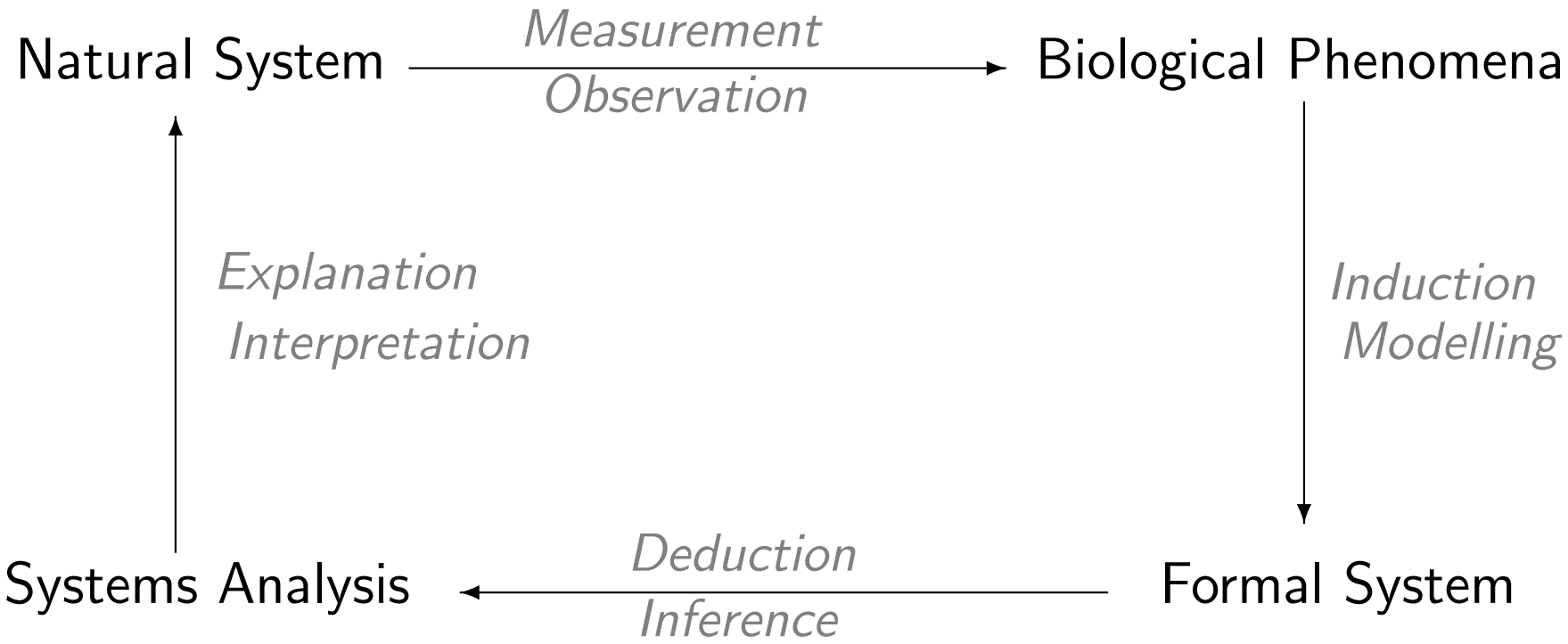
- It involves taking a systems theoretic view of biological processes — analysing inputs and outputs and the relationships between them.
- A radical shift from earlier reductionist approaches, systems biology aims to provide a conceptual basis and a methodology for reasoning about biological phenomena.

Systems Biology Methodology



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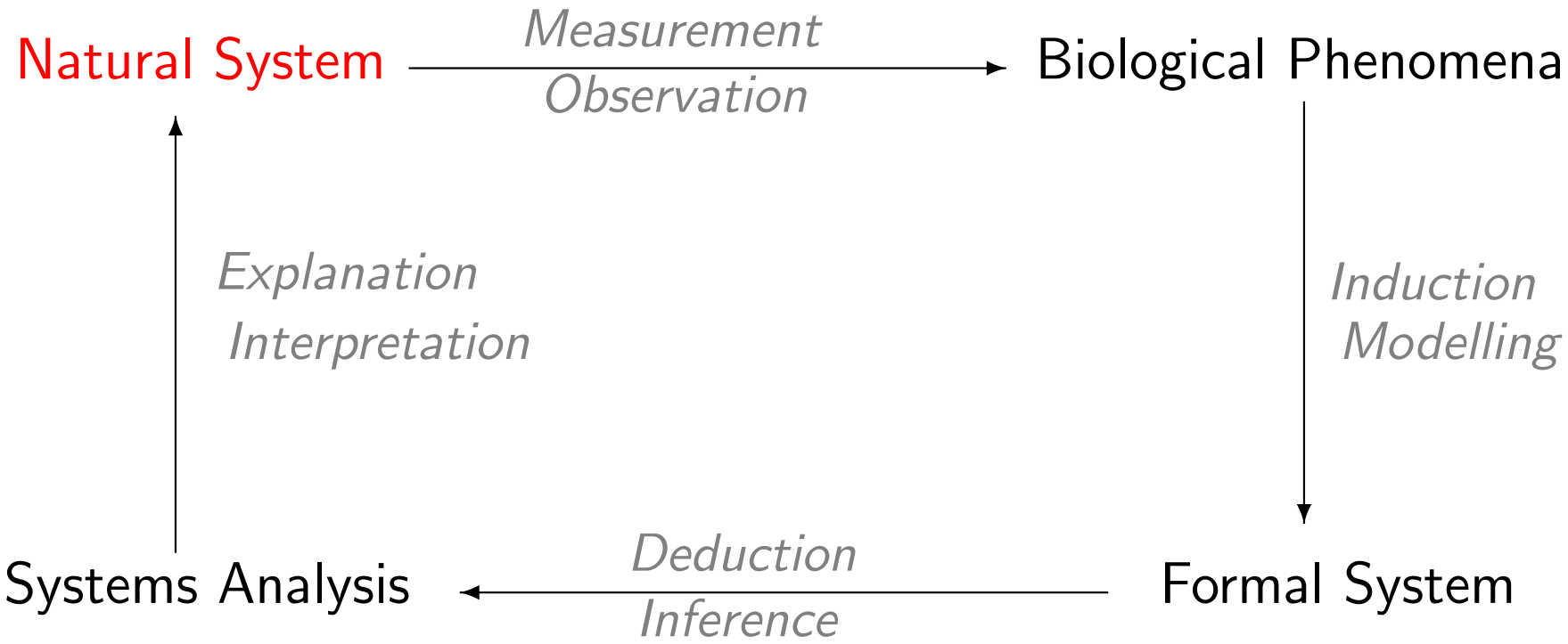

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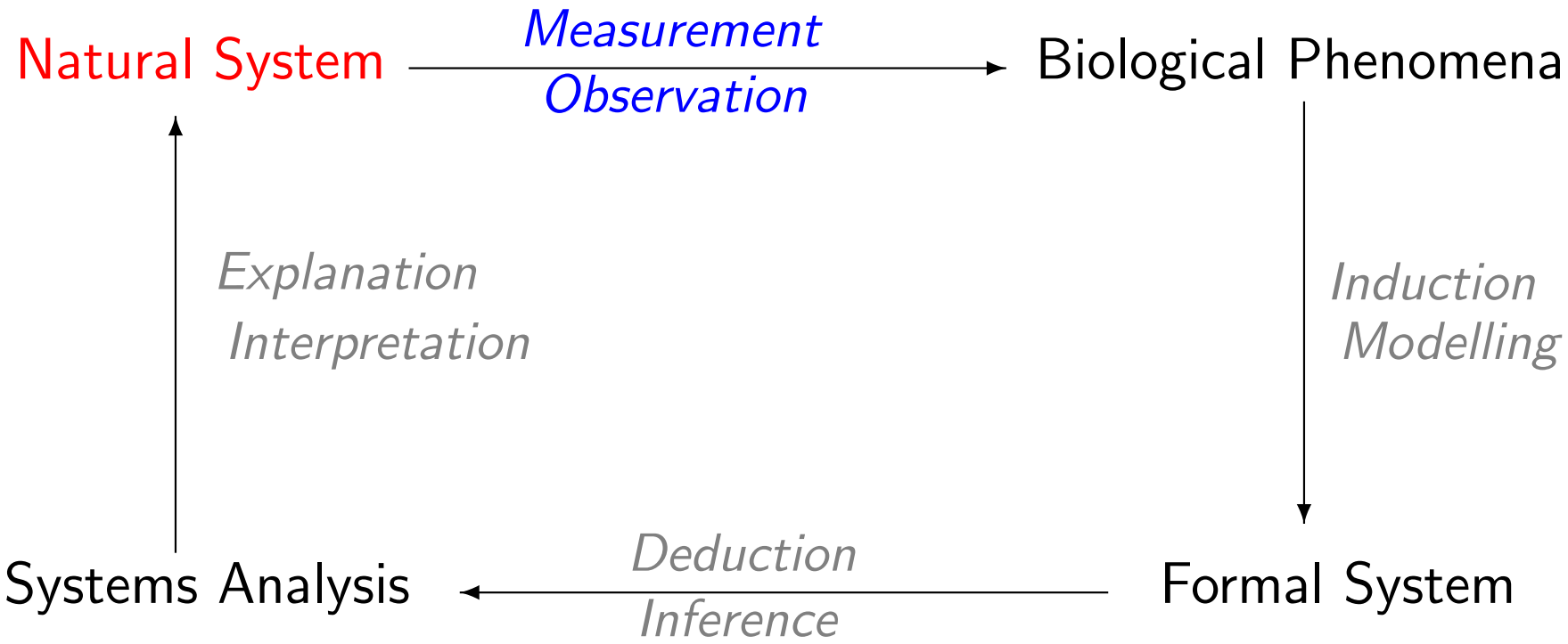

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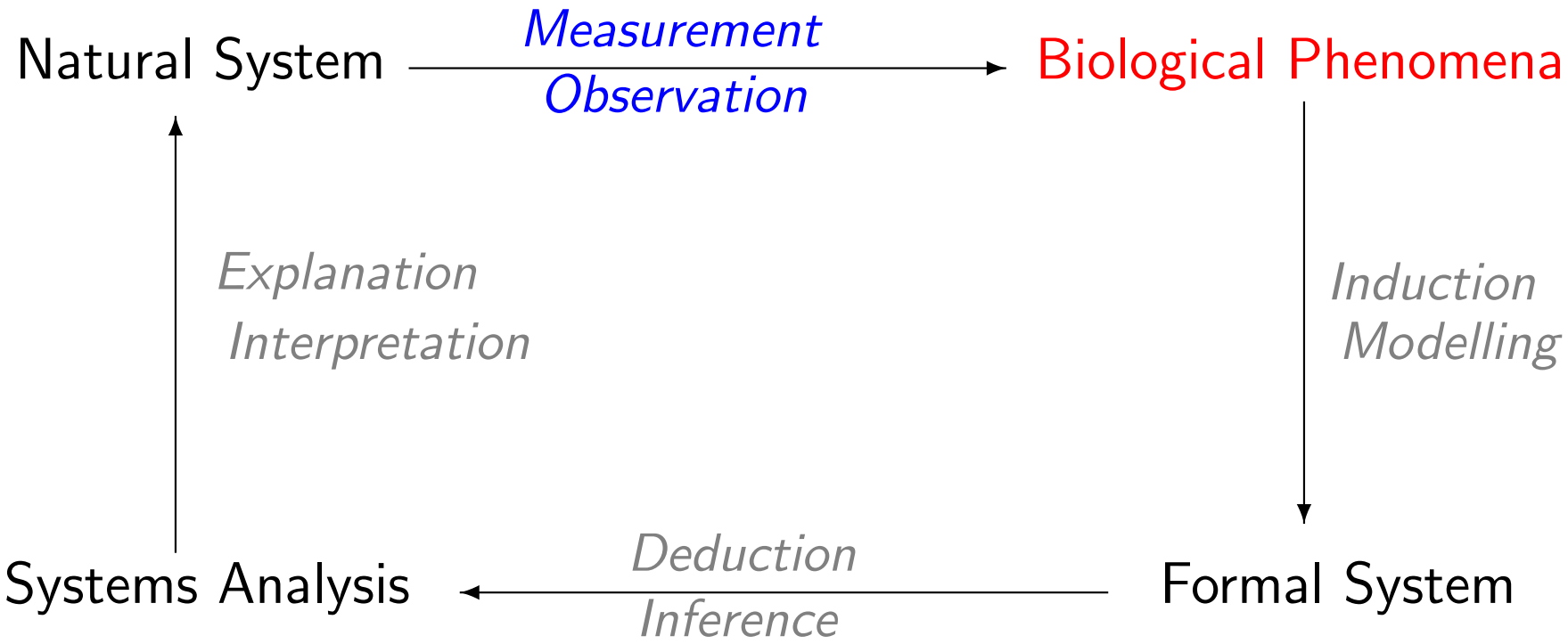

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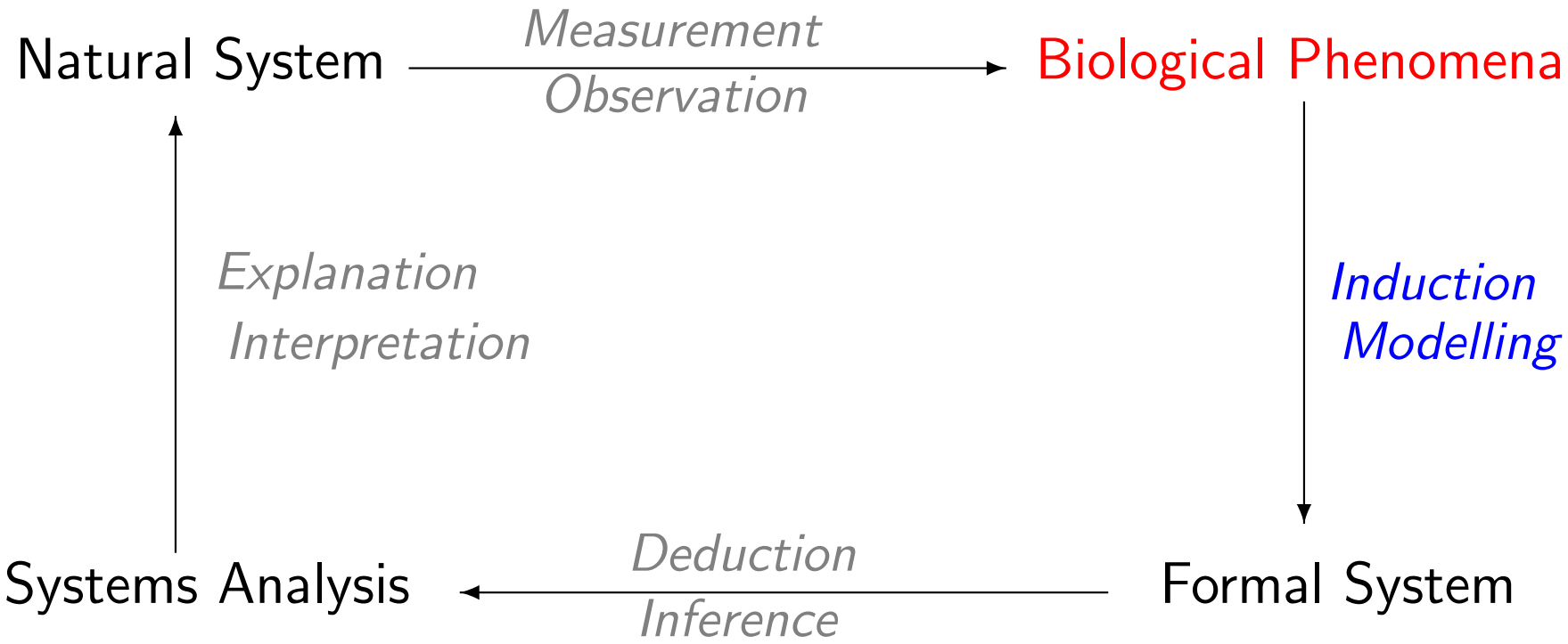

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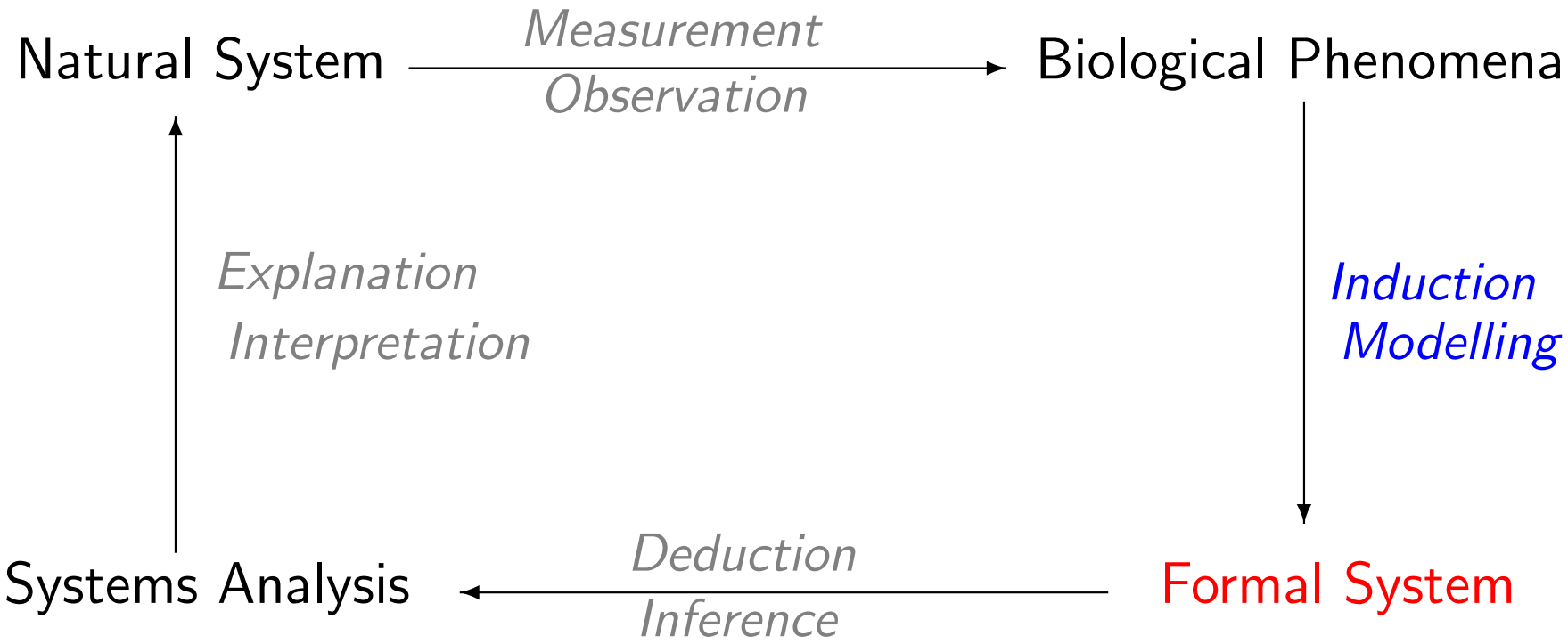

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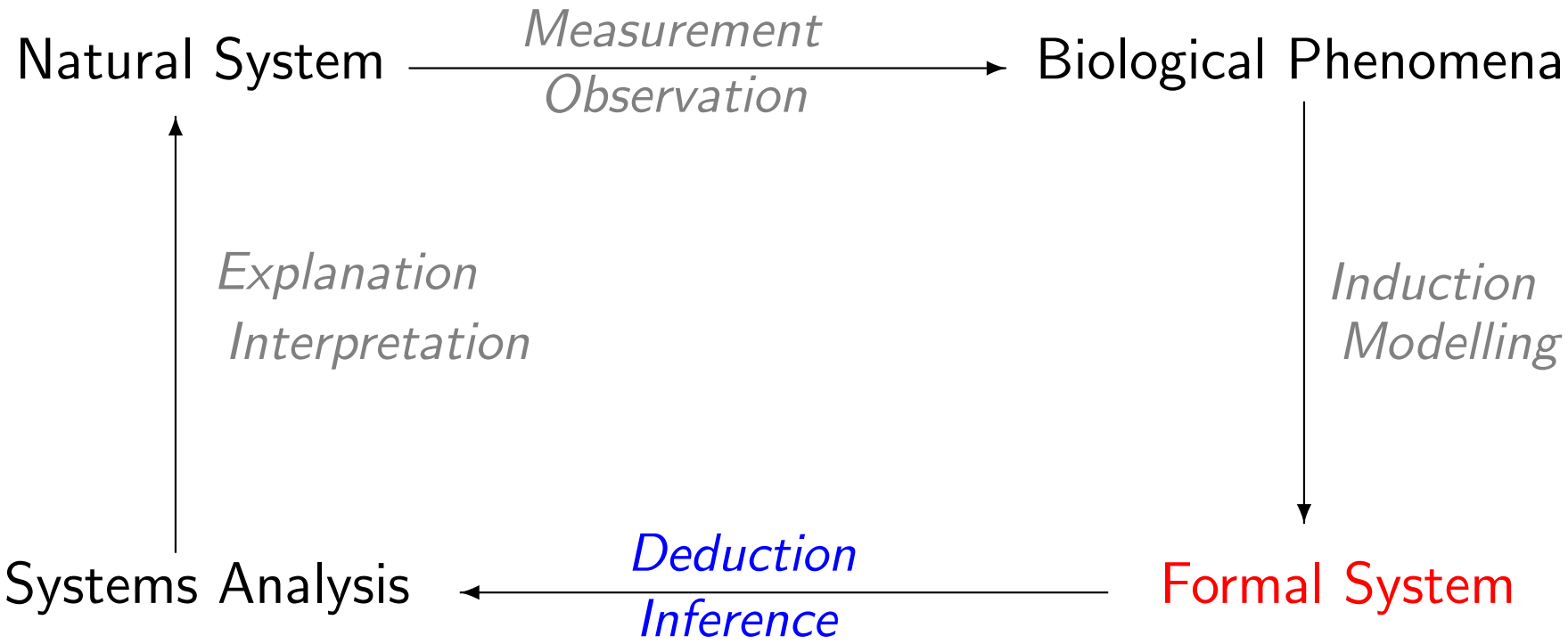

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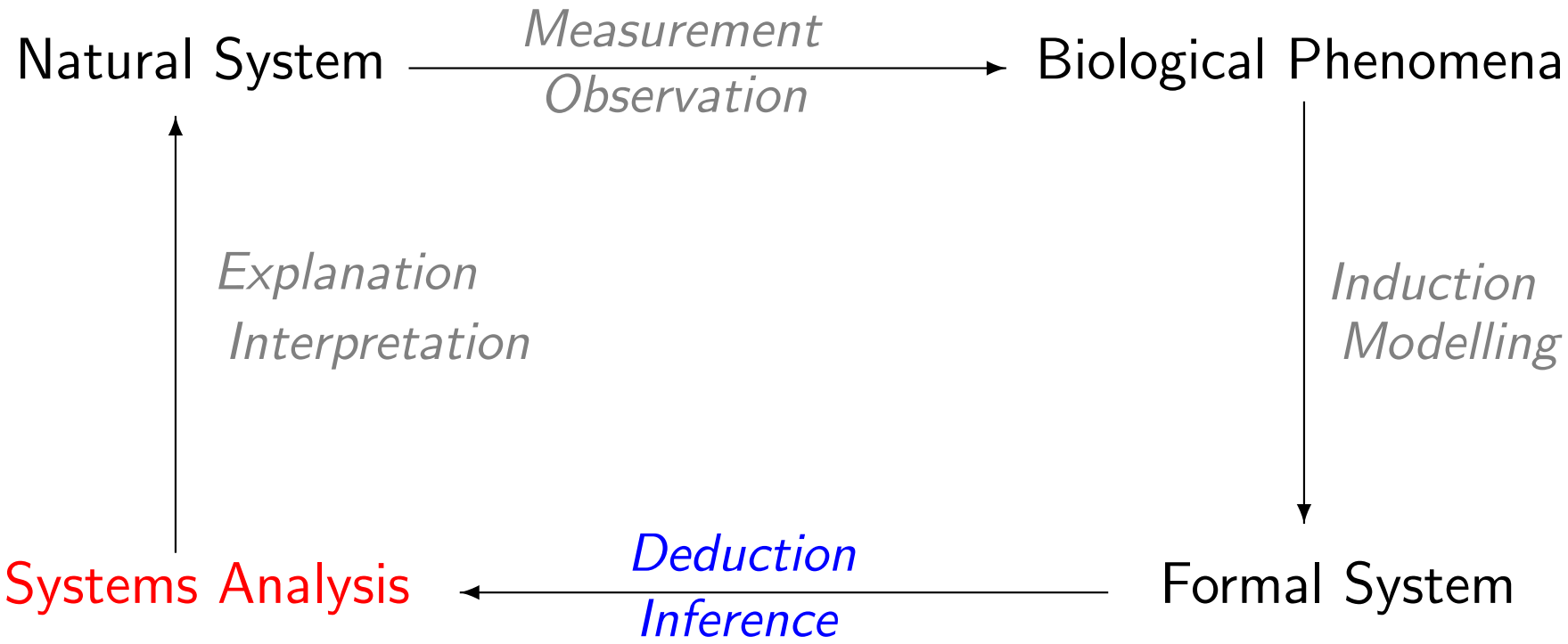

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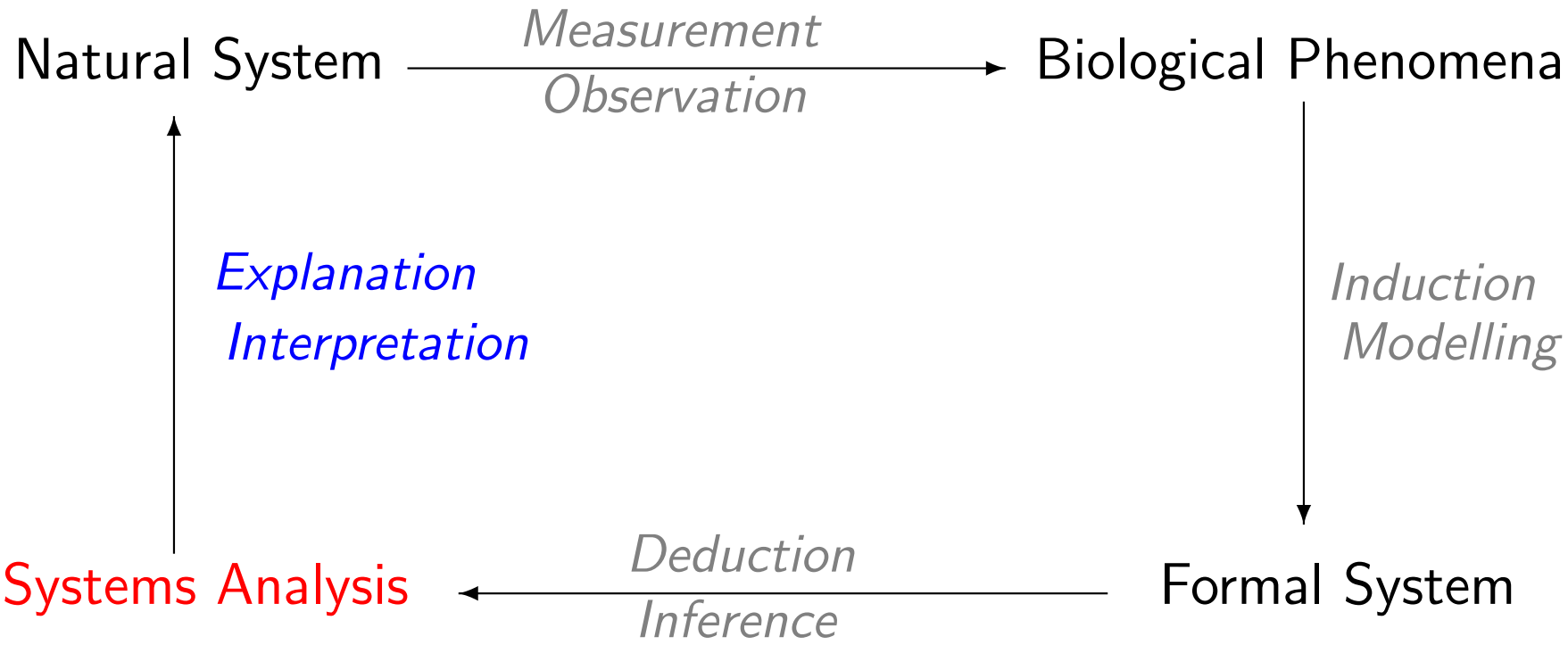

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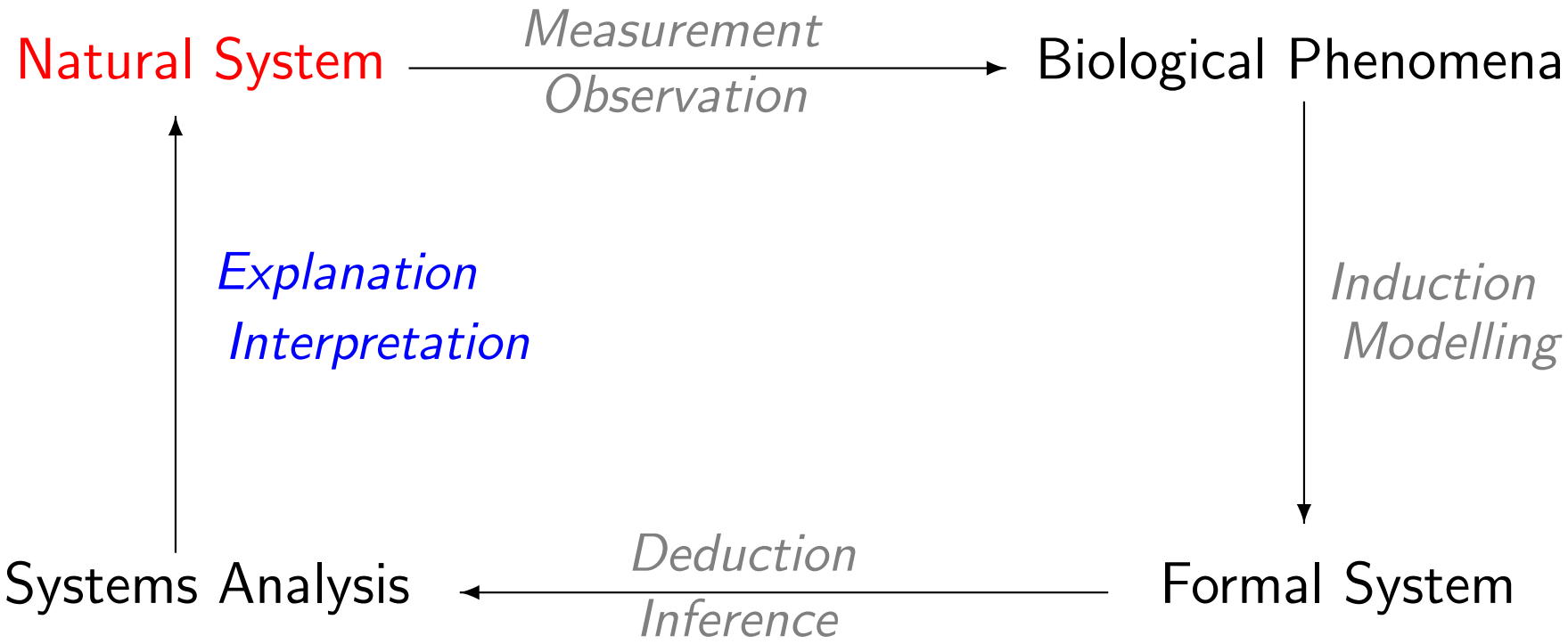

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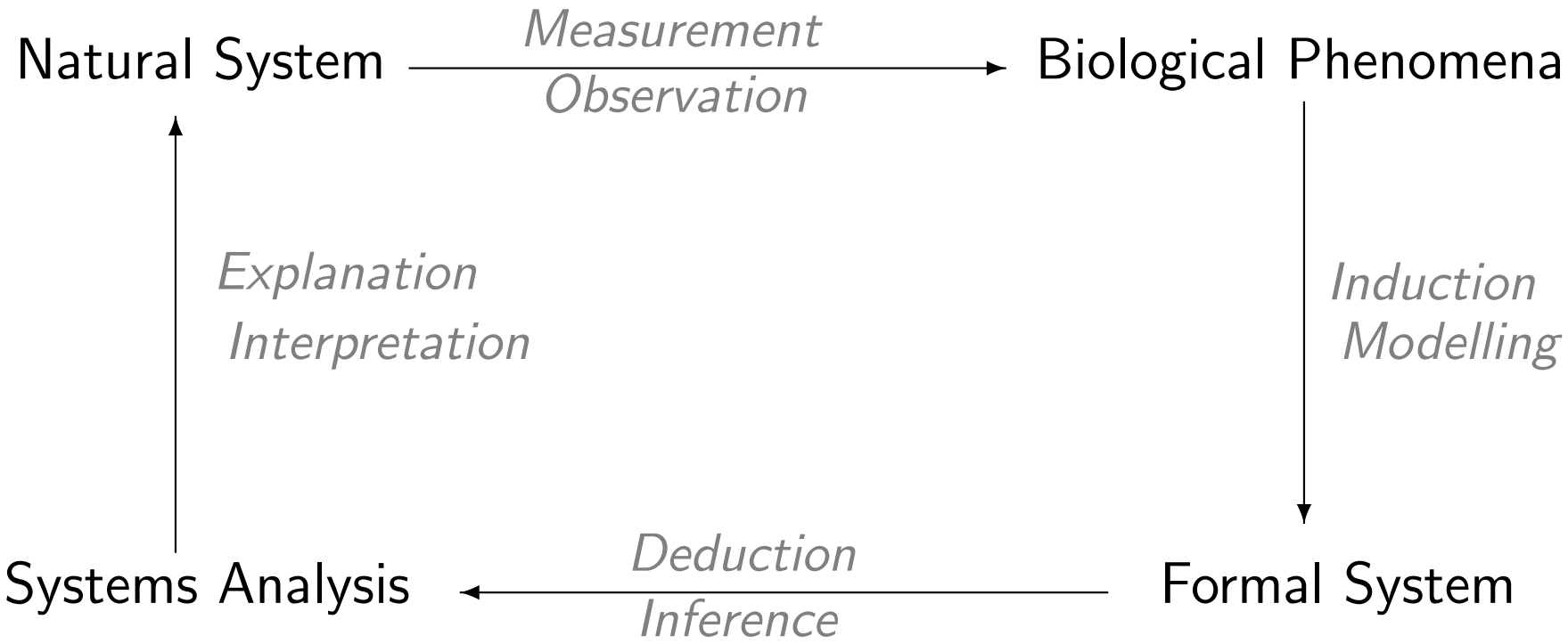

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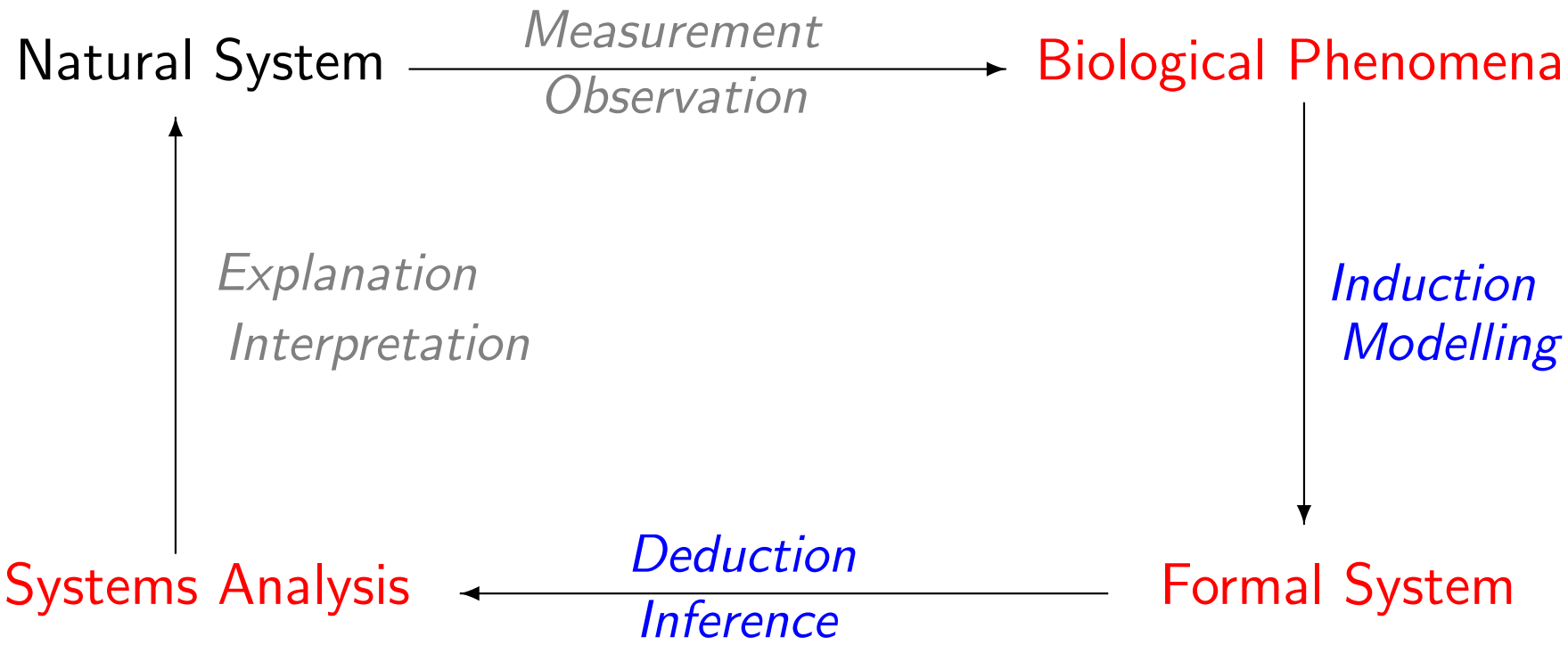

Signal transduction pathways

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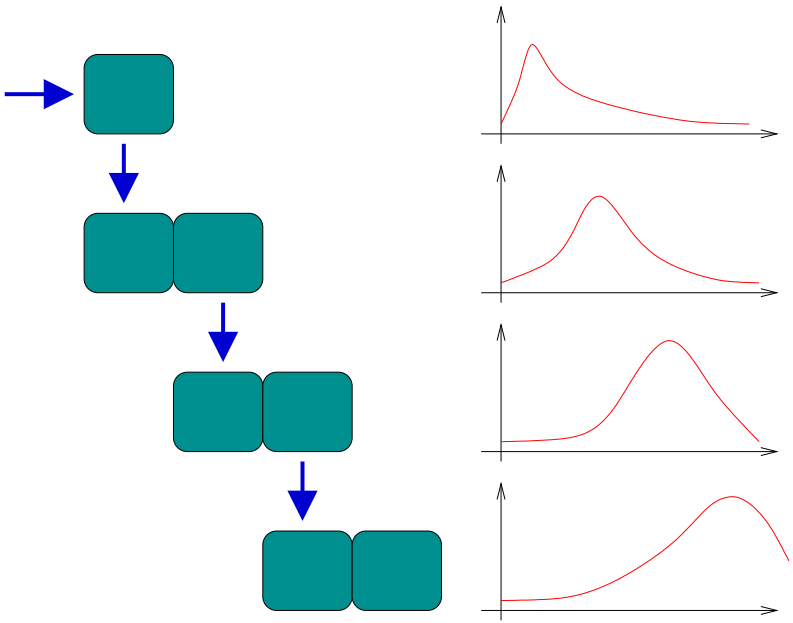

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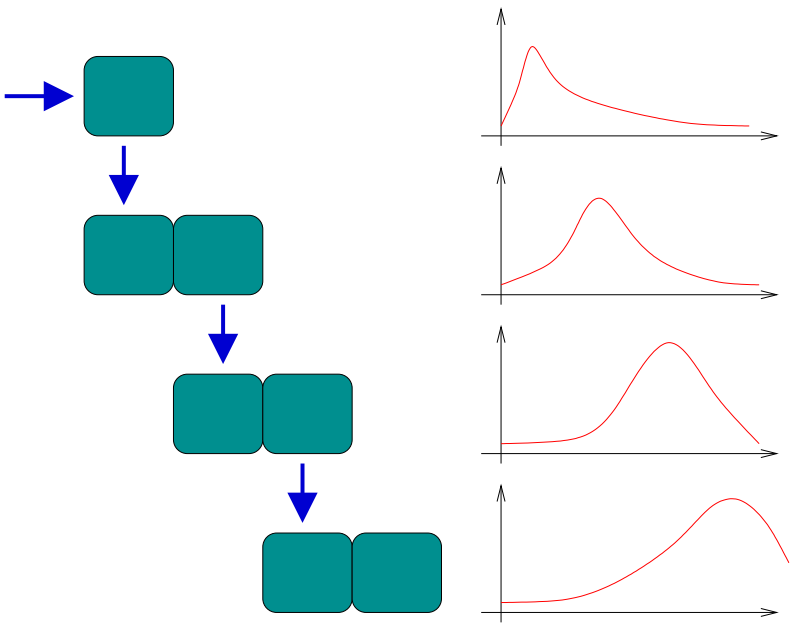

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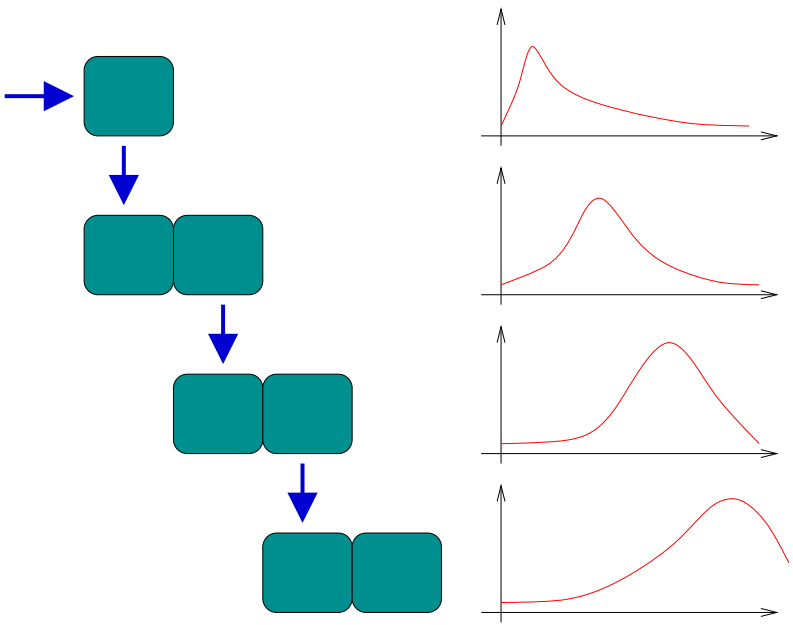

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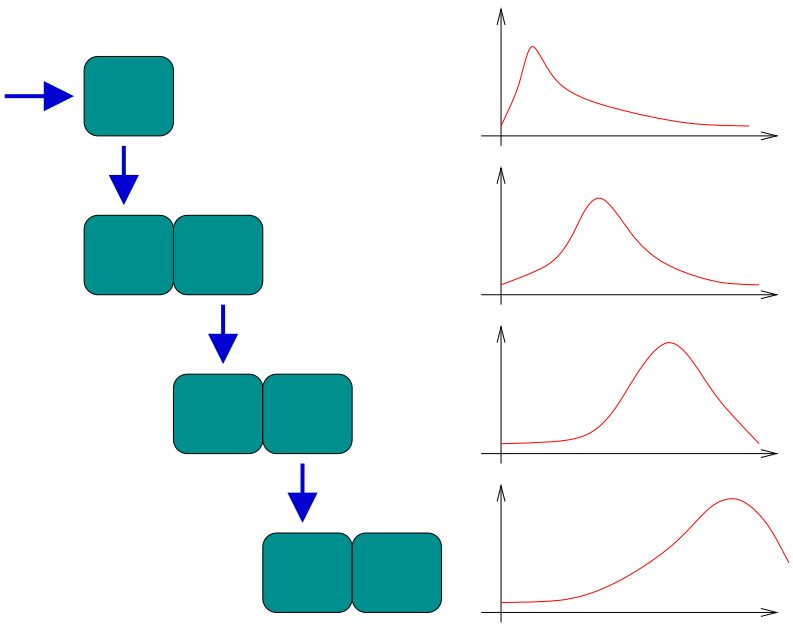

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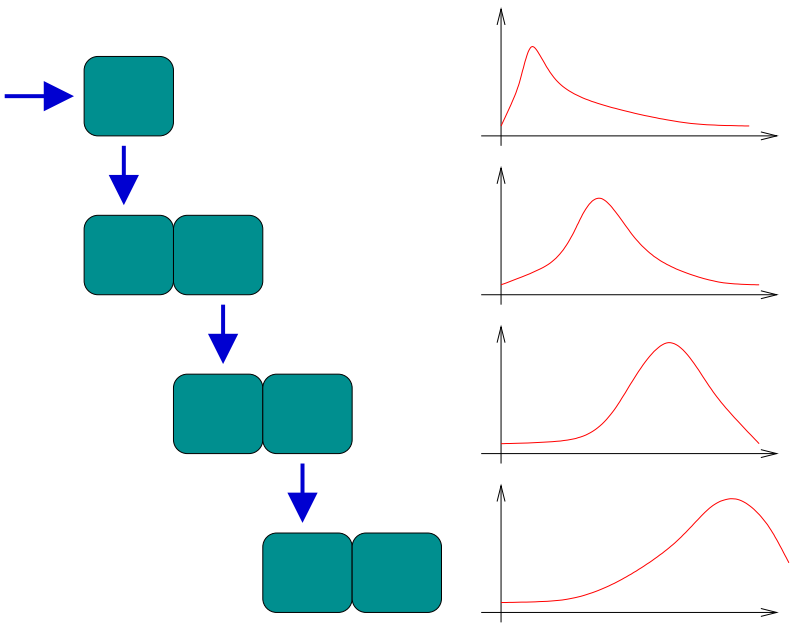
- Signals propagate through a series of protein accumulations.



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- These data 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.

Formal Systems

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

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For example, for a reaction $A + B \xrightarrow{k} C$, the reaction rate equation is:

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k[A][B]$$

$$\frac{d[C]}{dt} = k[A][B]$$

Limitations of Ordinary Differential Equations

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- This is a simplification, because in reality chemical reactions involve discrete, random collisions between individual molecules.
- As we consider smaller and smaller systems, the validity of a continuous approach becomes ever more tenuous.

Stochastic: Propensity function

As explicitly derived by Gillespie, the stochastic model uses basic Newtonian physics and thermodynamics to arrive at a form often termed the propensity function that gives the probability a_μ of reaction μ occurring in time interval $(t, t + \mathrm{d}t)$.

$$a_\mu \mathrm{d}t = h_\mu c_\mu \mathrm{d}t$$

where the M reaction mechanisms are given an arbitrary index μ $(1 \leq \mu \leq M)$, h_μ denotes the number of possible combinations of reactant molecules involved in reaction μ, and c_μ is a stochastic rate constant.

Stochastic: Chemical Master Equation

Applying this leads us to an important *partial differential equation* (PDE) known as the Chemical Master Equation.

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

Does not lend itself to either analytic nor numerical solutions.

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(Chapman-Kolmogorov equations of the CTMC)

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As with the chemical master equation, the SSA converges, in the limit of large numbers of reactants, to the same solution as the law of mass action.

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- Previous experience in the performance arena has shown us that there can be benefits to interposing a formal model between the system and the underlying mathematical model.
- Moreover taking this "high-level programming" style approach offers the possibility of different "compilations" to different mathematical models.

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Using Stochastic Process Algebras

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- Structure can also be apparent.
- Equivalence relations allow formal comparison of high-level descriptions.
- There are well-established techniques for reasoning about the behaviours and properties of models, supported by software. These include qualitative and quantitative analysis, and model checking.

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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Alternative mappings from the process algebra to underlying mathematics are then readily available.

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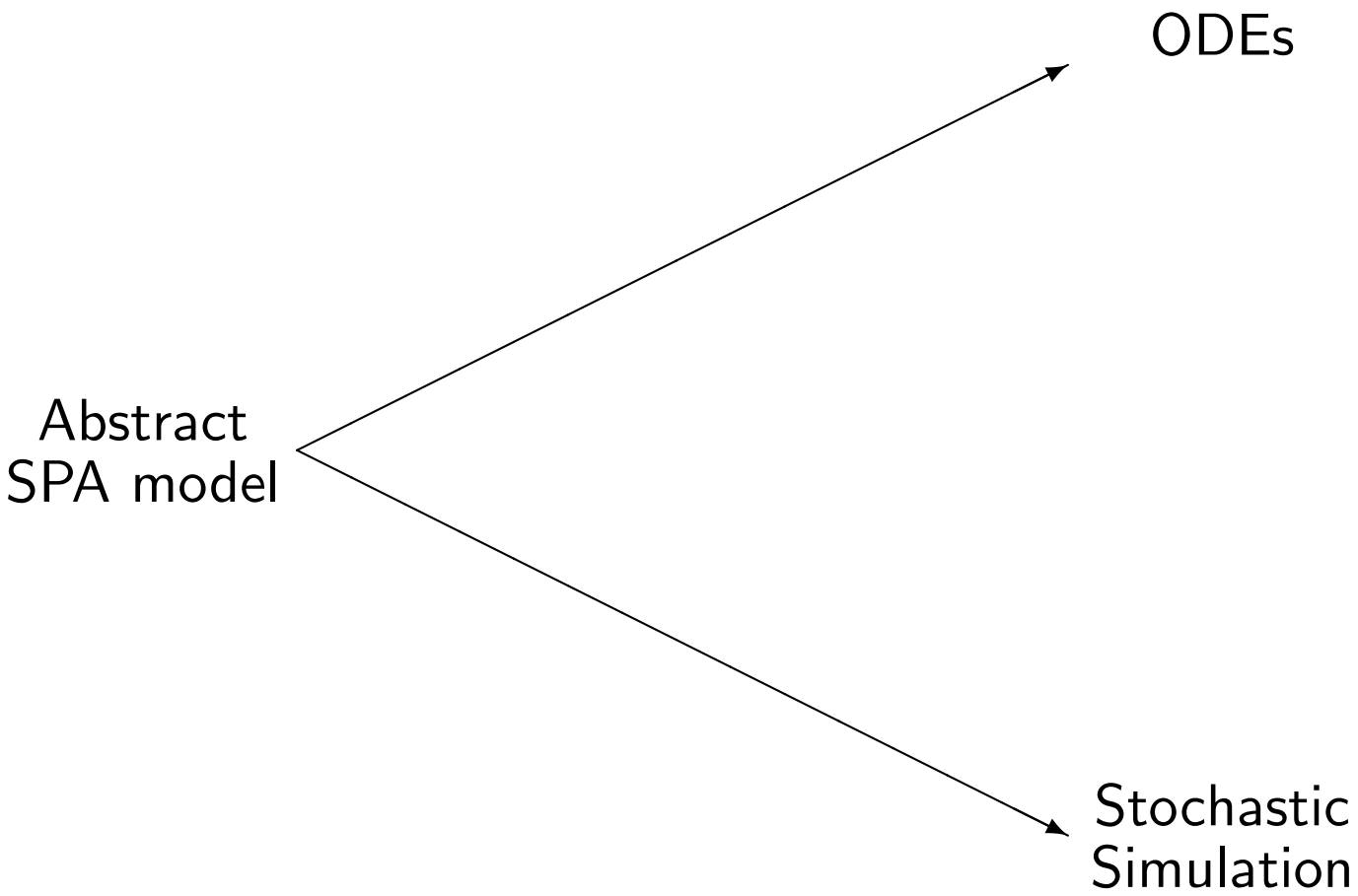

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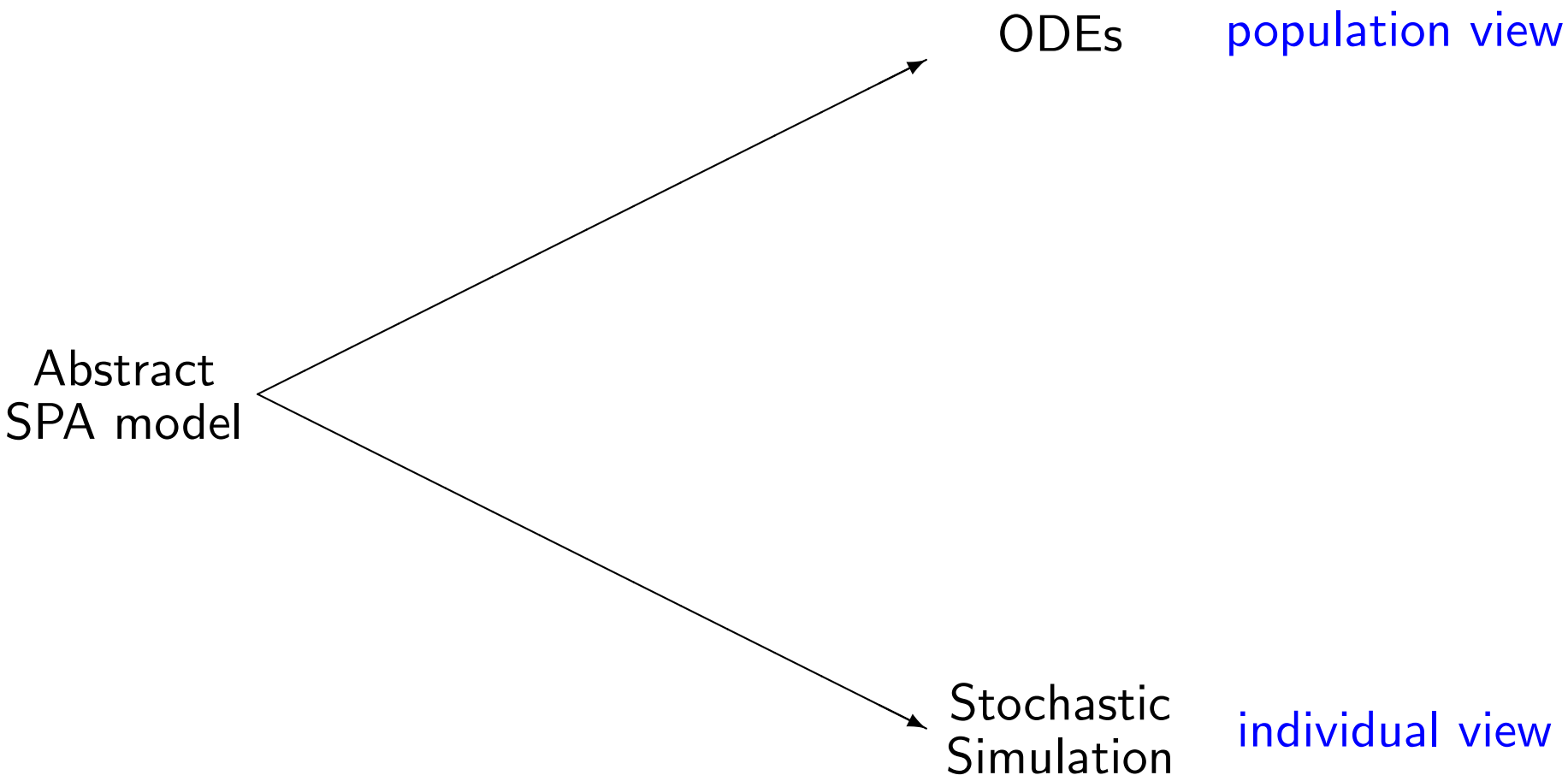

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- The data that we have available to parameterise models is sometimes speculative rather than precise. This suggests that it can be useful to use semiquantitative models rather than quantitative ones.

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.

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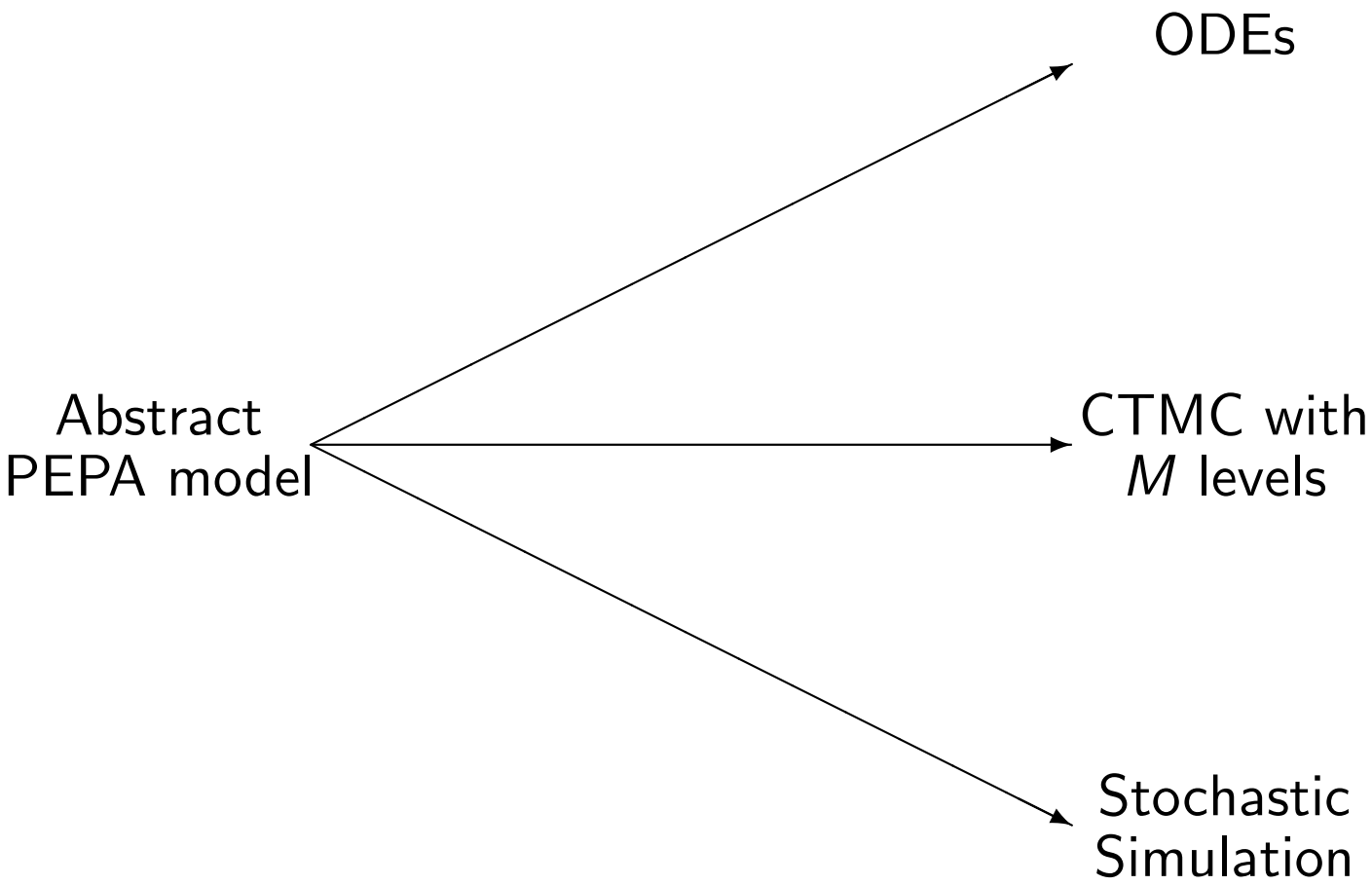

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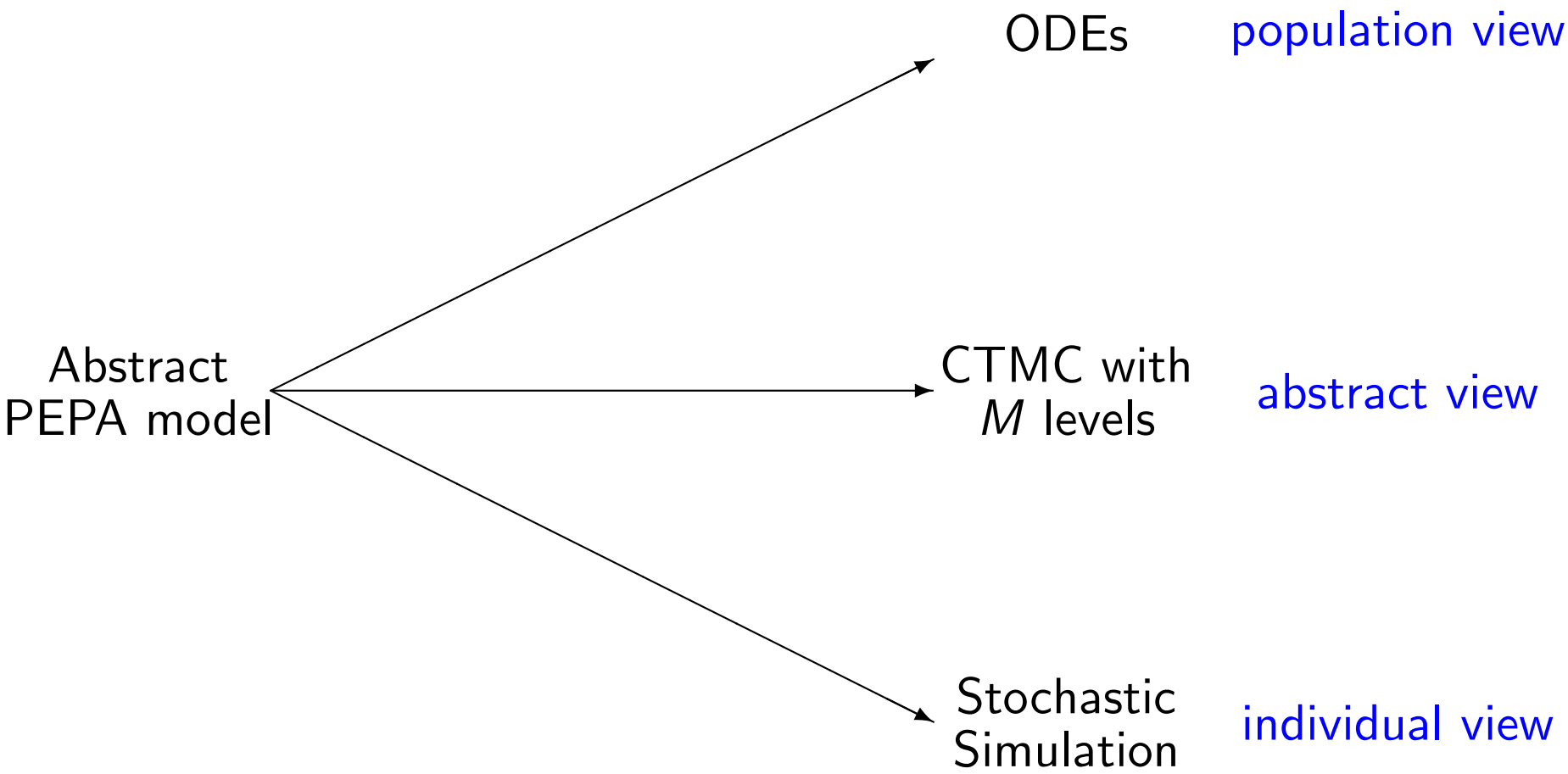

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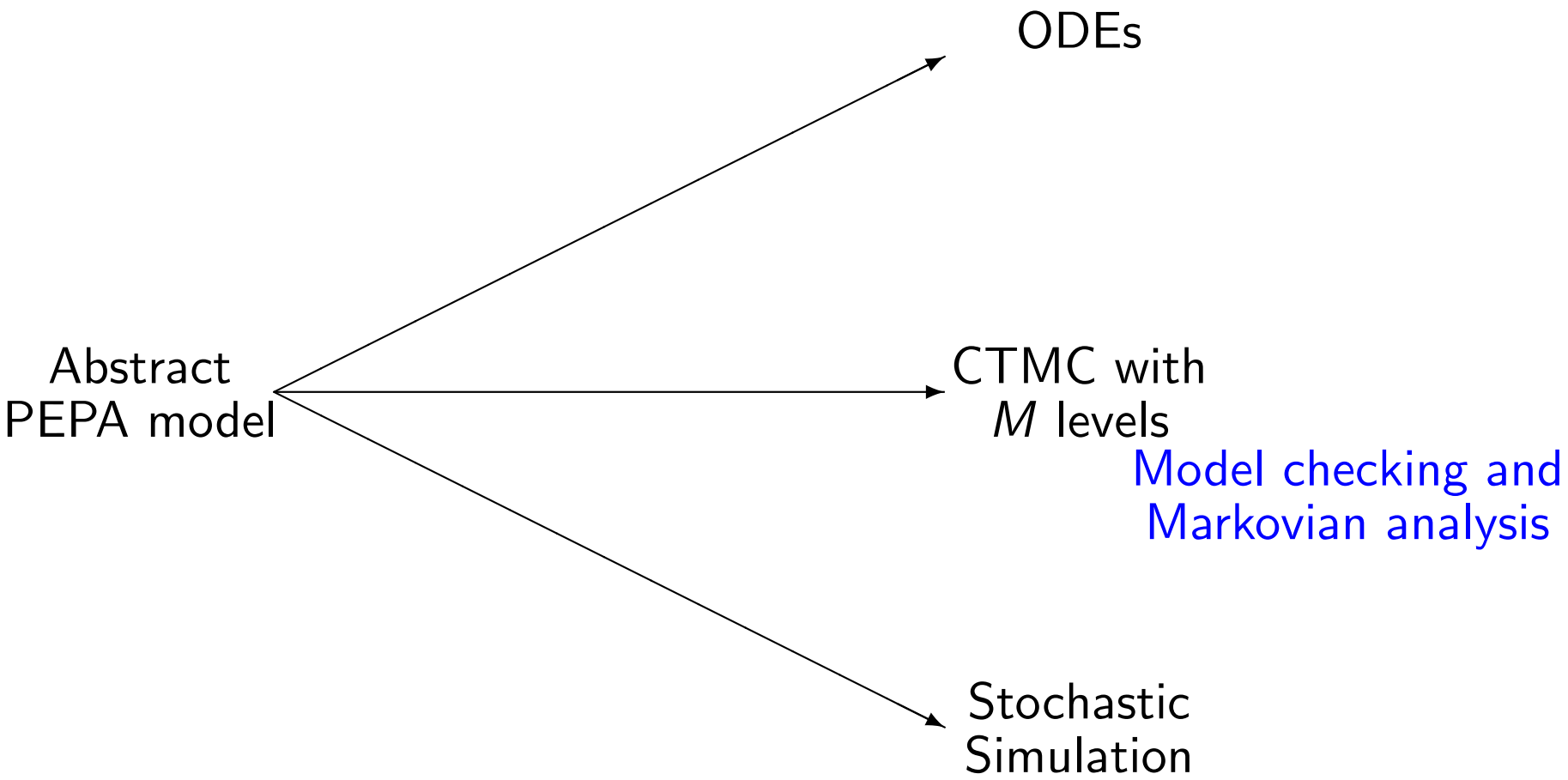

PEPA: Performance Evaluation Process Algebra

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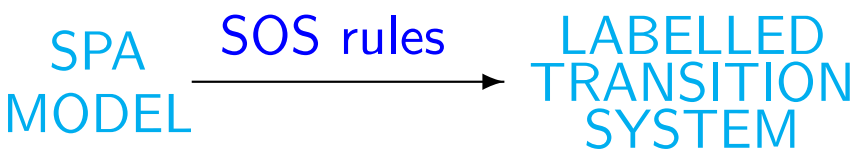

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SPA MODEL $\xrightarrow[\text{analysis}]{\text{syntactic}}$ RATE EQUATIONS $\xrightarrow[\text{algorithm}]{\text{Gillespie's}}$ STOCHASTIC SIMULATION

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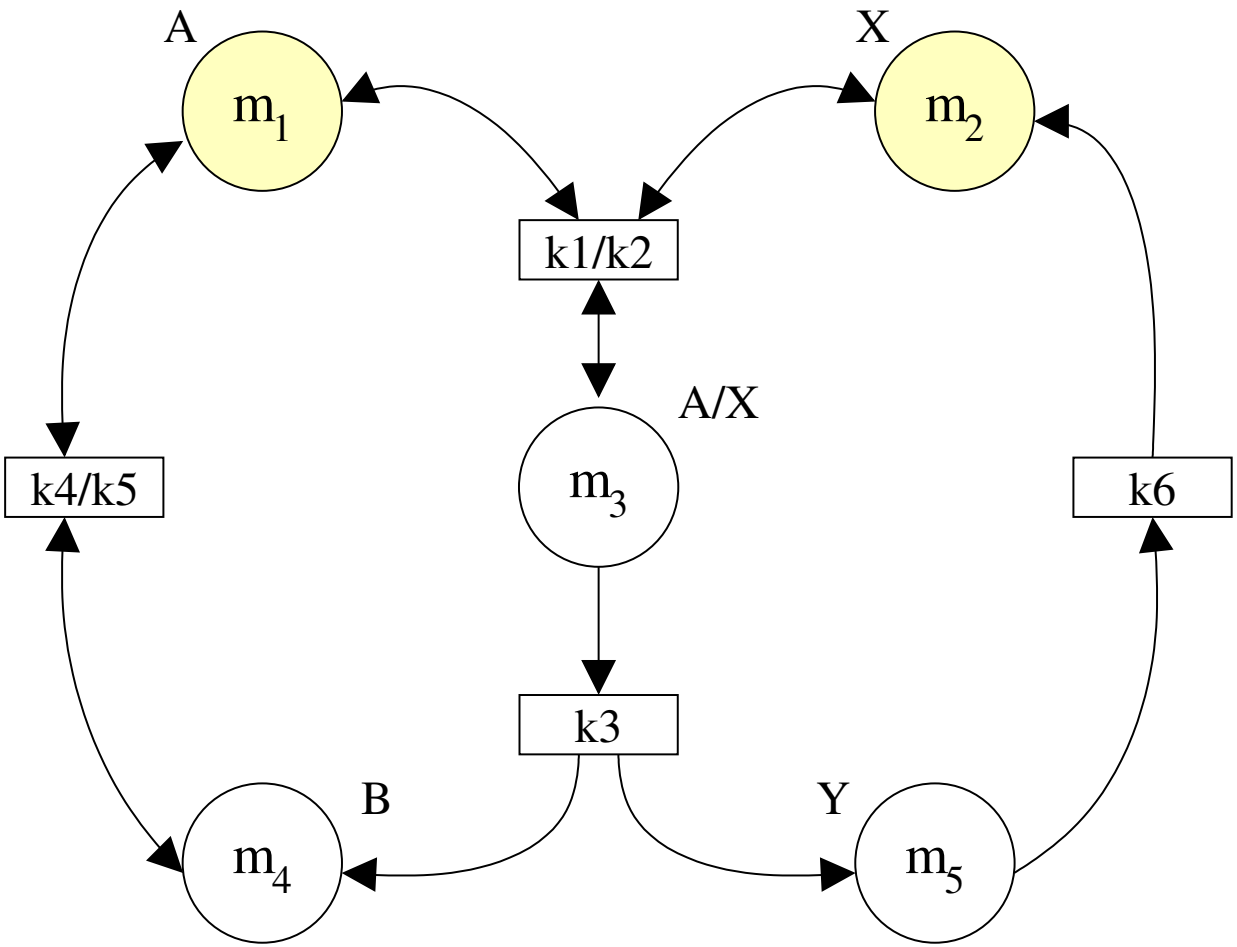
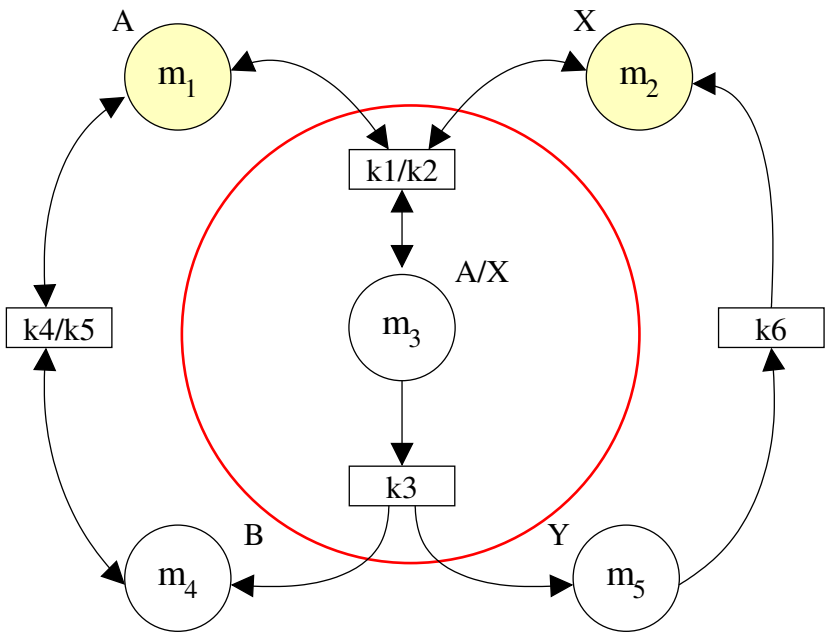
Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.

Small synthetic example network



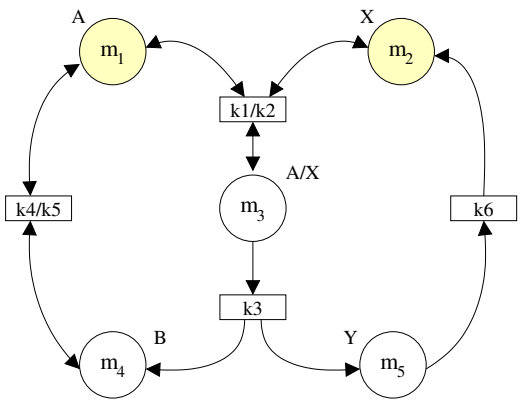
Small synthetic example network in PEPA (1)



$$A/X_H \stackrel{def}{=} (k2react, k2).A/X_L + (k3react, k3).A/X_L$$

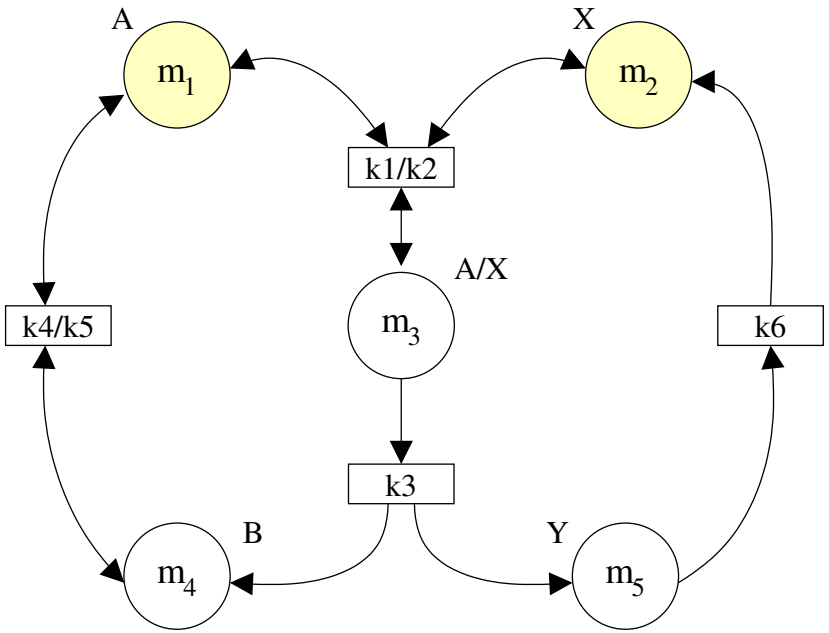
$$A/X_L \stackrel{def}{=} (k1react, k1).A/X_H$$

Small synthetic example network in PEPA (2)



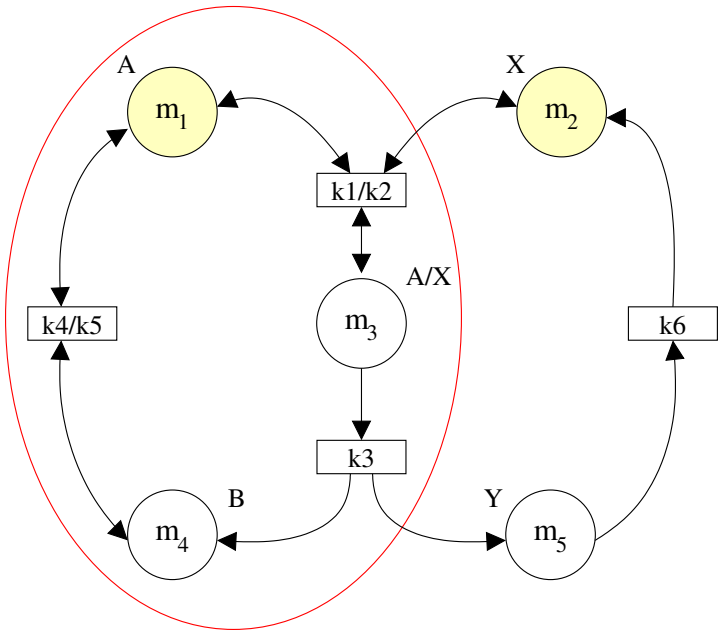
$$
\begin{aligned}
A_H &\stackrel{def}{=} (k1react, k1).A_L + (k5react, k5).A_L \\
A_L &\stackrel{def}{=} (k2react, k2).A_H + (k4react, k4).A_H \\
X_H &\stackrel{def}{=} (k1react, k1).X_L \\
X_L &\stackrel{def}{=} (k2react, k2).X_H + (k6react, k6).X_H \\
A/X_H &\stackrel{def}{=} (k2react, k2).A/X_L + (k3react, k3).A/X_L \\
A/X_L &\stackrel{def}{=} (k1react, k1).A/X_H \\
B_H &\stackrel{def}{=} (k4react, k4).B_L \\
B_L &\stackrel{def}{=} (k5react, k5).B_H + (k3react, k3).B_H \\
Y_H &\stackrel{def}{=} (k6react, k6).Y_L \\
Y_L &\stackrel{def}{=} (k3react, k3).Y_H
\end{aligned}
$$

Small synthetic example network in PEPA (3)



$$(((A_H \underset{\{k1react,k2react\}}{\bowtie} X_H) \underset{\{k1react,k2react\}}{\bowtie} A/X_L) \underset{\{k3react,k4react,k5react\}}{\bowtie} B_L) \underset{\{k3react,k6react\}}{\bowtie} Y_L$$

Small synthetic example network in PEPA (4)



$$PathwayA_1 \stackrel{def}{=} (k1react, k1).PathwayA_2 + (k5react, k5).PathwayA_3$$

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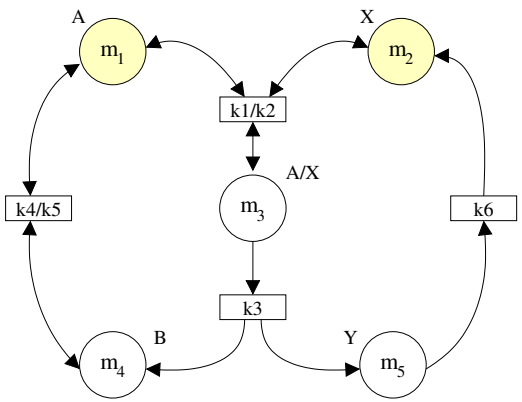
Small synthetic example network in PEPA (5)



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\begin{aligned}
PathwayA_1 &\stackrel{def}{=} (k1react, k1).PathwayA_2 \\
&\quad + (k5react, k5).PathwayA_3 \\
PathwayA_2 &\stackrel{def}{=} (k2react, k2).PathwayA_1 \\
&\quad + (k3react, k3).PathwayA_3 \\
PathwayA_3 &\stackrel{def}{=} (k4react, k4).PathwayA_1 \\
PathwayX_1 &\stackrel{def}{=} (k1react, k1).PathwayX_2 \\
PathwayX_2 &\stackrel{def}{=} (k2react, k2).PathwayX_1 \\
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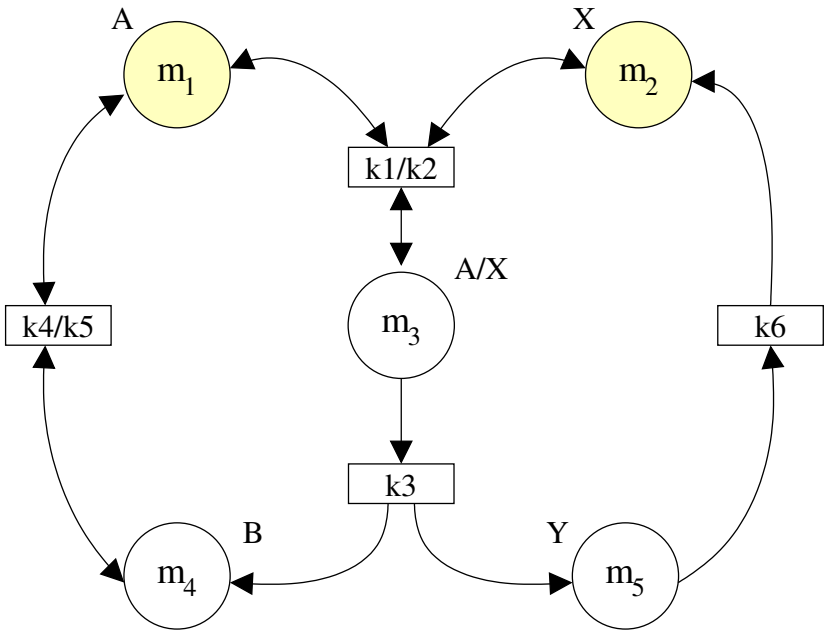
\end{aligned}
$$

Small synthetic example network in PEPA (6)



$$PathwayA_1 \underset{\{k1react, k2react, k3react\}}{\bowtie} PathwayX_1$$

State spaces

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the reactant-based model of A becomes:

$$\begin{aligned} A_2 &\stackrel{def}{=} (k1react, 2 \times k1).A_1 + (k5react, 2 \times k5).A_1 \\ A_1 &\stackrel{def}{=} (k1react, k1).A_0 + (k5react, k5).A_0 \\ &\quad + (k2react, k2).A_2 + (k4react, k4).A_2 \\ A_0 &\stackrel{def}{=} (k2react, 2 \times k2).A_1 + (k4react, 2 \times k4).A_1 \end{aligned}$$

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the configuration of the pathway model becomes:

$$(PathwayA_1 \parallel PathwayA_1) \underset{\{k1react, k2react, k3react\}}{\bowtie} (PathwayX_1 \parallel PathwayX_1)$$

Markovian analysis

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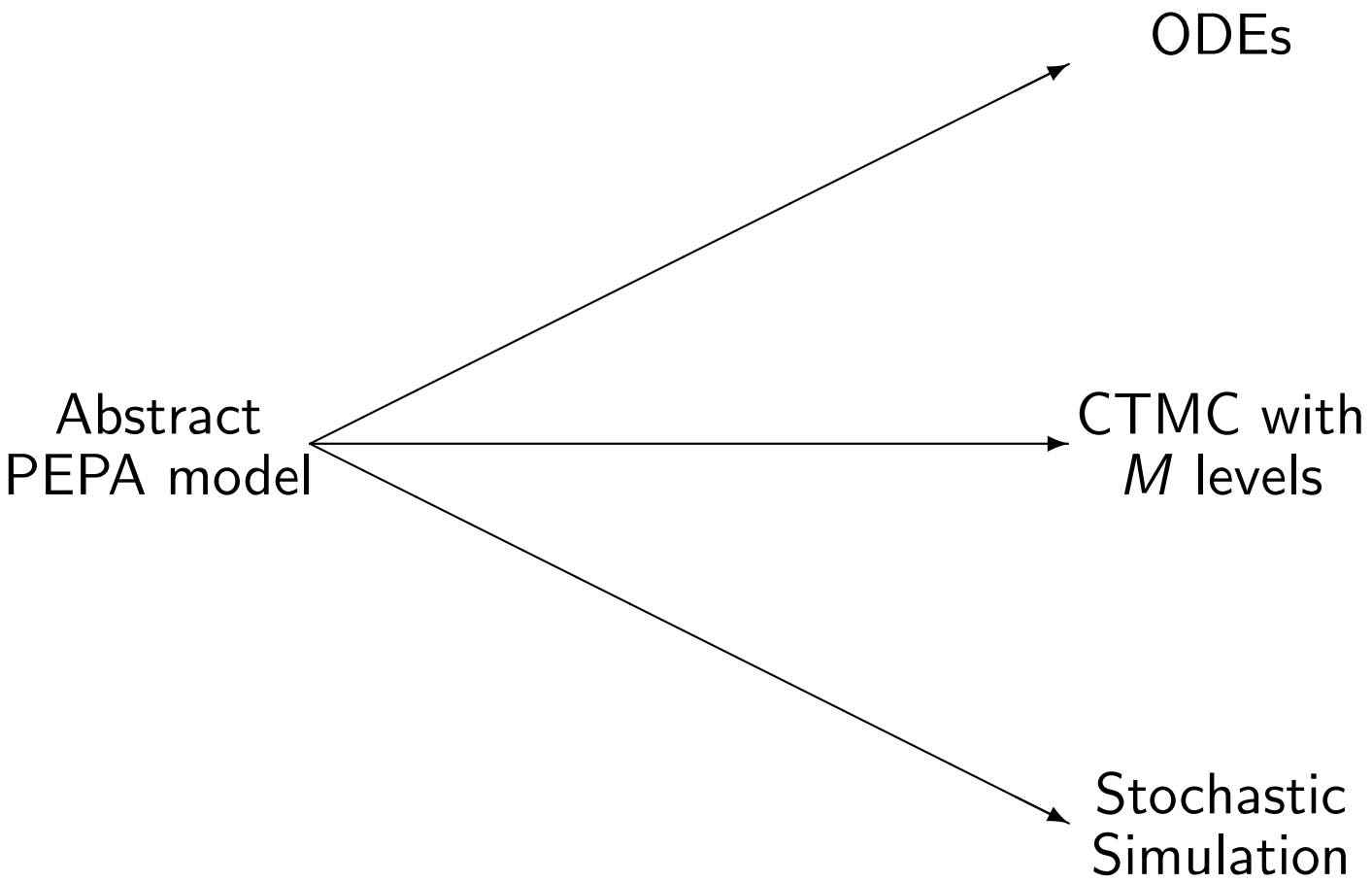
- Stochastic model checking is available via the PRISM model checker, assessing the probable validity of properties expressed in CSL (Continuous Stochastic Logic).

Equivalent Representations?



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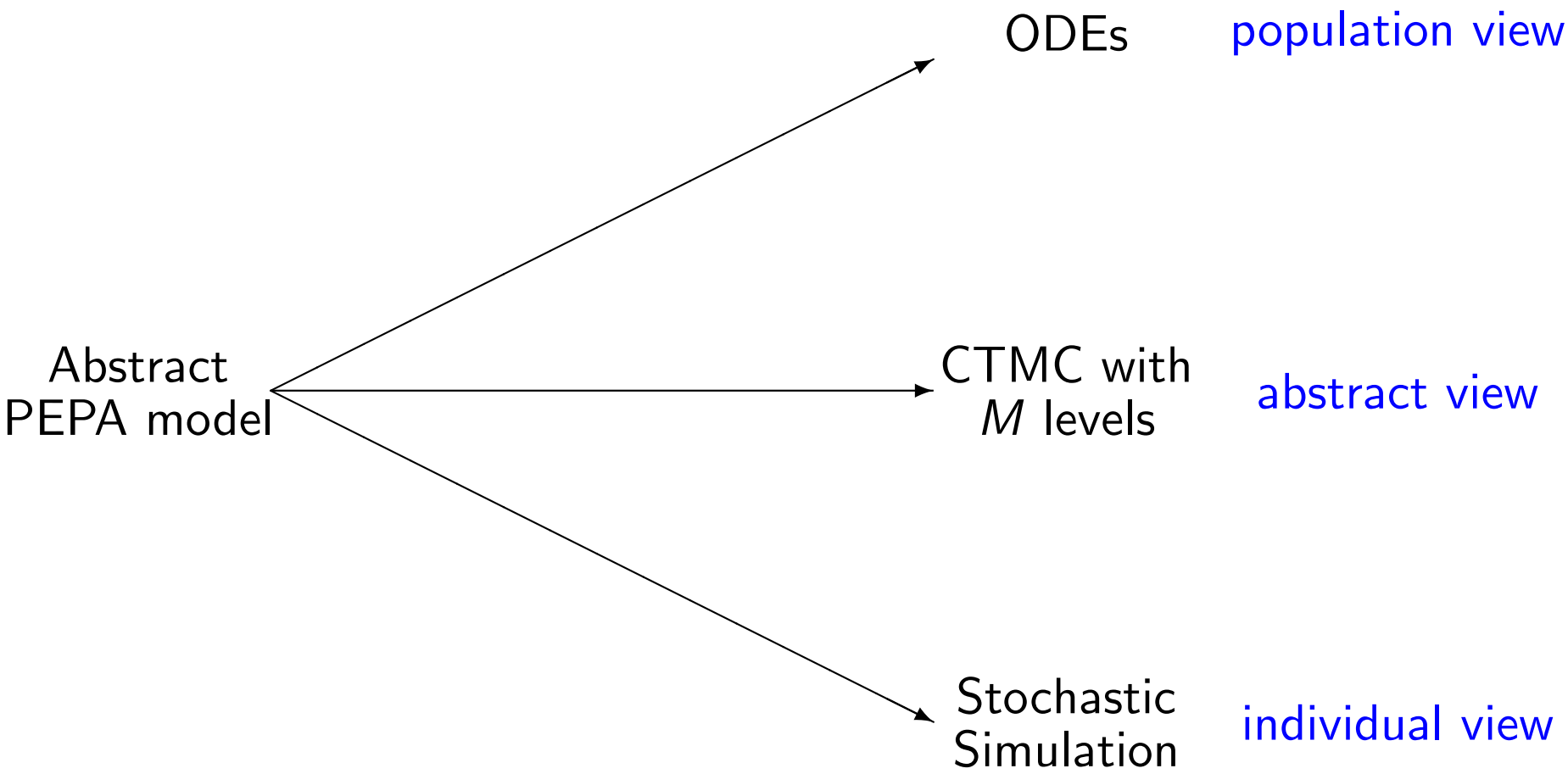

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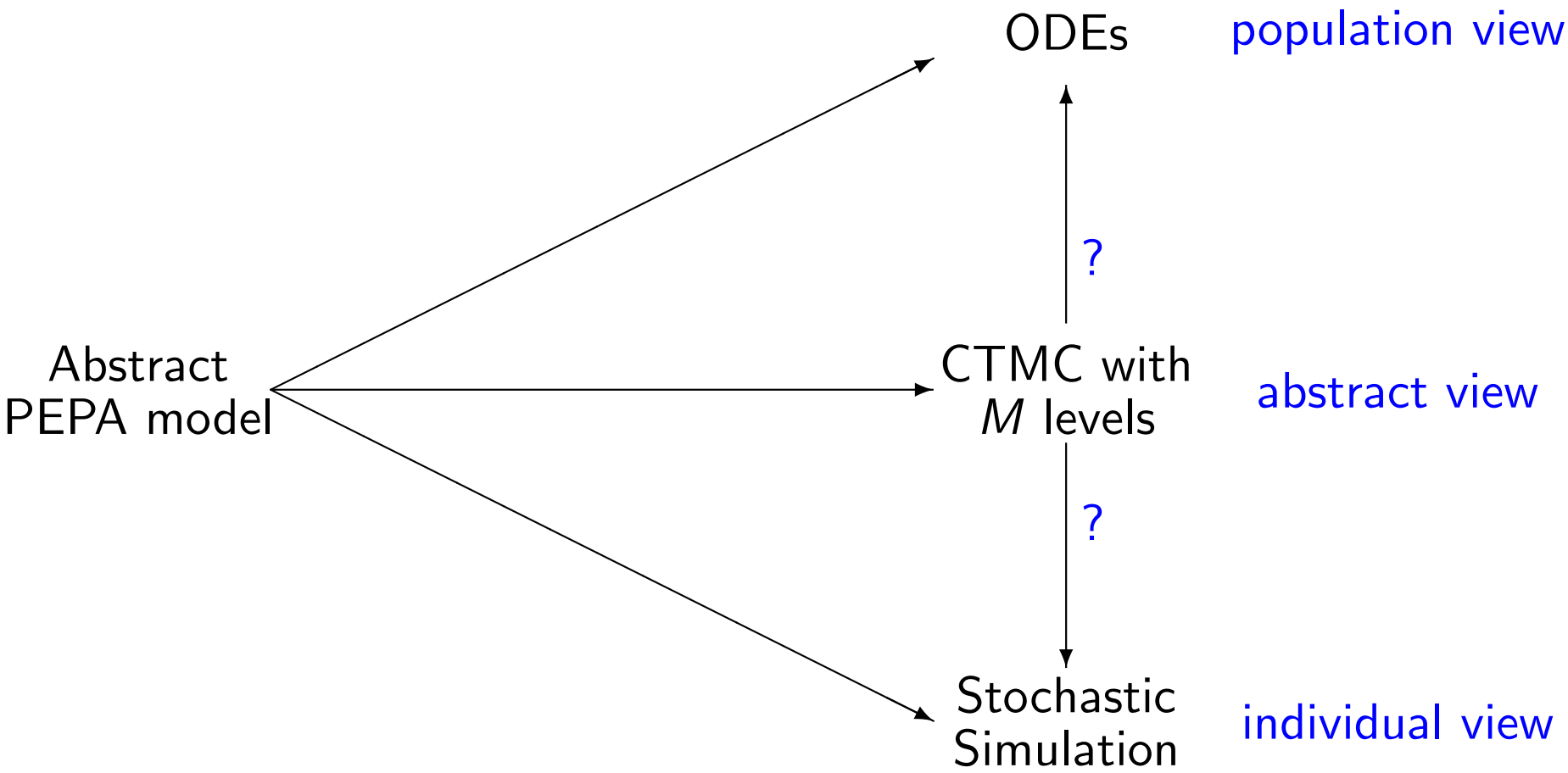

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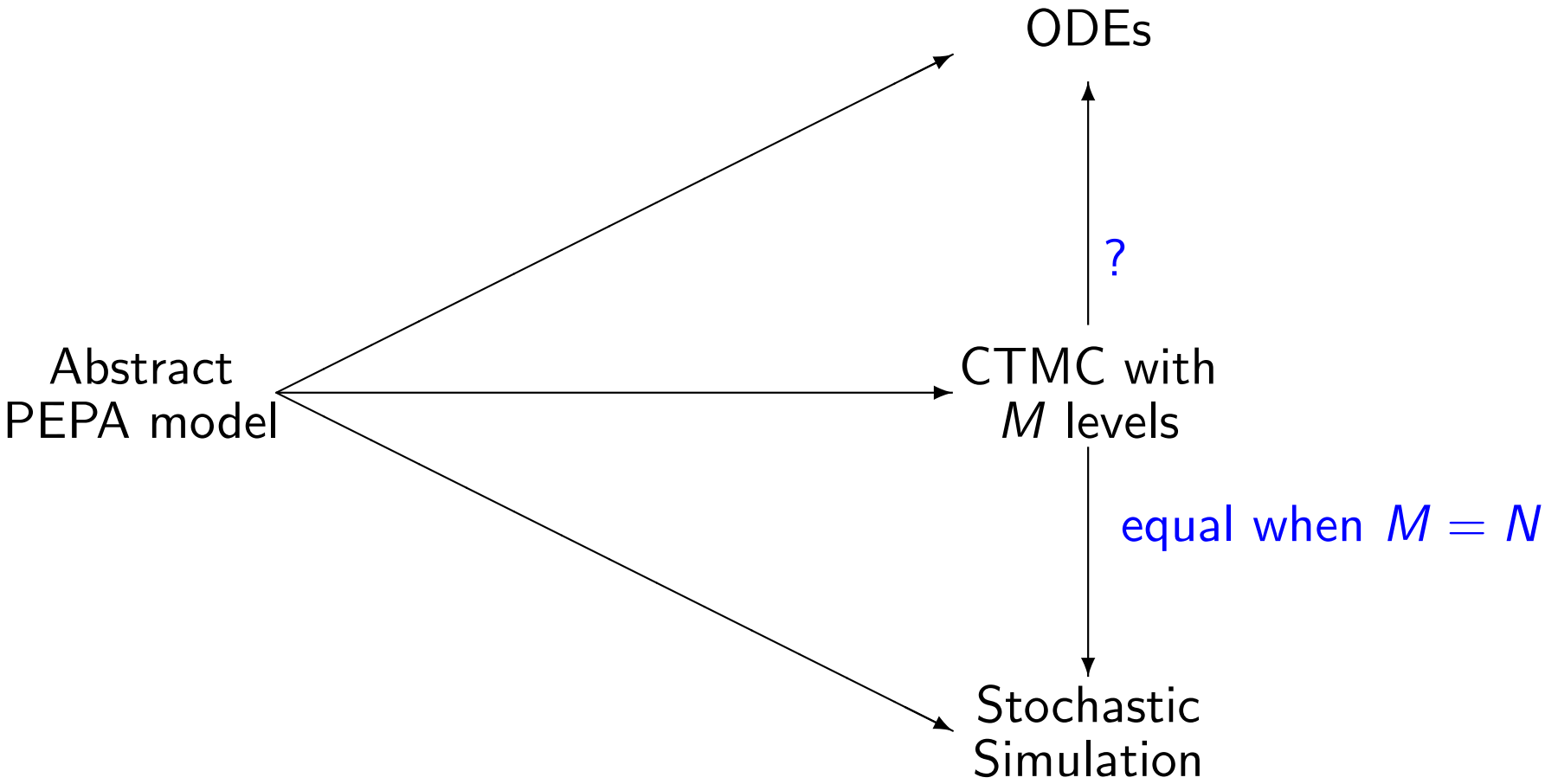

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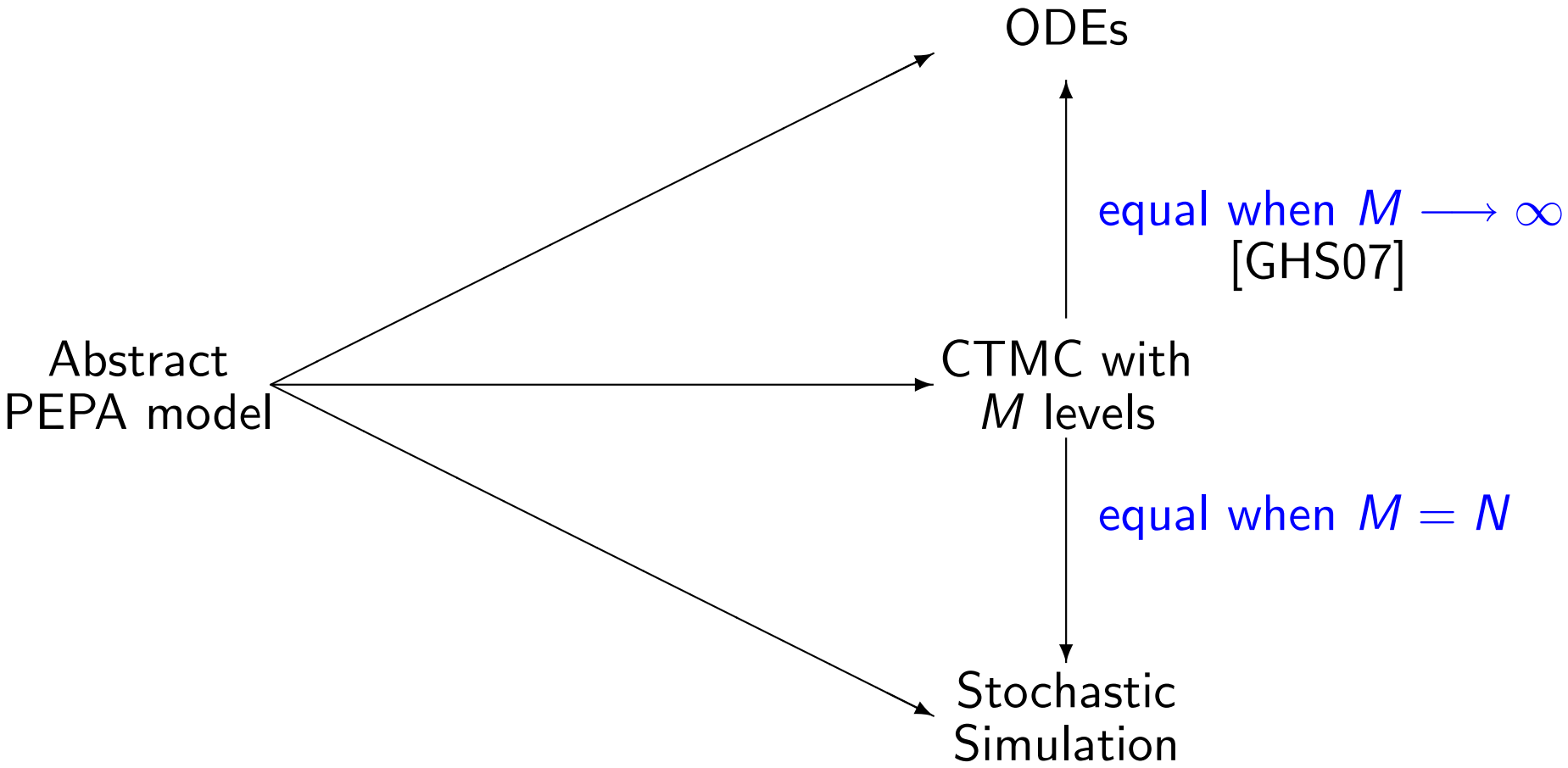

Relating CTMC and ODE models

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- We show that the CTMCs we construct from the PEPA models are density dependent and so satisfy Kurtz's theorem.
- Moreover the ODEs which we arrive at in the limit are identical to the ODEs derived syntactically from the PEPA model.

Density Dependent CTMC

A family of CTMCs is called density dependent if and only if there exists a continuous function $f(x, l), x \in \mathbb{R}^h, l \in \mathbb{Z}^h$, such that the infinitesimal generators of X_N are given by:

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- $q_{k,k+1}$ denotes an entry in the infinitesimal generator matrix;
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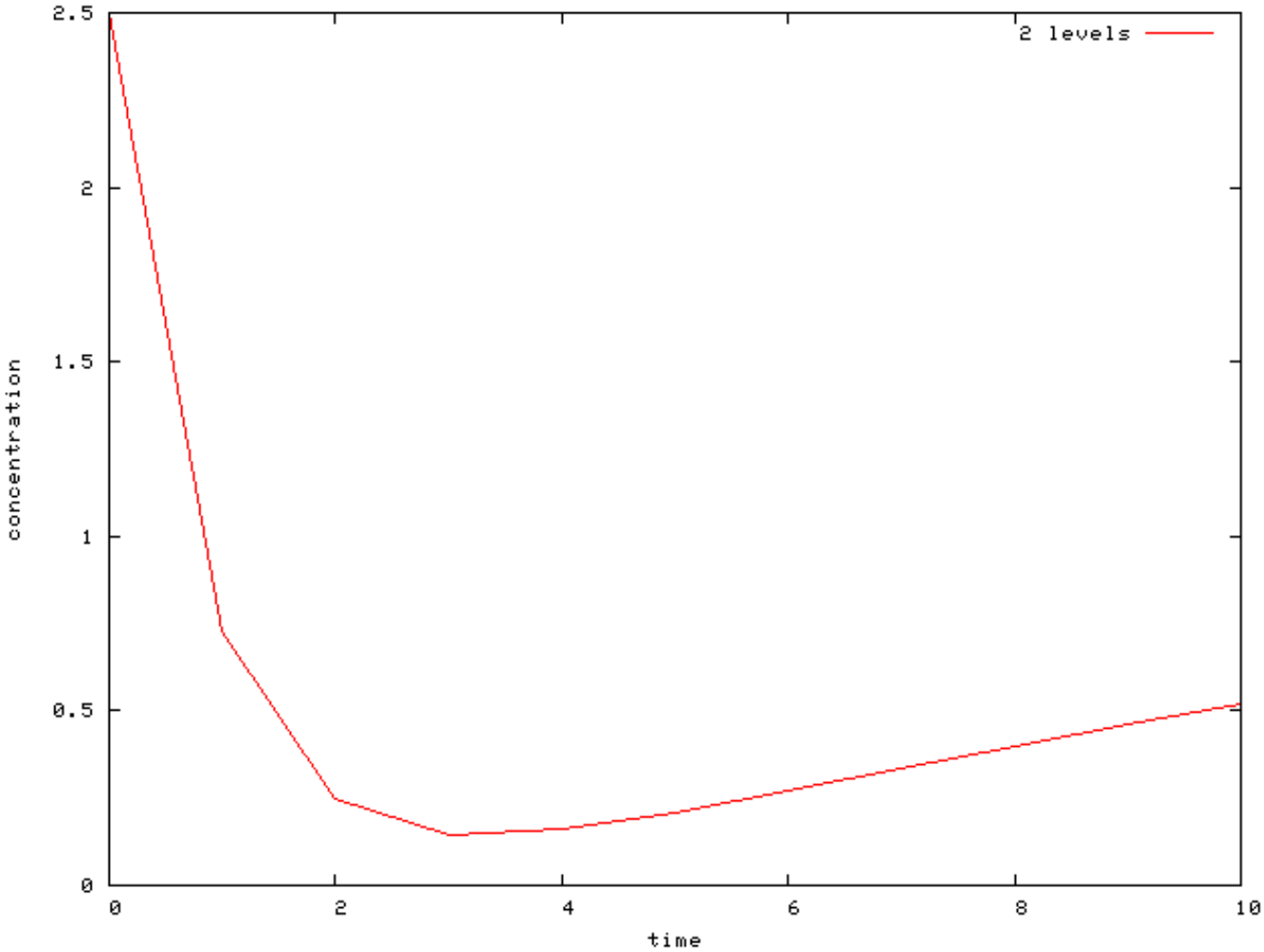
- l is a transition vector i.e. it records the adjustment to the number of copies of each state of each entity (species) after the transition is taken.

An illustration: the small example revisited



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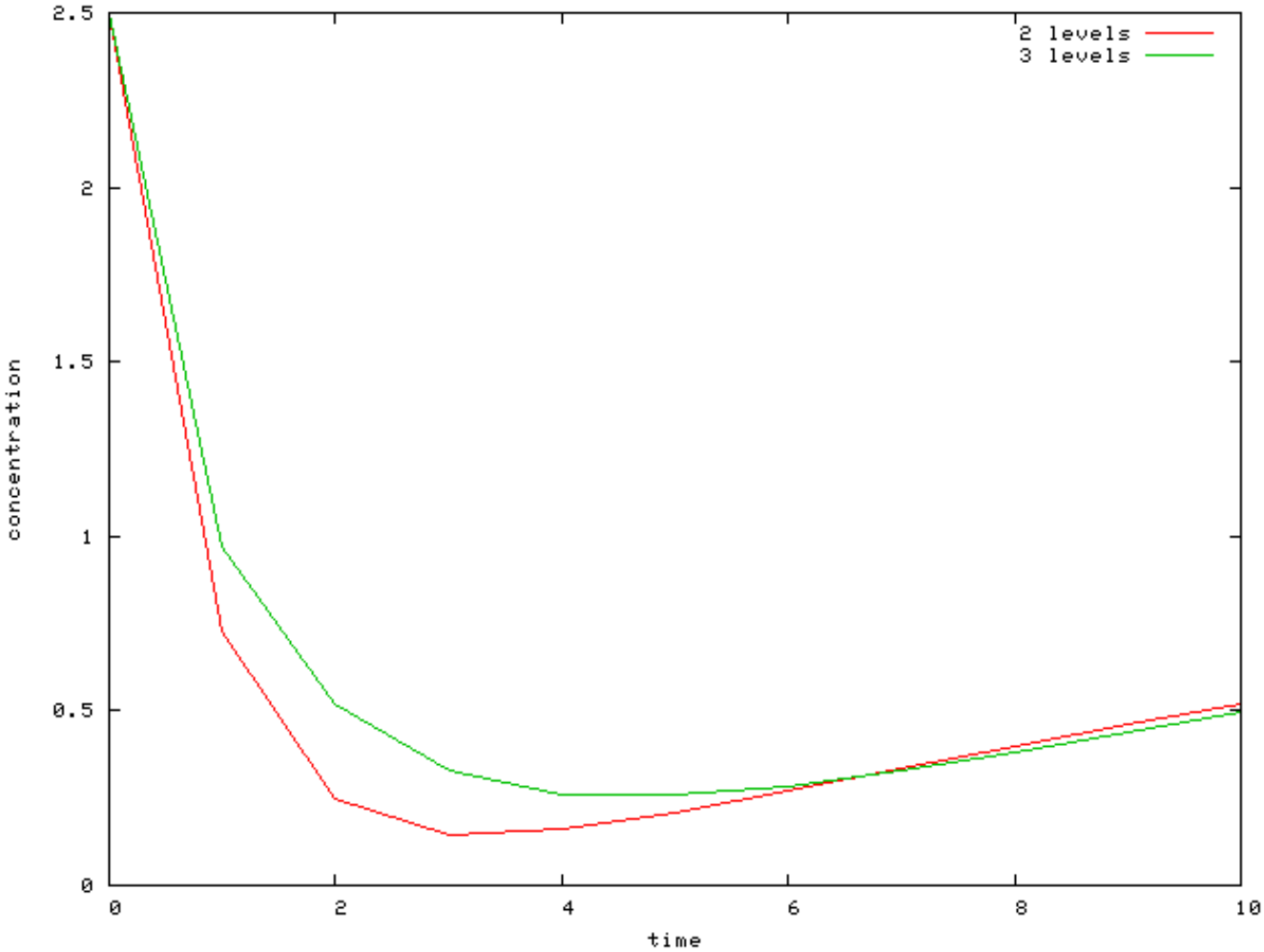

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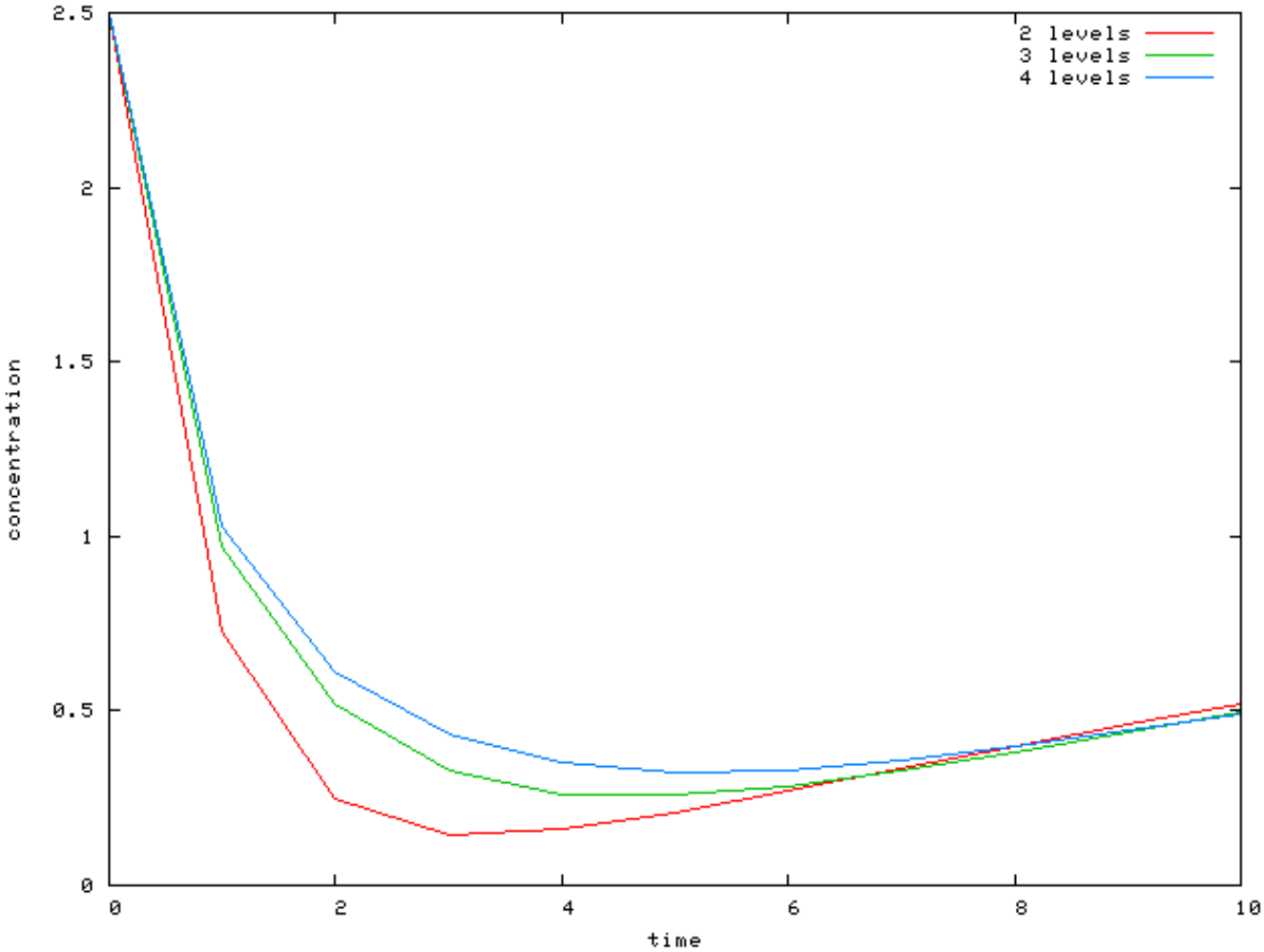

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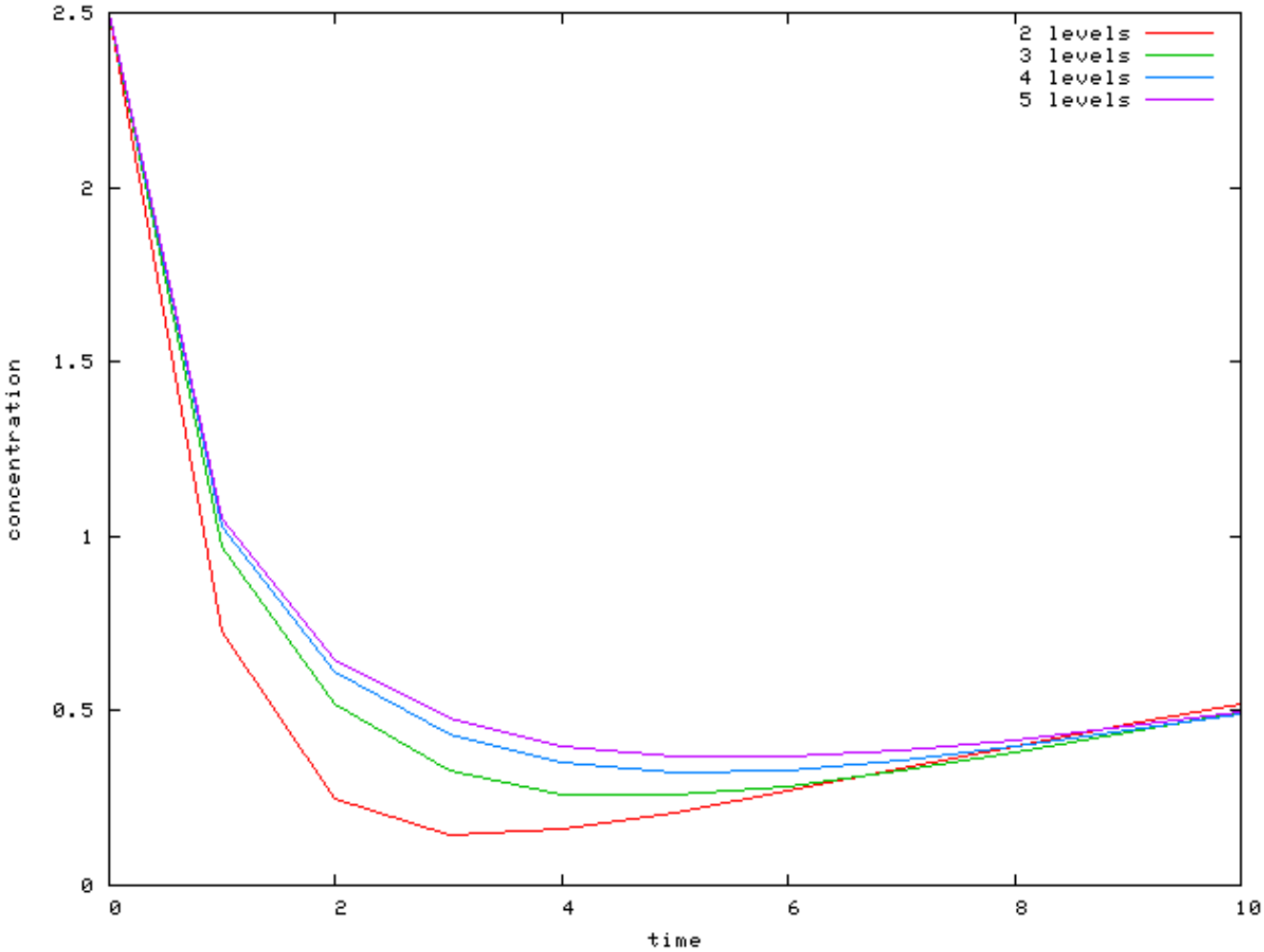

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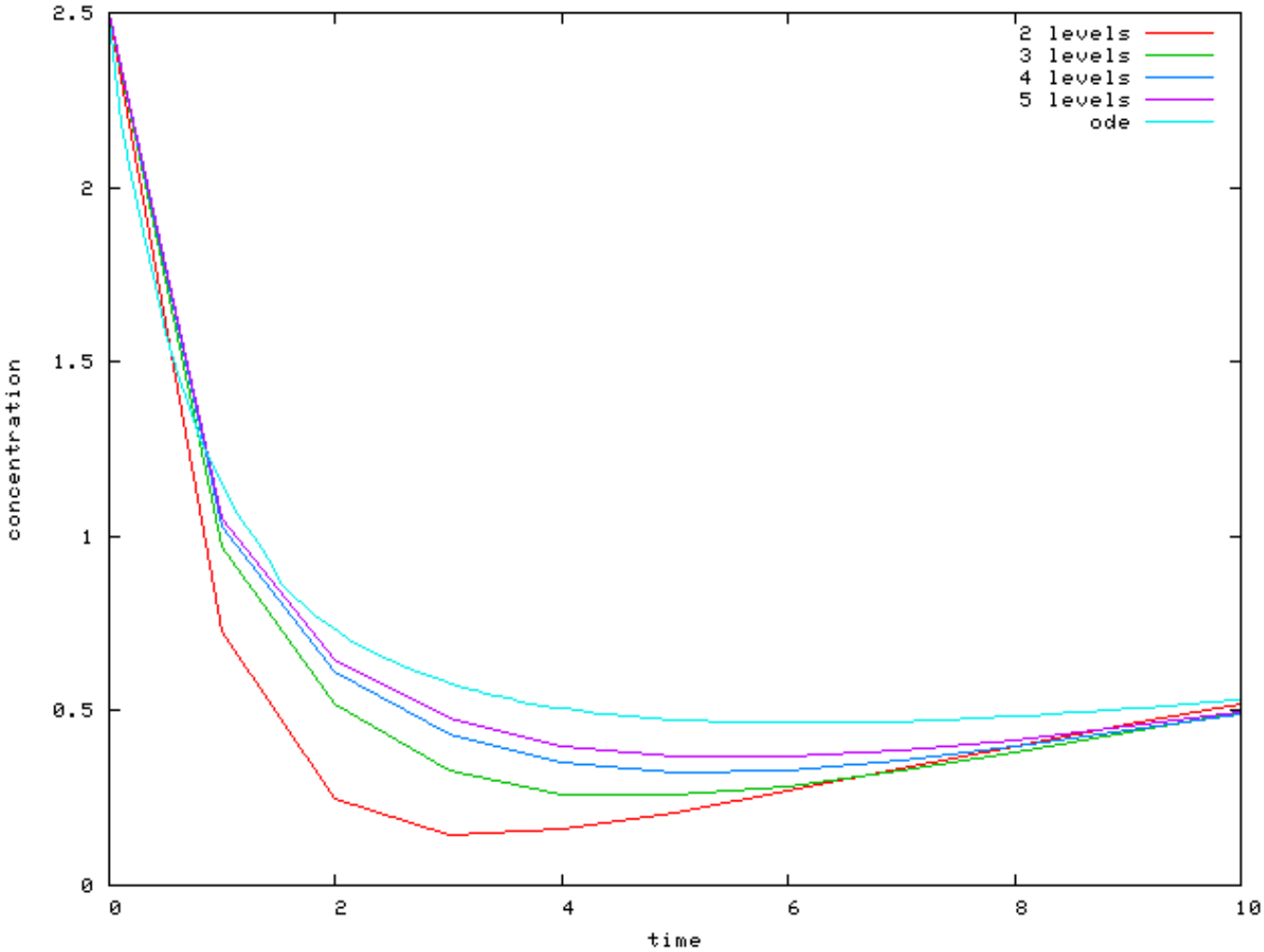

Outline

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Summary

- Abstract modelling offers a compromise between the individual-based and population-based views of systems which biologists commonly take.
- Moveover we can undertake additional analysis based on the discretised population view.
- Further work is needed to establish a better relationship between this view and the population view — empirical evidence has shown that 6 or 7 levels are often sufficient to capture exactly the same behaviour as the ODE model.
- In the future we hope to investigate the extent to which the process algebra compositional structure can be exploited during model analysis.

Conclusions

- Ultimately we want to understand the functioning of cells as useful levels of abstraction, and to predict unknown behaviour.

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- It remains an open and challenging problem to define a toolset 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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Acknowledgements: Engineering and Physical Sciences Research Council (EPSRC) and Biotechnology and Biological Sciences Research Council (BBSRC)