Modelling Biochemical Pathways with Stochastic Process Algebra

Jane Hillston.
LFCS, University of Edinburgh

9th May 2007

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- Performance Evaluation Process Algebra (PEPA) sought to address these problems by the introduction of a suitable process algebra.
- The project has sought to investigate and exploit the interplay between the process algebra and the continuous time Markov chain (CTMC).

PEPA Case Studies (1)

- Multiprocessor access-contention protocols (Gilmore, Hillston and Ribaudo, Edinburgh and Turin)
- Protocols for fault-tolerant systems (Clark, Gilmore, Hillston and Ribaudo, Edinburgh and Turin)
- Multimedia traffic characteristics (Bowman et al, Kent)
- Database systems (The STEADY group, Heriot-Watt University)
- Software Architectures (Pooley, Bradley and Thomas, Heriot-Watt and Durham)
- Switch behaviour in active networks (Hillston, Kloul and Mokhtari, Edinburgh and Versailles)

PEPA Case Studies (2)

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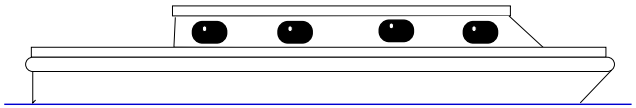

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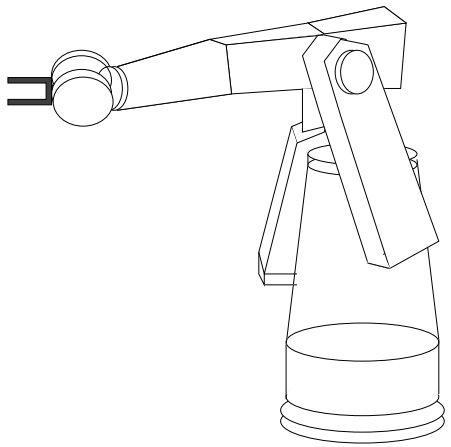

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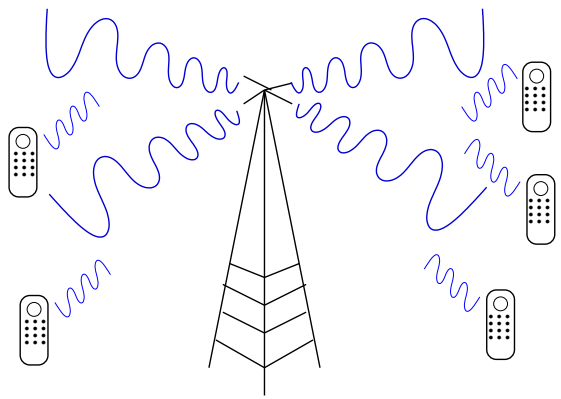

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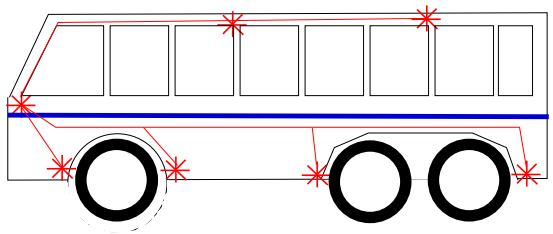

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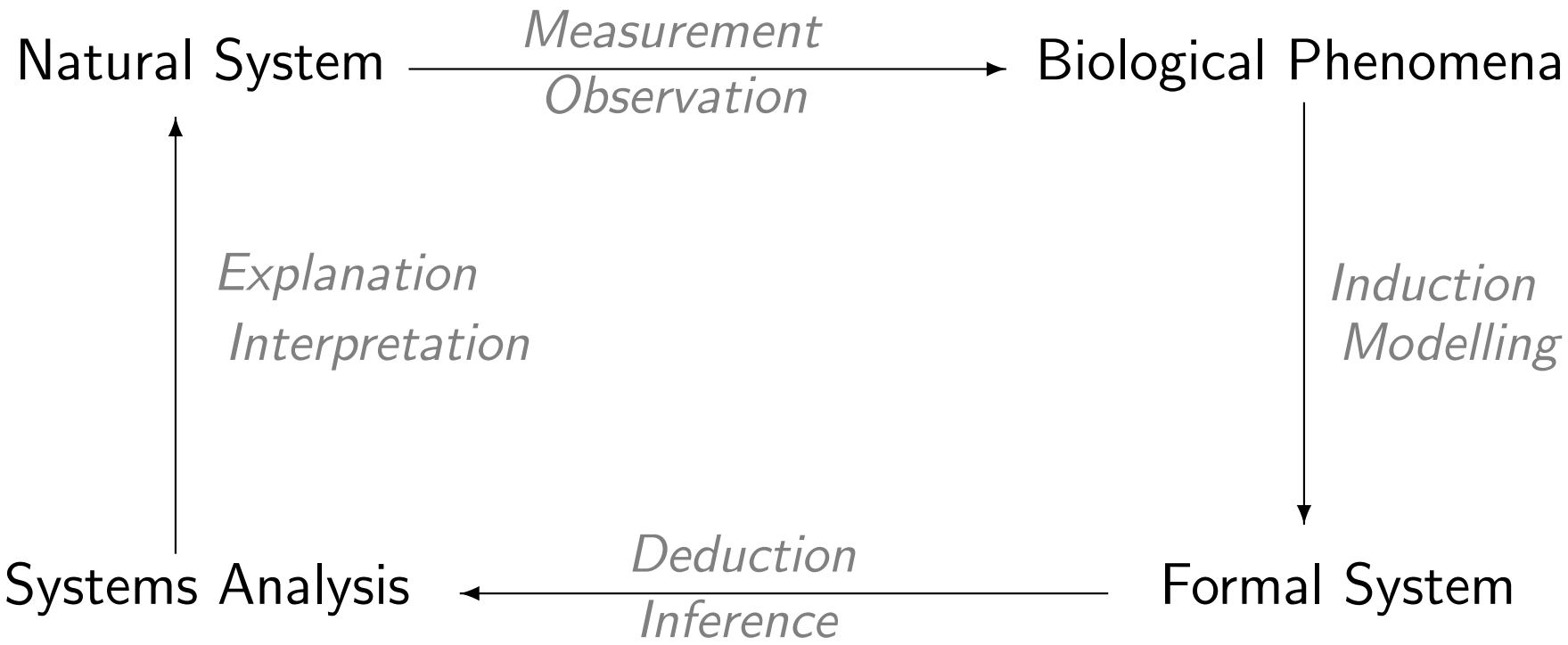
- Systems biology aims to develop a better understanding of the processes involved.
- It involves taking a systems theoretic view of biological processes — analysing inputs and outputs and the relationships between them.
- A radical shift from earlier reductionist approaches, systems biology aims to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

Systems Biology Methodology



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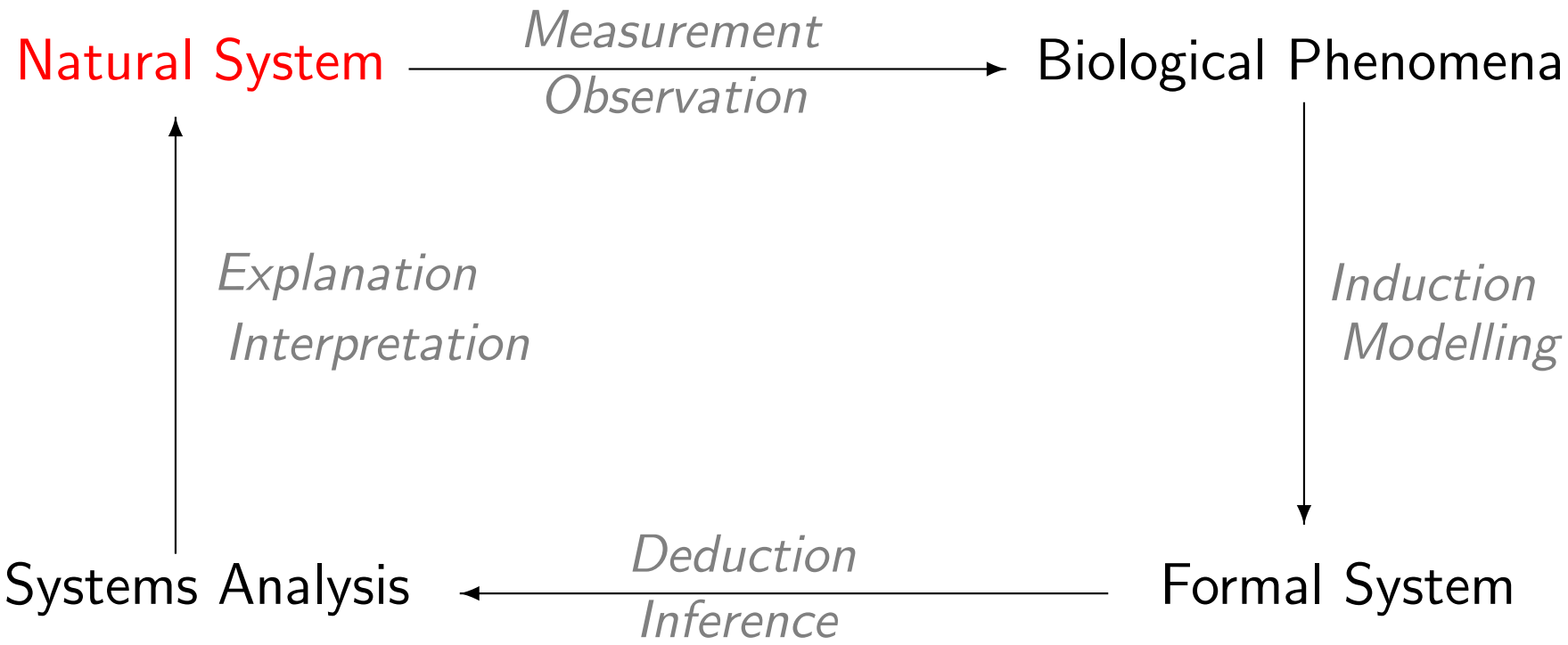

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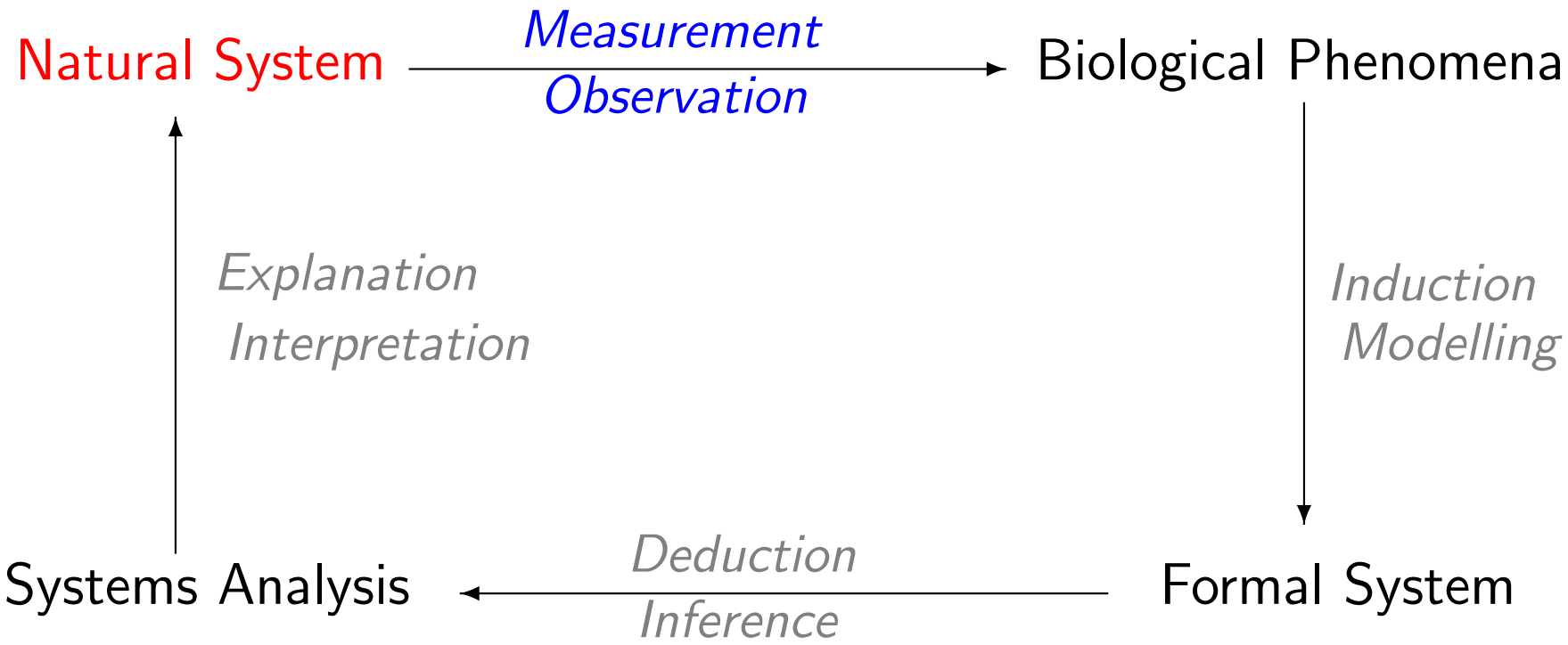

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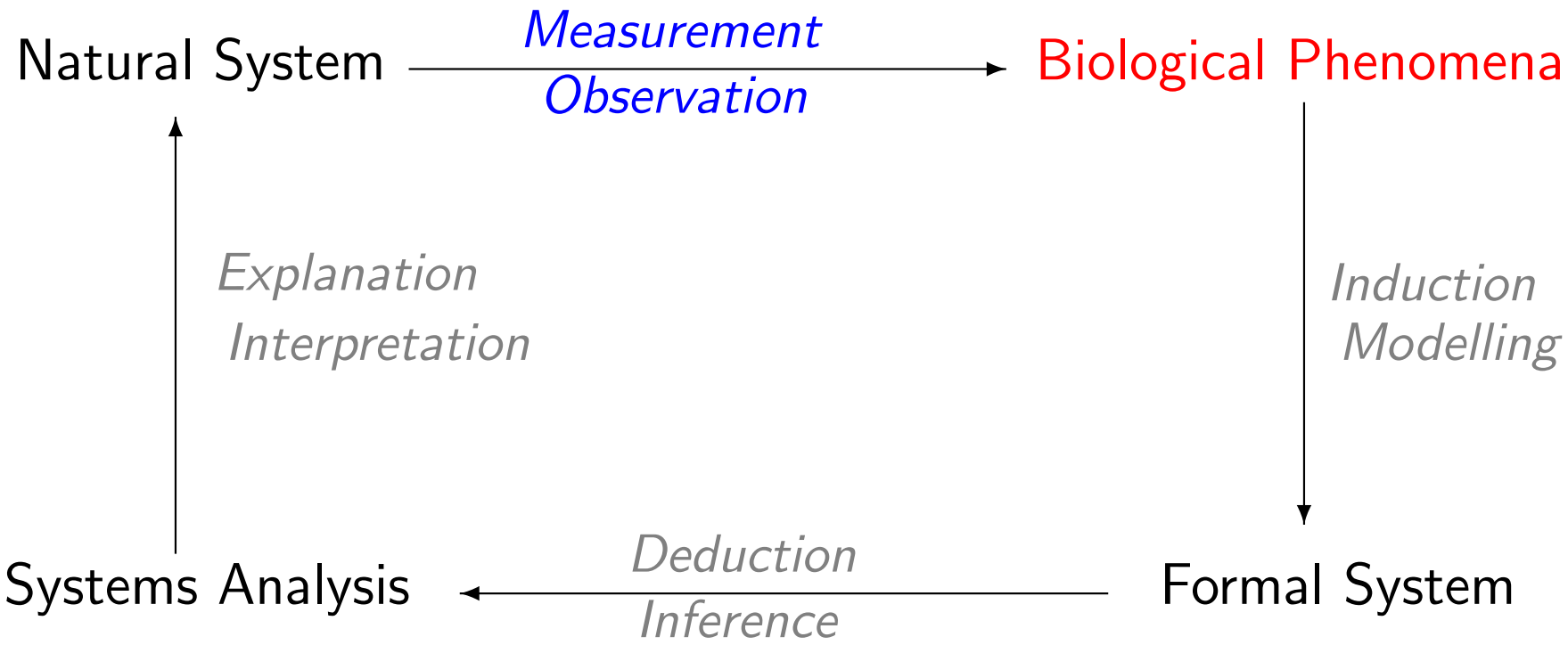

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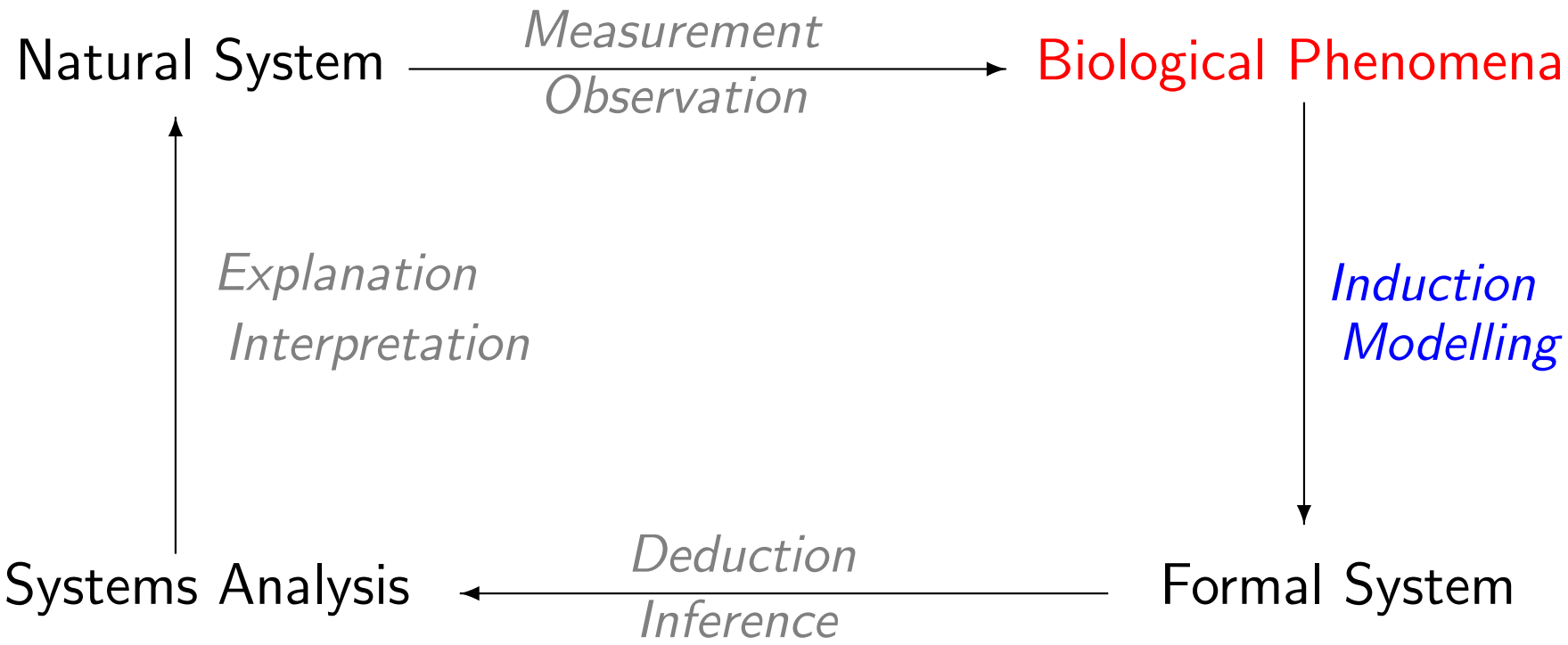

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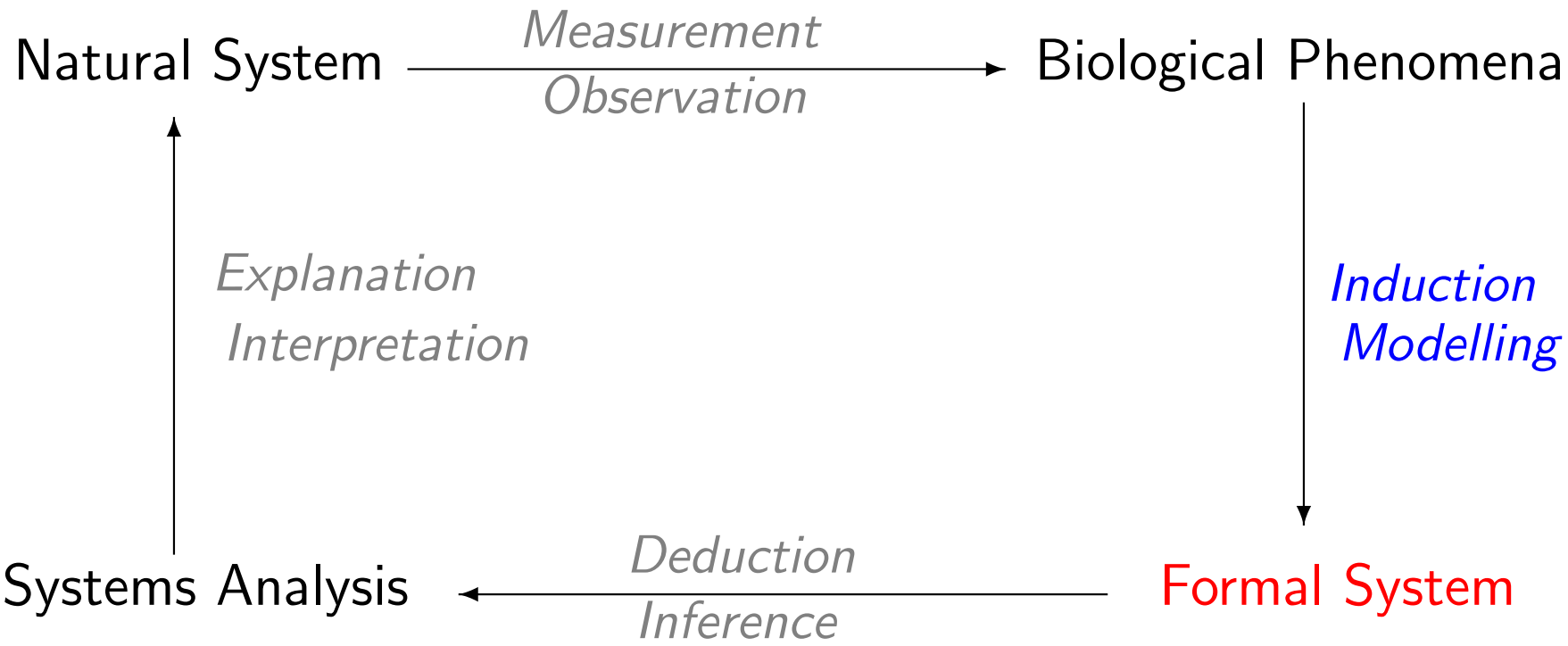

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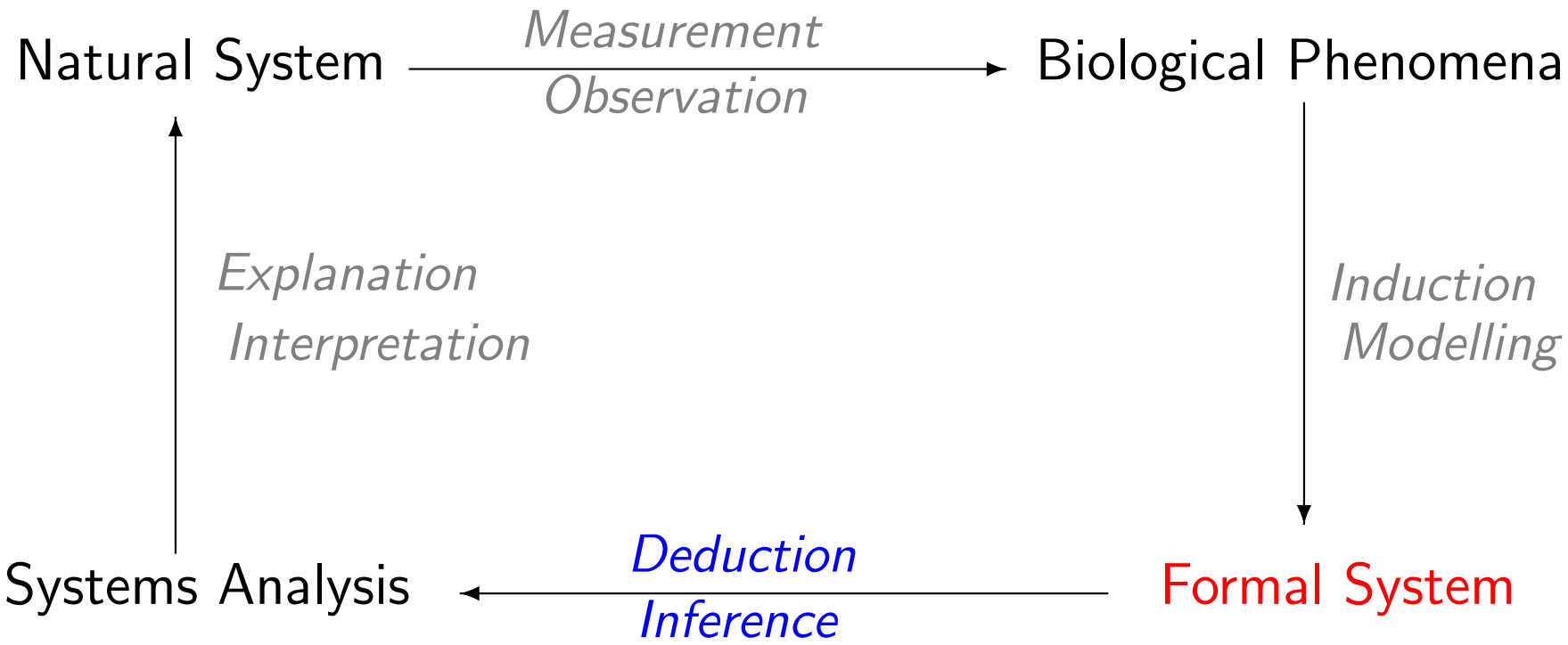

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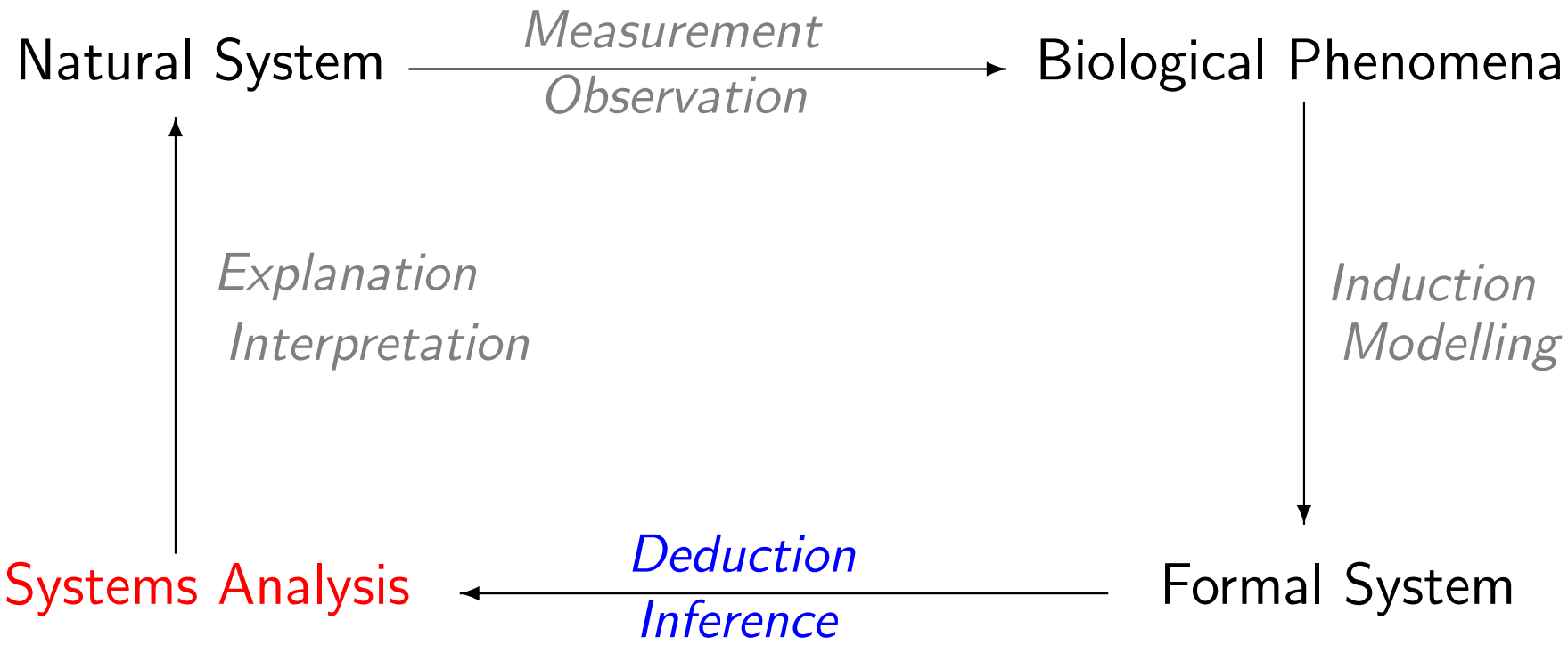

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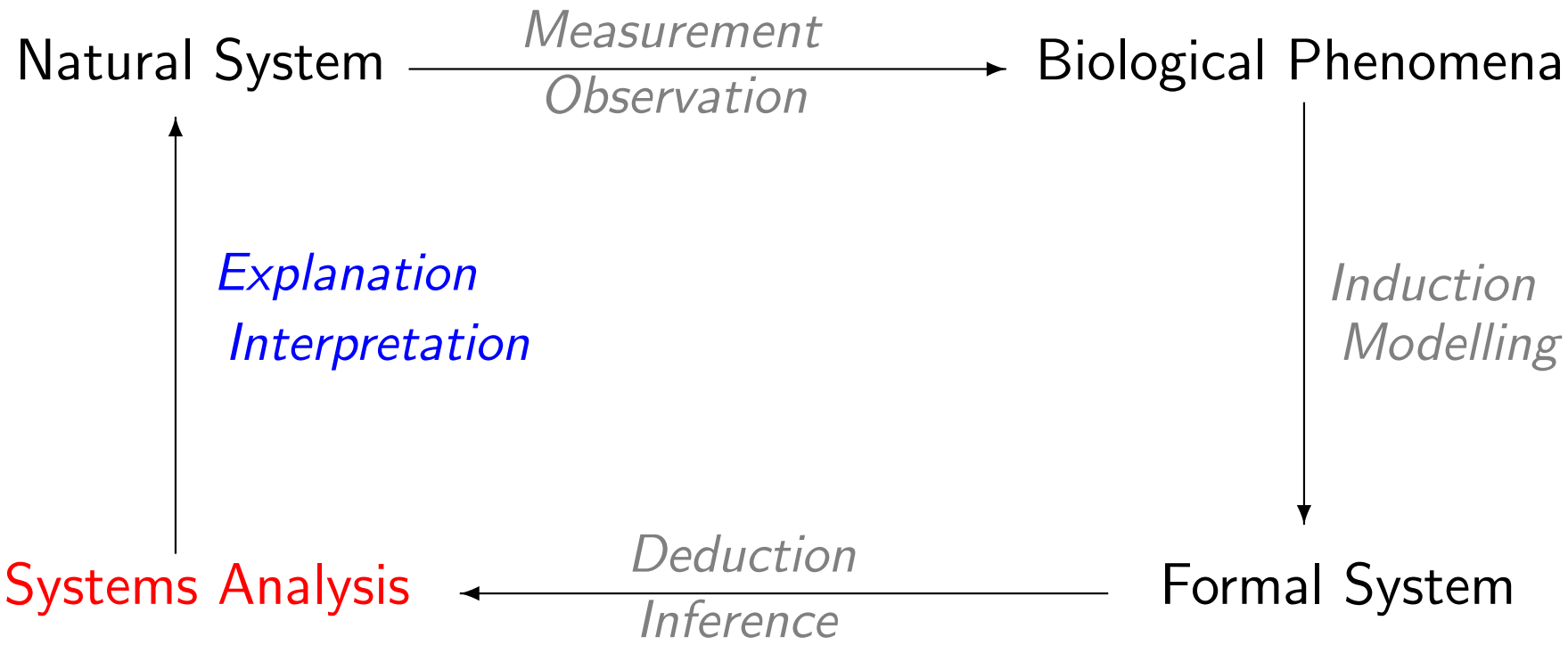

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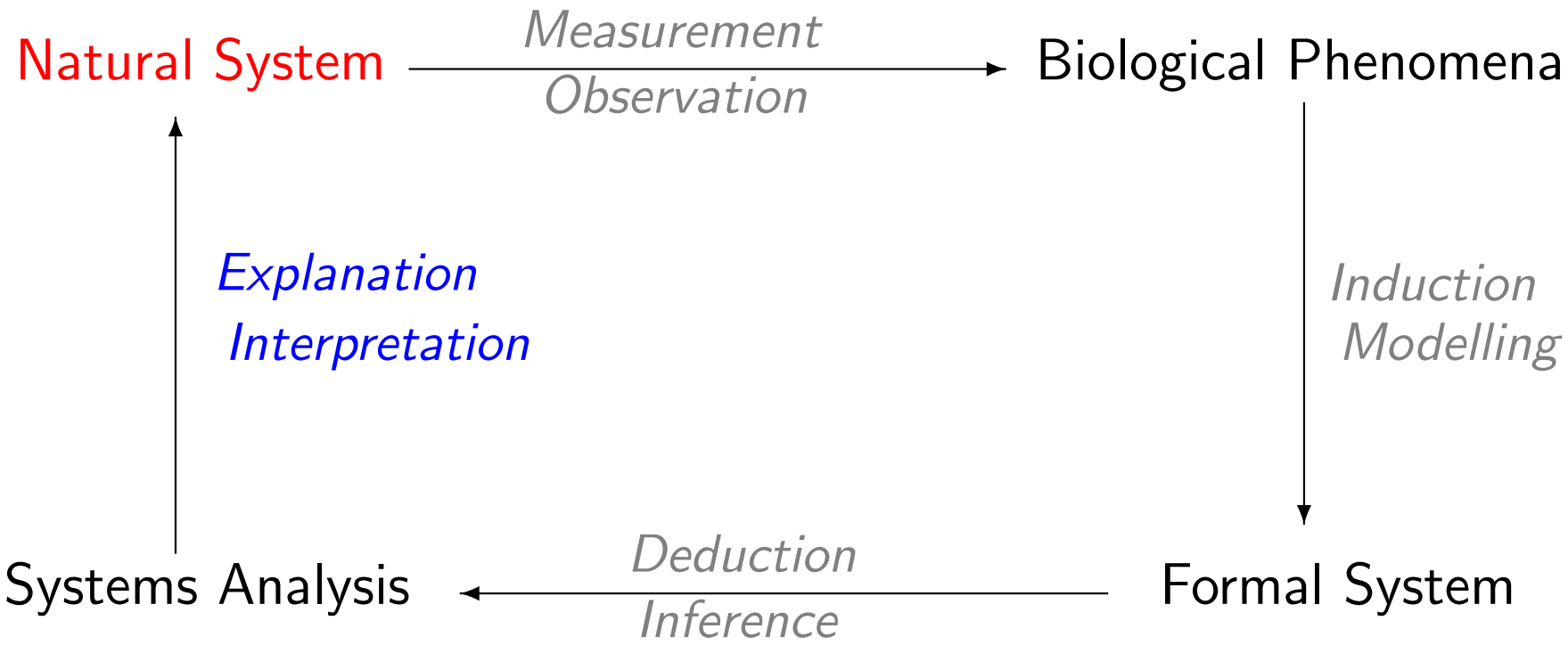

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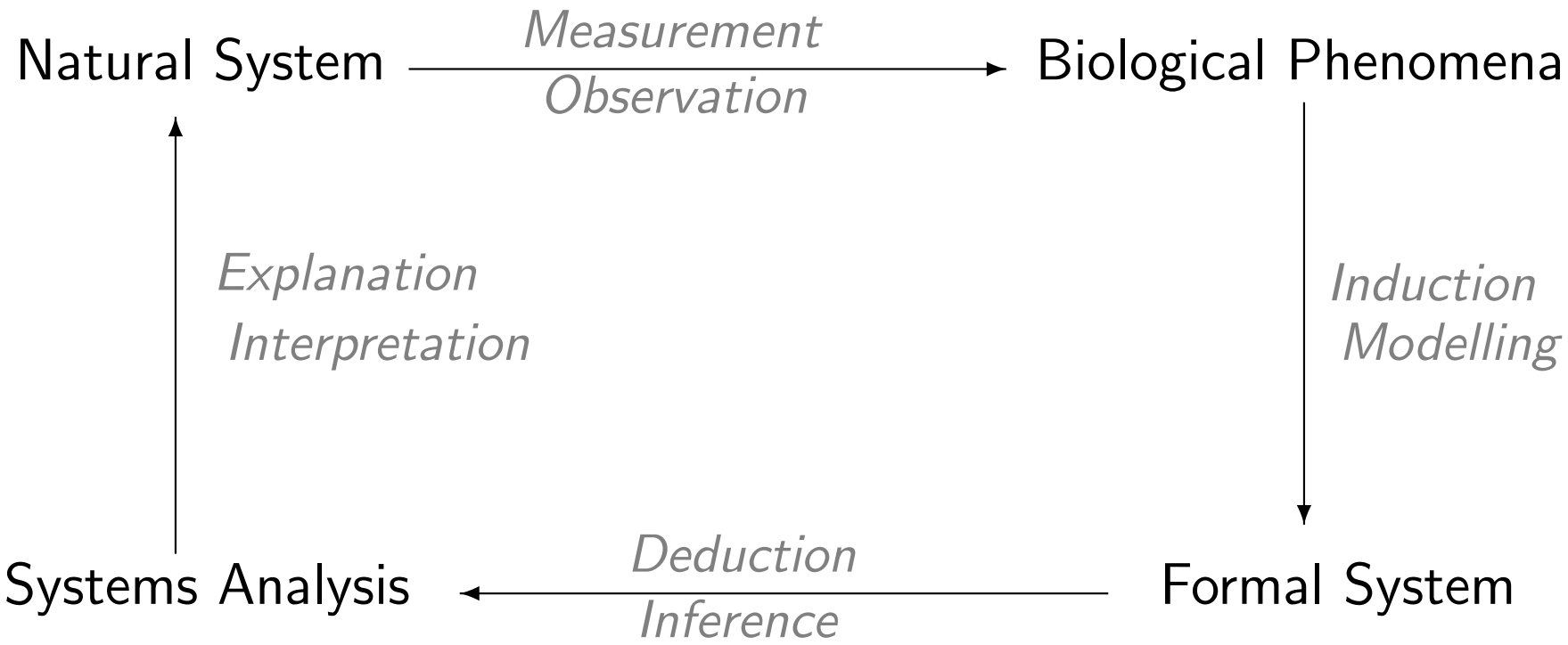

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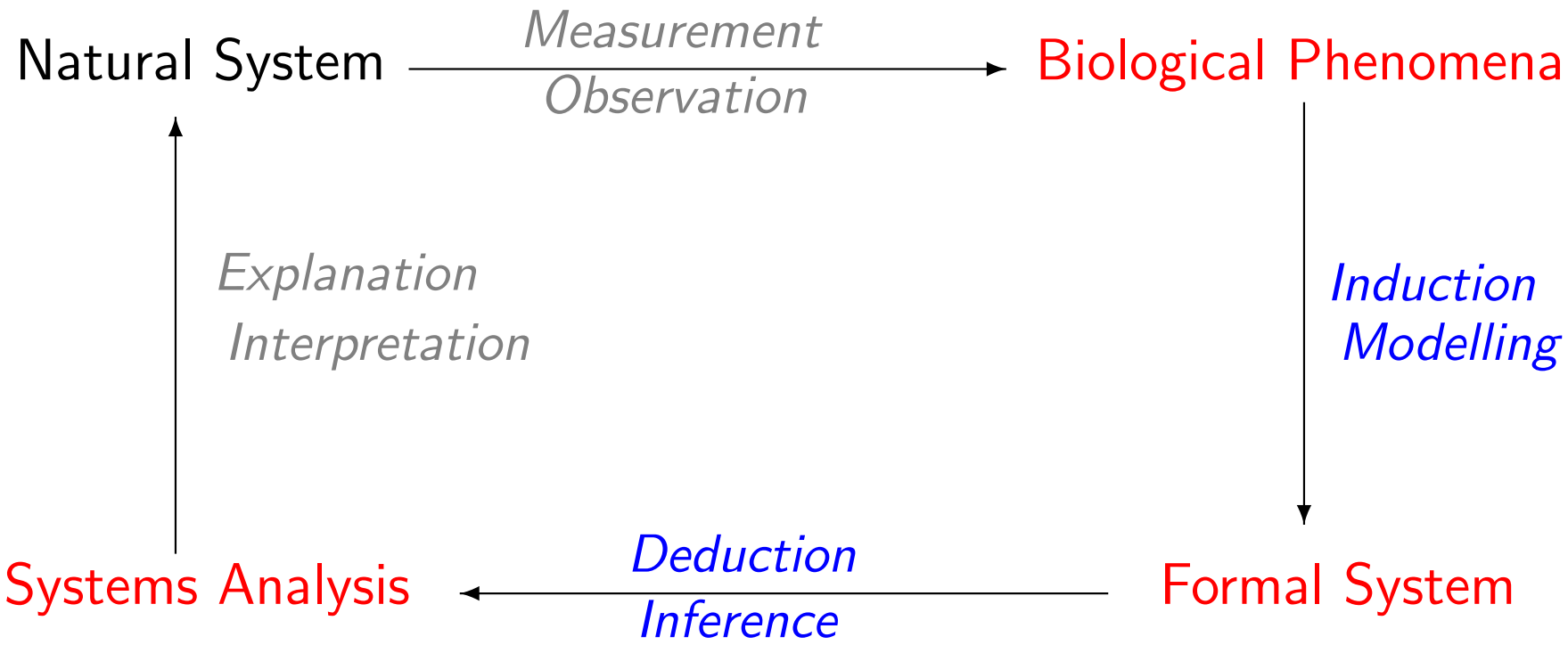

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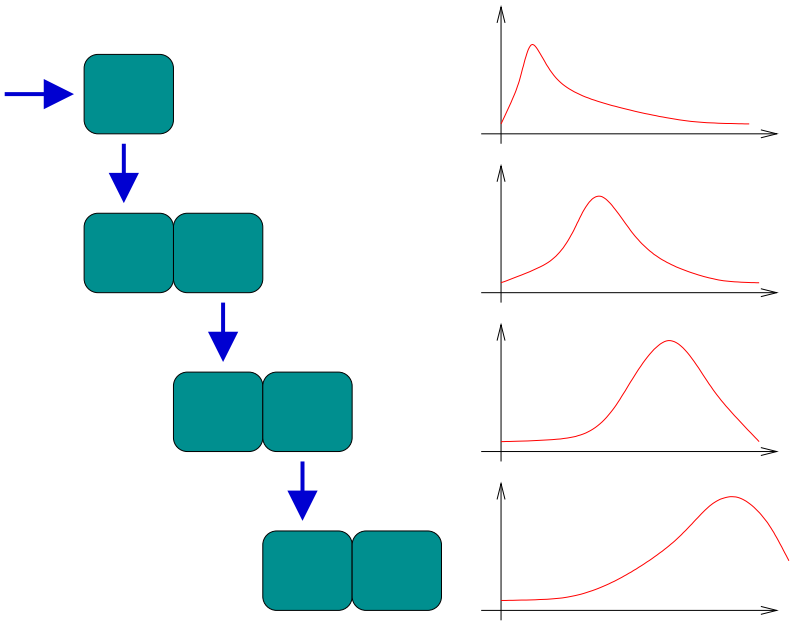
But these distinctions are to some extent arbitrary as models may include elements of more than one pathway type.

Signal transduction pathways

- All signalling is biochemical:



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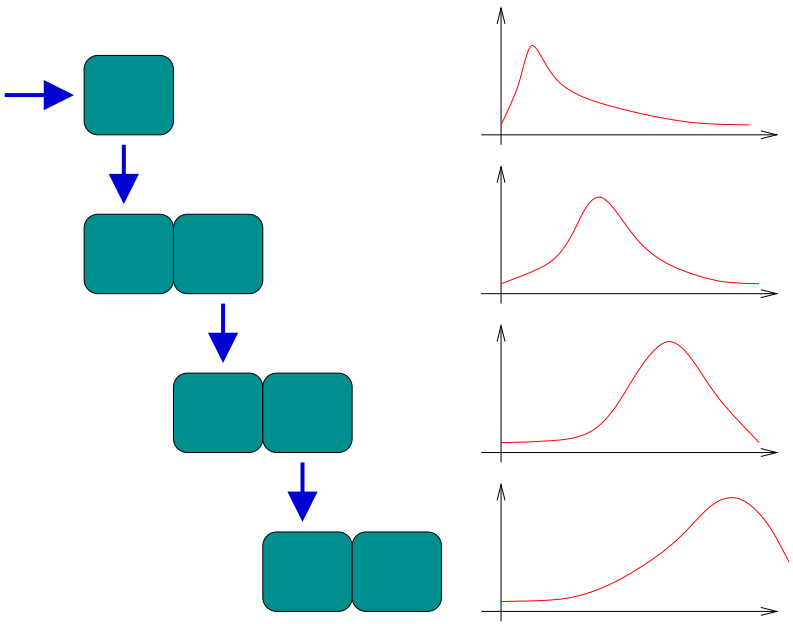

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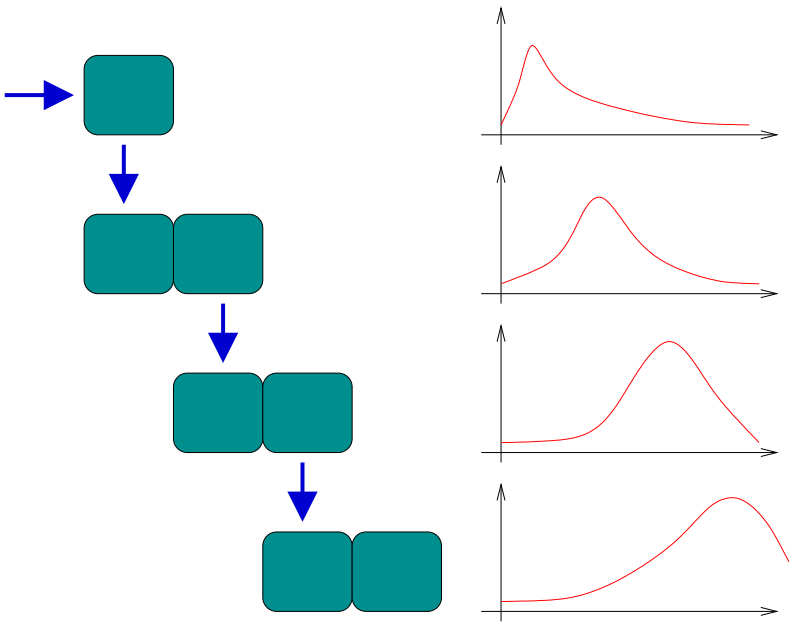

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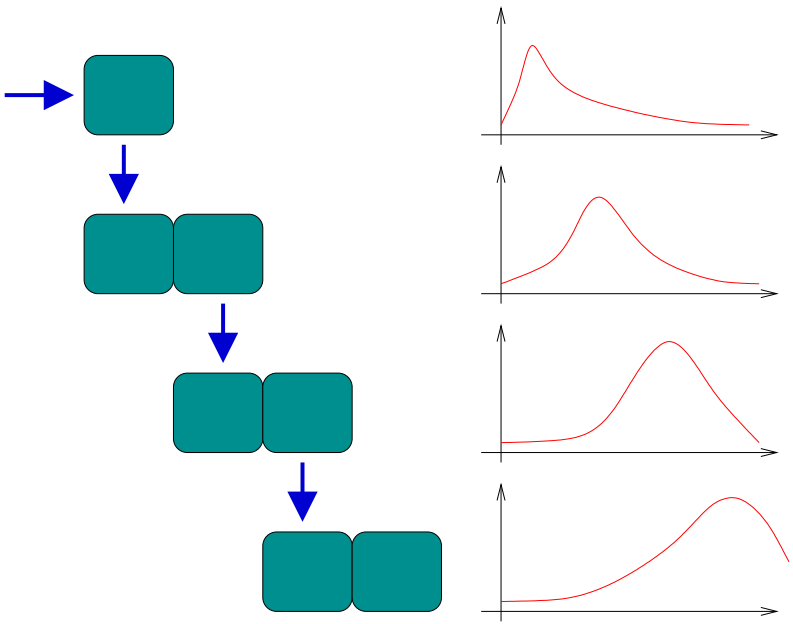

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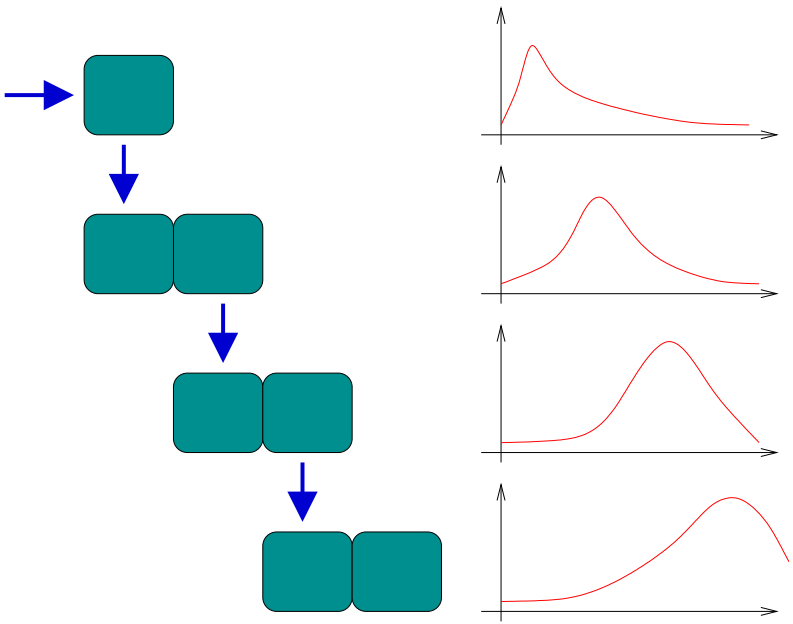
- Signals propagate through a series of protein accumulations.



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

Ordinary Differential Equations

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

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

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

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- This is based on the assumption that chemical reactions to be macroscopic under convective or diffusive stirring, continuous and deterministic.
- 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 (CME).

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

Does not lend itself to either analytic nor numerical solutions.

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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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- 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.

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- Moreover taking this "high-level programming" style approach offers the possibility of different "compilations" to different mathematical models.

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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

[Regev *et al* 2000]

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

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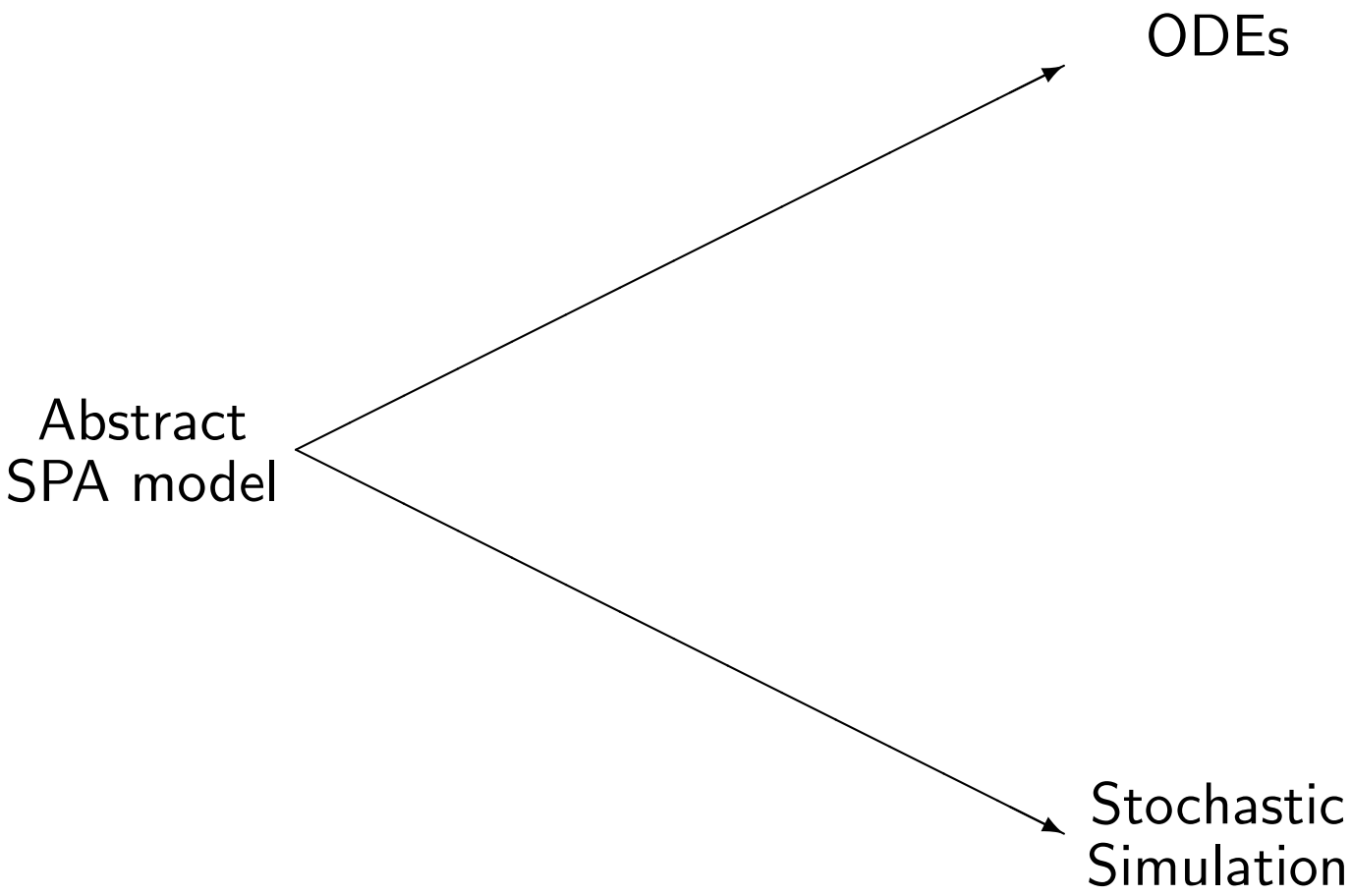
- The data that we have available to parameterise models is sometimes speculative rather than precise. This suggests that it can be useful to use semiquantitative models rather than quantitative ones.

Alternative Representations



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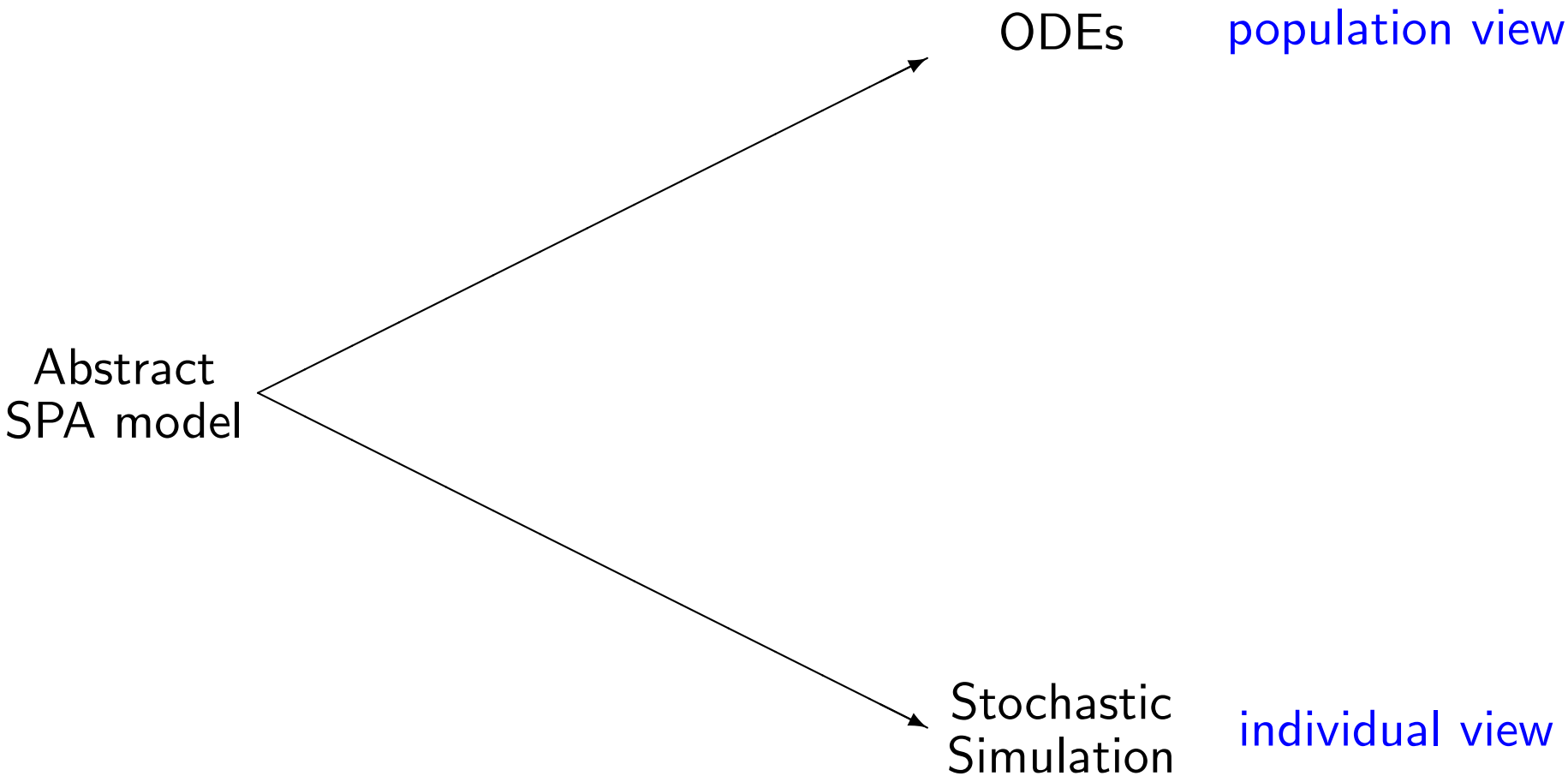
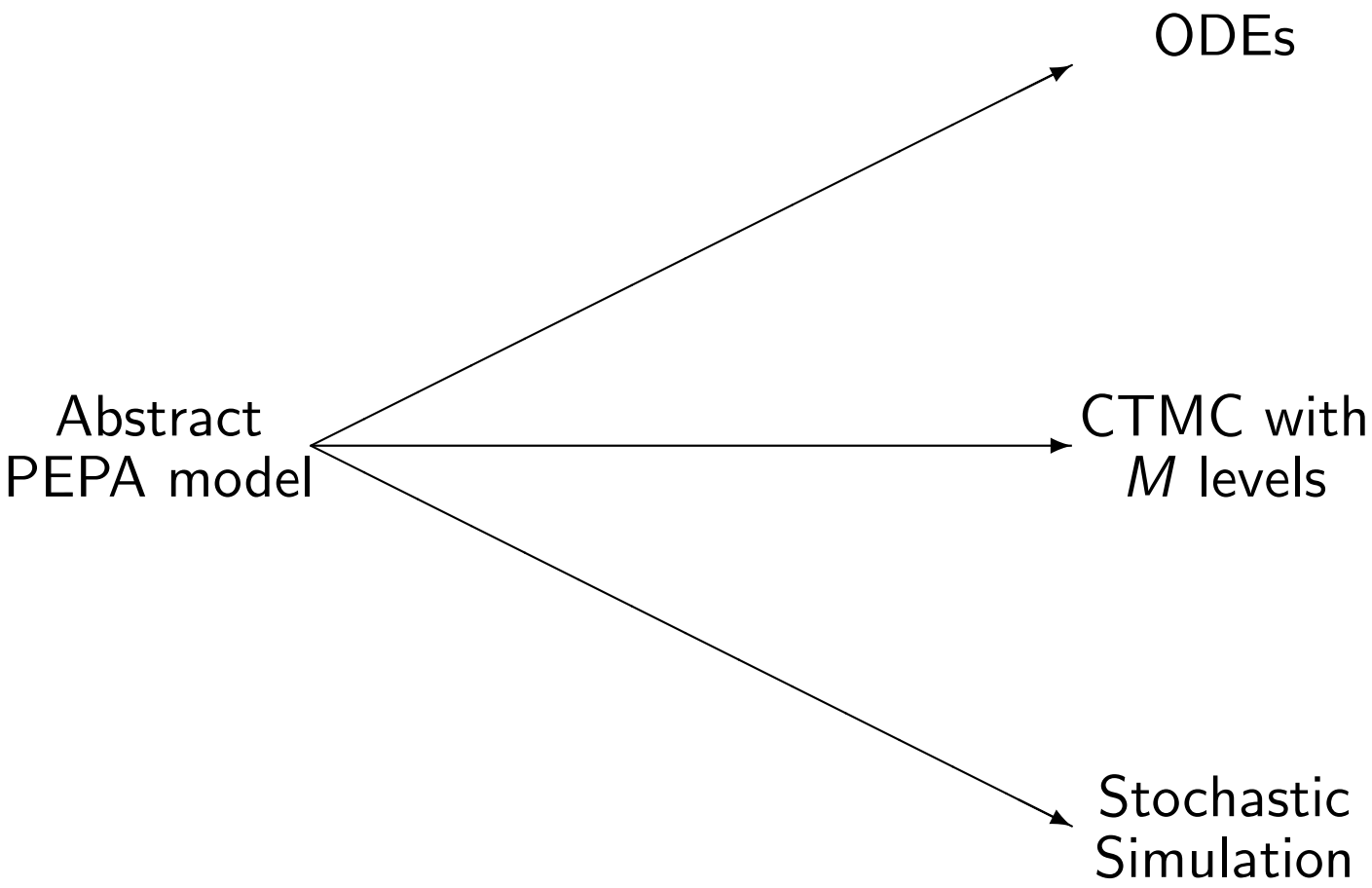


Discretising the population view

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



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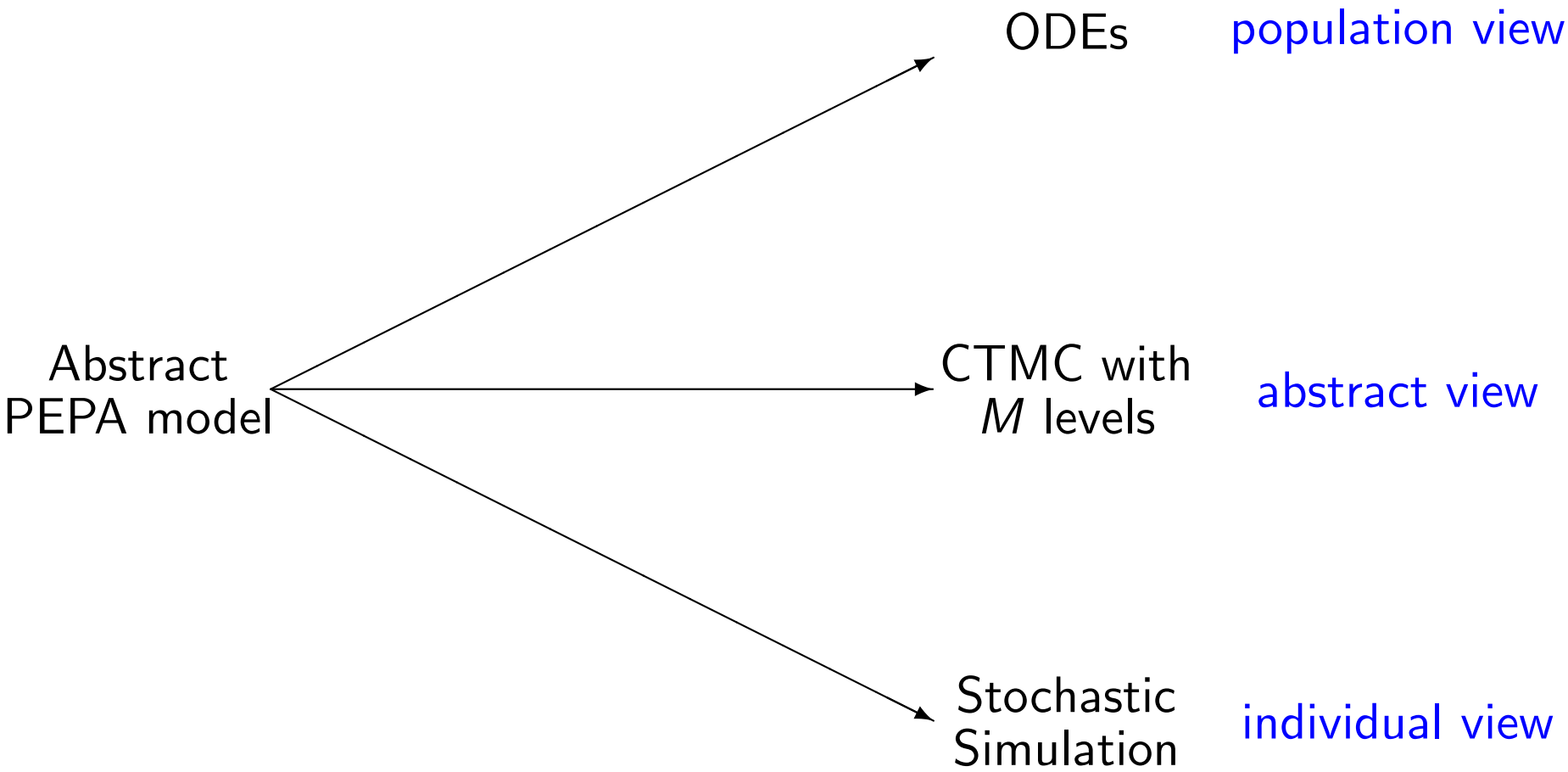

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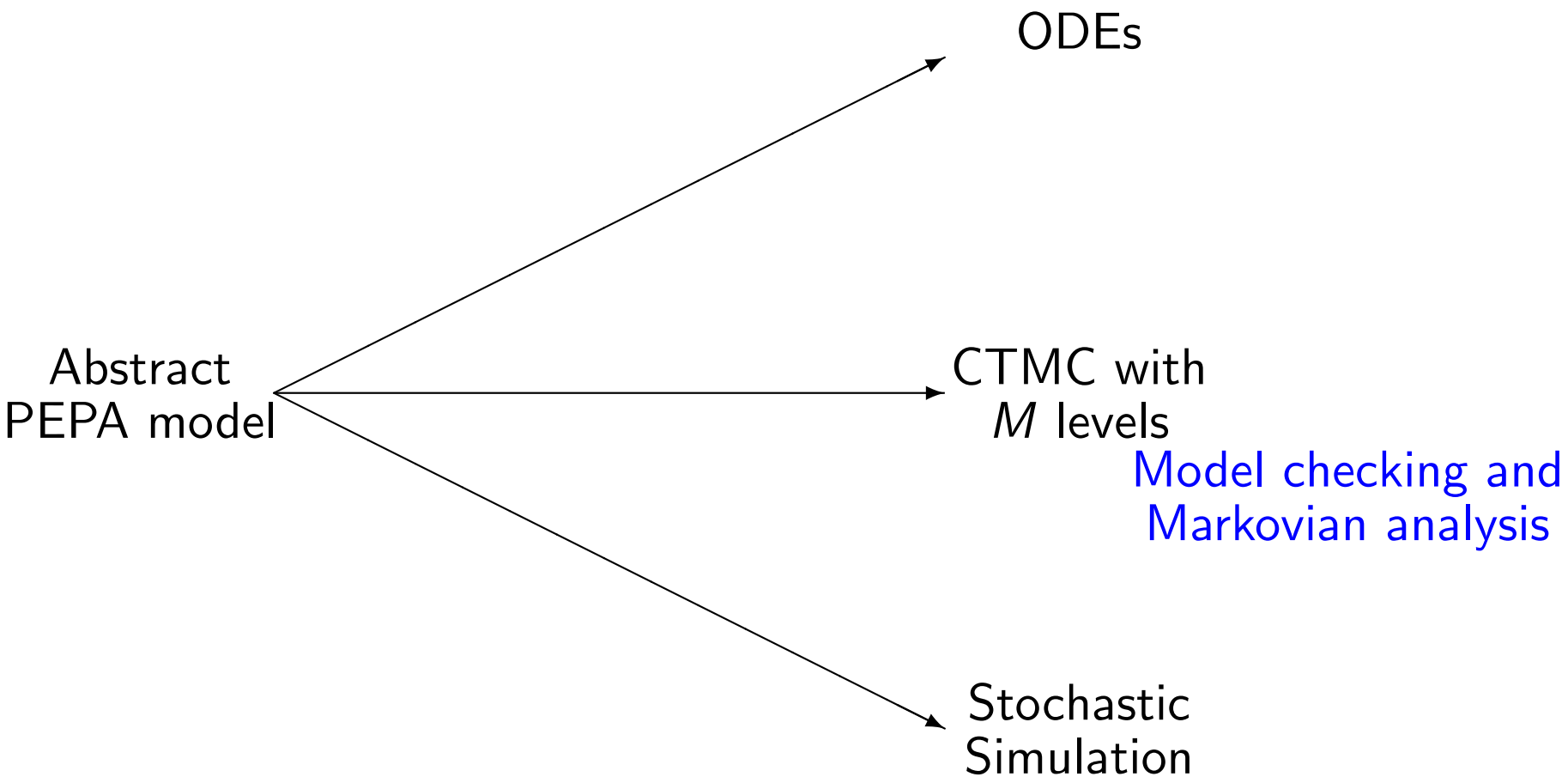

PEPA: Performance Evaluation Process Algebra

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\begin{aligned}
S &::= (\alpha, r).S \mid S + S \mid A \\
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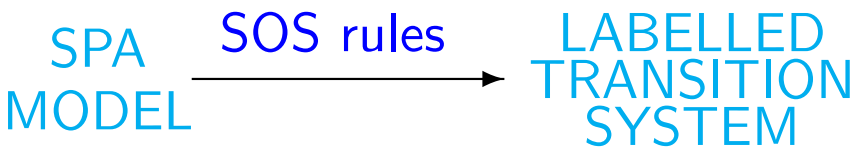

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SPA MODEL $\xrightarrow{\text{SOS rules}}$ LABELLED TRANSITION SYSTEM $\xrightarrow[\text{diagram}]{\text{state transition}}$ CTMC **Q**

Q is the infinitesimal generator matrix characterising the CTMC.

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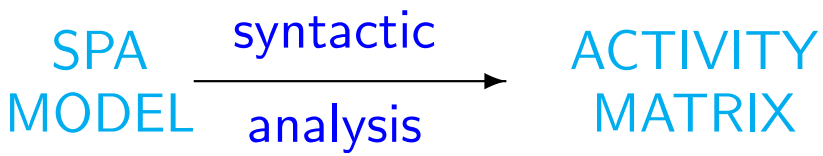

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Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.

Markovian analysis

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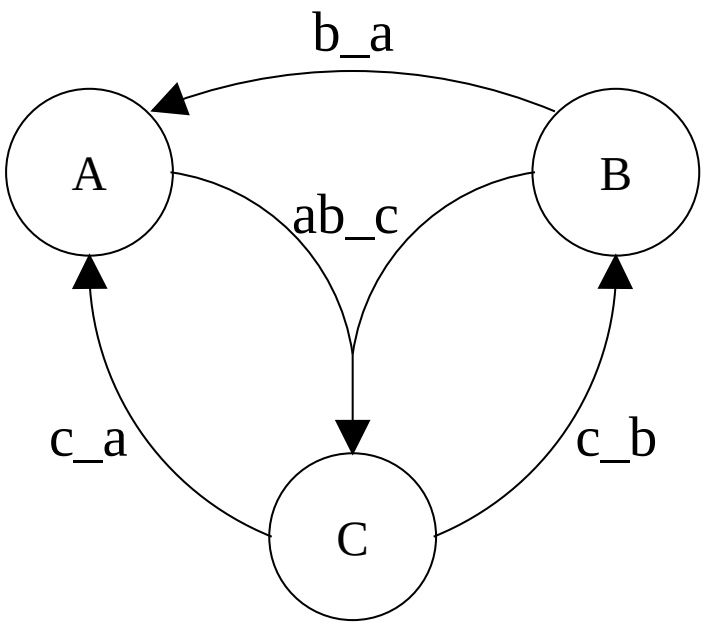
- Stochastic model checking is available via the PRISM model checker, assessing the probable validity of properties expressed in CSL (Continuous Stochastic Logic).

Reagent-centric modelling [CGH04]

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

PEPA reagent-centric example



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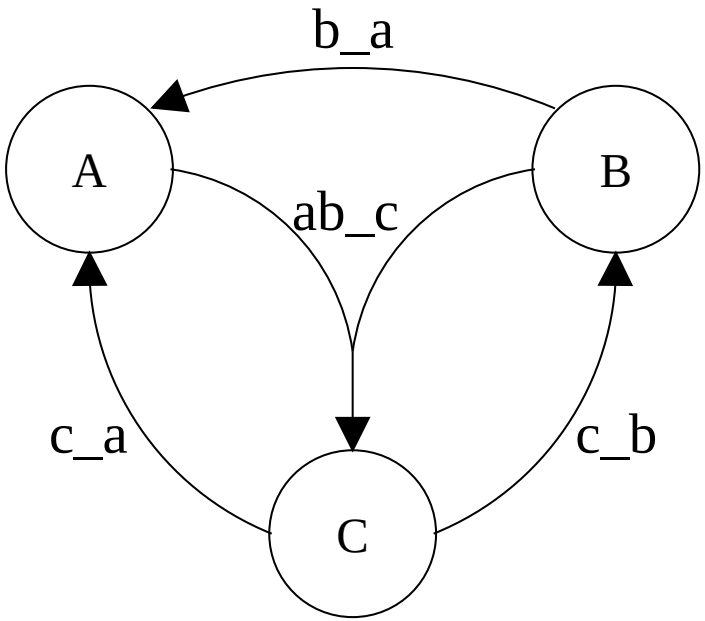

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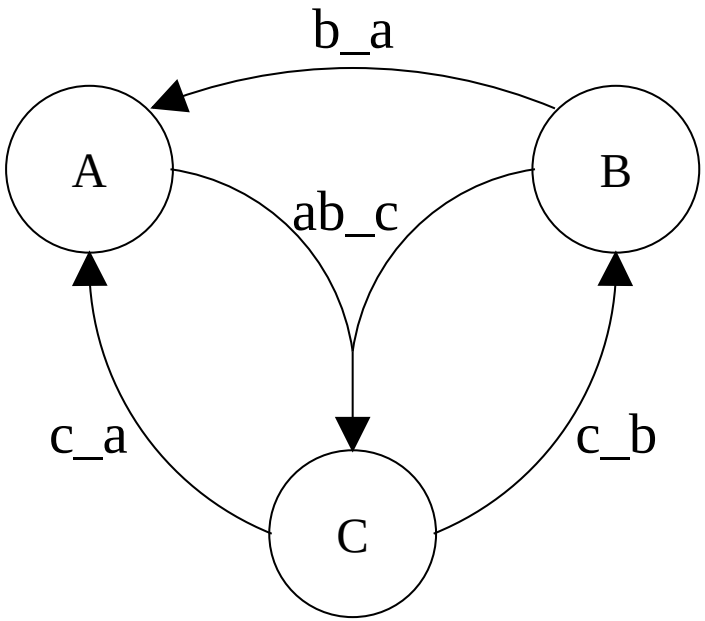

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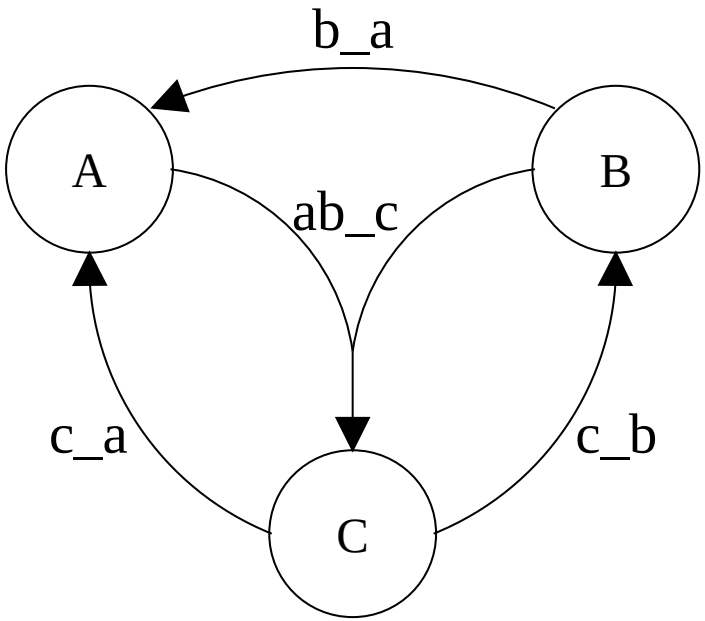

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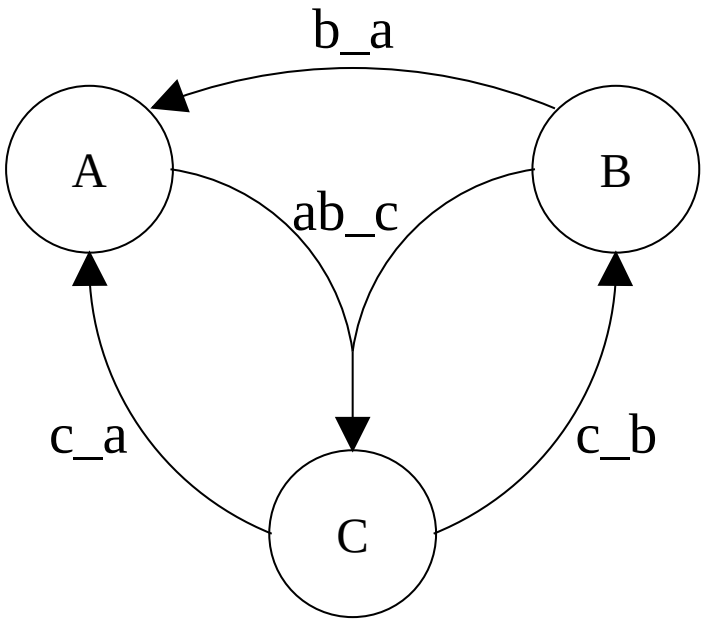

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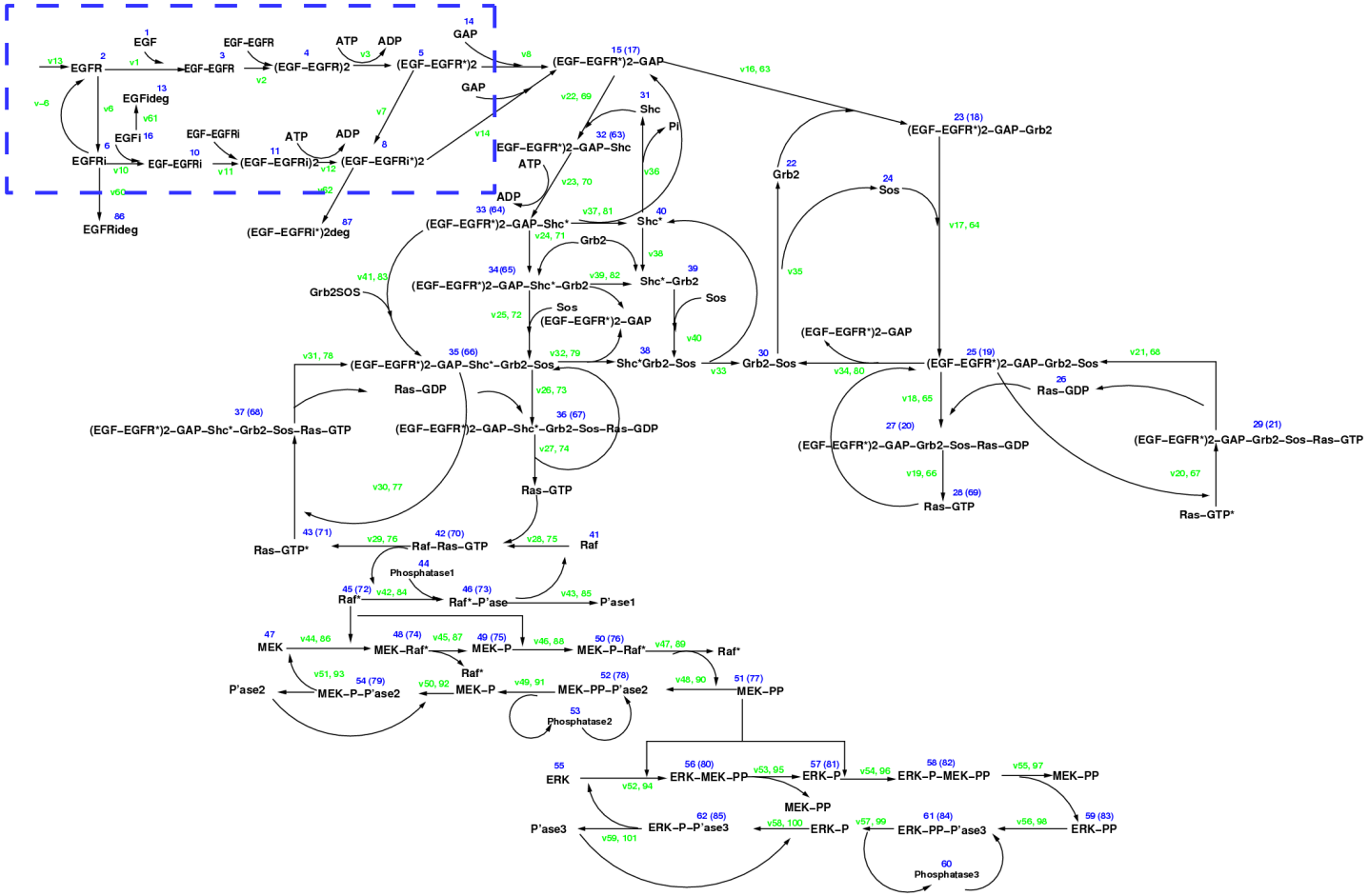
$$(A_H \underset{\{ab\_c, b\_a\}}{\bowtie} B_H) \underset{\{ab\_c, c\_a, c\_b\}}{\bowtie} C_L$$

Case Study: Schoeberl *et al.*'s model of the MAPK Cascade [CDGH06]

- Published in *Nature Biotechnology* 20:370-375 in 2002.
- Influential, cited by more than 150 subsequent published papers.
- Consists of 94 reagent species involved in 125 reactions.
- Substantial ODE model consisting of 94 state variables and 95 parameters.
- Original model constructed "by hand", with help of a graphical representation.
- Original analysis based on numerical integration platform of the Matlab numerical computing platform.

The MAP Kinase Cascade



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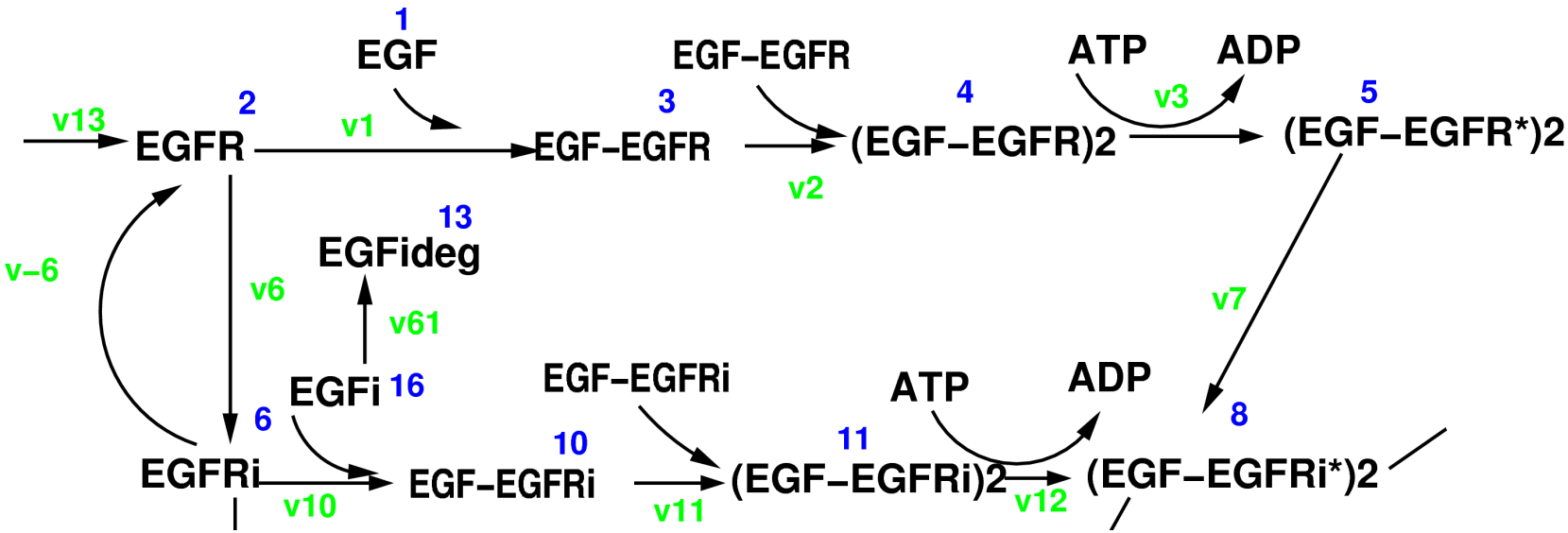

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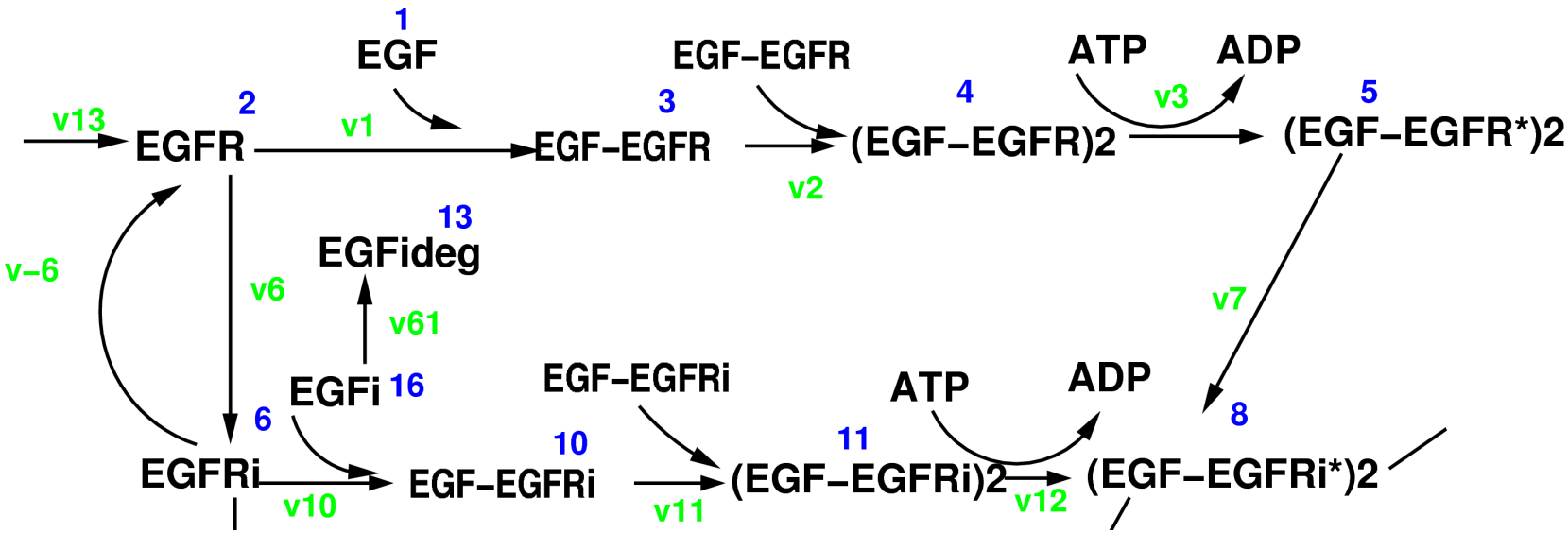

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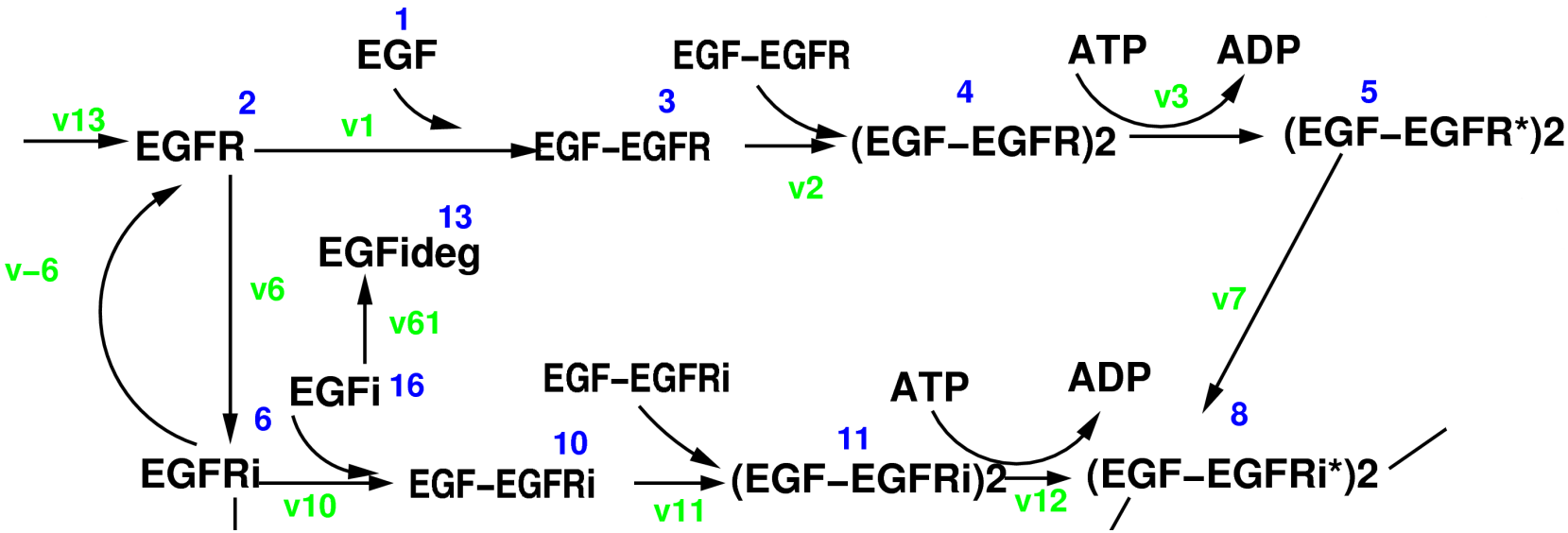

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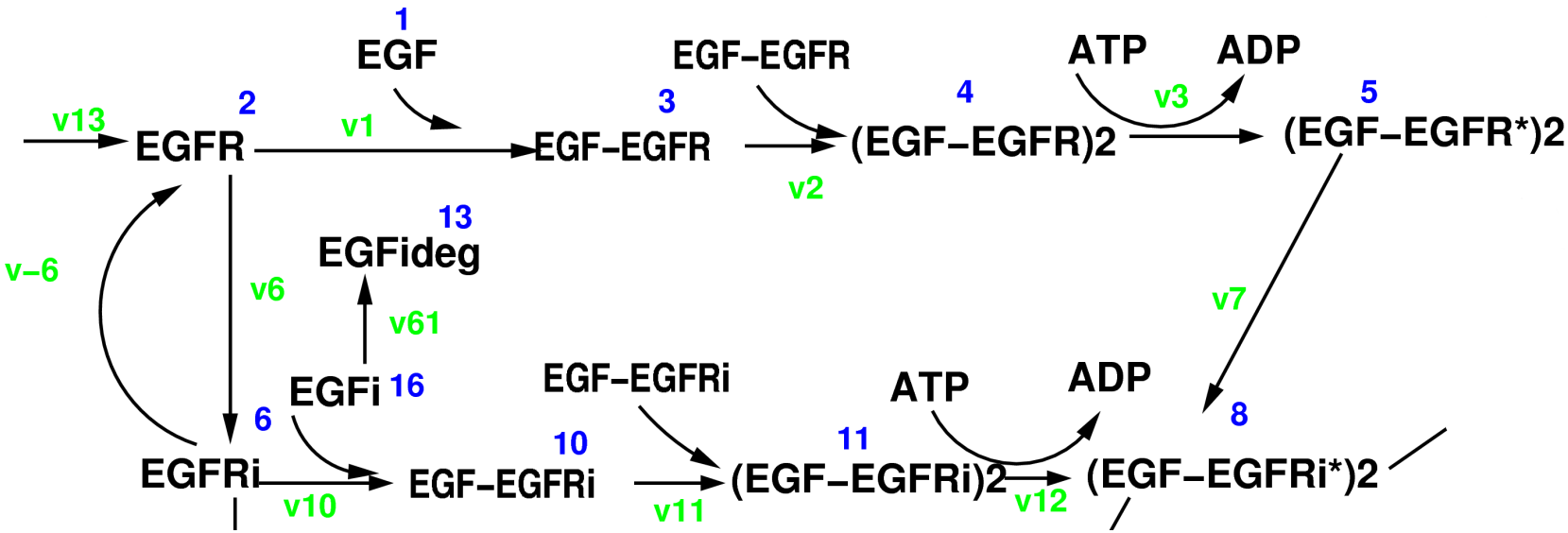

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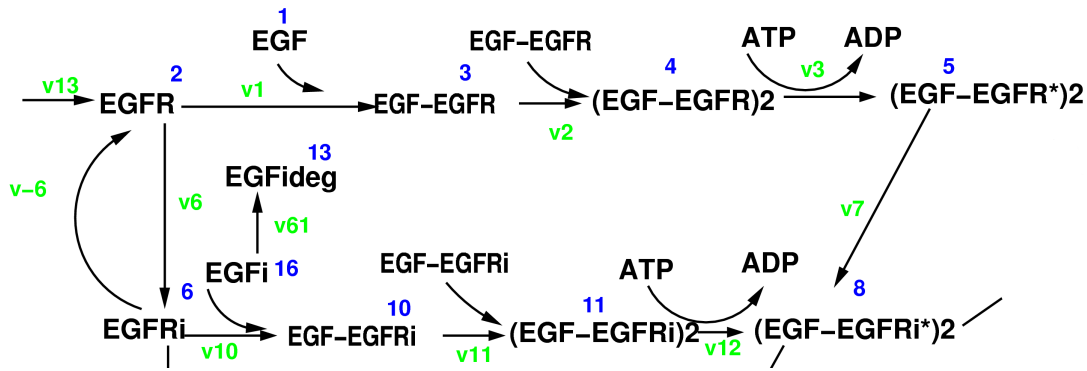
- An infinite supply of EGF is assumed;
- Reaction *v7* is uni-directional whereas all others are reversible.

Extracts from the model of the MAP Kinase Cascade



$$\mathrm{EGF_H} \stackrel{def}{=} (v_1, k_1).\mathrm{EGF_H}$$

$$\mathrm{EGFR_H} \stackrel{def}{=} (v_1, k_1).\mathrm{EGFR_L} + (v_6, k_6).\mathrm{EGFR_L}$$

$$\mathrm{EGFR_L} \stackrel{def}{=} (v_{\text{-}1},\ k_{\text{-}1}).\mathrm{EGFR_H} + (v_{\text{-}6},\ k_{\text{-}6}).\mathrm{EGFR_H} + (v_{13}, k_{13}).\mathrm{EGFR_H}$$

$$\text{EGF-EGFR}_\mathrm{H} \stackrel{def}{=} (v_2, k_2).\text{EGF-EGFR}_\mathrm{L} + (v_{\text{-}1}, k_{\text{-}1}).\text{EGF-EGFR}_\mathrm{L}$$

$$\text{EGF-EGFR}_\mathrm{L} \stackrel{def}{=} (v_1, k_1).\text{EGF-EGFR}_\mathrm{H} + (v_{\text{-}2}, k_{\text{-}2}).\text{EGF-EGFR}_\mathrm{H}$$

The PEPA model

Similar PEPA definitions were constructed for each of the 94 species in the pathway.

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In order to complete the model we also needed to capture the interactions (i.e. cooperations) between the reagents. In this case we assumed that whenever reagents participated in reactions with the same name they did so in cooperation.

Validation of the PEPA model

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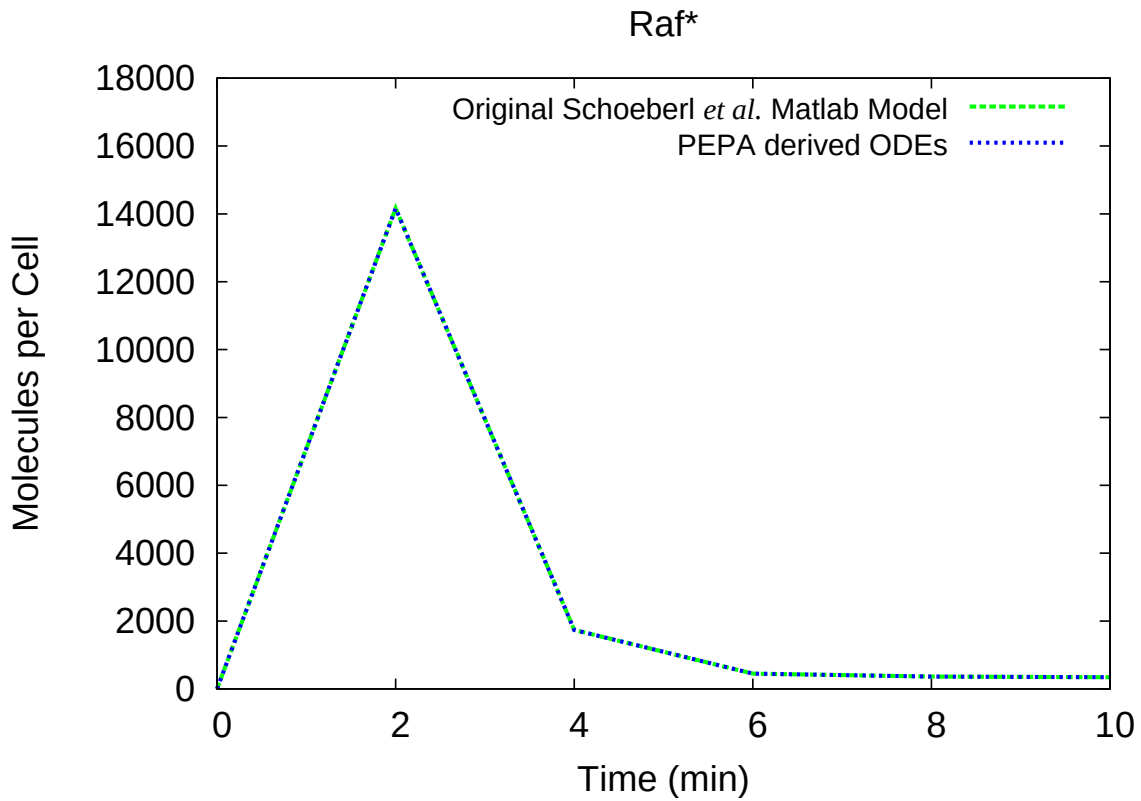
- Then we used an alternative mapping from the PEPA to generate a stochastic simulation of the system.

Comparing Original Results and PEPA Derived ODEs



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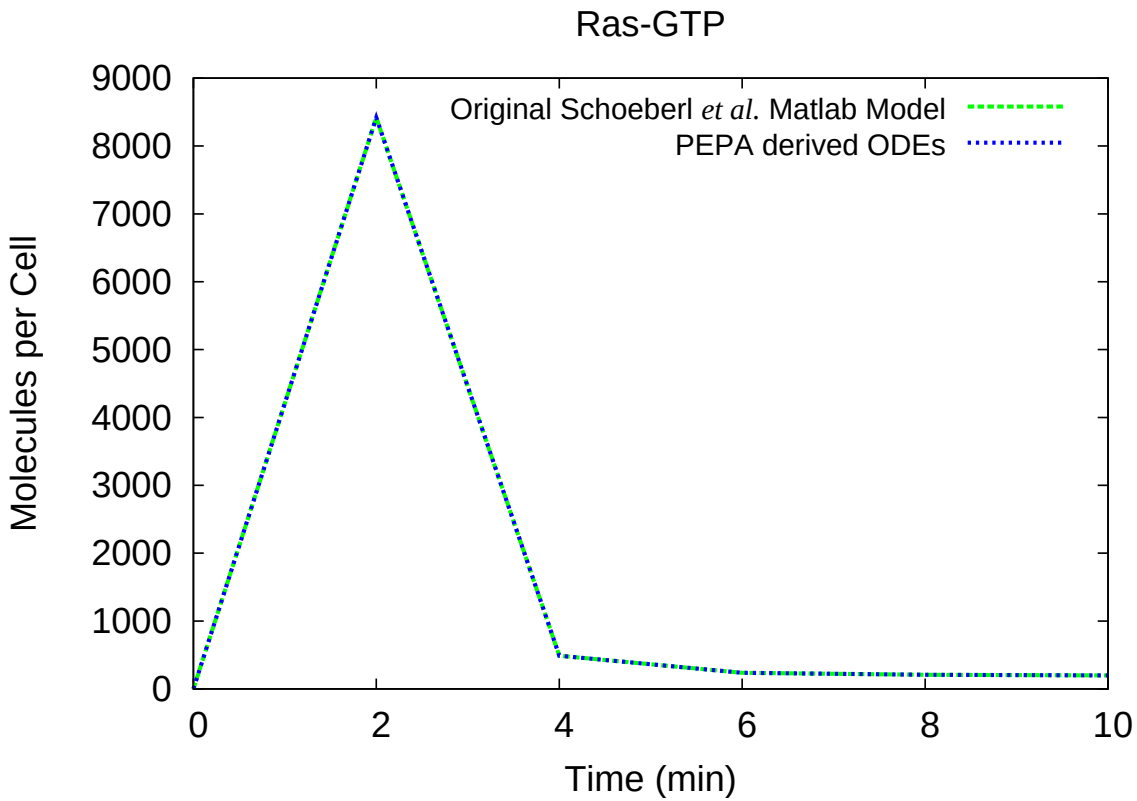
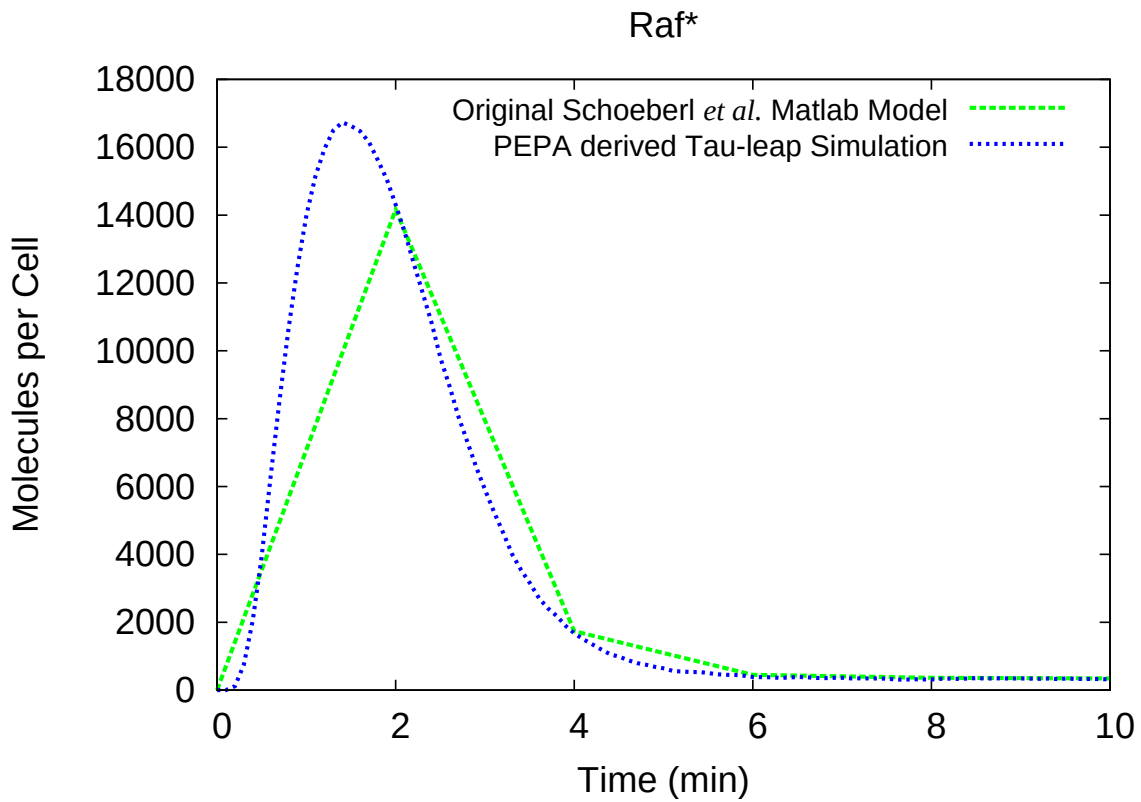


The PEPA derived ODEs return the same results as the Schoeberl *et al.* Matlab model.

Comparing Original Results and PEPA Derived Stochastic Simulation



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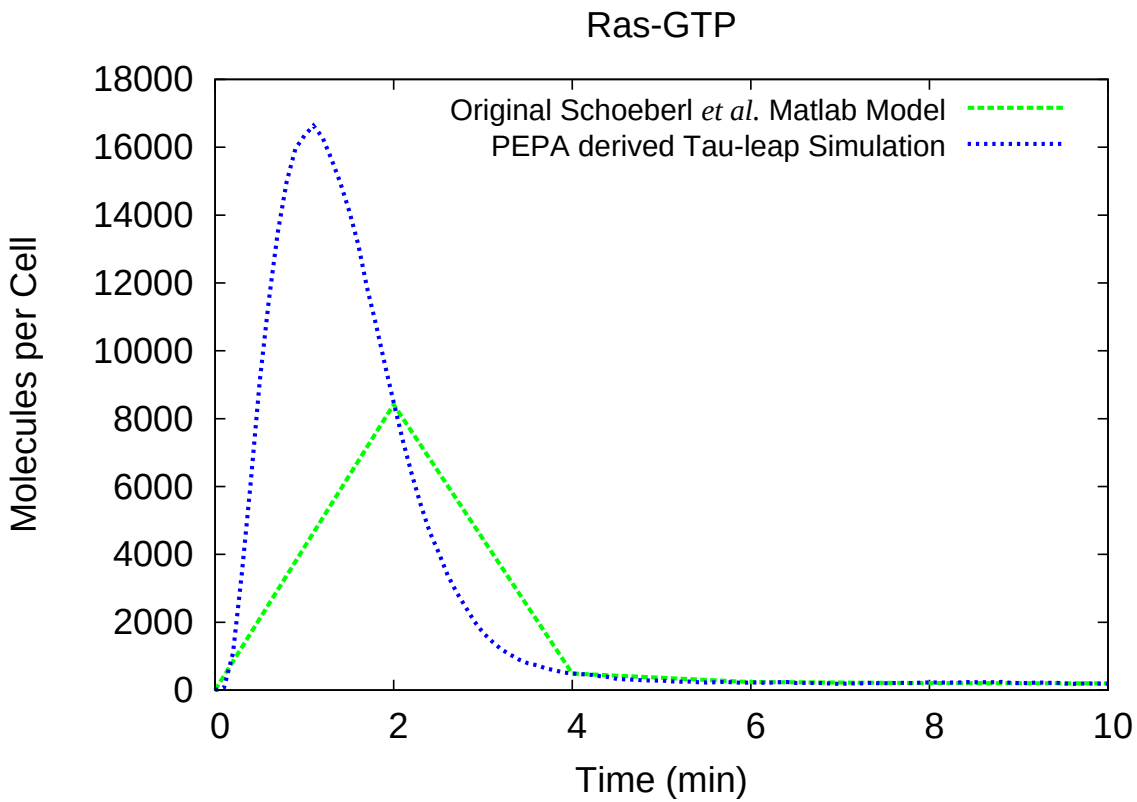
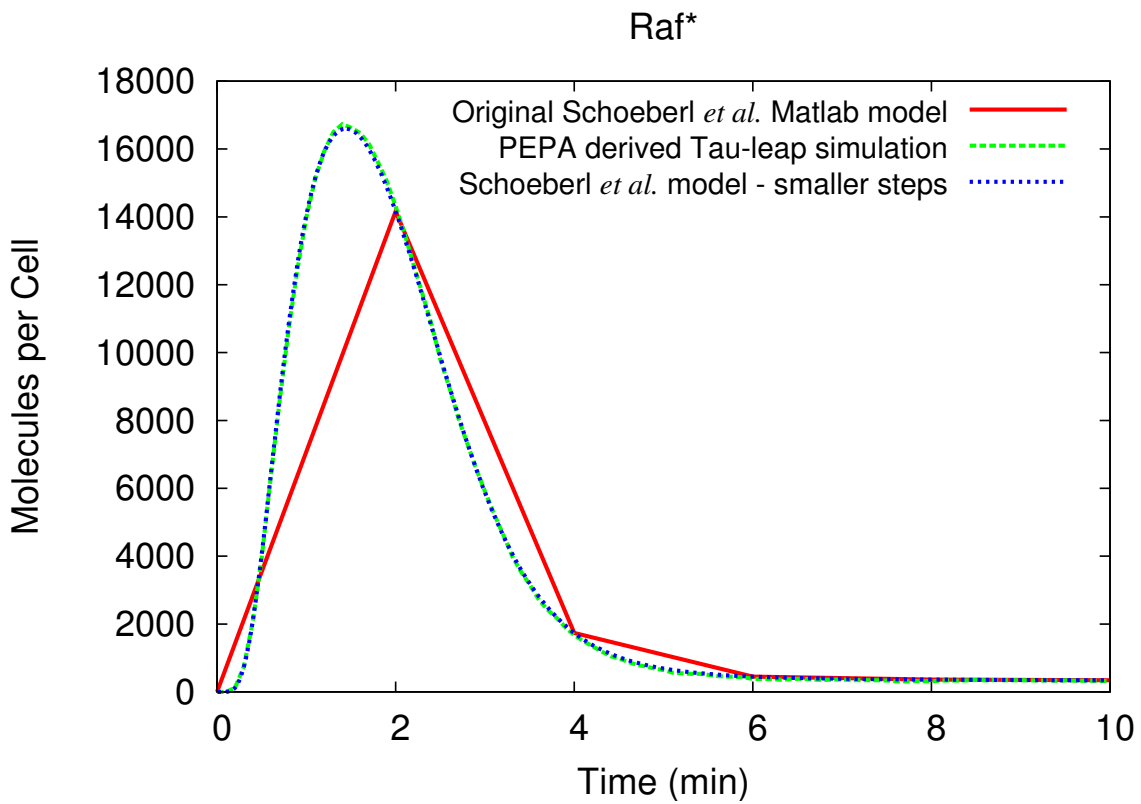


Corrected Time Step in Matlab Model



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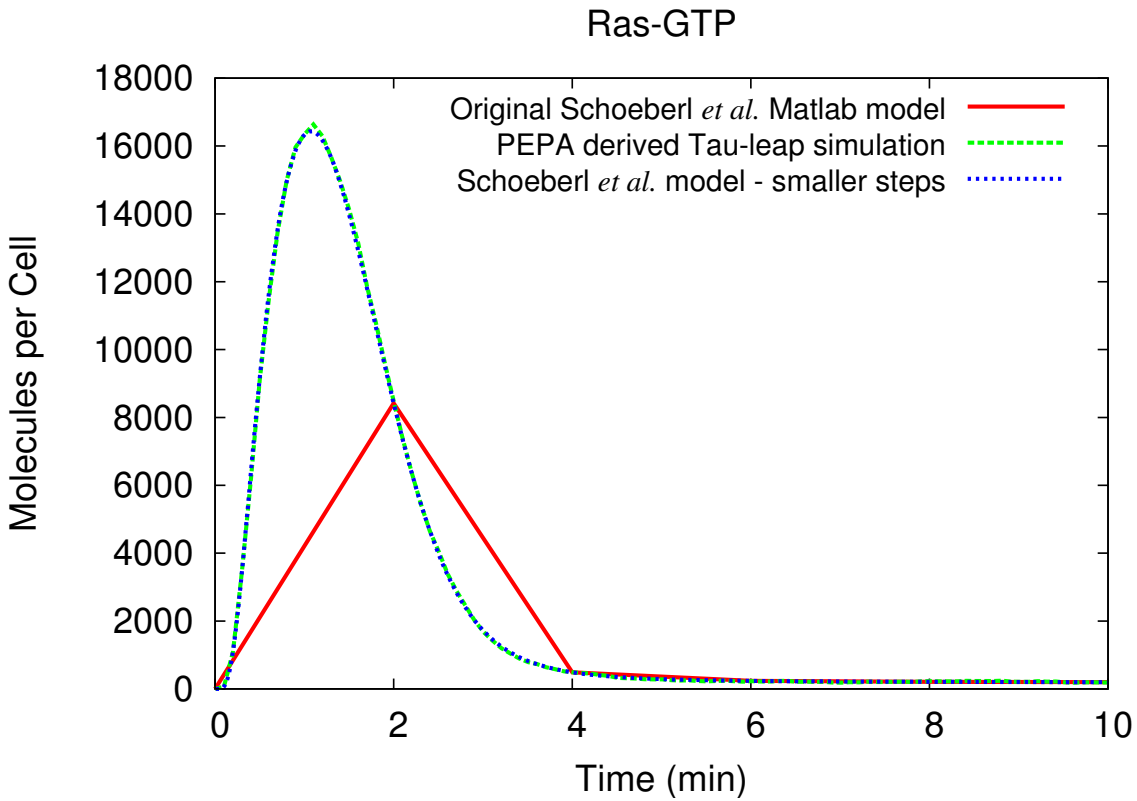


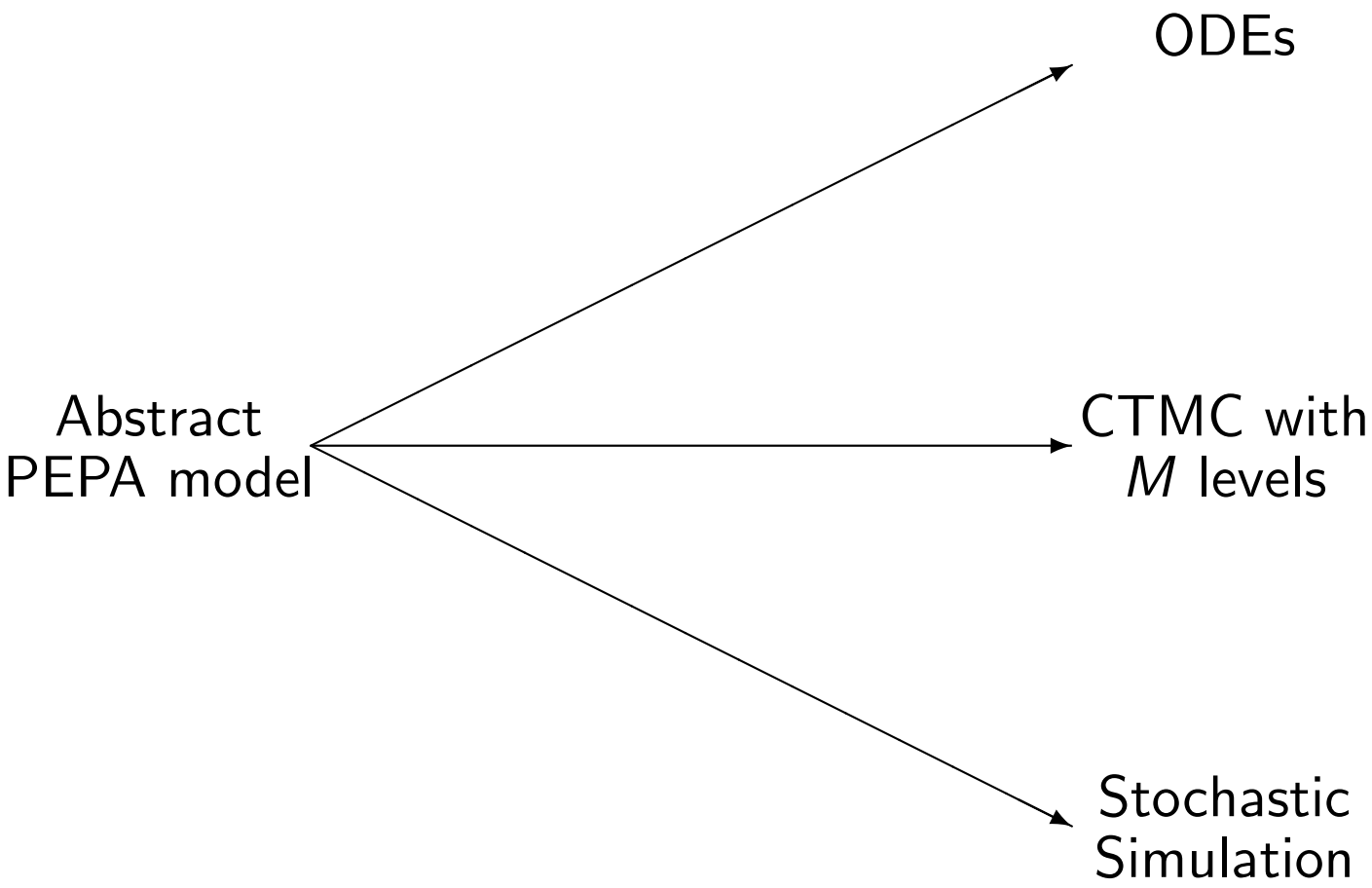
The original parameters for the Matlab model stepped over the true peak.

On-going work

On-going work on this case study is working on a Markovian analysis of the system.

This involves developing the model to have multiple levels rather than the simple distinction between high and low which is all that is needed in order to generate the ODE and stochastic simulation models.

Equivalent Representations?



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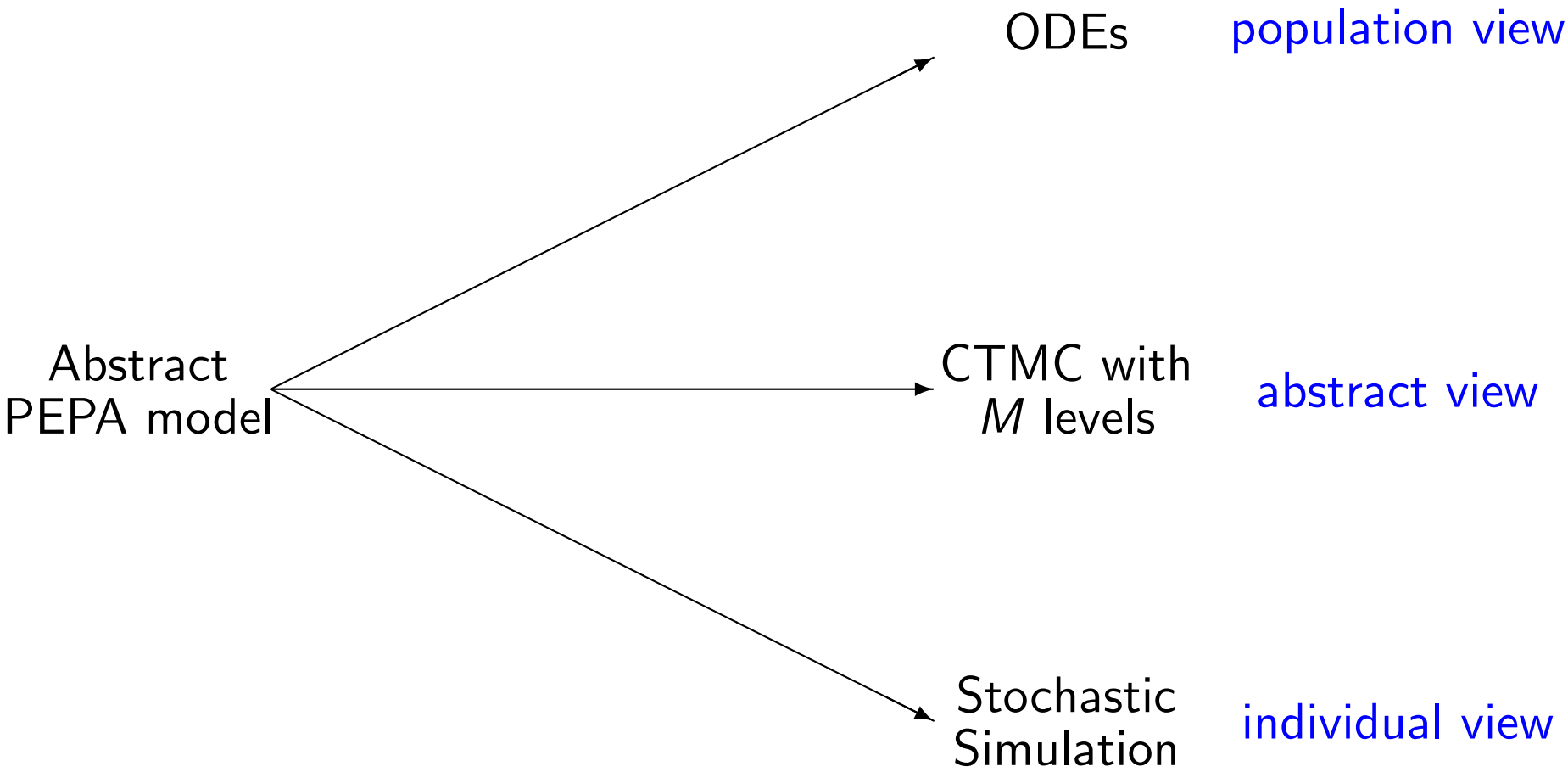

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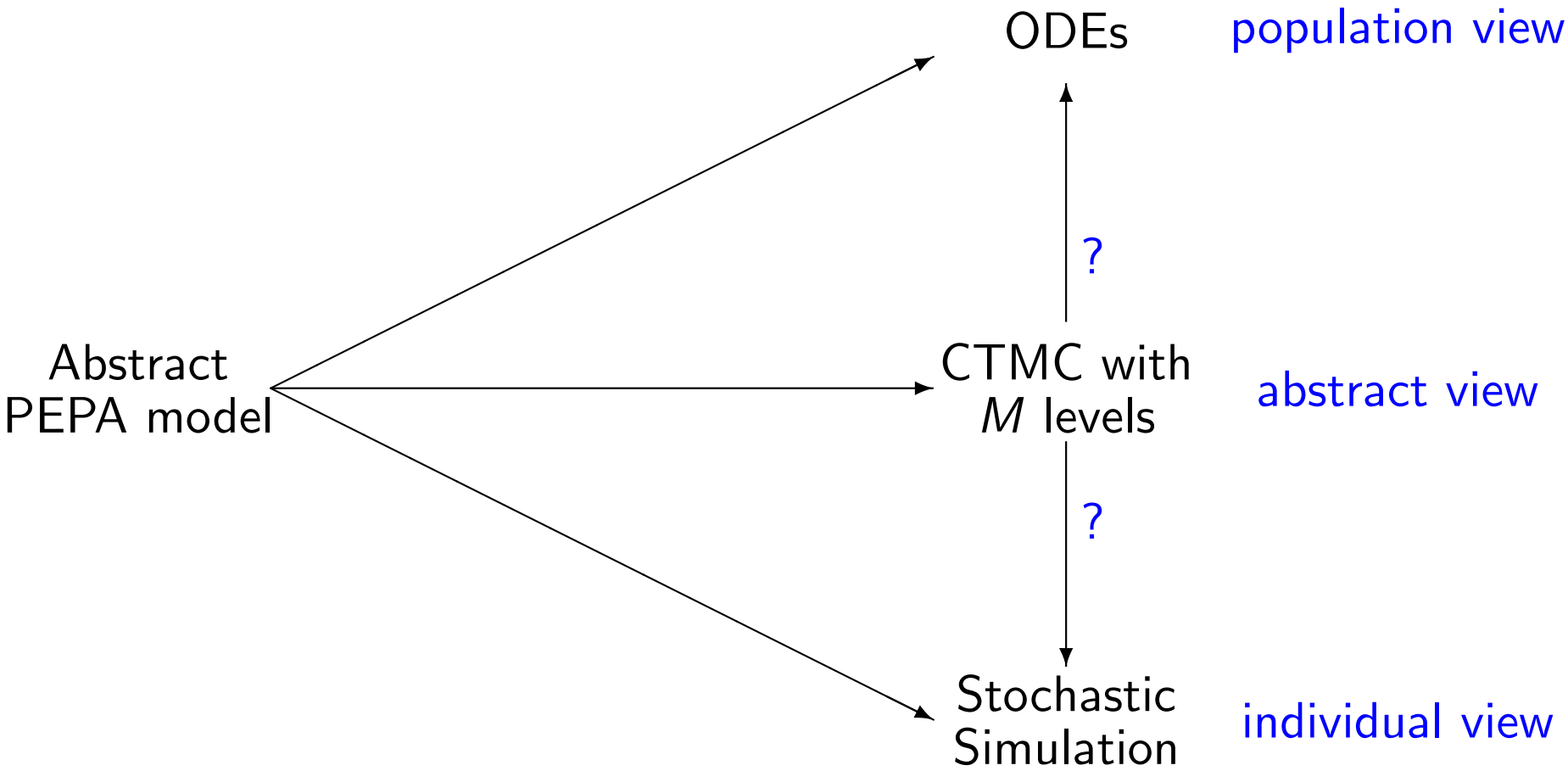

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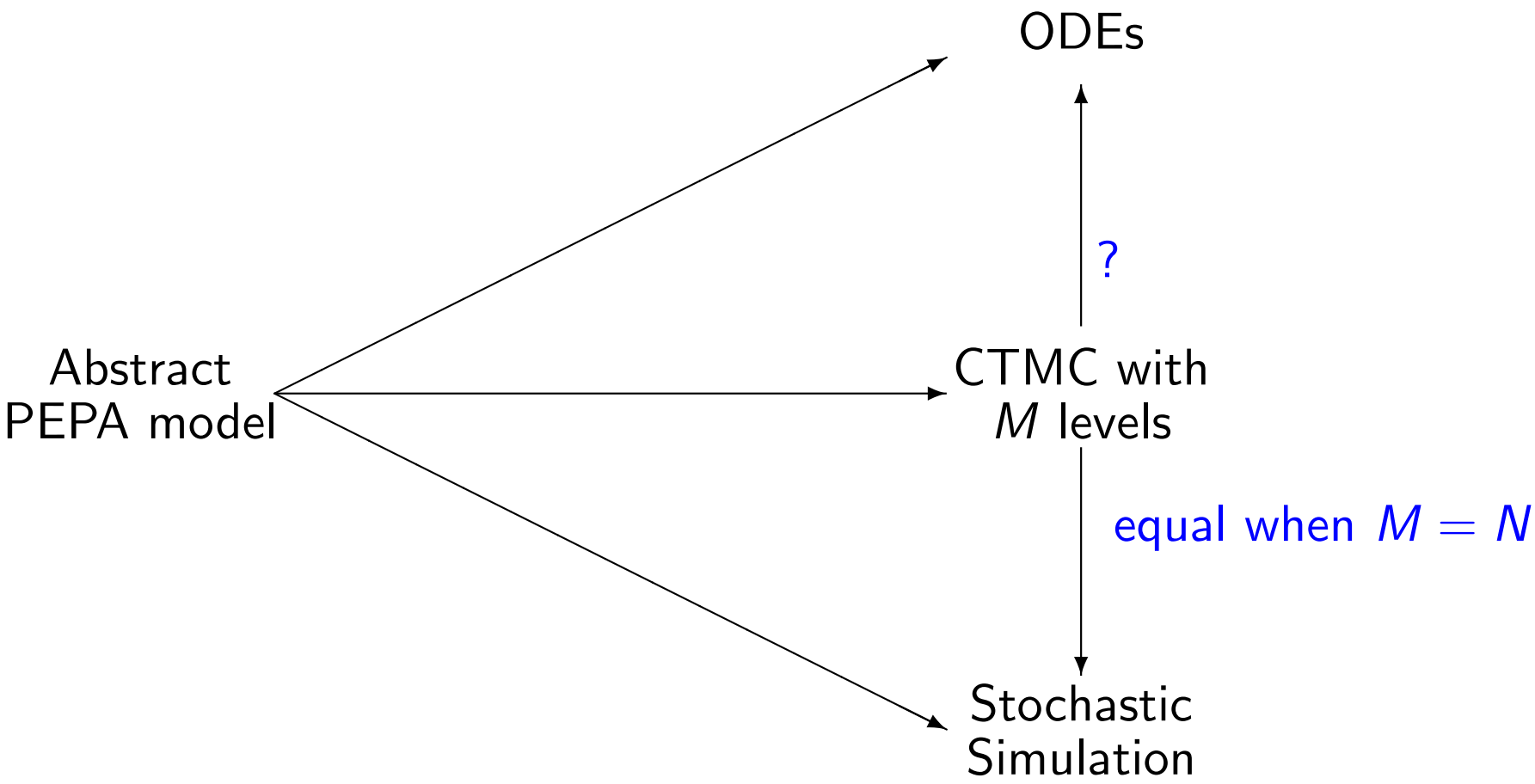

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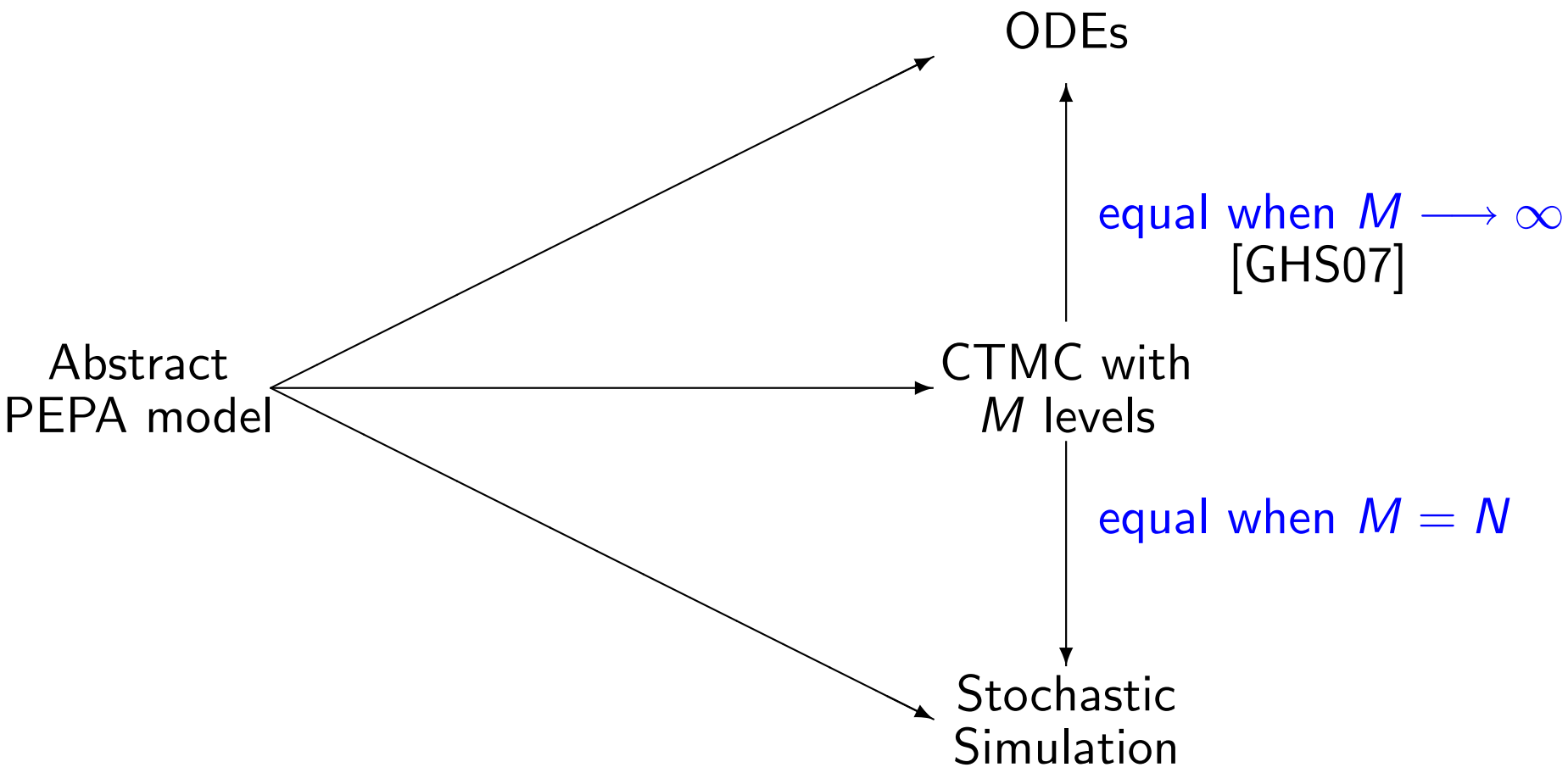

Relating CTMC and ODE models

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- Kurtz's theorem states that a sequence of pure jump Markov processes converge to a limit which coincides with a set of ODEs [Kurtz 70]. In particular this holds for a class of CTMCs which are density dependent.
- We show that the CTMCs we construct from the PEPA+ models are density dependent and so satisfy Kurtz's theorem.

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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- k is a numerical state vector and
- 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.

Outline

Summary

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- 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.

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- The abstract Markovian models allow quantities of interest such as "response times" to be expressed as probability distributions rather than single estimates. This may allow better reflection of wet lab data which showns variability.
- Promising recent work by Girolami *et al.* on assessing candidate models which attempt to cover both unknown structure and unknown kinetic rates with respect to experimental data, using Bayesian reasoning.

Conclusions

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  - 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)