Modelling Biochemical Pathways with Stochastic Process Algebra

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- The project has sought to investigate and exploit the interplay between the process algebra and the continuous time Markov chain (CTMC).

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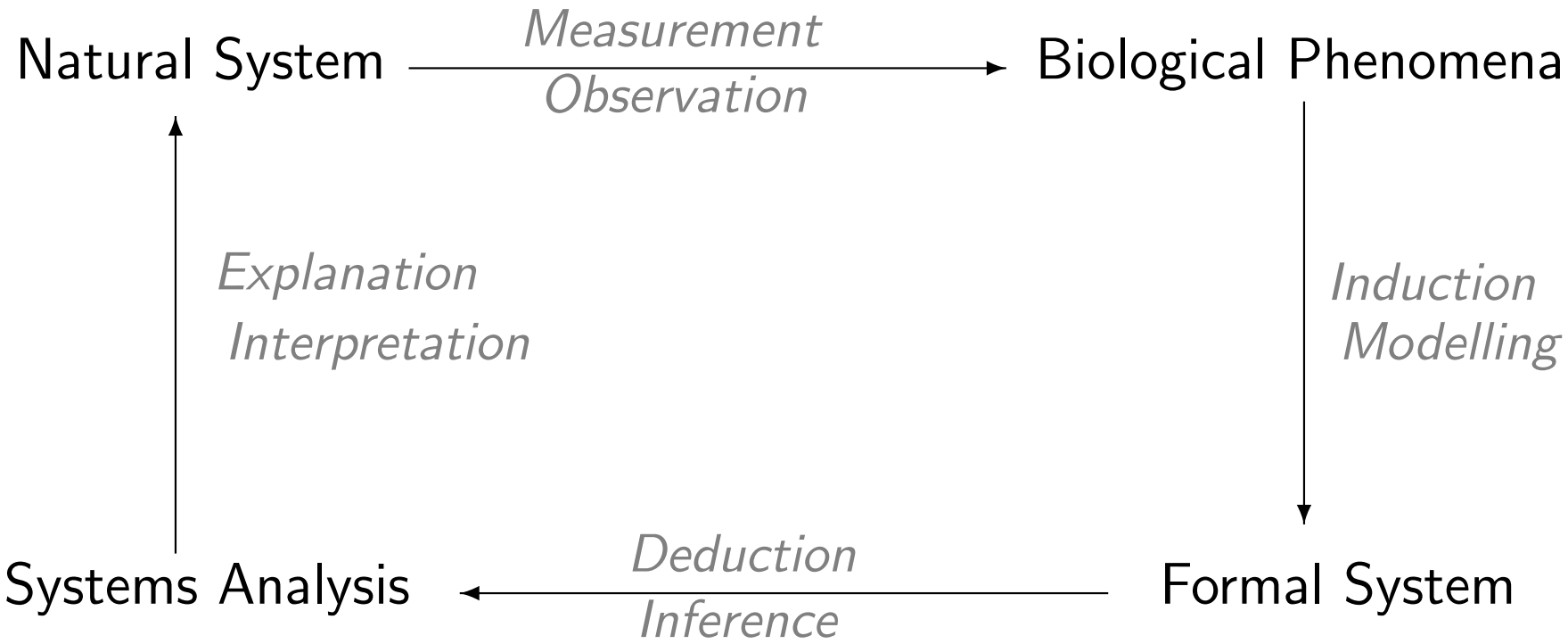
- Systems biology aims to develop a better understanding of the processes involved.
- It involves taking a systems theoretic view of biological processes — analysing inputs and outputs and the relationships between them.
- A radical shift from earlier reductionist approaches, systems biology aims to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

Systems Biology Methodology



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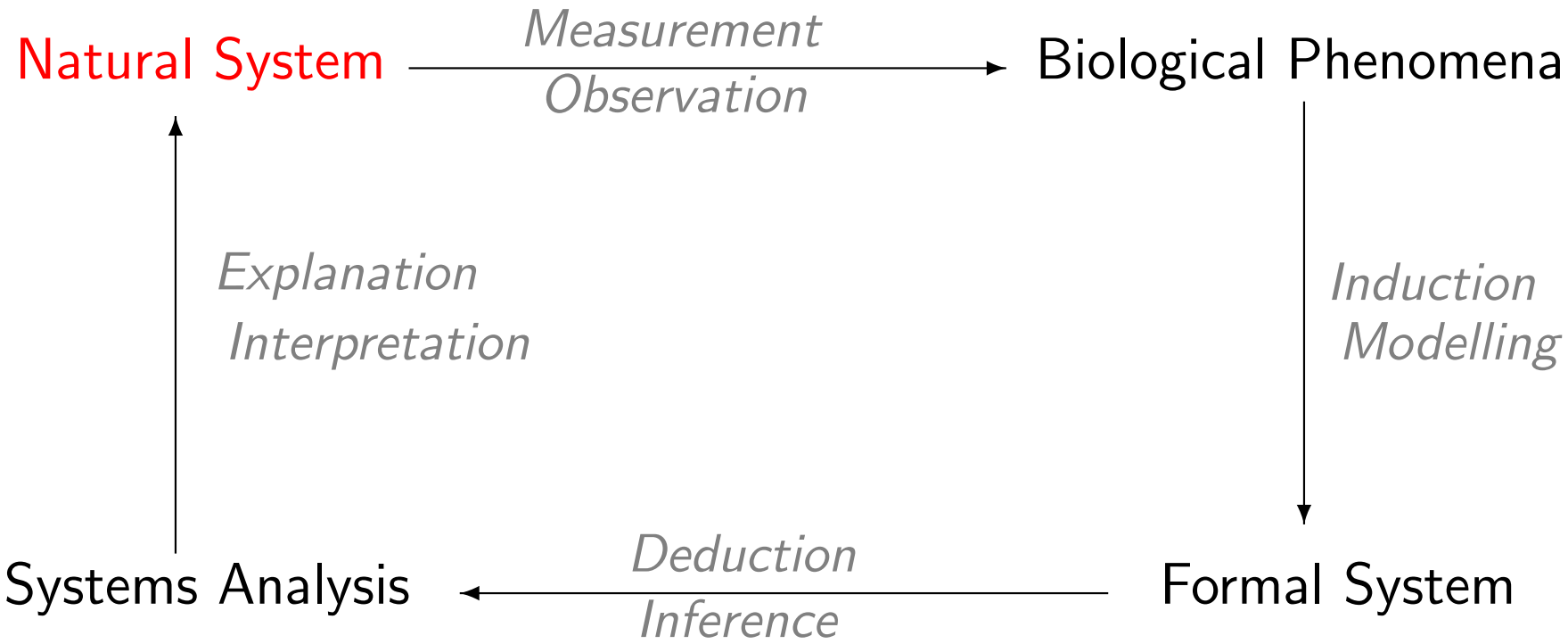

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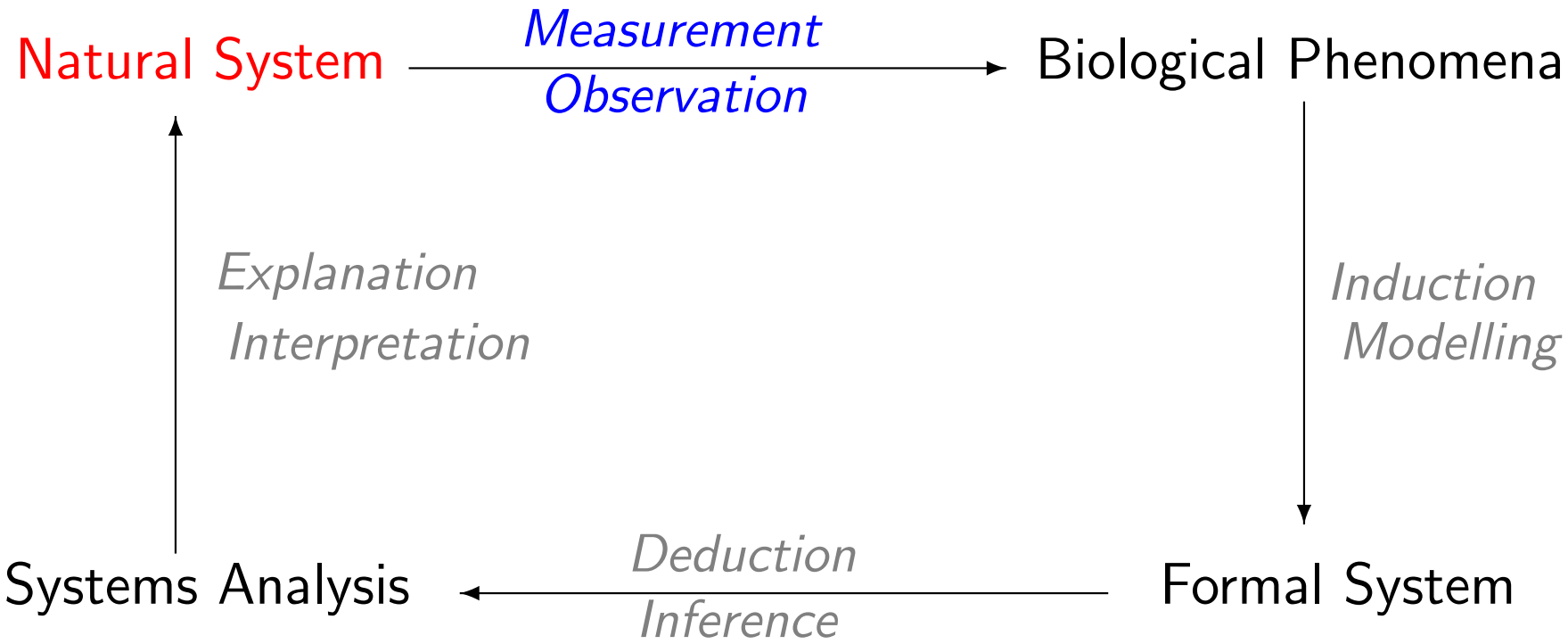

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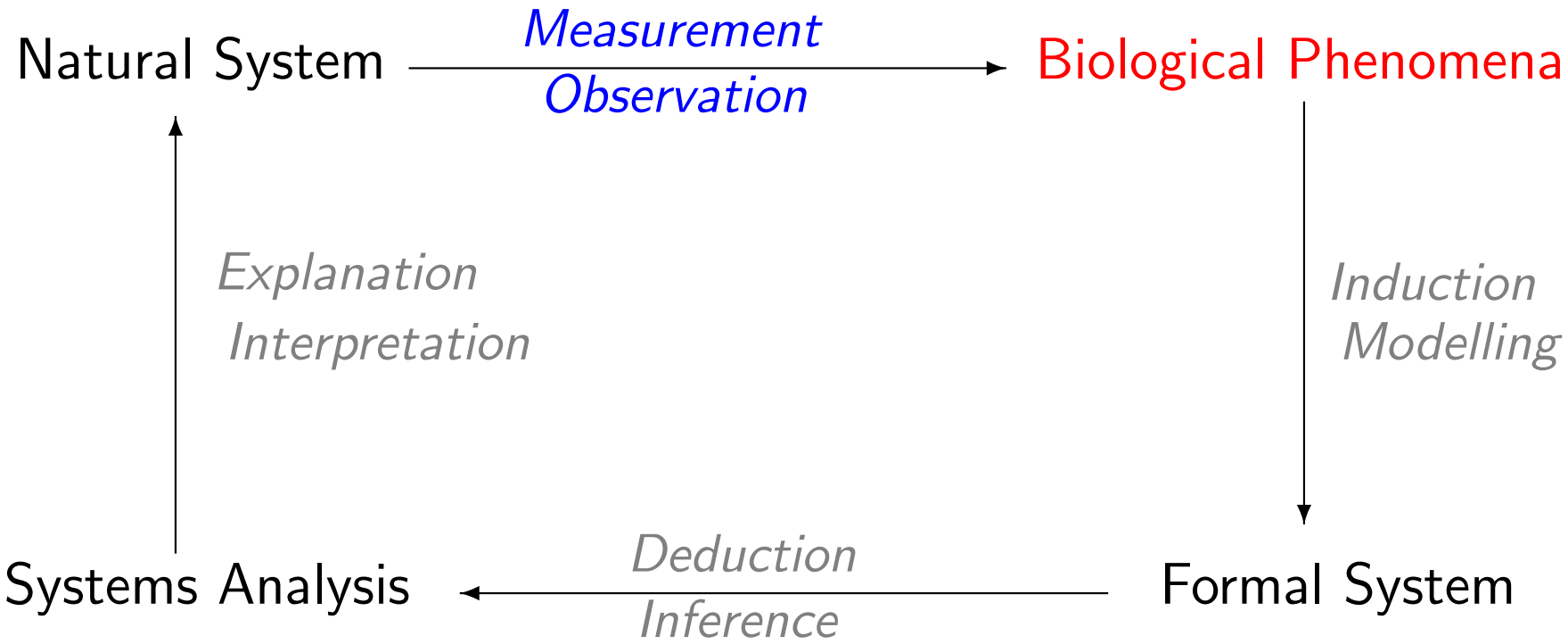

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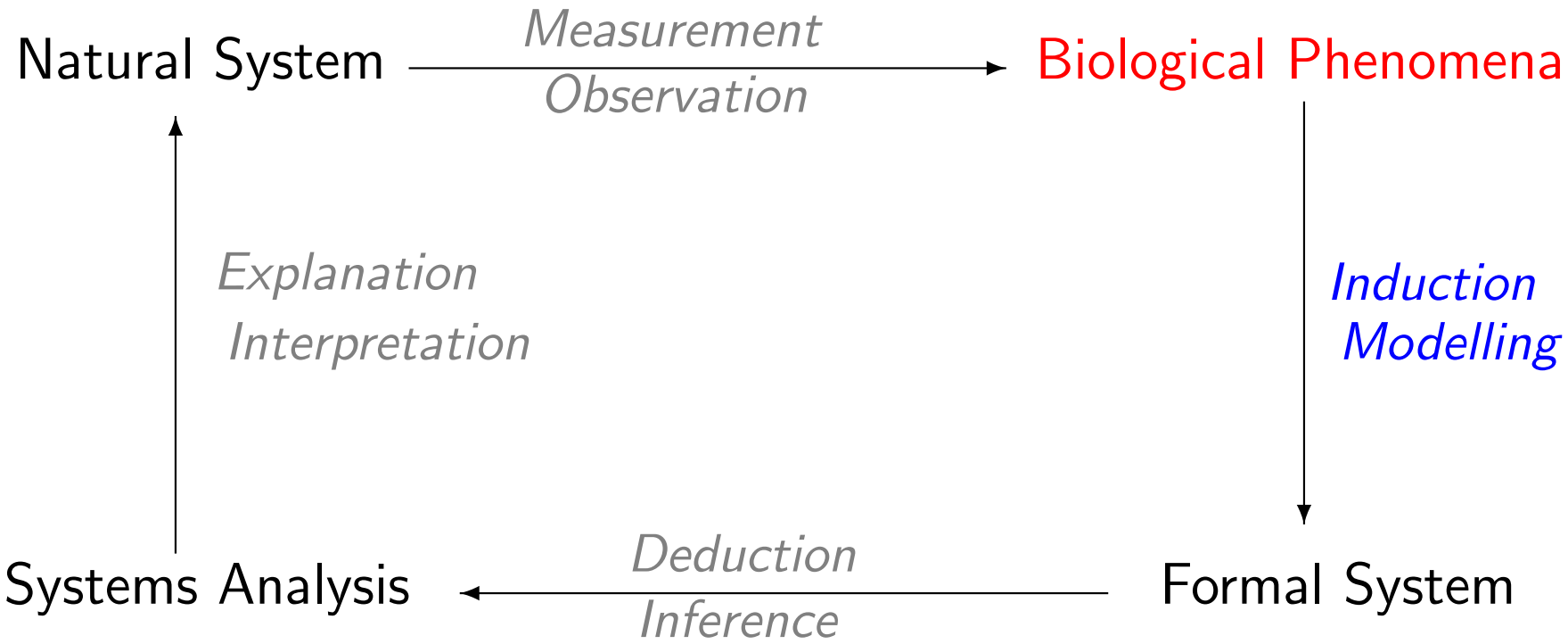

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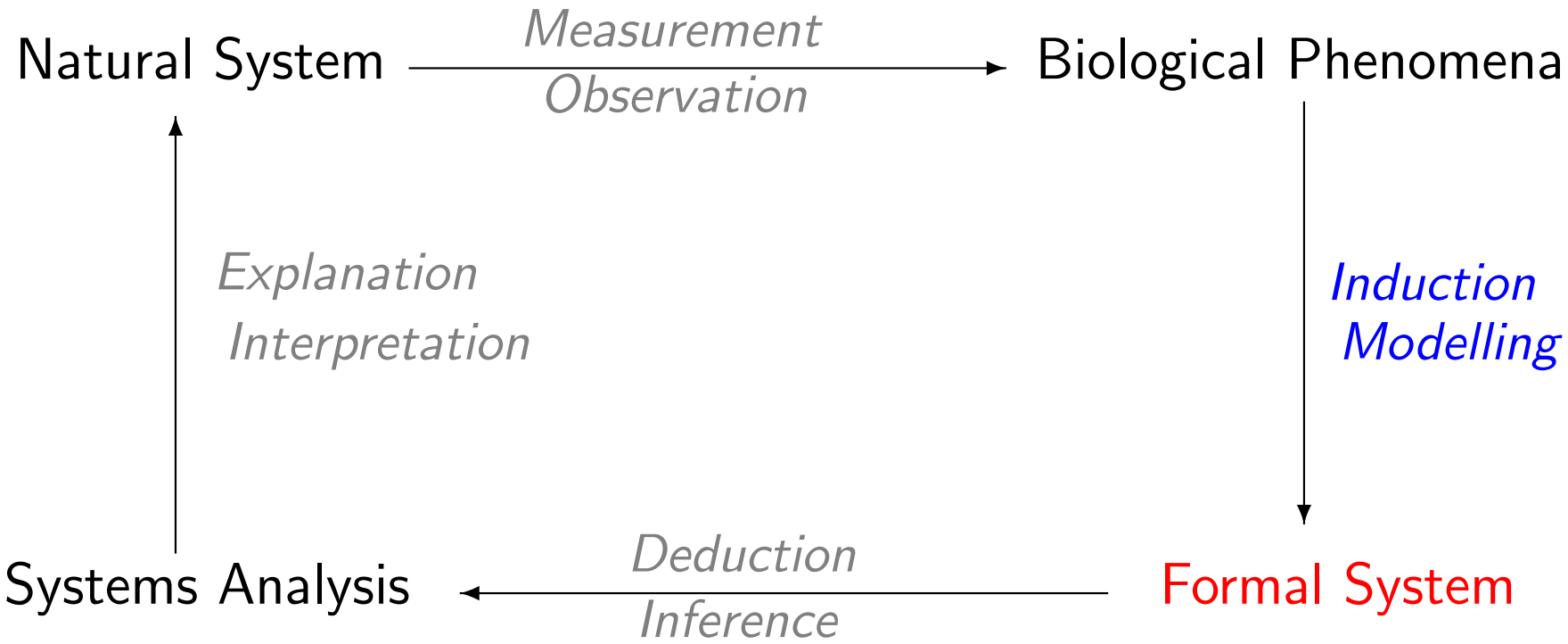

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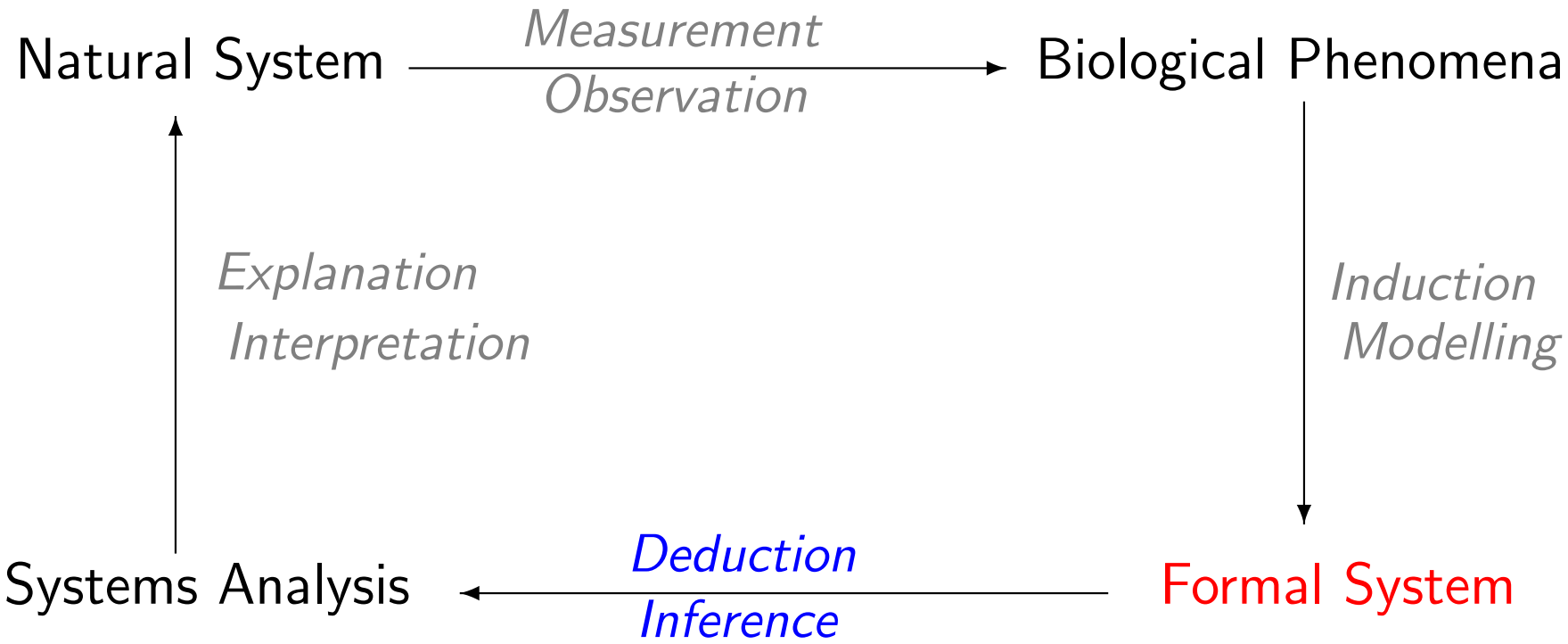

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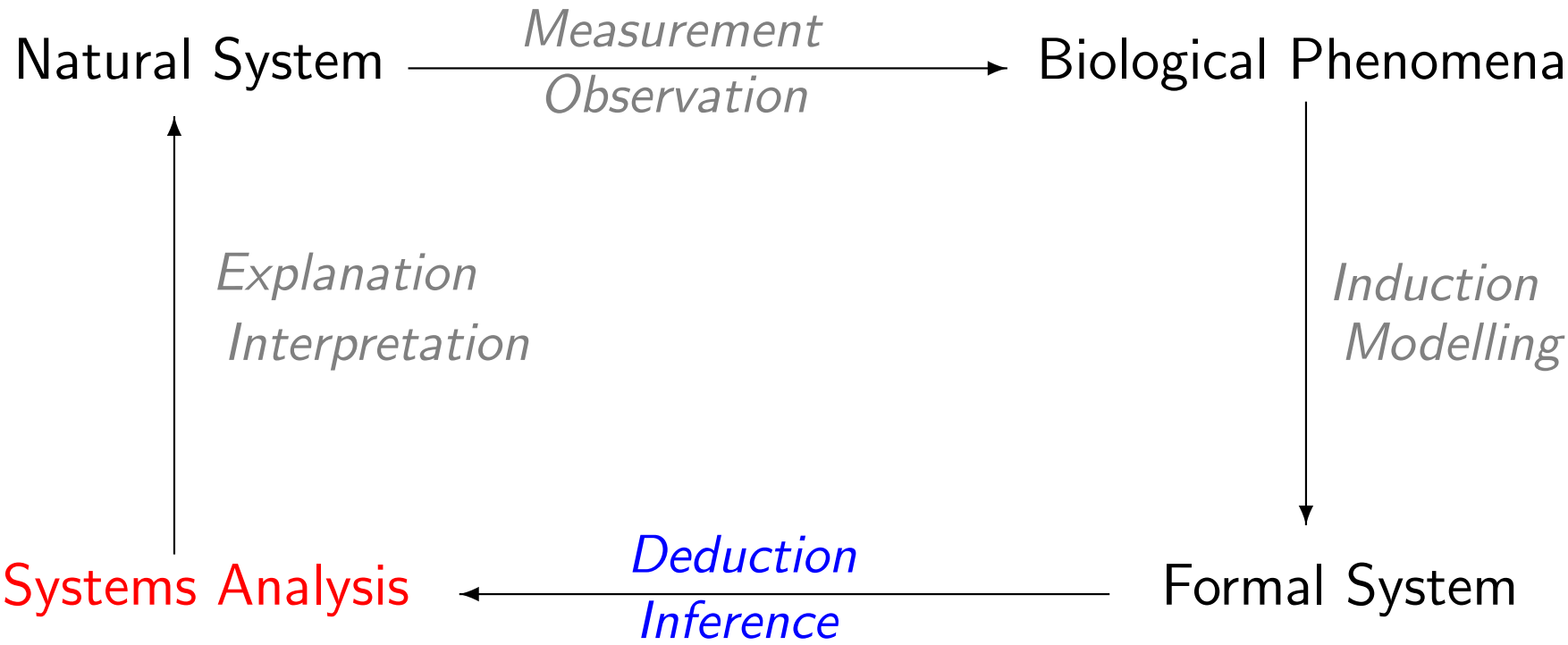

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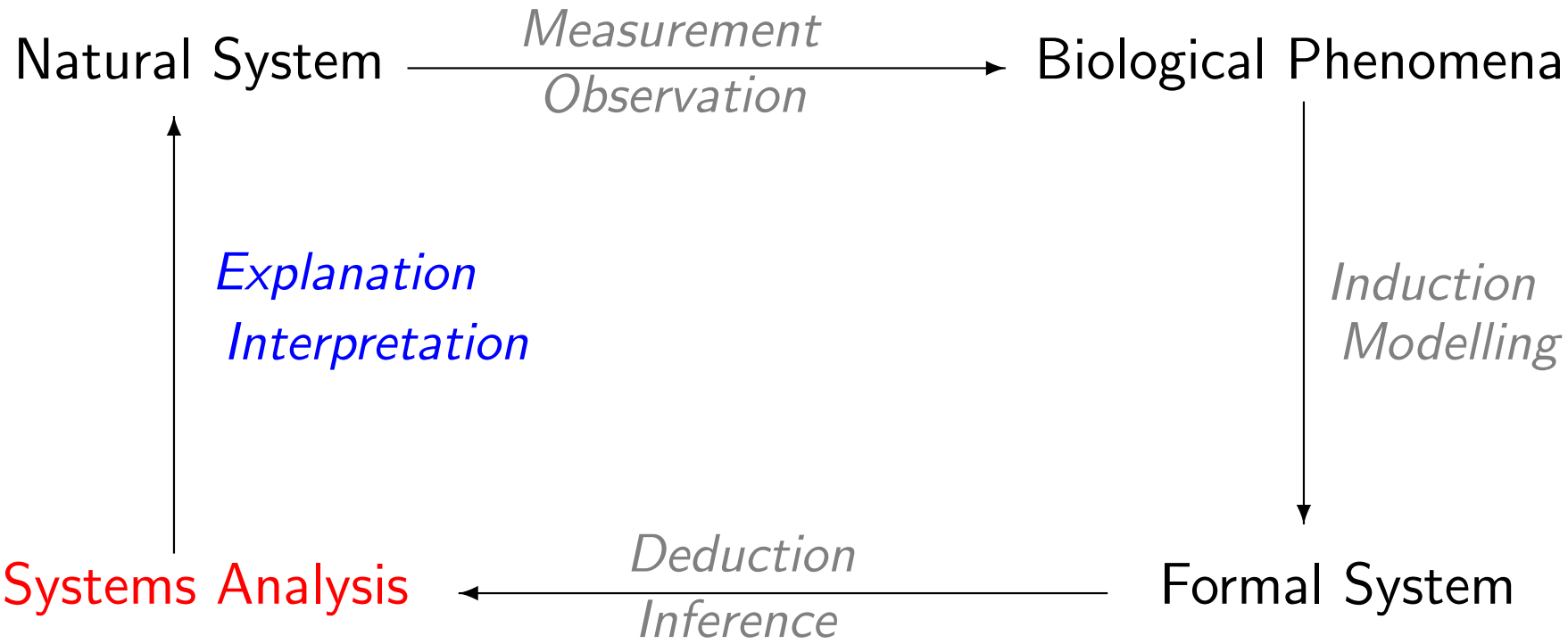

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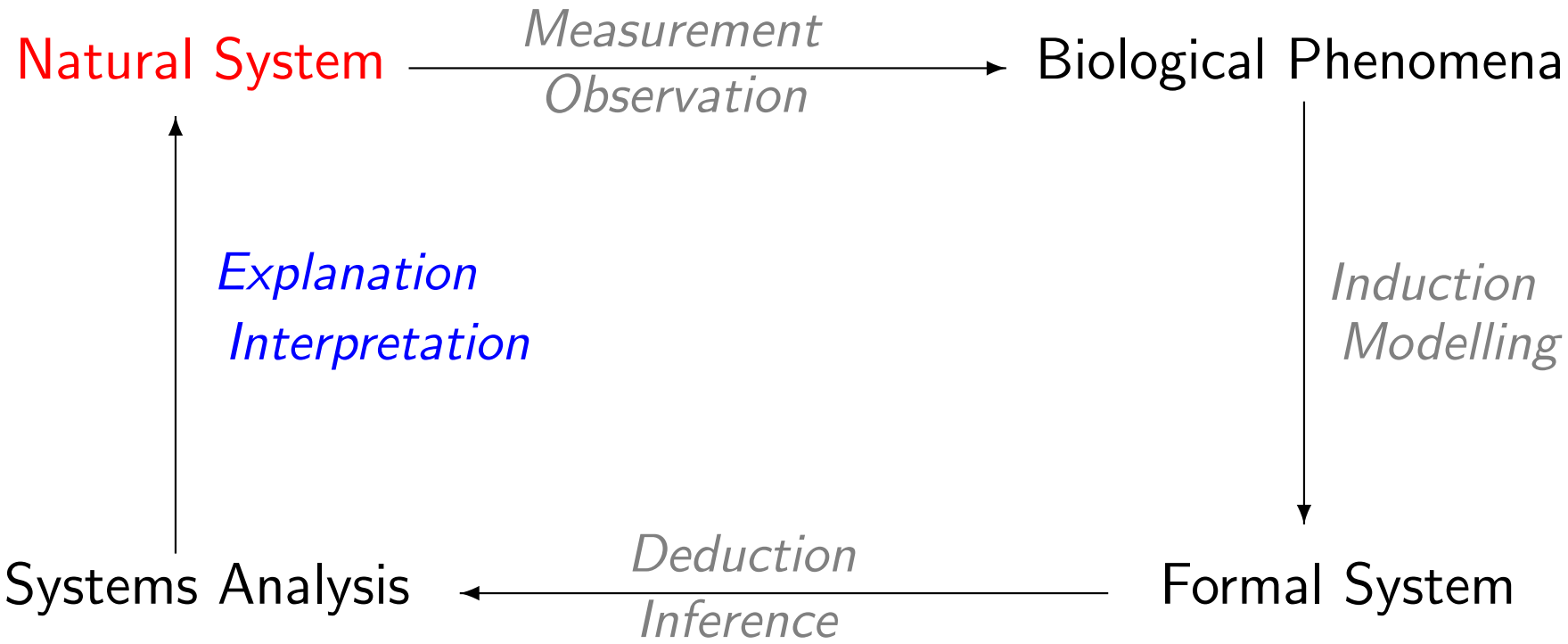

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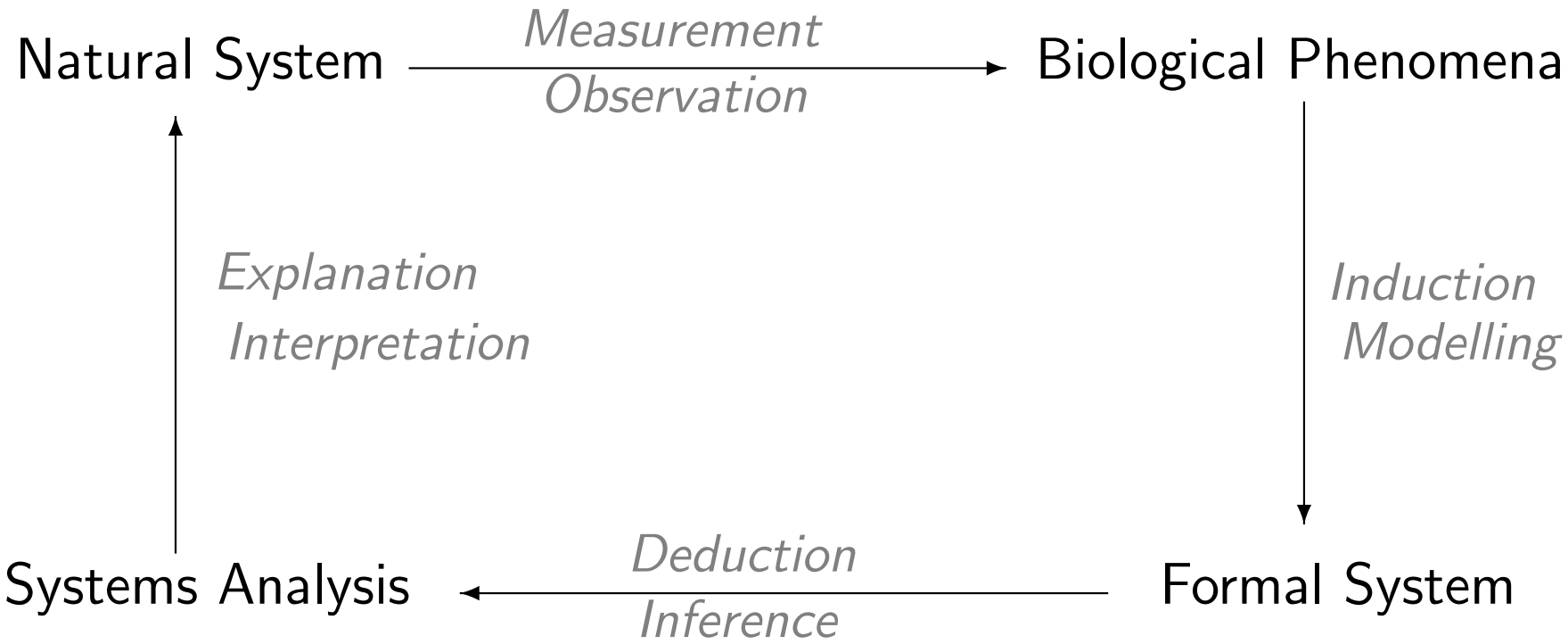

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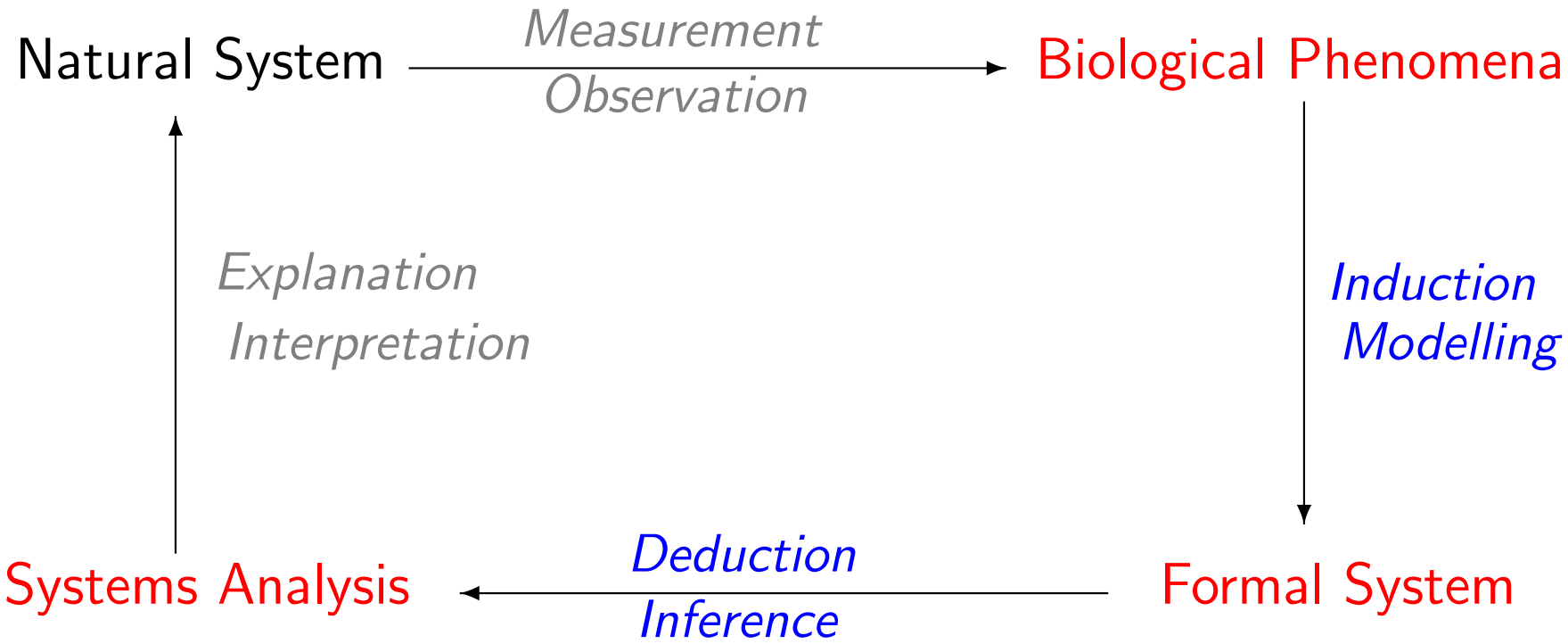

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- The biological phenomena to be studied will clearly depend on the type of system being investigated.
- A grand challenge for systems biology is to develop multi-scale models which seek to account for high-level behaviour (at the level of the whole organisms) at all levels down to the intra-cellular processes.

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

Signal transduction pathways

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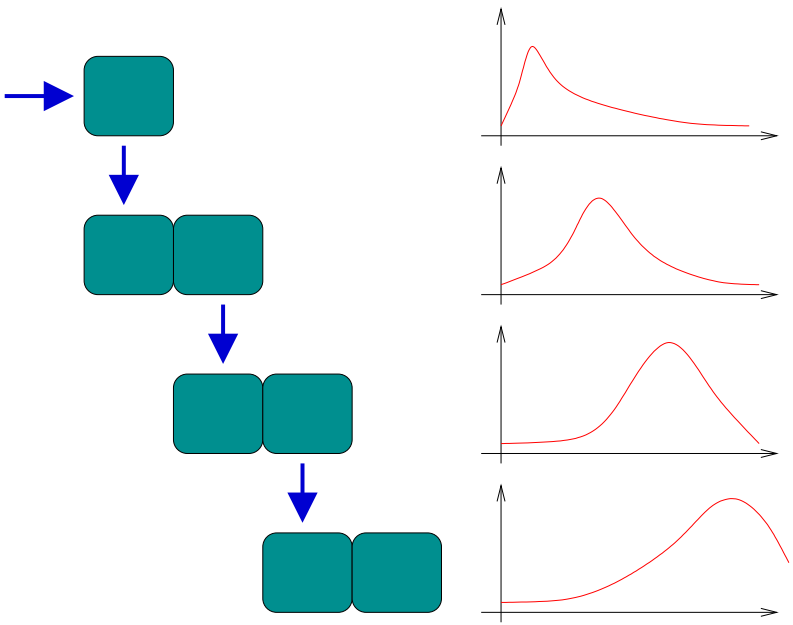

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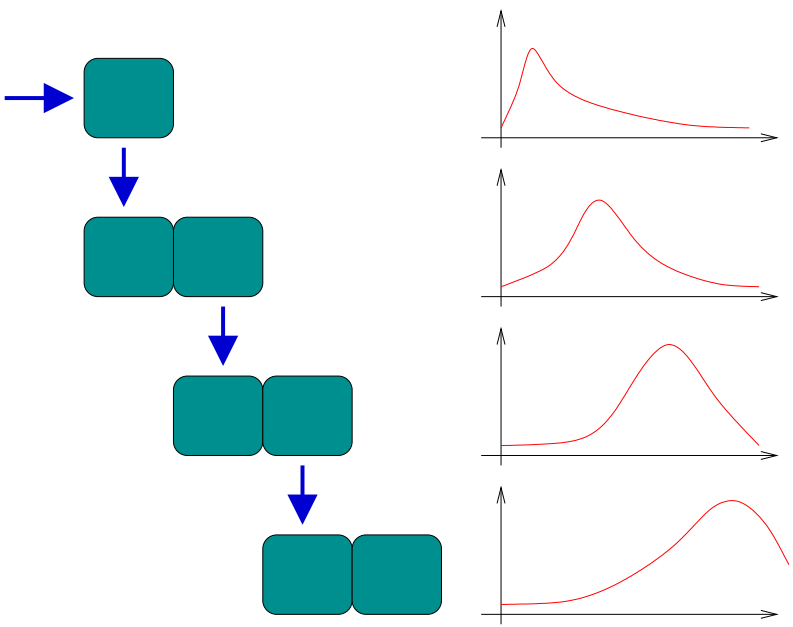

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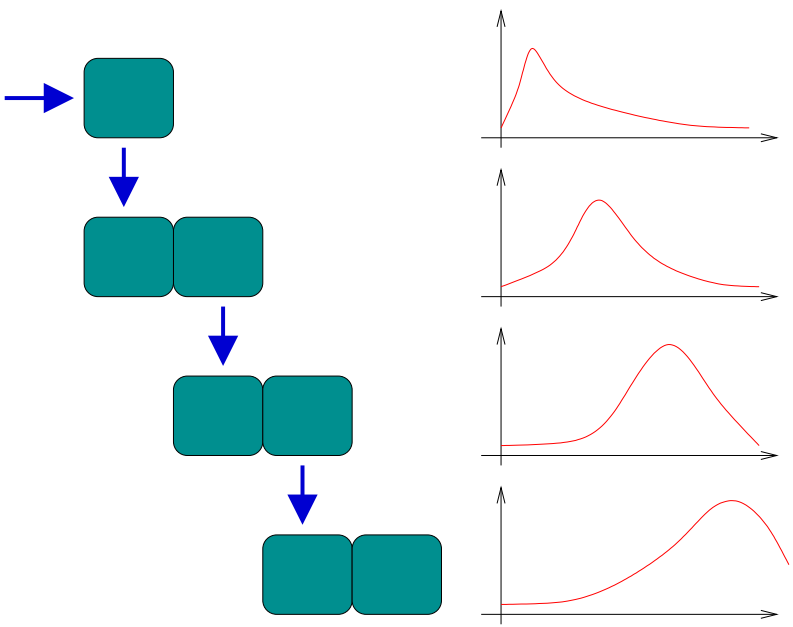

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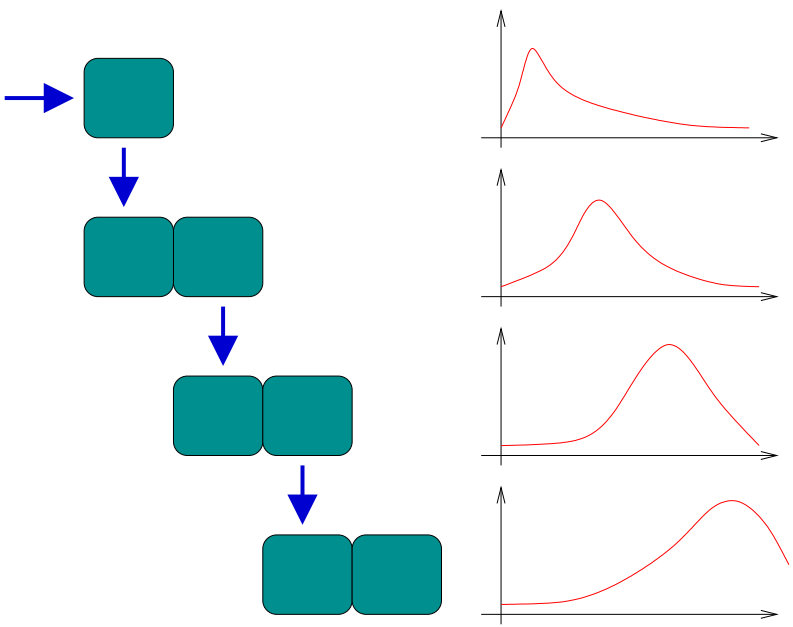

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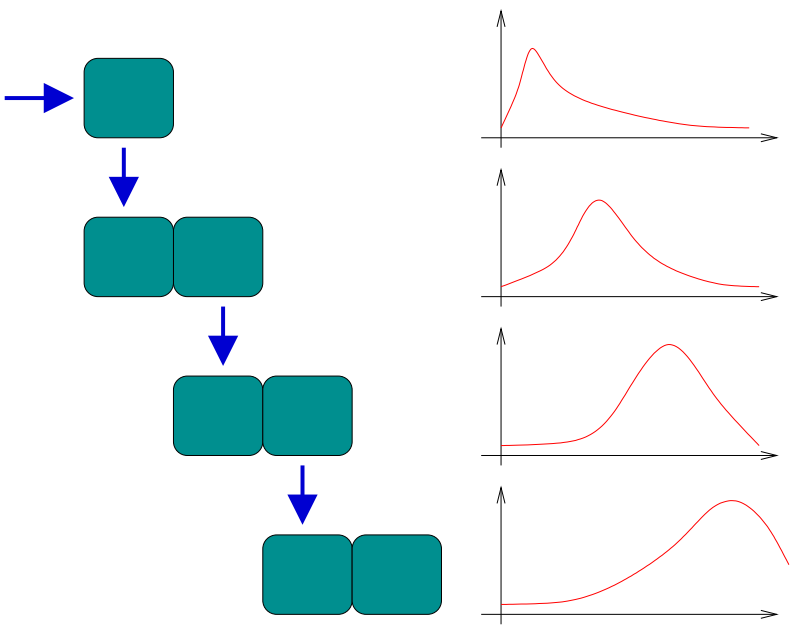
- Signals propagate through a series of protein accumulations.



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

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

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

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

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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, and re-arranging the former, leads us to an important *partial differential equation* (PDE) known as the Chemical Master Equation (CME).

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

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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 are the data that can be collected from wet lab experiments.
- The accumulation of protein is a stochastic process affected by several factors in the cell (temperature, pH, etc.).
- Thus it is more realistic to talk about a distribution rather than a deterministic time.

Case Study: Circadian Rhythms – Overview

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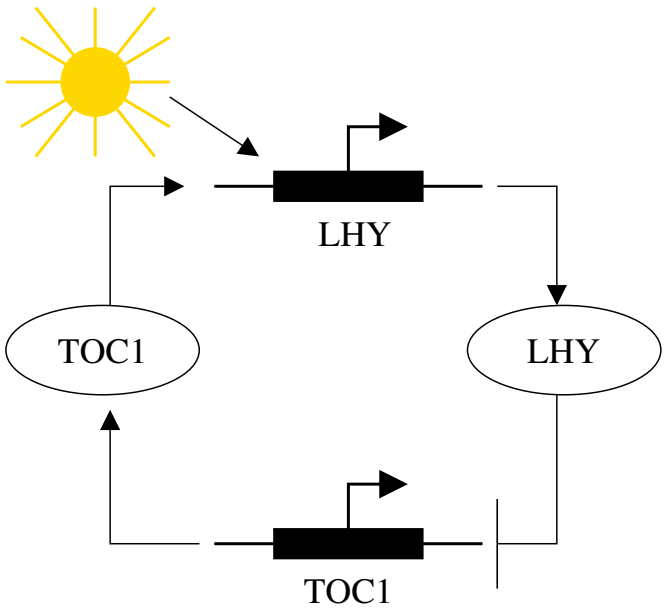
It is held up as an exemplar of what systems biology is trying to achieve, and the breakthroughs that it can bring about when it is successful.

Case Study: Circadian Rhythms – Initial Model

From initial experiments Locke *et al.* identified a two genes and two proteins which appeared to operate in a simple loop:



An initial mathematical model (ODEs) was constructed to capture this model.

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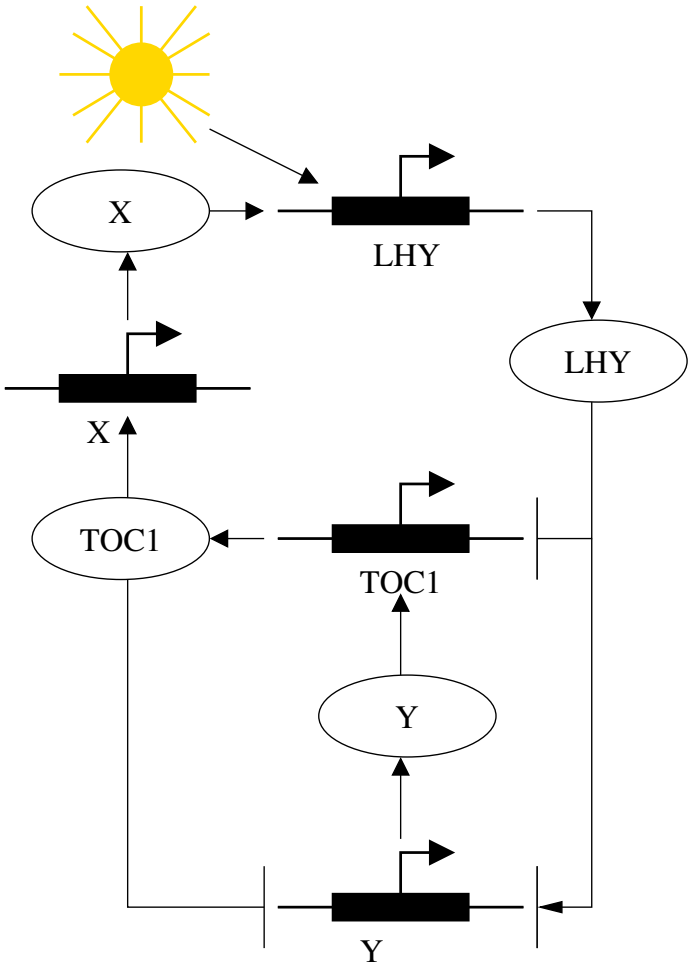
These mathematical experiments conjectured a network with two interacting loops.

Case Study: Circadian Rhythms – Elaborated Model



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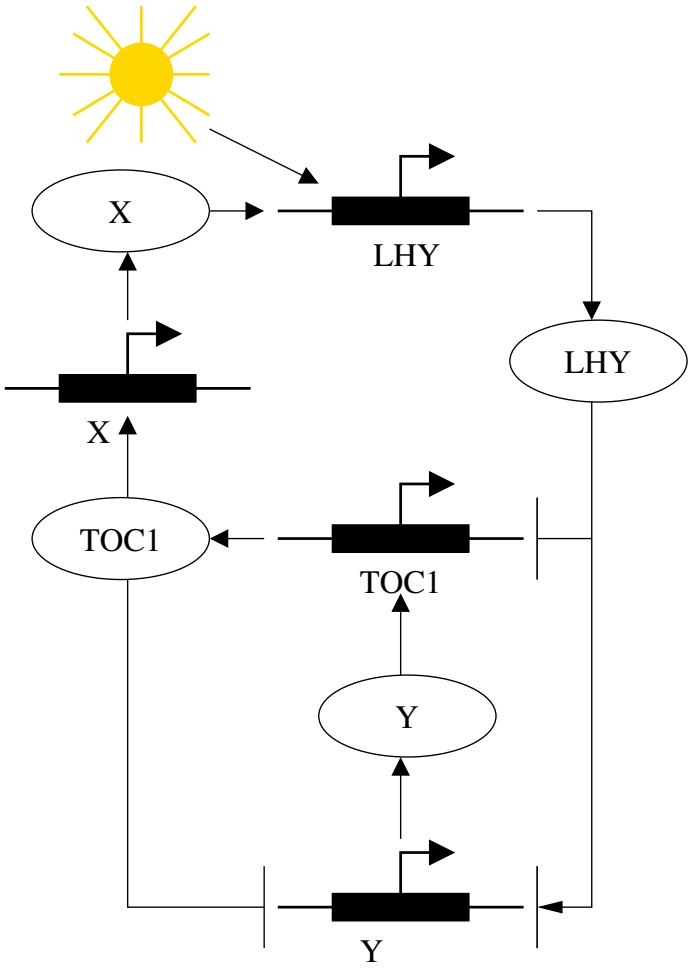

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The simulation results from this model showed much better agreement with the observed data.

Case Study: Circadian Rhythms – Validating the Model

The researchers then sought to identify the "new" genes X and Y.

Searching the literature elicited several candidate genes which previous experimental studies had suggested were implicated in the circadian rhythm.

In particular, "knockout" data for one, GIGANTEA (GI), coincided with the pattern from simulation experiments of the original model with a single loop.

Subsequent wet lab experiments have reinforced this impression that GI is gene Y.

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- The experiments showed that MGS was not viable: the cell could not survive in simulation.
- 76 genes were found to be functionally duplicated and 7 additional genes were added to form VICE.

Case Study: The VICE project – In silico experimentation

- Many different alternative gene sets were possible on the basis of the original model and experiments.

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- The steady state distribution of the concentrations of virtual metabolites was similar to that measured for bacteria experimentally.

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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.

Outline

Individual vs. Population behaviour

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- These should be regarded as alternatives, each being appropriate for some models. The challenge then becomes when to use which approach.
- Note that given a large enough number of molecules an "individuals" model will (in many circumstances) be indistinguishable from the a "population" level model.

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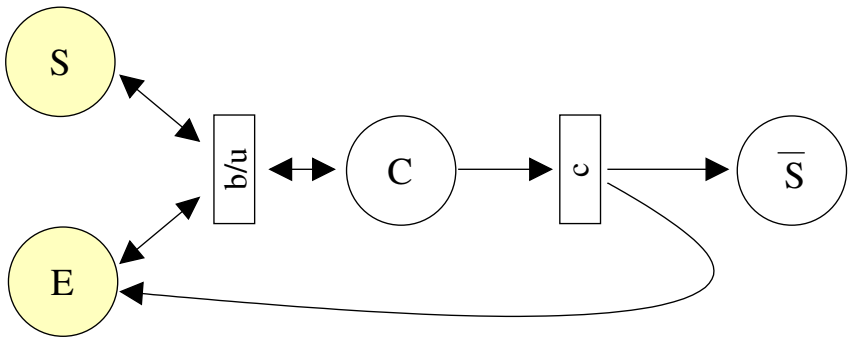
- When a large number of such reactions occur, the randomness of the individual reactions can cancel each other out and the apparent behaviour exhibits less variability.
- However, in some systems the variability in the stochastic behaviour plays a crucial role in the dynamics of the system.

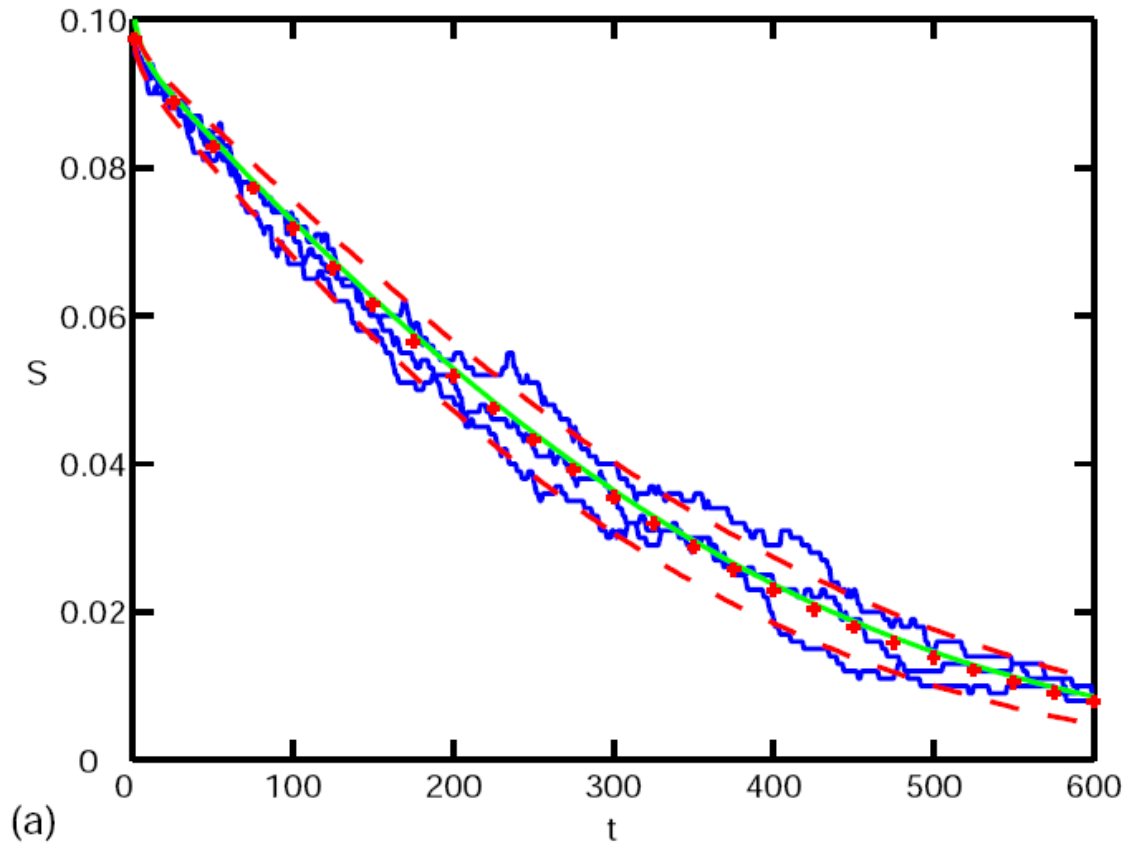
Comparing stochastic simulation and ODEs

Consider a Michaelis Menten reaction in which a substrate S is transformed to a product $\overline{S}$ via a complex C formed with an enzyme E.



It is relatively straightforward to contrast the results of the two methods. We compare the results of 2000 runs of the stochastic algorithm simulating a system with initial molecular populations $S_0 = 100, E_0 = 10, C_0 = 0, \overline{S}_0 = 0$ and a volume of 1000 units.

Results for $S_0 = 100, E_0 = 10, C_0 = 0, \overline{S}_0 = 0$ (vol 1000)



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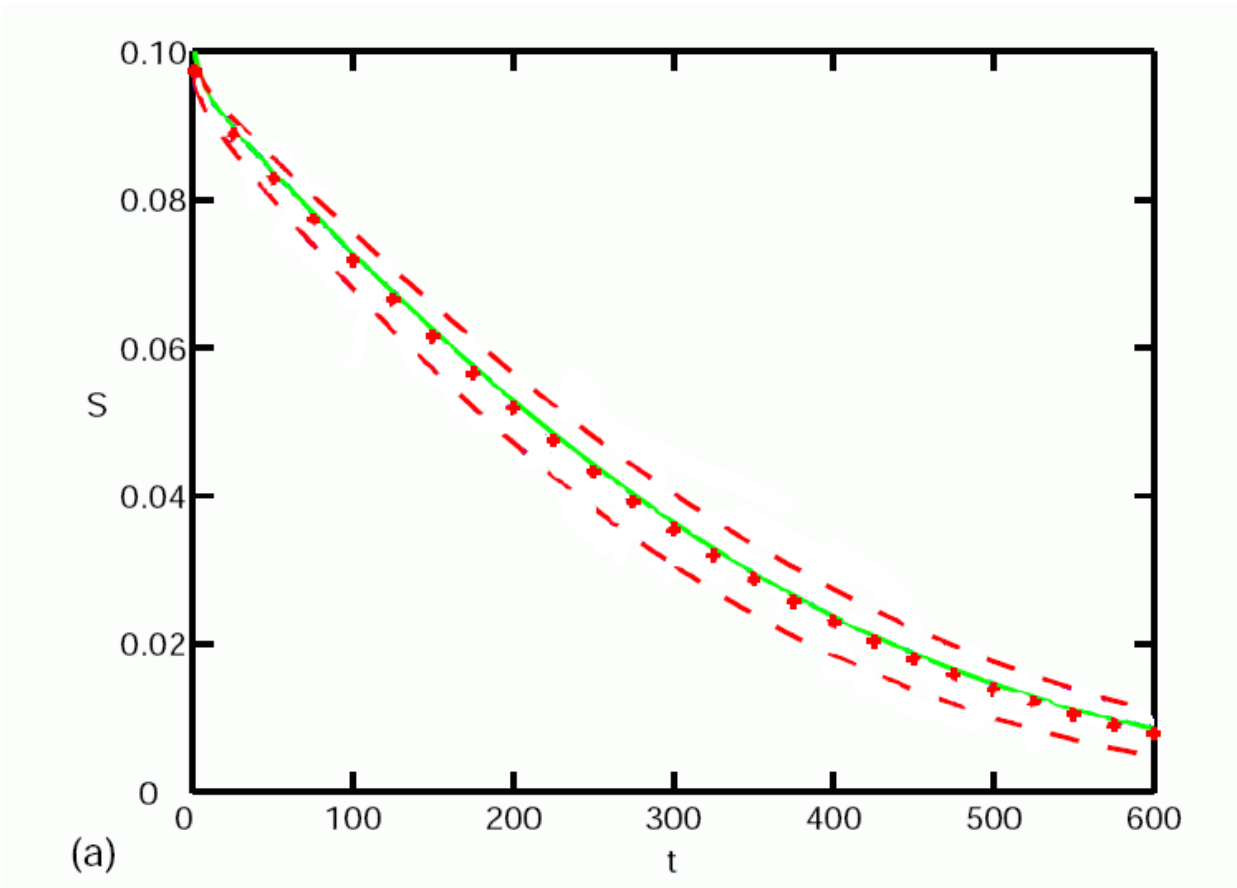

In vivo behaviour compared with model behaviour

However, it is worth bearing in mind that an actual *in vivo* biochemical reaction would follow just one of the many random curves that average together producing the closely fitting mean. This curve may deviate significantly from that of the deterministic approach, and thus call into question its validity.

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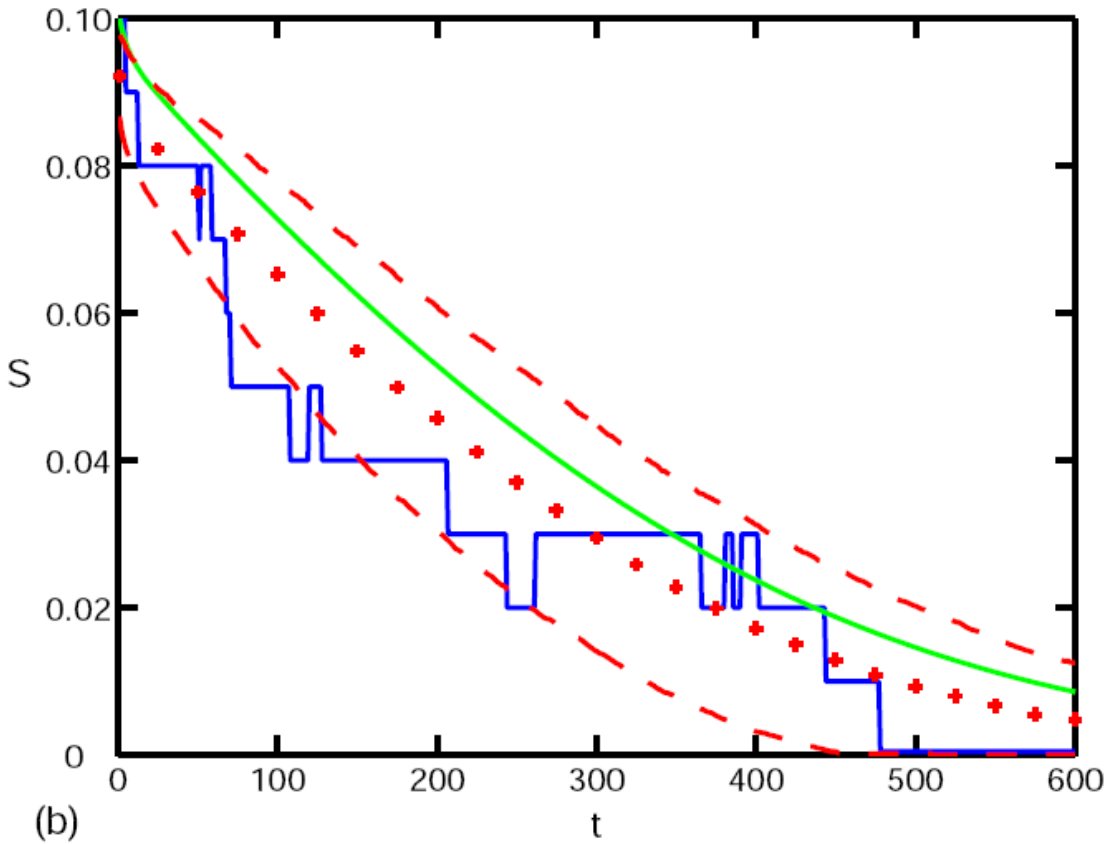
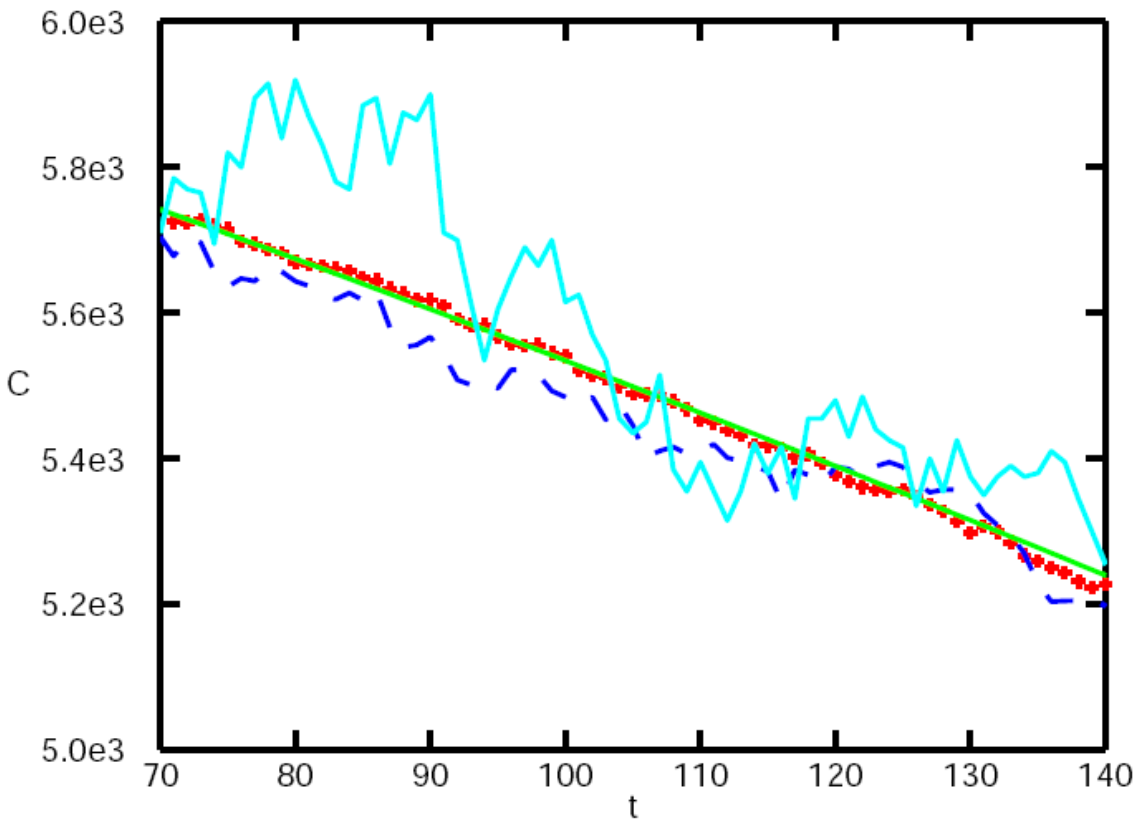
But this does not mean that the randomness exhibited by a particular stochastic simulation trajectory will be the same as the randomness of a particular *in vivo* reaction. Indeed, a set of stochastic simulation trajectories (ensemble) is usually averaged before any conclusions are drawn.

Comparing results at lower population sizes

$S_0 = 10, E_0 = 1, C_0 = 0, \overline{S}_0 = 0$ (vol 100)



Mean results for 11, 110 and 1100 molecules



Circadian clock

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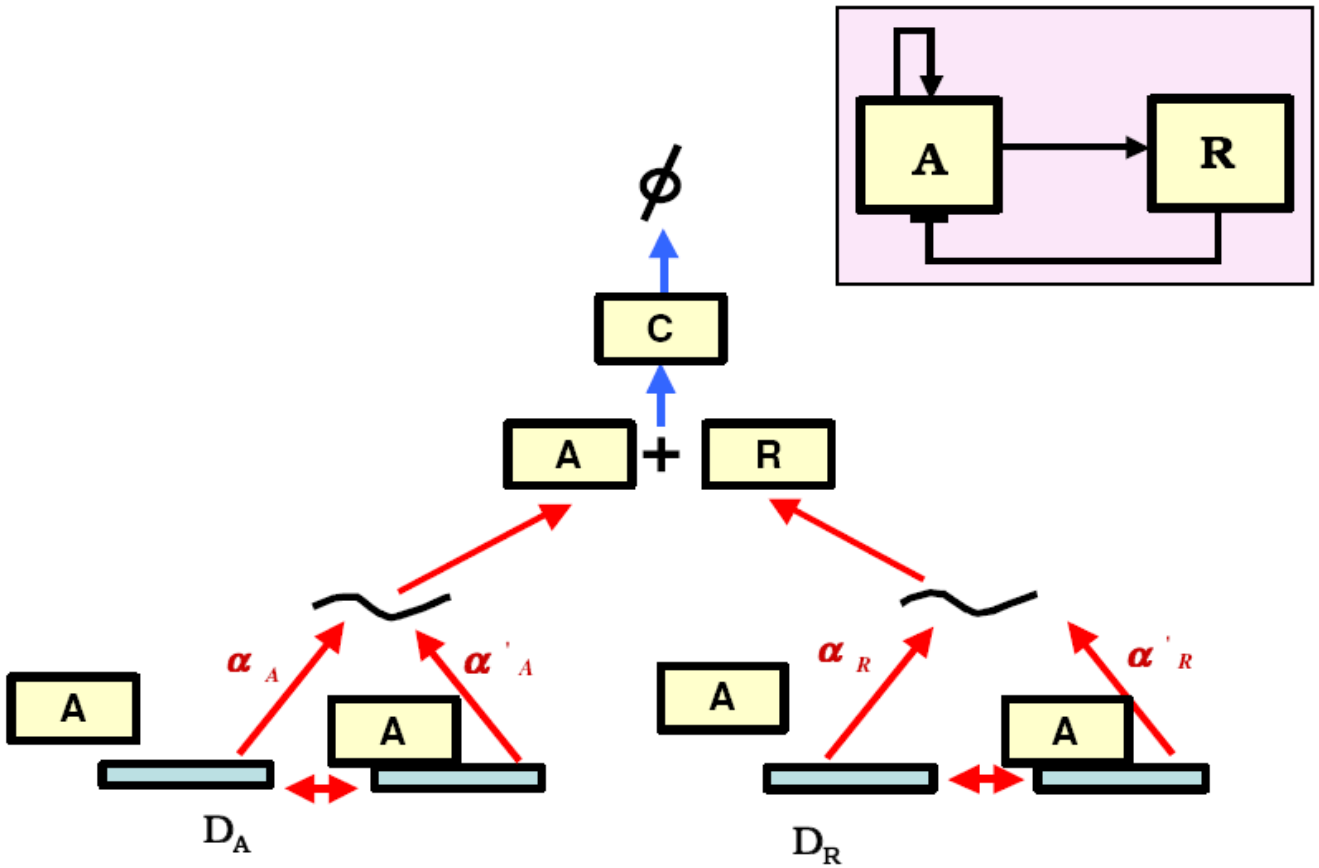
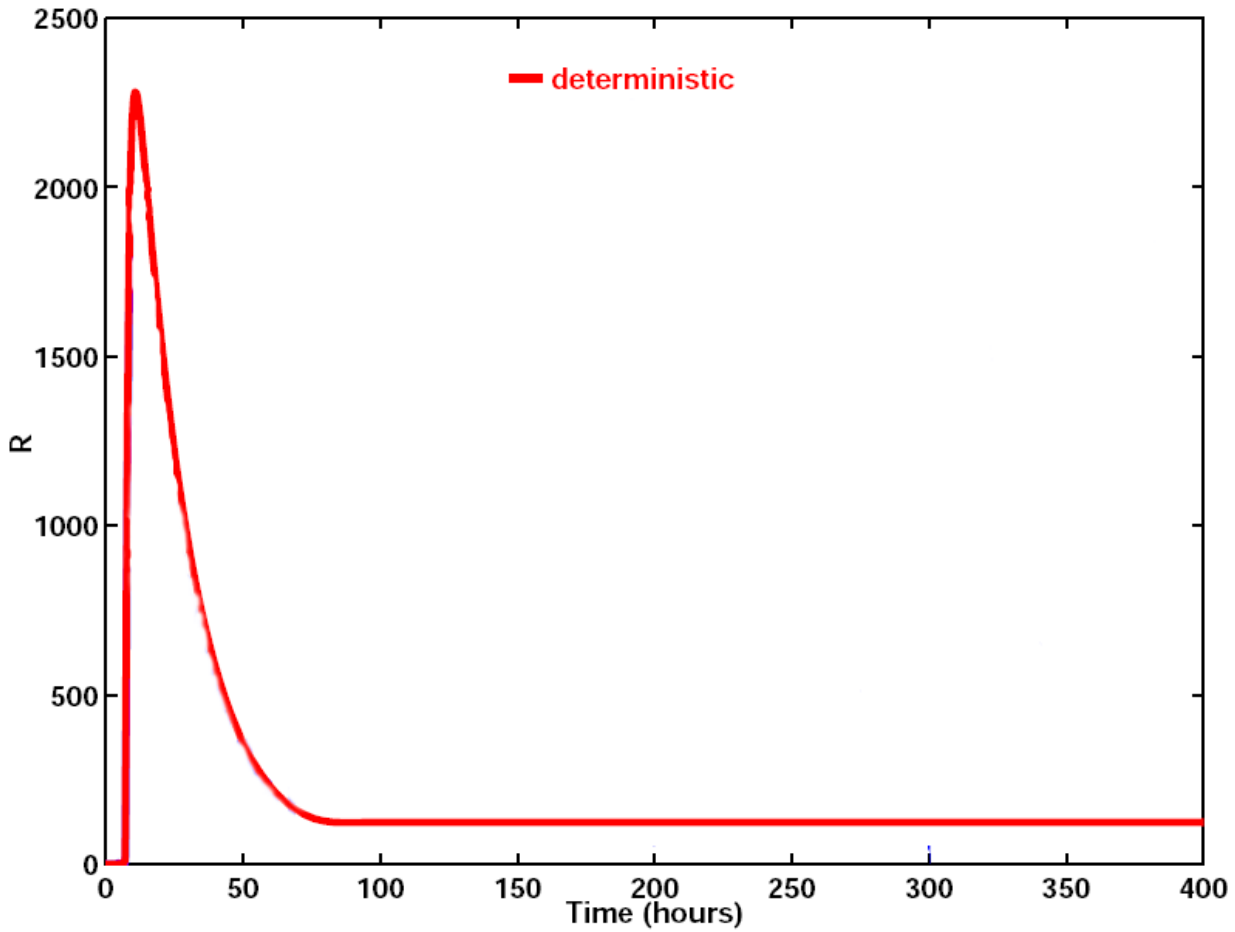
- The activator A binds to the A and R promoters and increases their expression rate. Thus, A implements a positive loop acting on its own transcription.
- Conversely, R sequesters A to form a complex C, therefore inhibiting it from binding to the gene promoter and acting as a negative feedback loop.

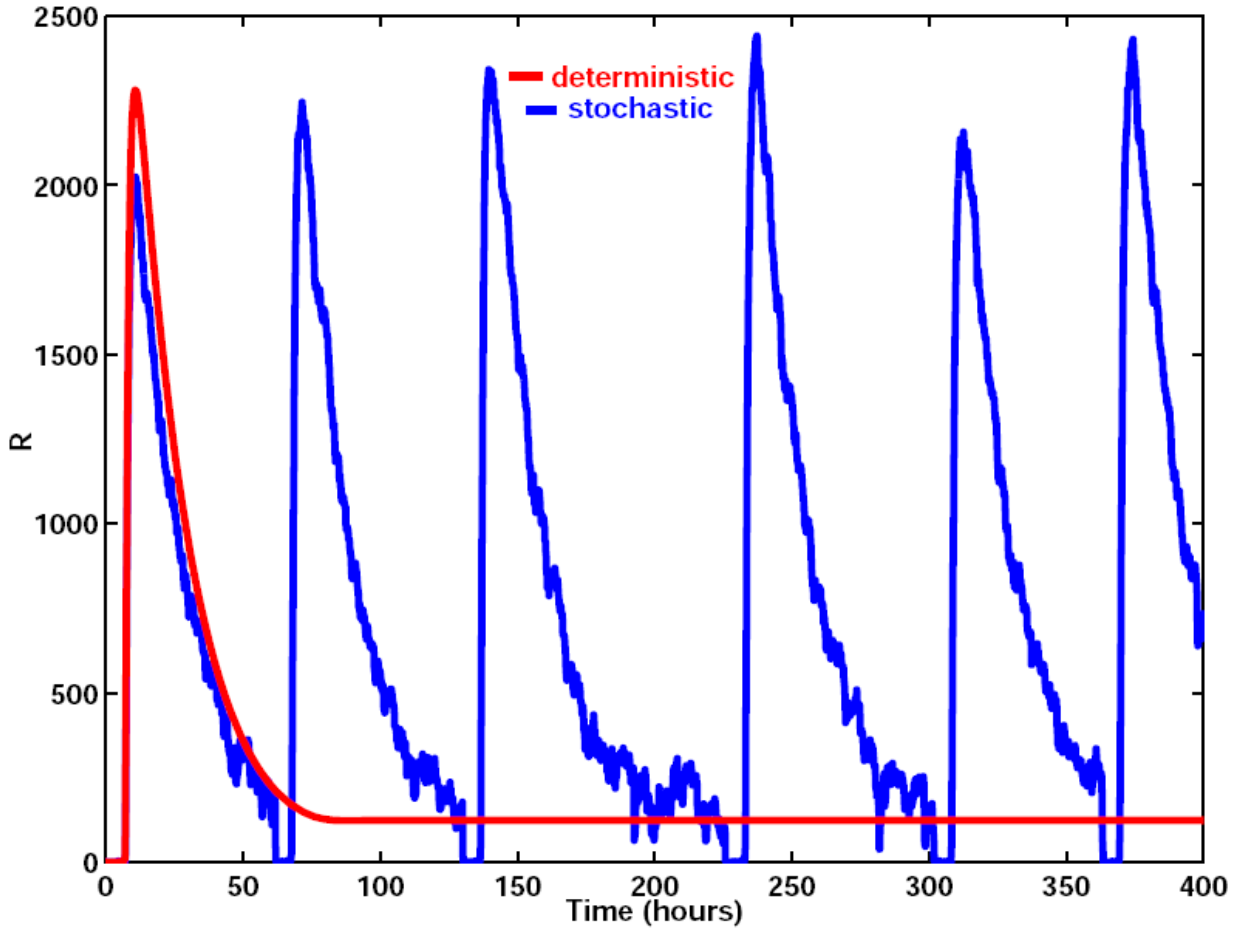
Circadian clock (cartoon)



Circadian clock (deterministically . . .)



Circadian clock (. . . and stochastically)



Conclusions from the Circadian Clock

- For some parameter values a differential equation model exhibits autonomous oscillations.
- These oscillations disappear from the deterministic model as the degradation rate of the repressor δ_R is decreased.
- The system of ODEs undergoes a bifurcation at this point and exhibits a unique stable deterministic equilibrium.
- However, if the effects of molecular noise are incorporated the oscillations in the stochastic system pertain.
- This phenomenon is a manifestation of coherence resonance, and illustrates the crucial interplay between noise and dynamics.

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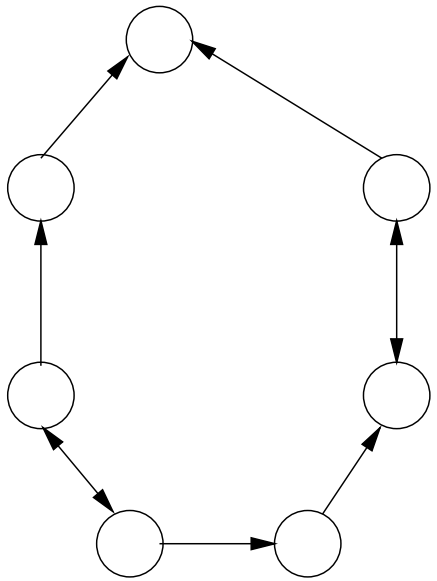
Others such as Cornish-Bowden are much more skeptical and cite the problem of infinite regress as being insurmountable.

The problem of *Infinite Regress*



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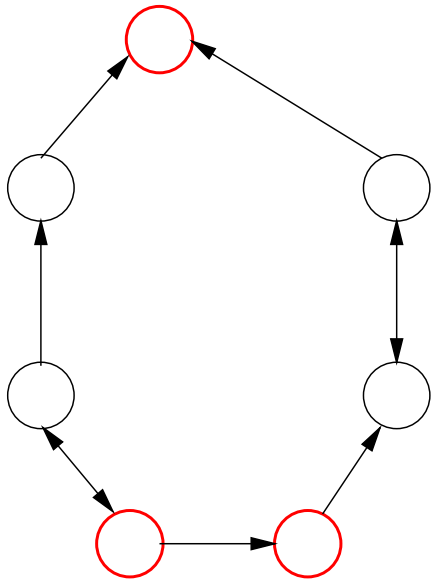

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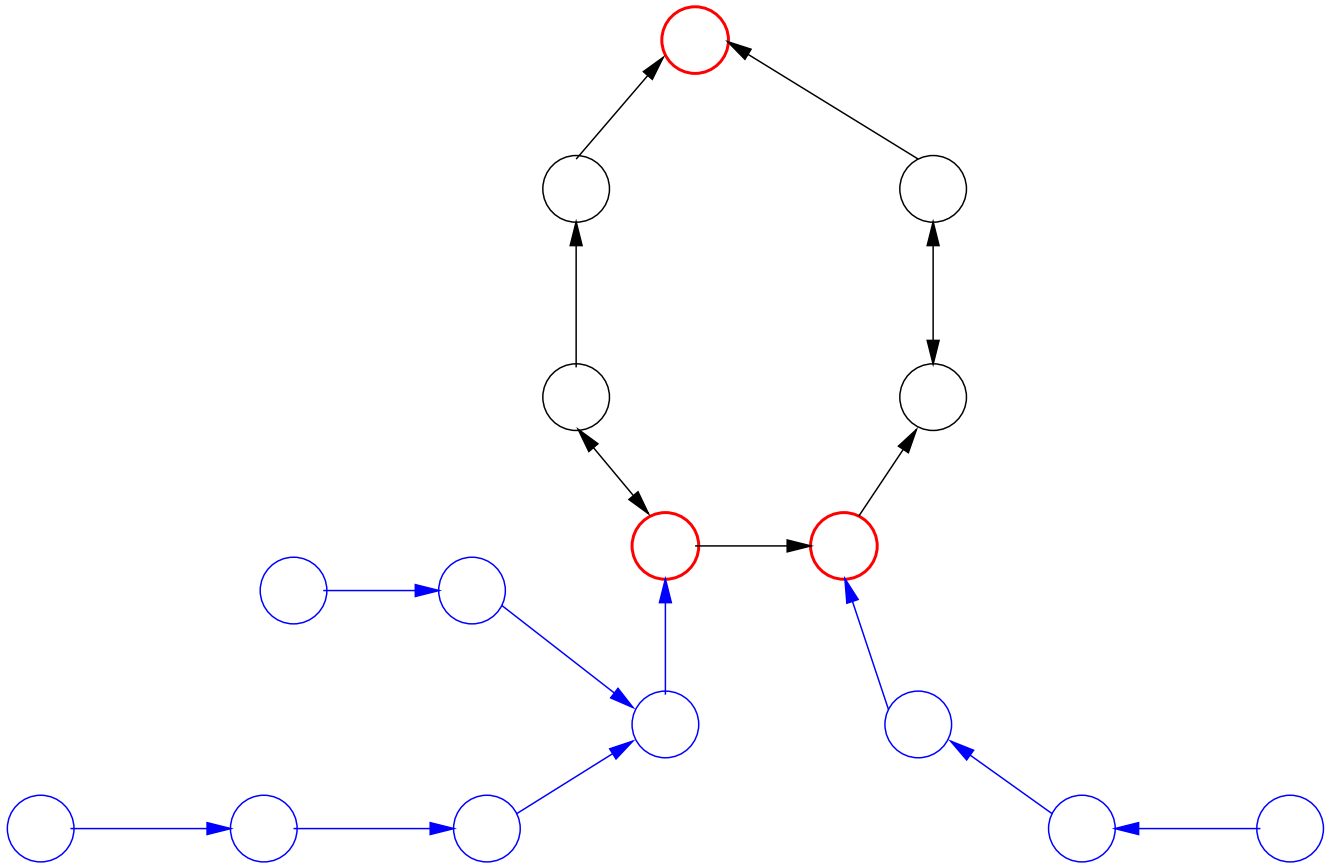

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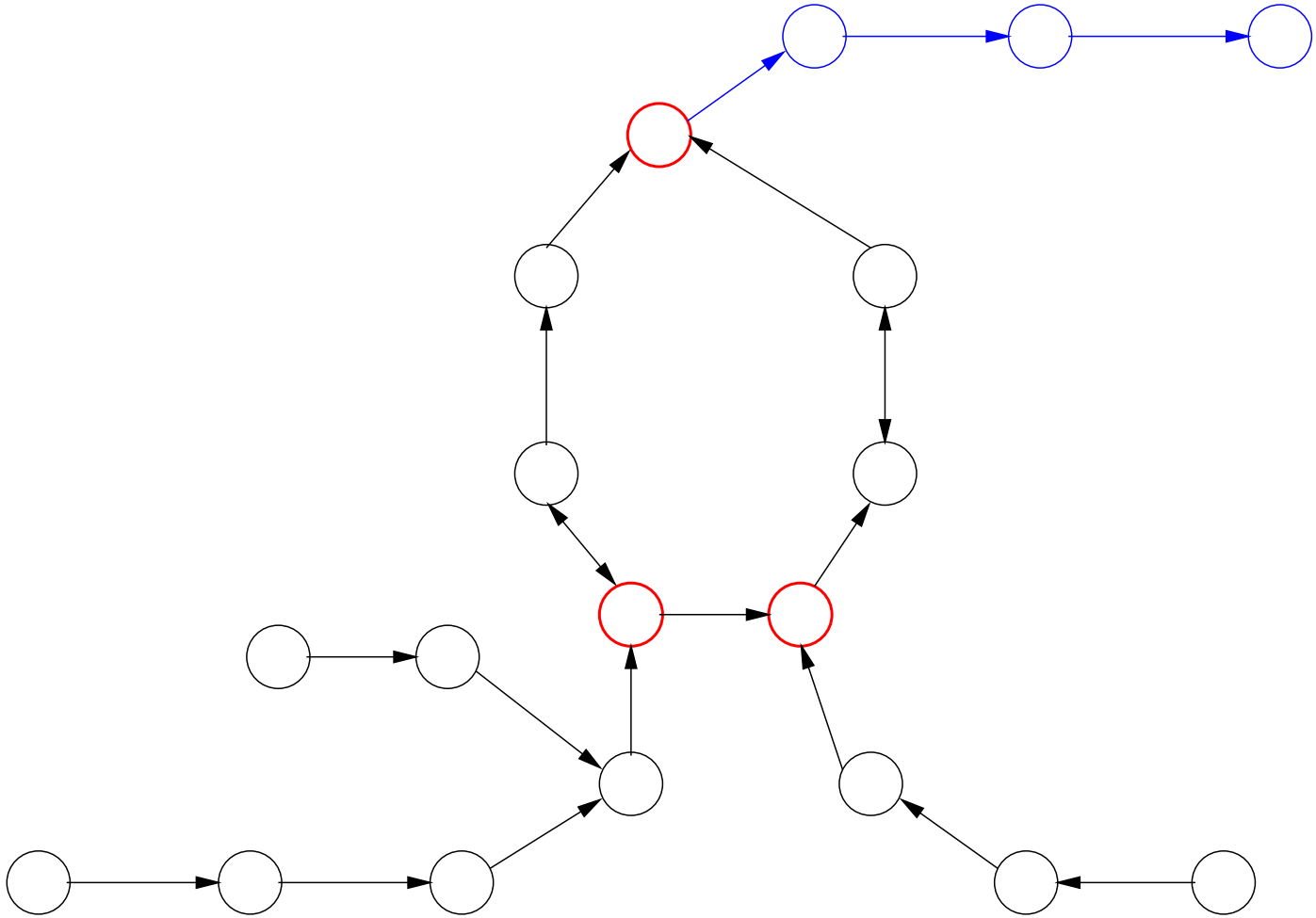

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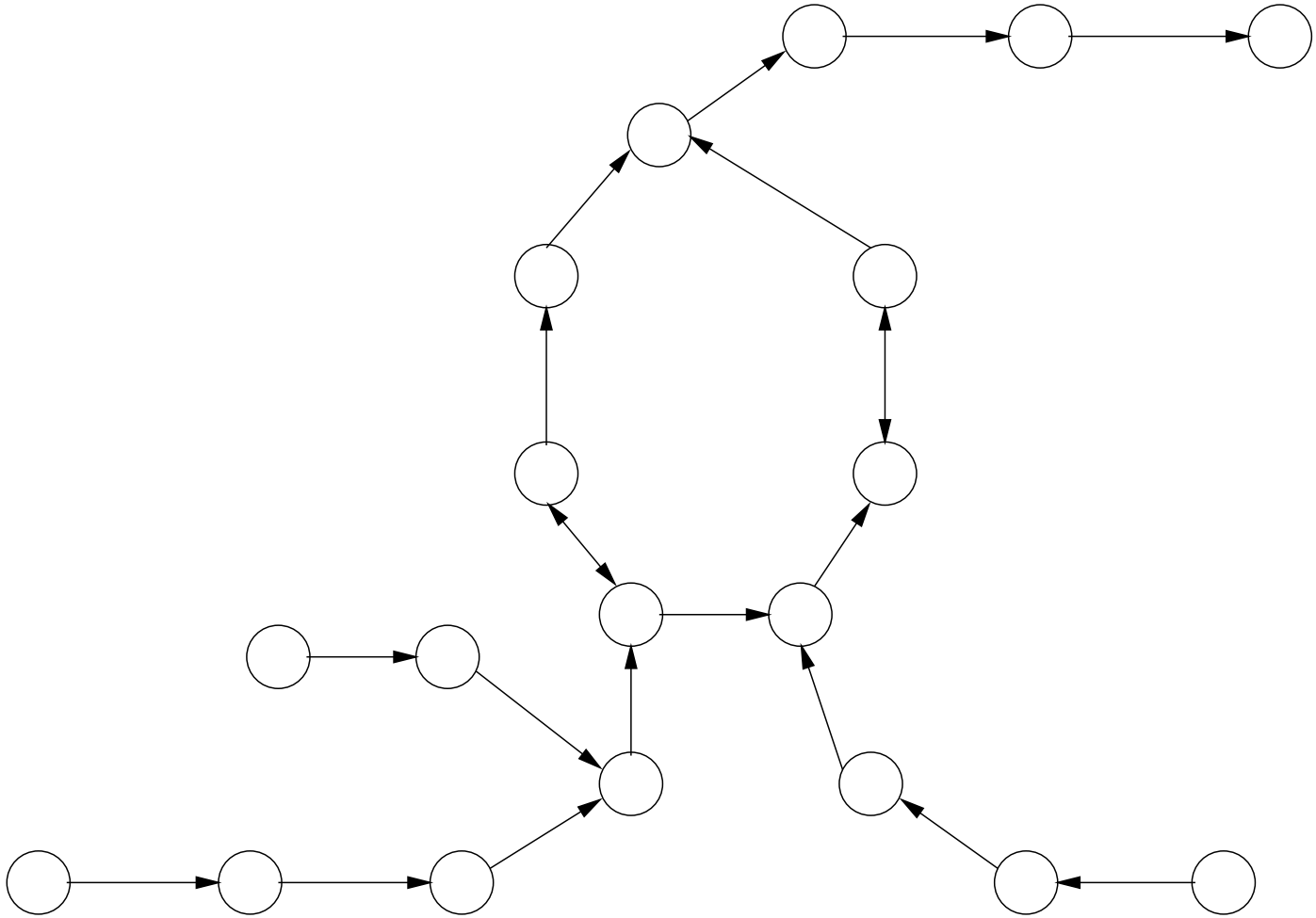

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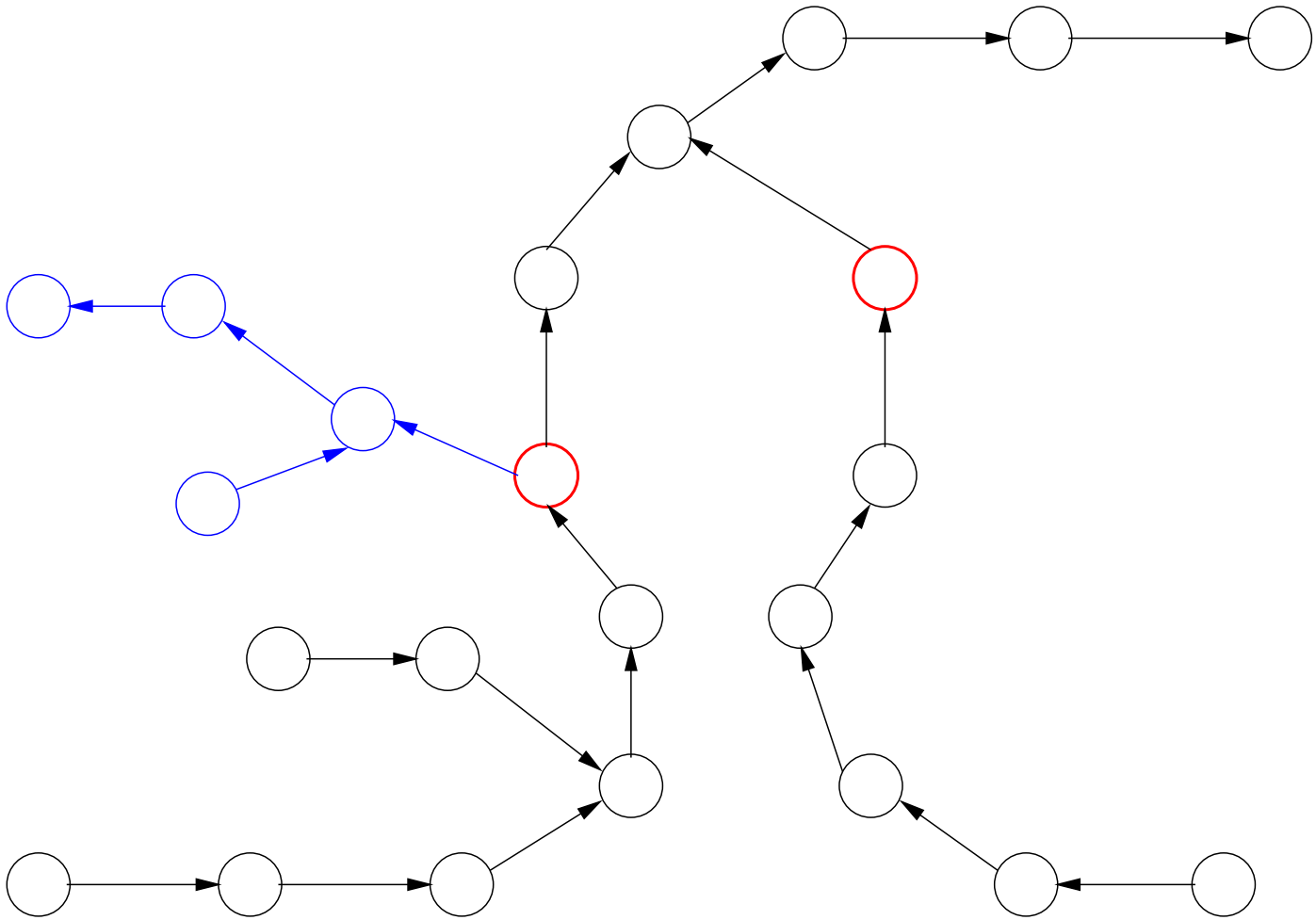

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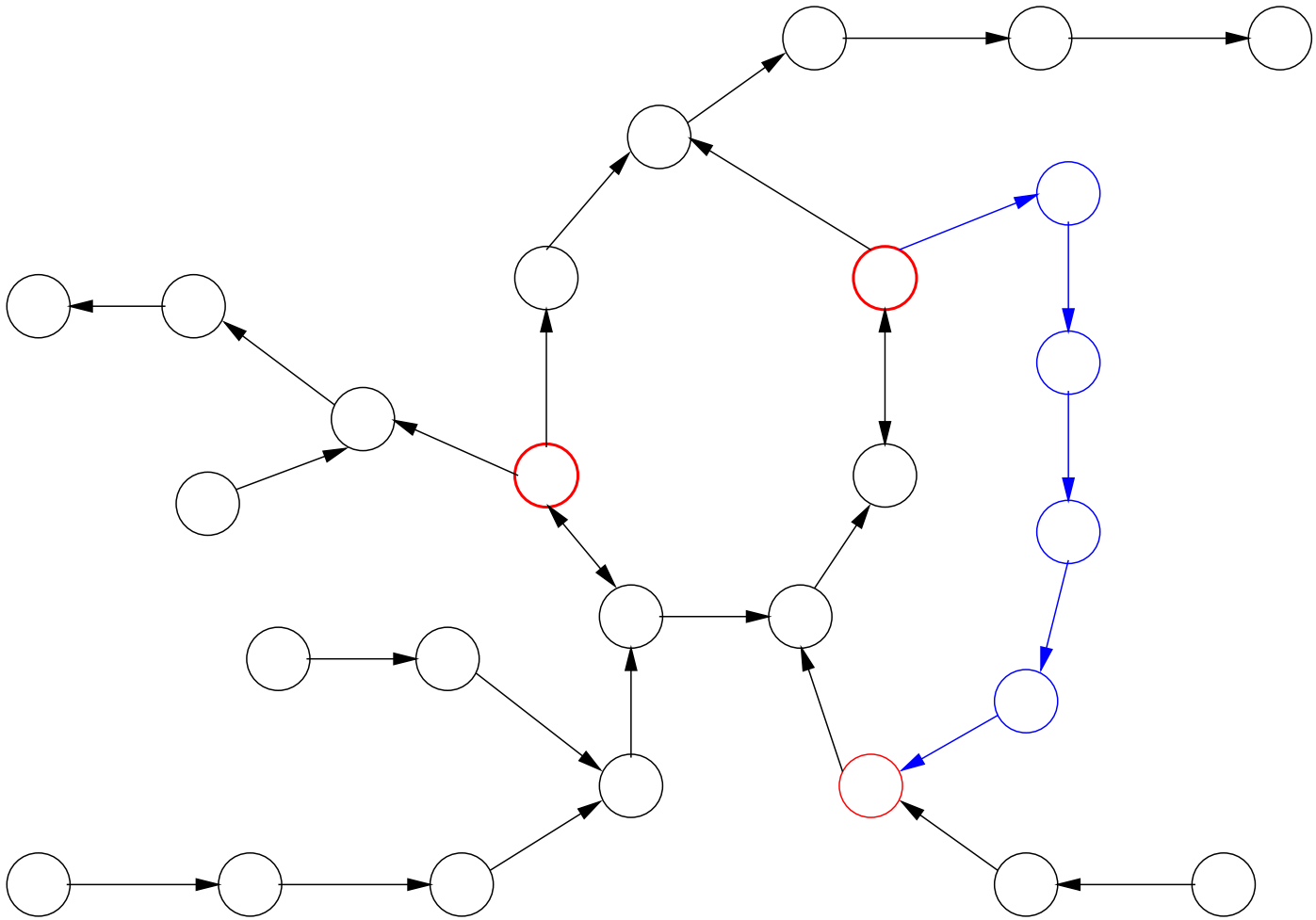

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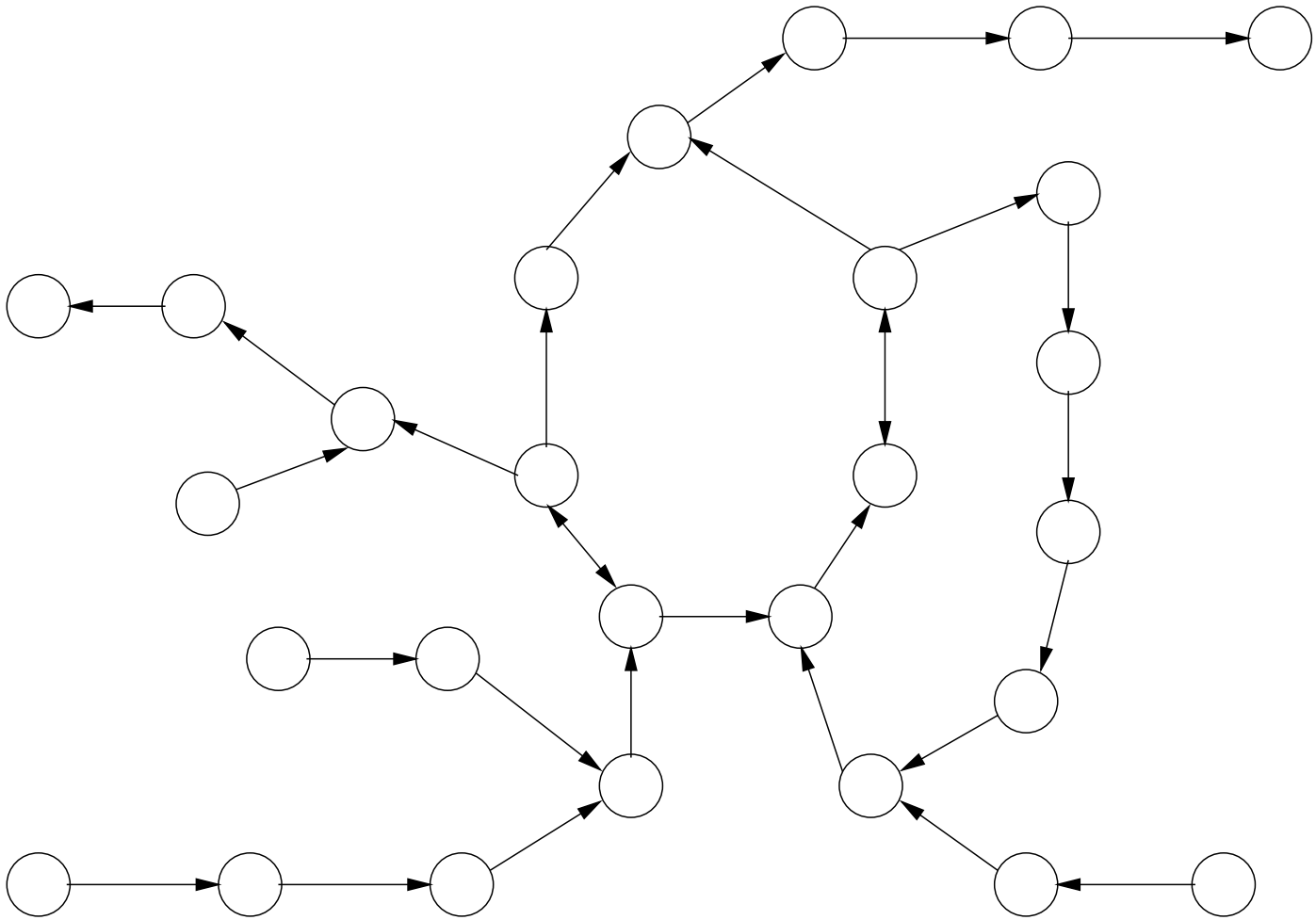

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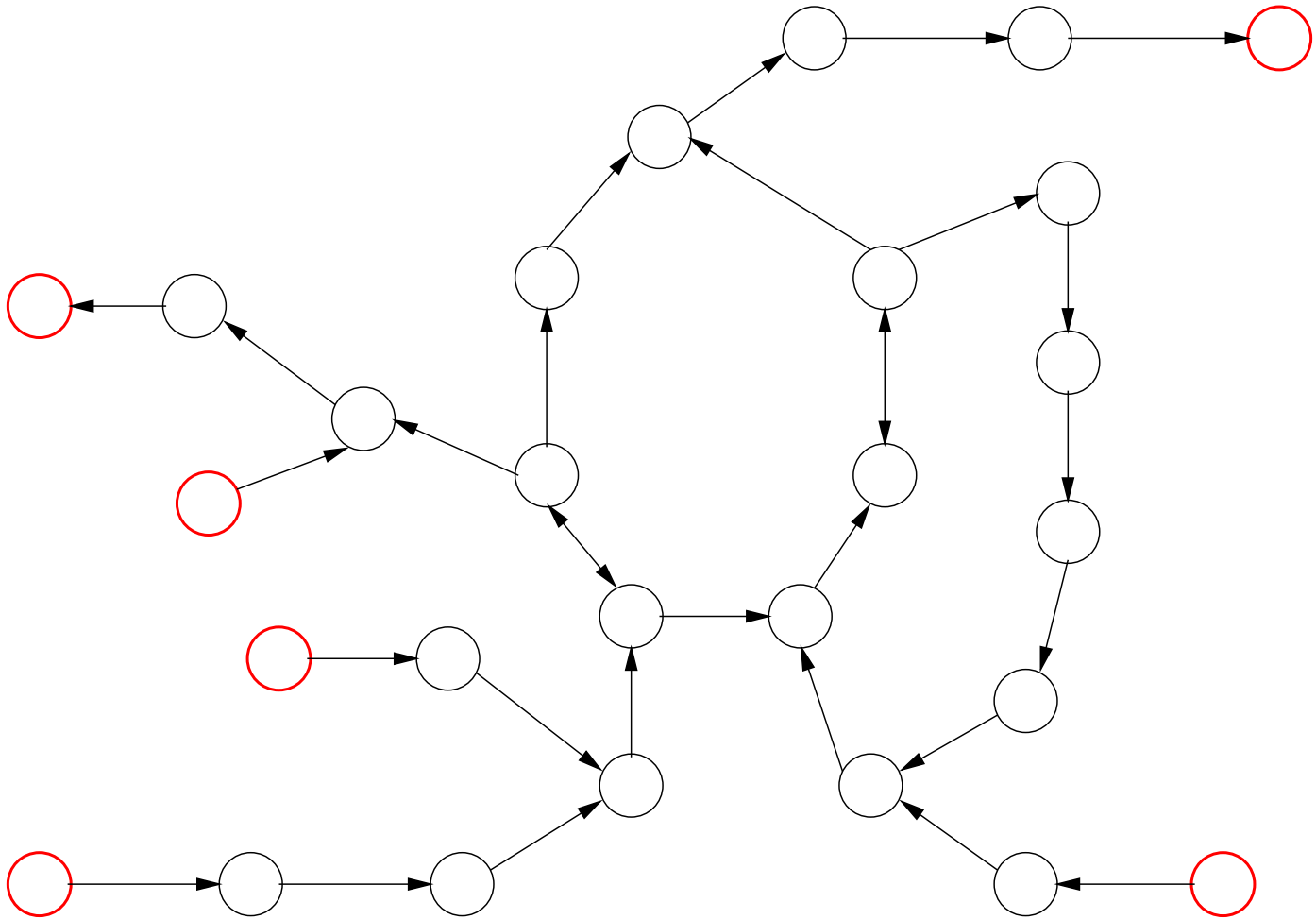

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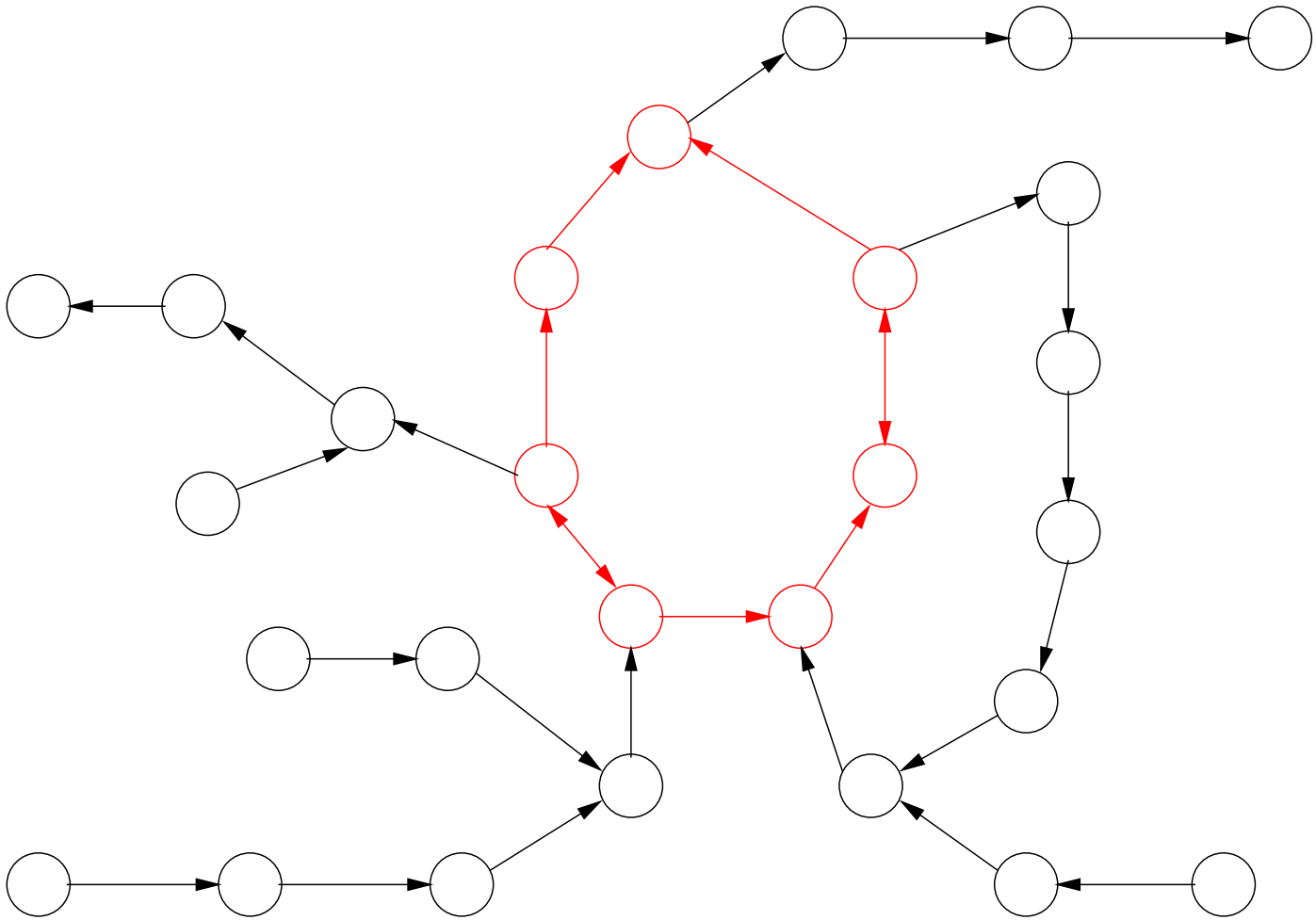

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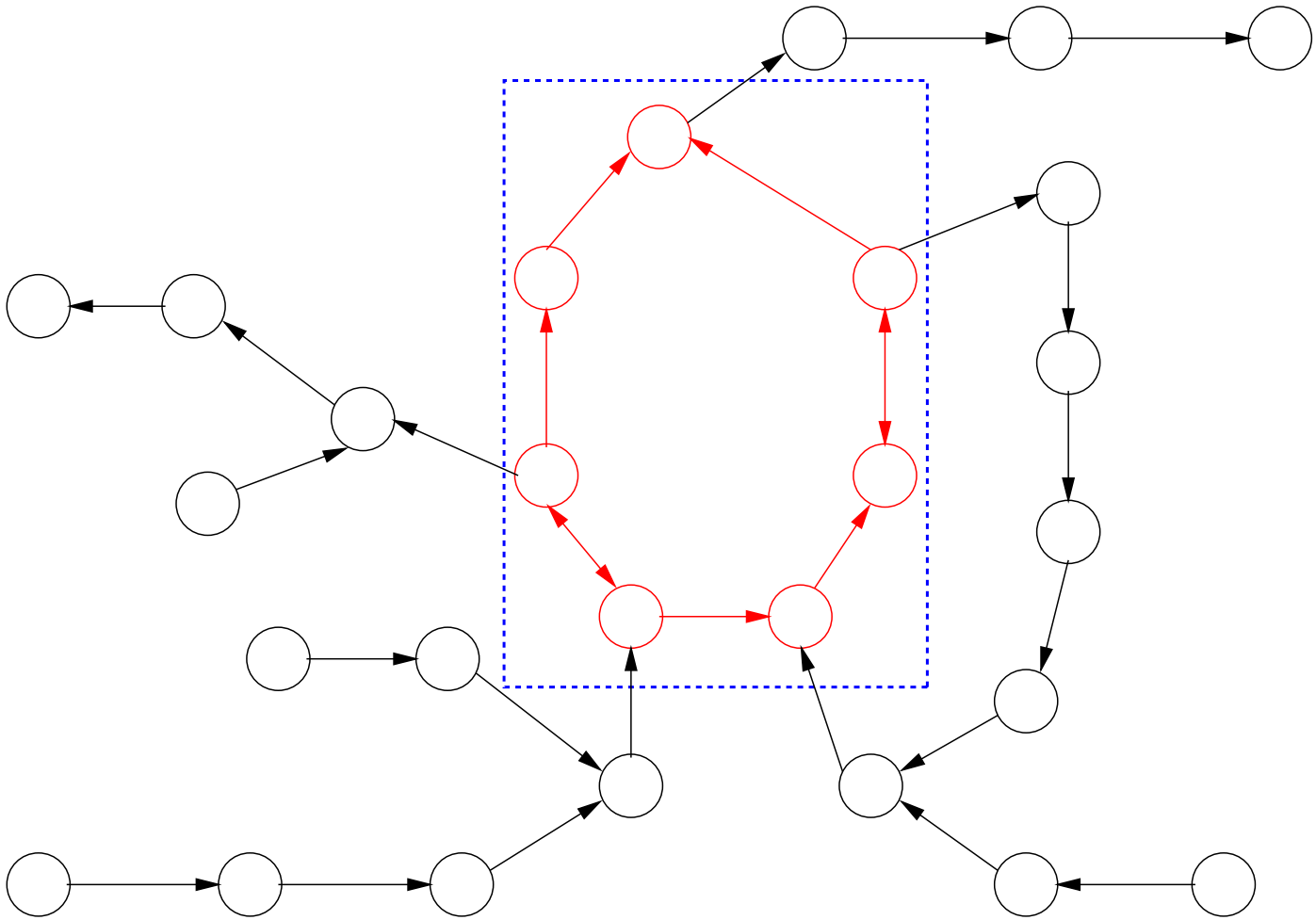

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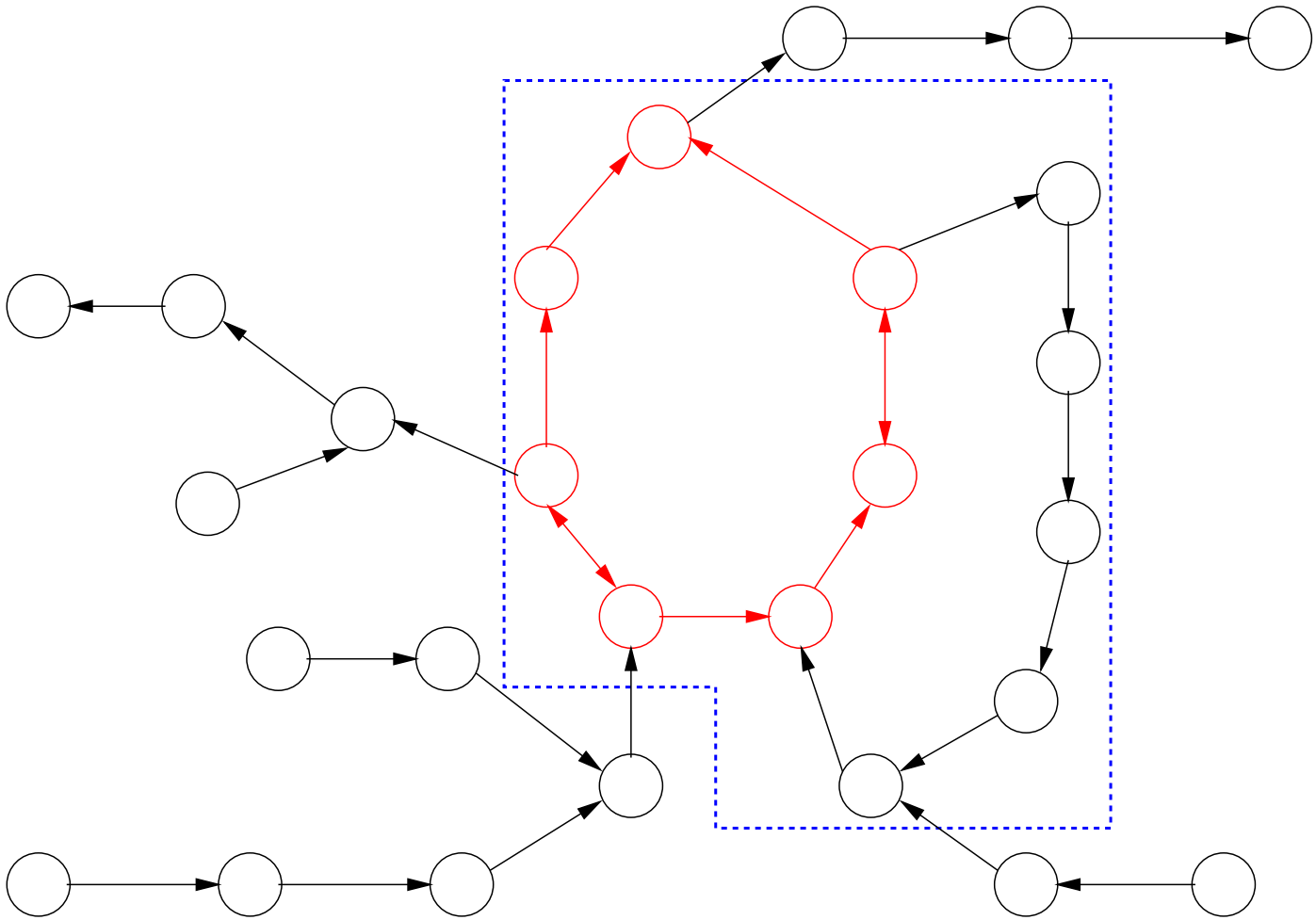

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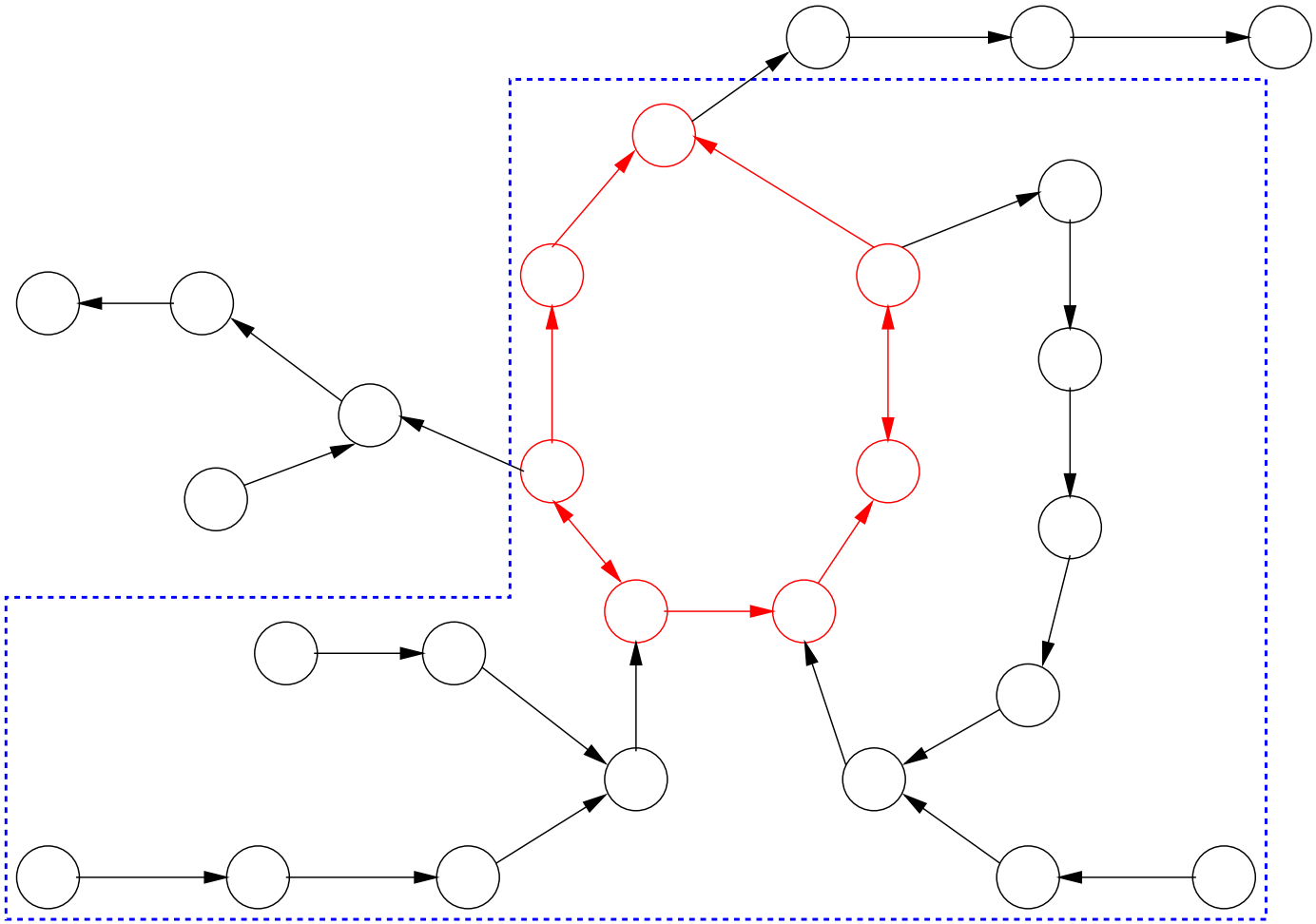

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Even when data exists the quality is often very poor.

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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.

PEPA: Performance Evaluation Process Algebra

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S &::= (\alpha, r).S \mid S + S \mid A \\
P &::= S \mid P \underset{L}{\bowtie} P \mid P/L
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Q is the infinitesimal generator matrix characterising the CTMC.

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

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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- Process algebra based analyses such as comparing models (e.g. for equivalence or simulation) and model checking are only possible is the state space is not prohibitively large.

Mapping biological systems to process algebra

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In our mapping we focus on species (c.f. a type rather than an instance, or a class rather than an object).

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.

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

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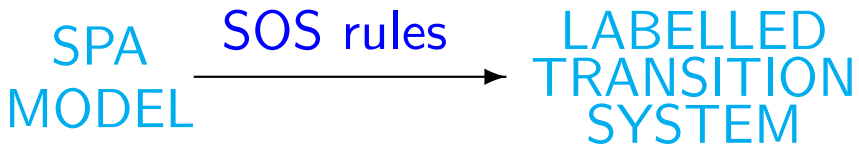

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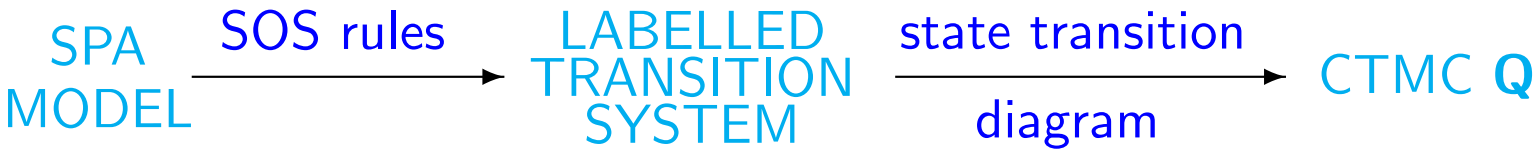

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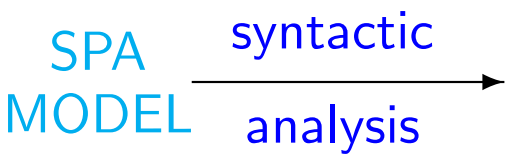

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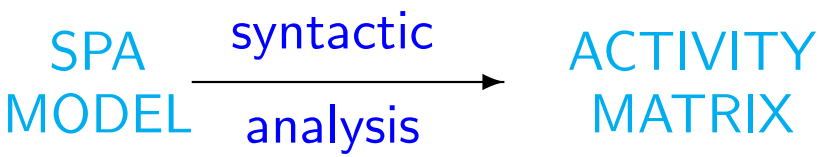

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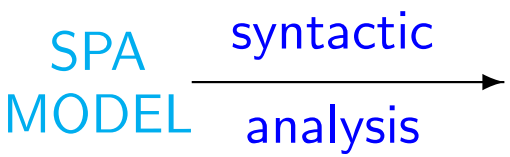

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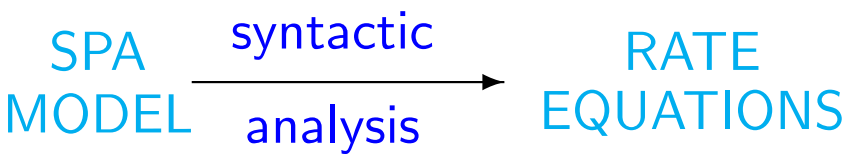

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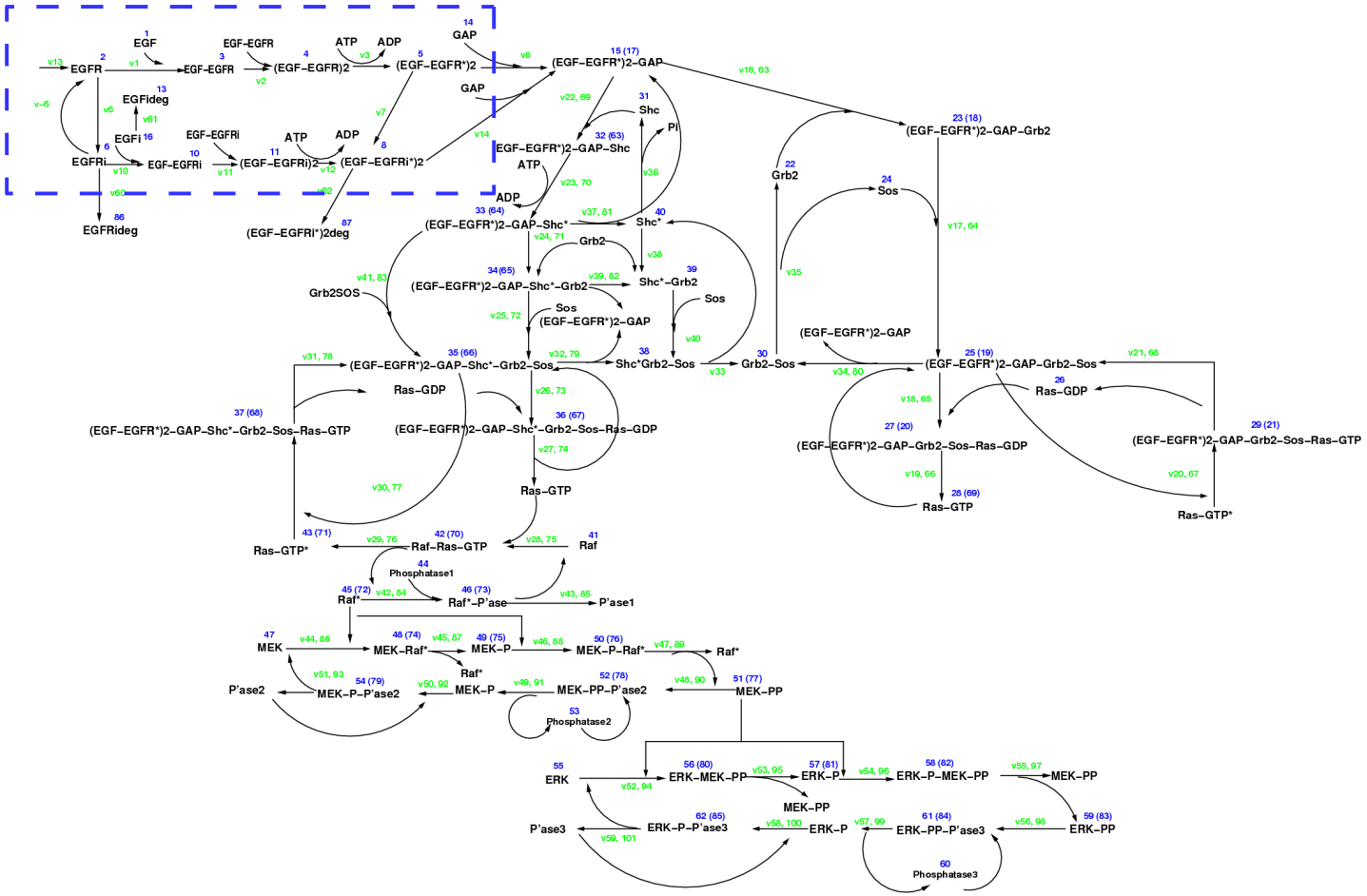
Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.

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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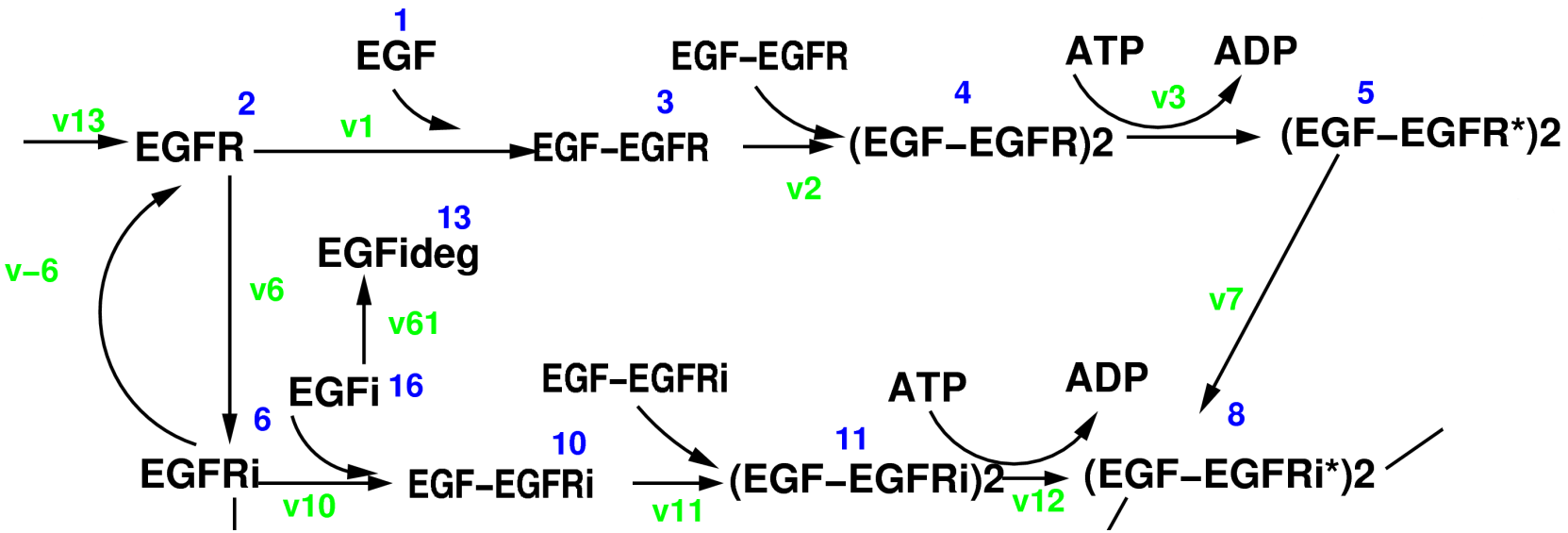

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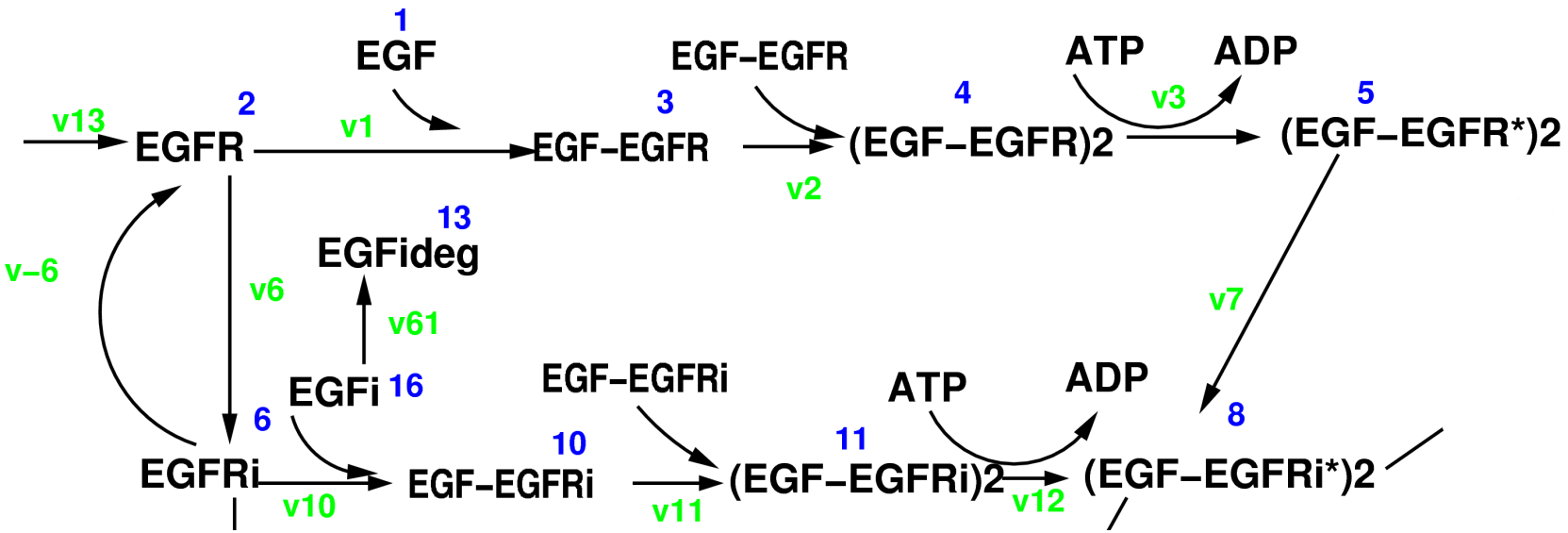

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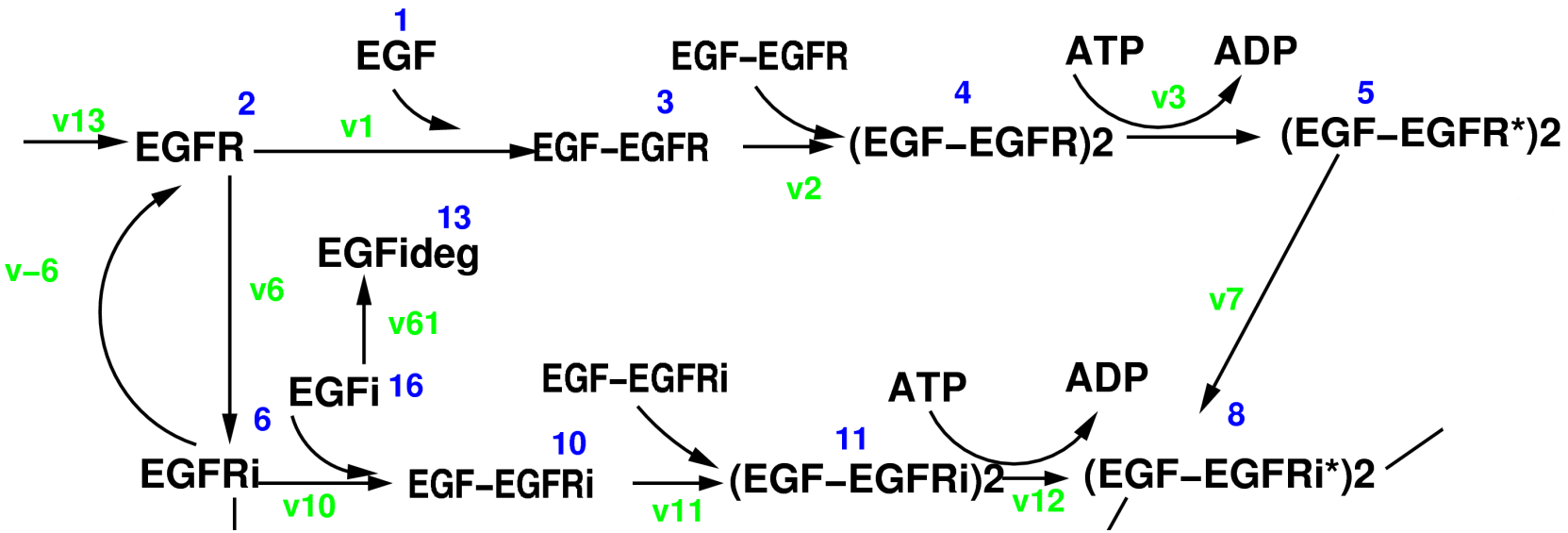

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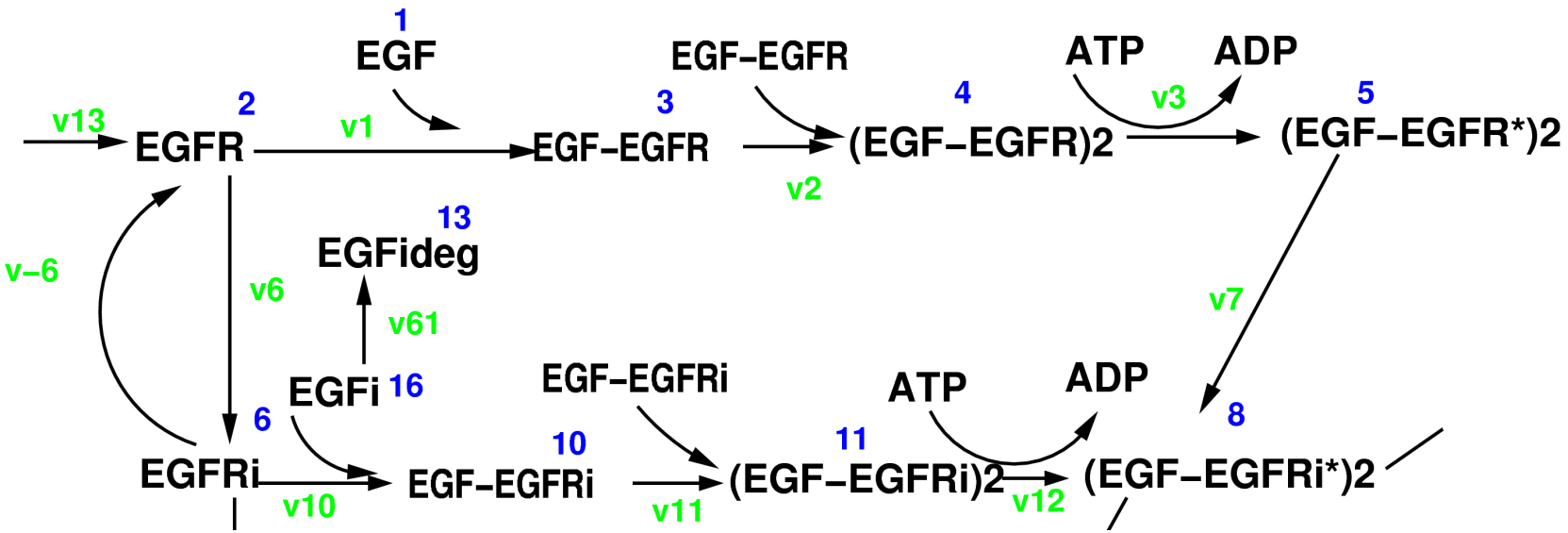

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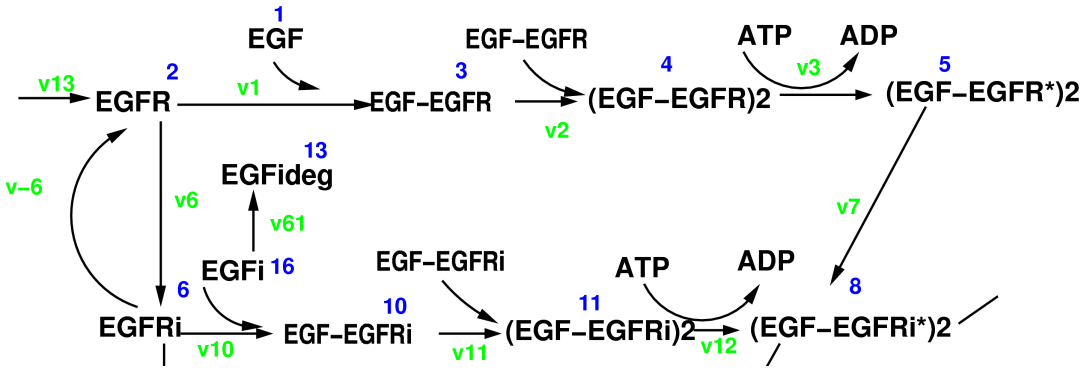
- An infinite supply of EGF is assumed;
- Reaction *v7* is uni-directional whereas all others are reversible.

Extracts from the model of the MAP Kinase Cascade



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

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

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

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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.

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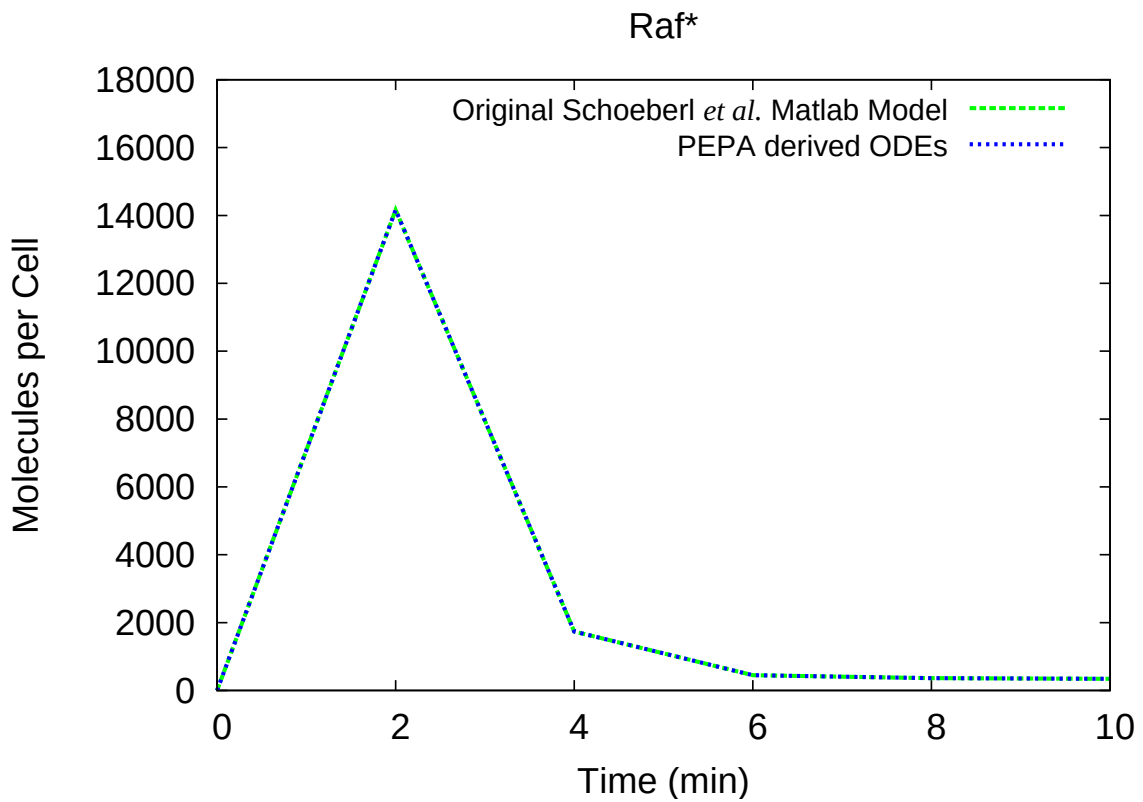
- Then we used an alternative mapping from the PEPA to generate a stochastic simulation of the system.

Comparing Original Results and PEPA Derived ODEs



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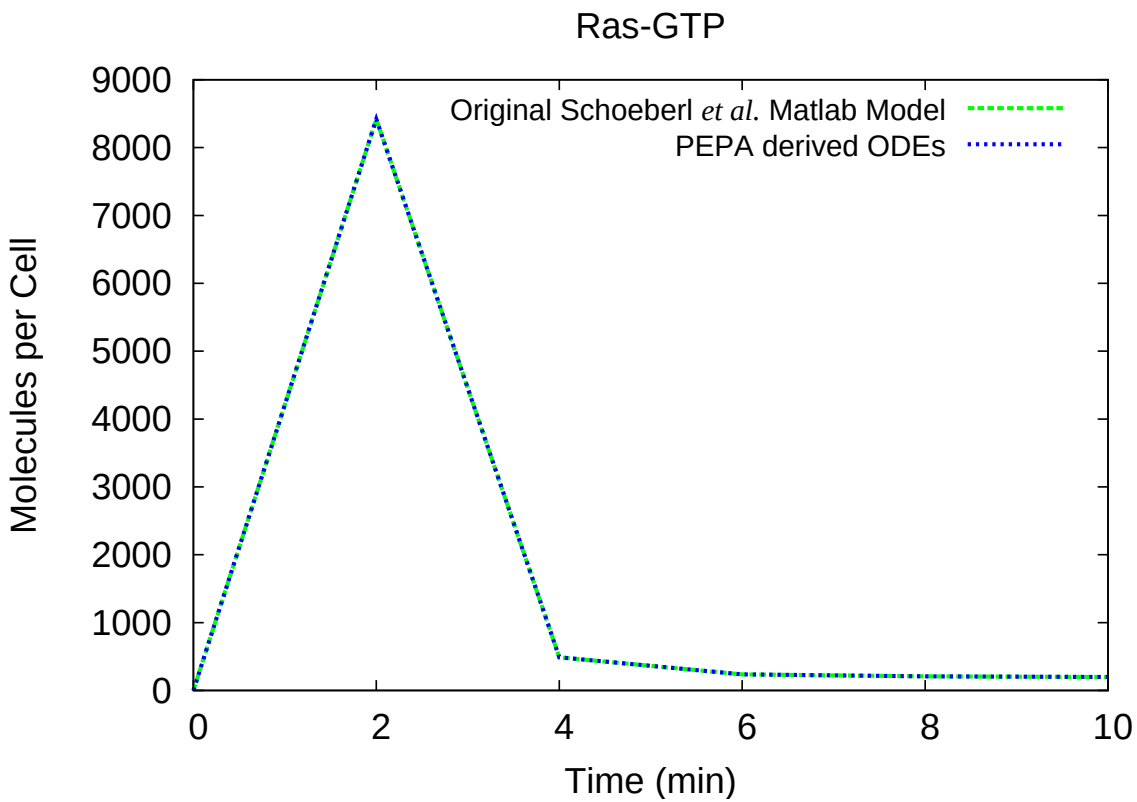
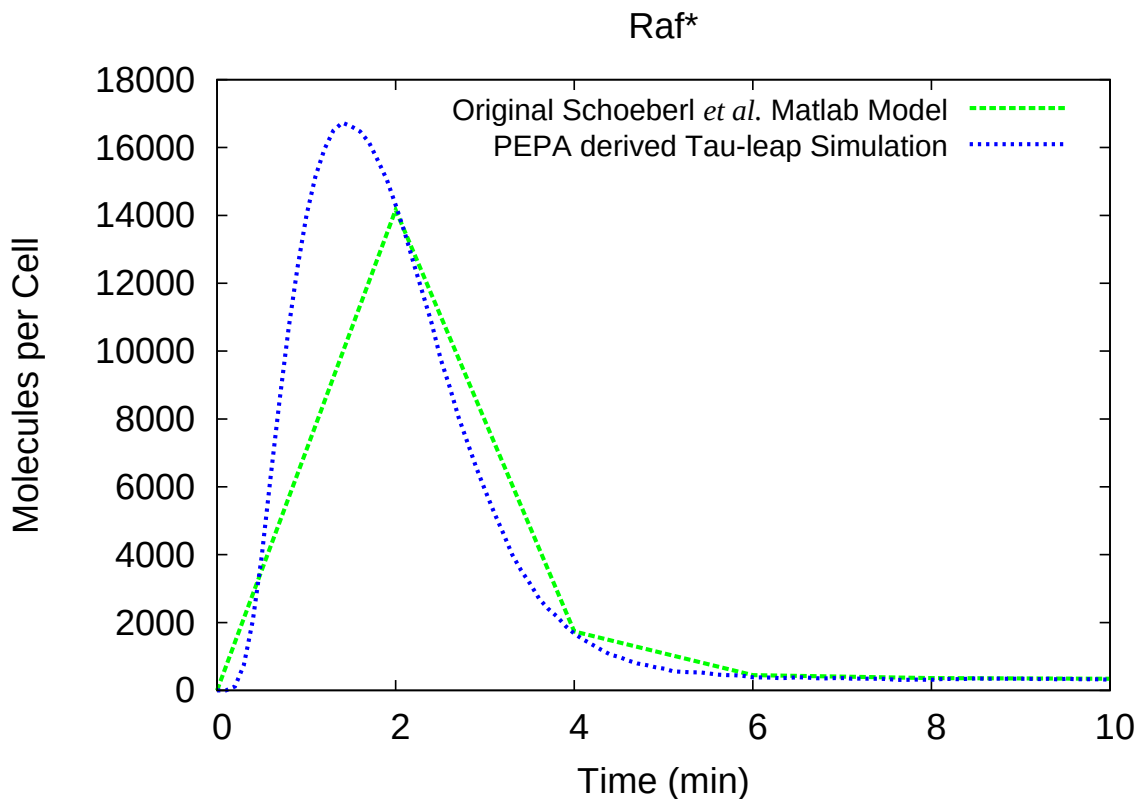


The PEPA derived ODEs return the same results as the Schoeberl *et al.* Matlab model.

Comparing Original Results and PEPA Derived Stochastic Simulation



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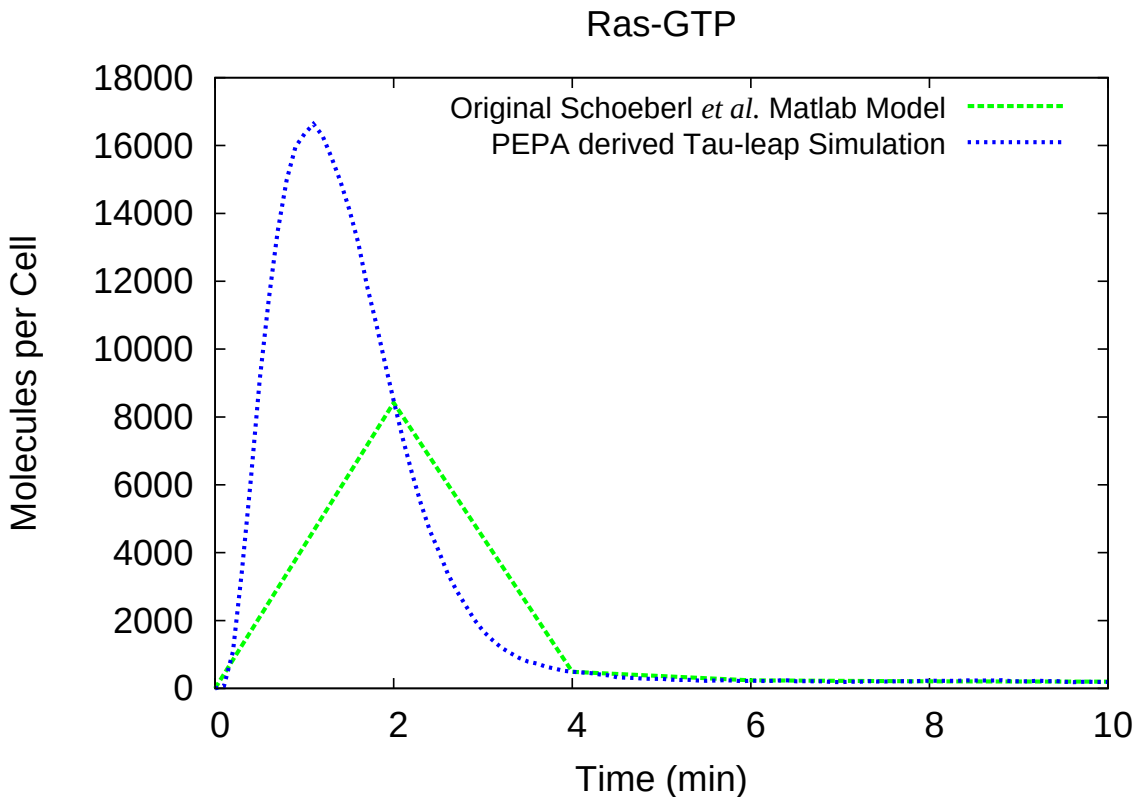
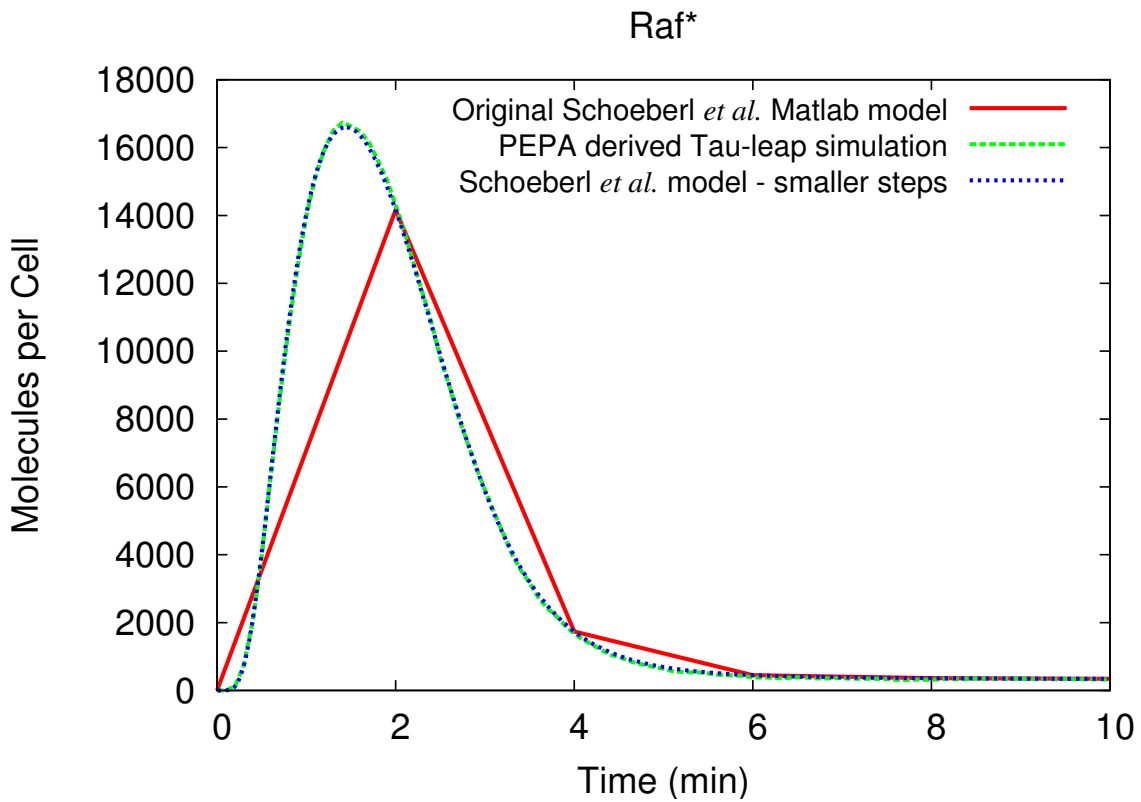


Corrected Time Step in Matlab Model



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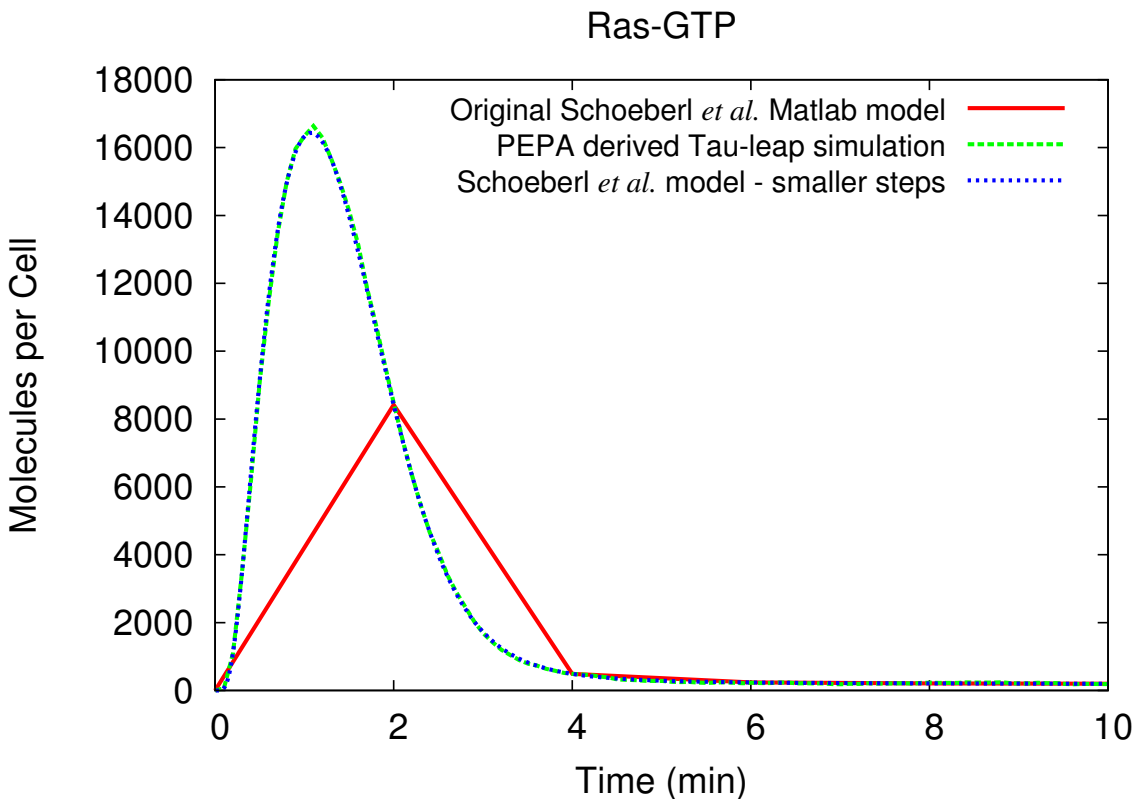

The original parameters for the Matlab model stepped over the true peak.

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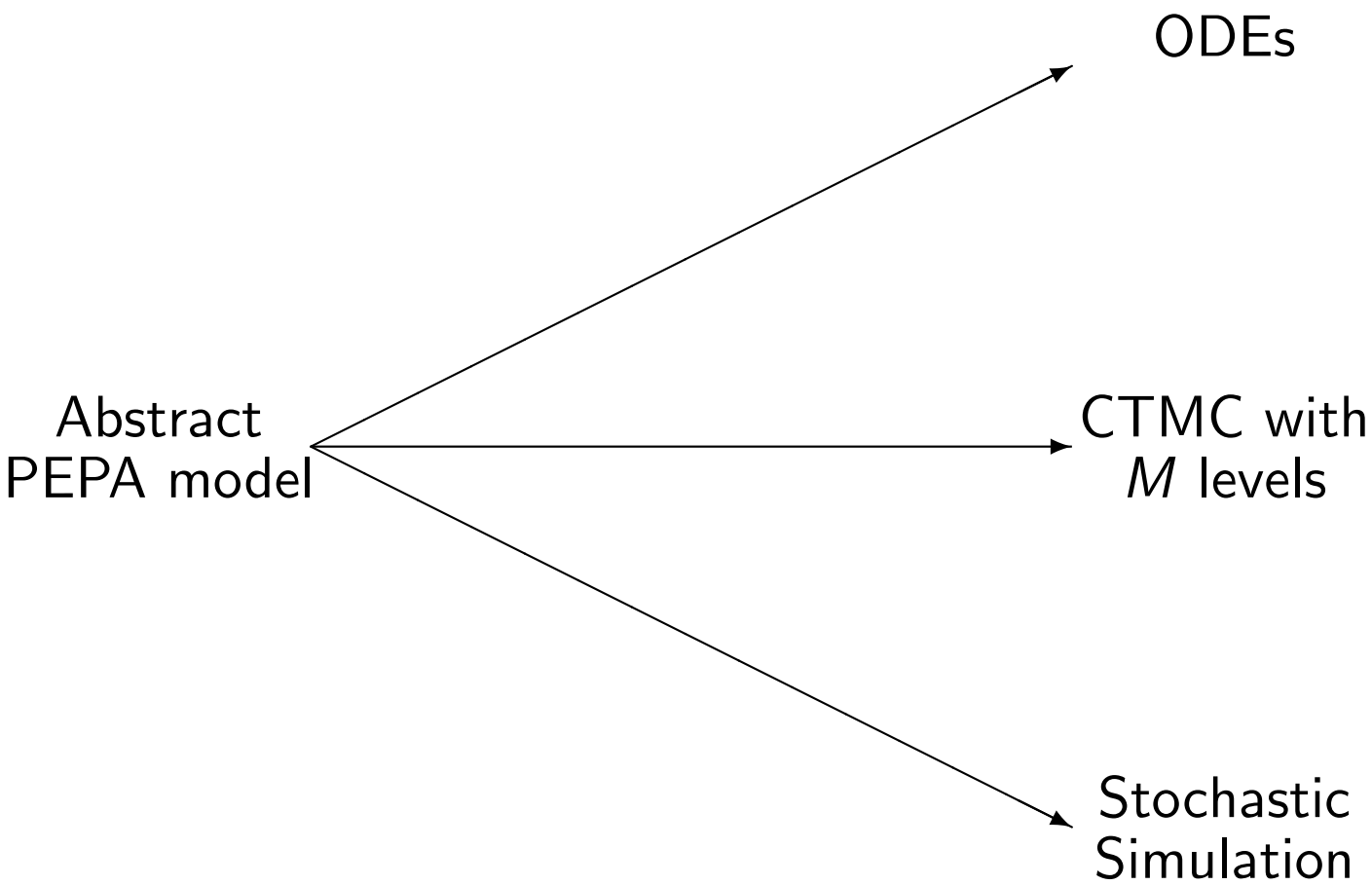

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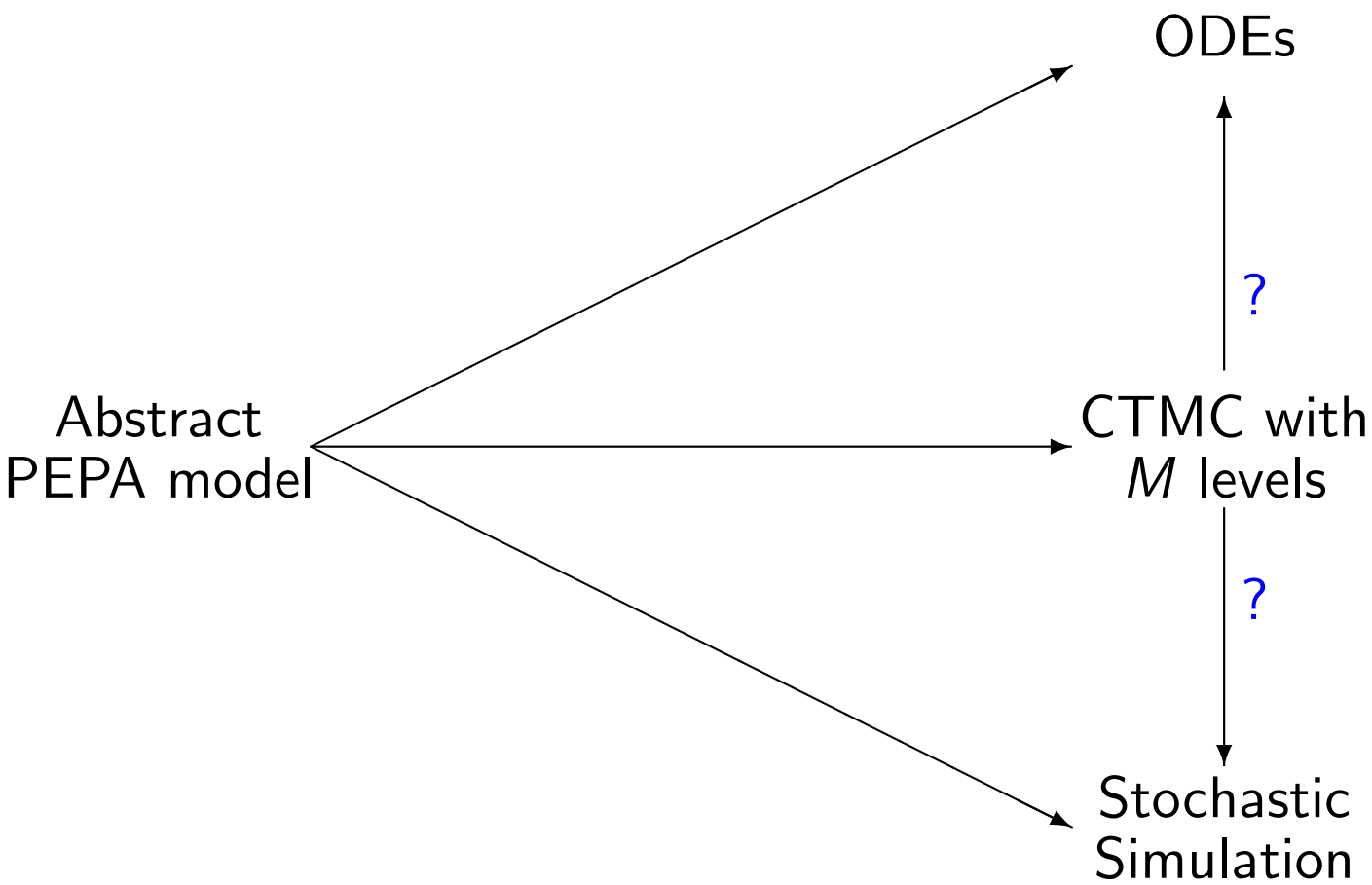

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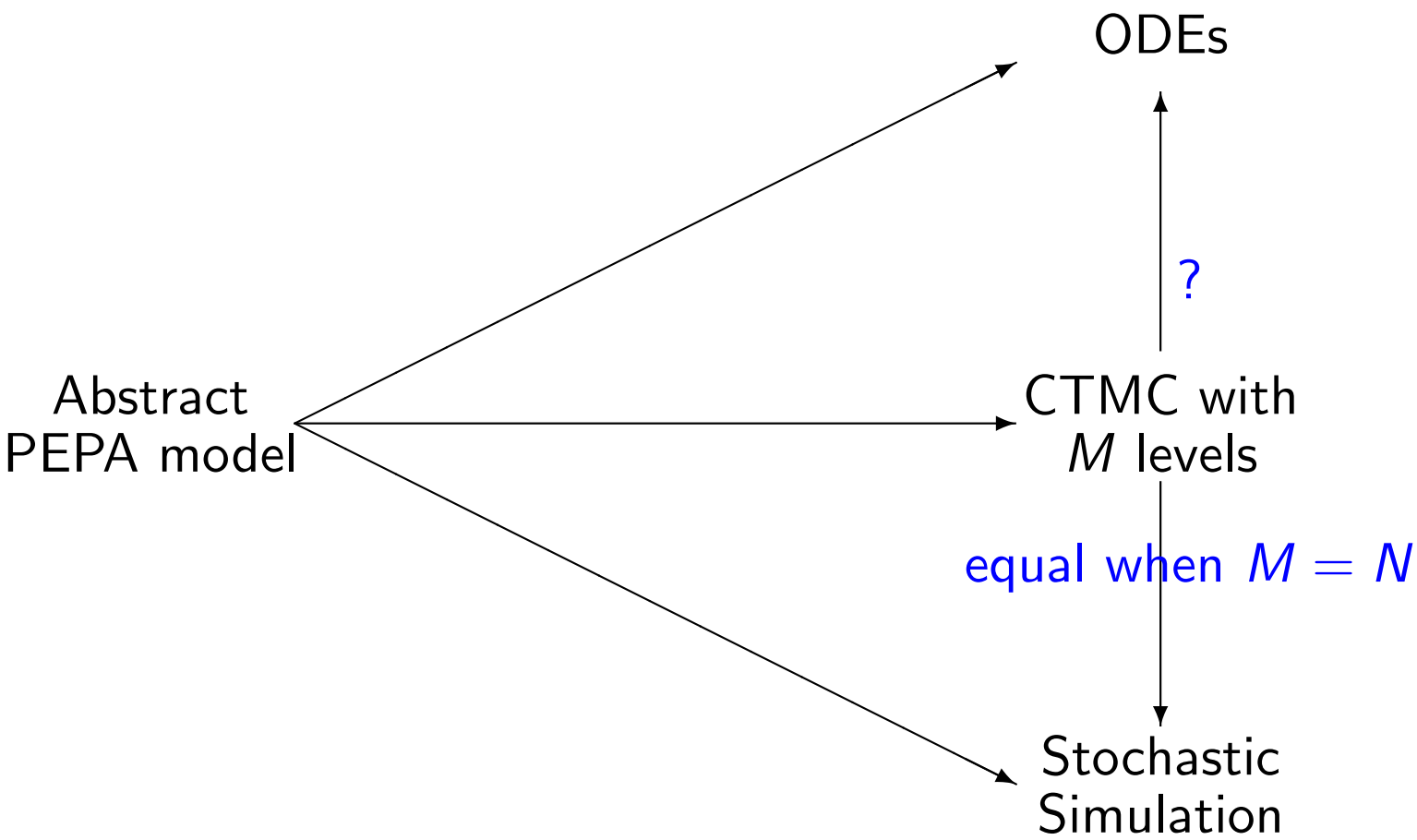

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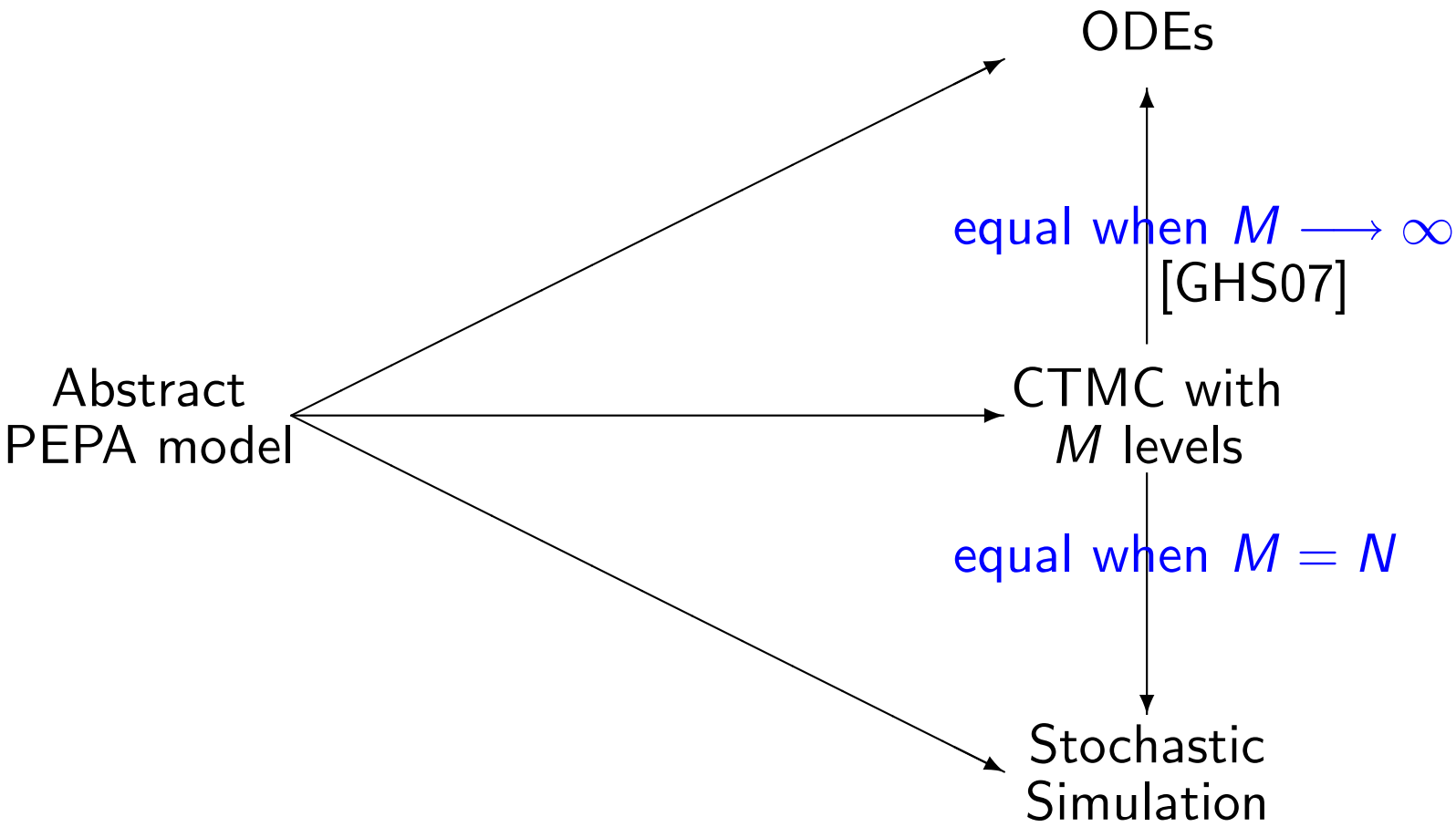

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- In the future we hope to investigate the extent to which the process algebra compositional structure can be exploited during model analysis.

Challenges cont.

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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 candidates 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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  - New models of computations that are biologically inspired.

Thank You!

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Collaborators: Muffy Calder, Federica Ciocchetta, Adam Duguid, Nil Geisweiller, Stephen Gilmore and Marco Stenico.

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