Calculi for Systems Biology

Jane Hillston.
LFCS, University of Edinburgh

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Joint work with Federica Ciocchetta

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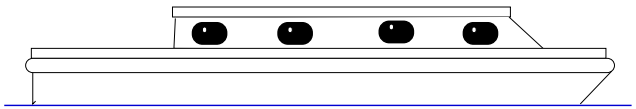
- The project has sought to investigate and exploit the interplay between the process algebra and the continuous time Markov chain (CTMC).

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)

- Locks and movable bridges in inland shipping in Belgium (Knapen, Hasselt)



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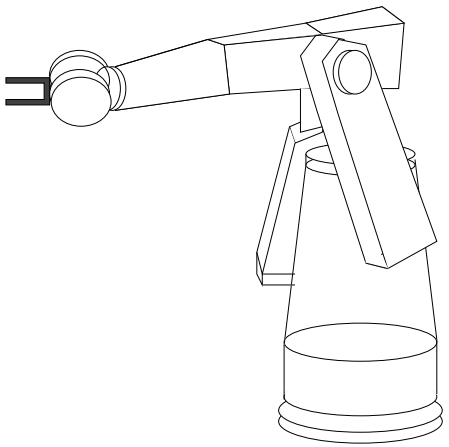

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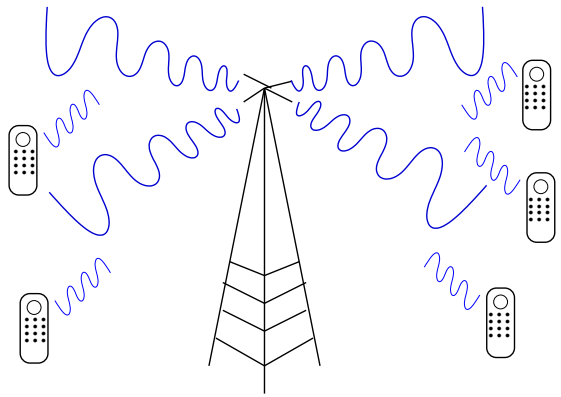

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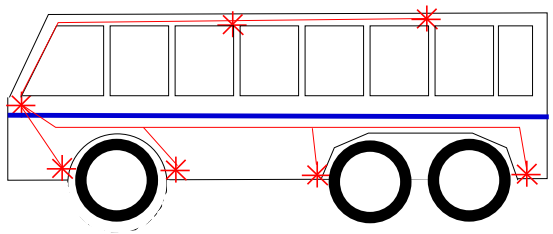
- Automotive diagnostic expert systems (Console, Picardi and Ribaudo, Turin)



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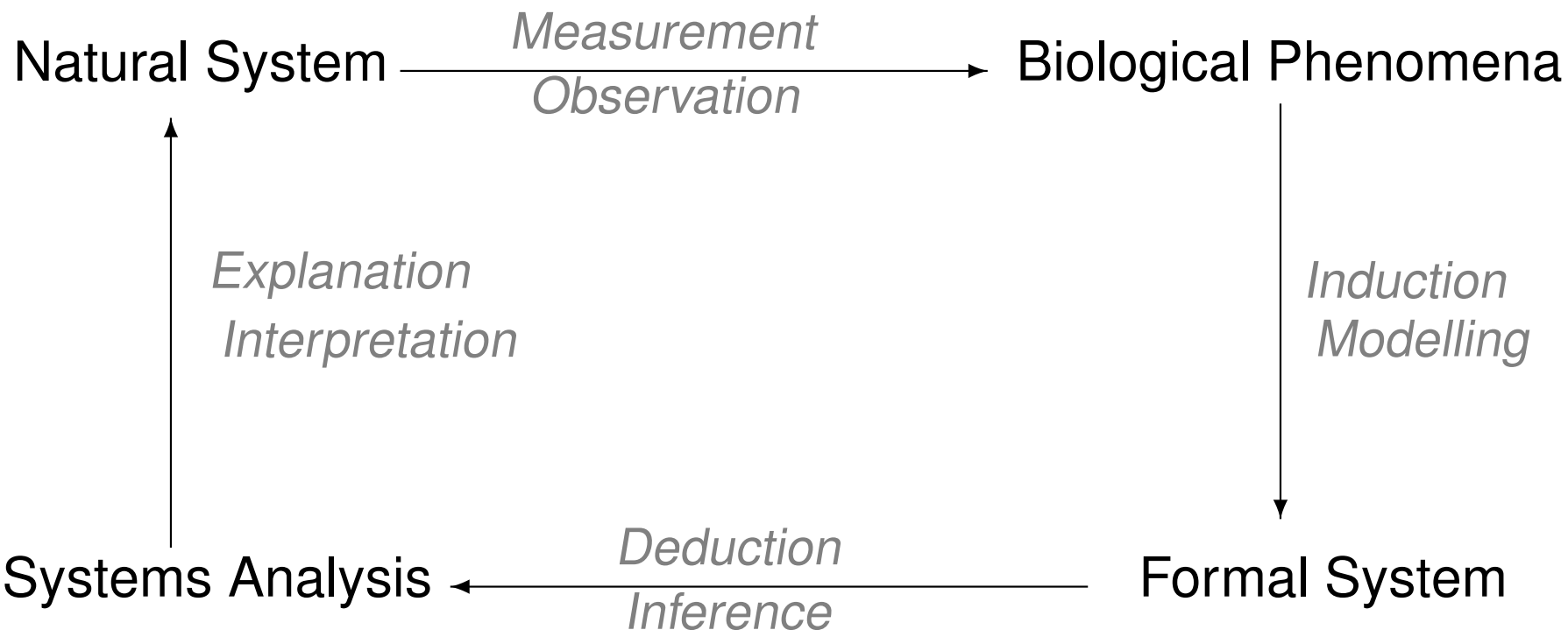
- Systems biology aims to develop a better understanding of the processes involved.
- It involves taking a systems theoretic view of biological processes — analysing inputs and outputs and the relationships between them.
- A radical shift from earlier reductionist approaches, systems biology aims to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

Systems Biology Methodology



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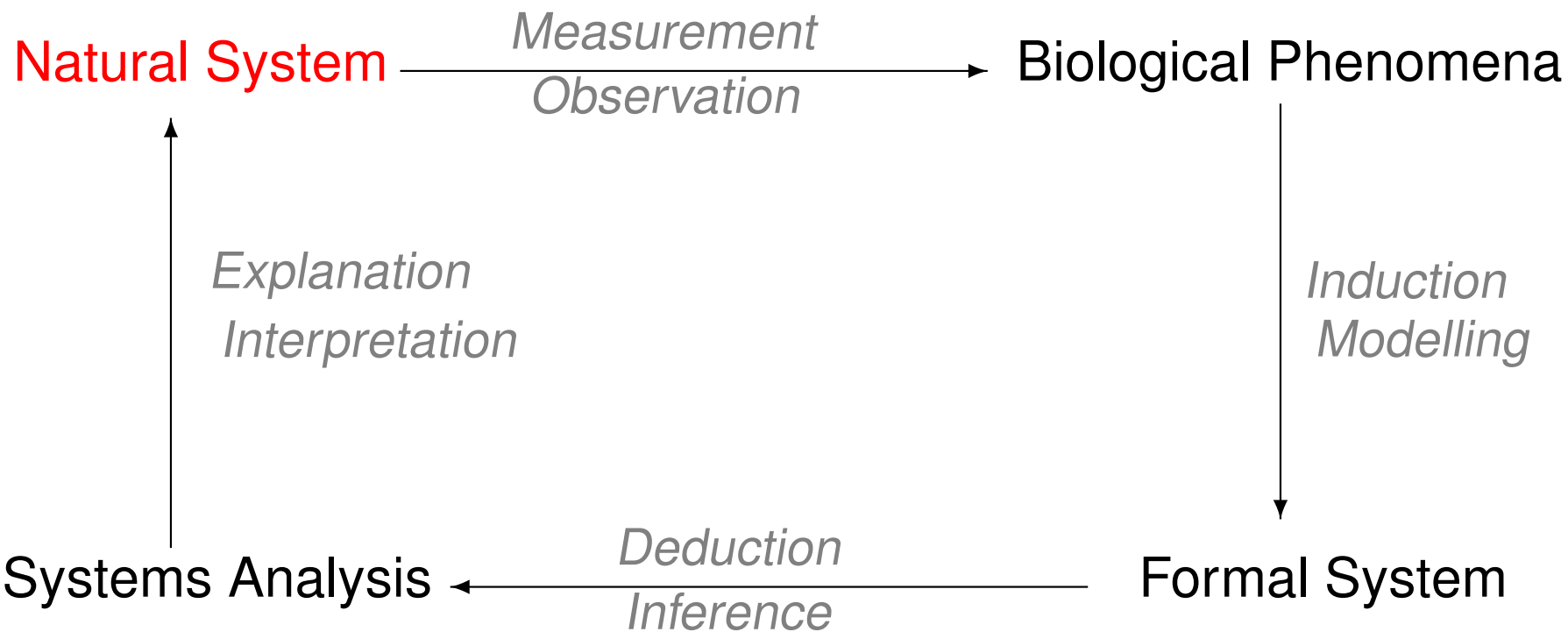

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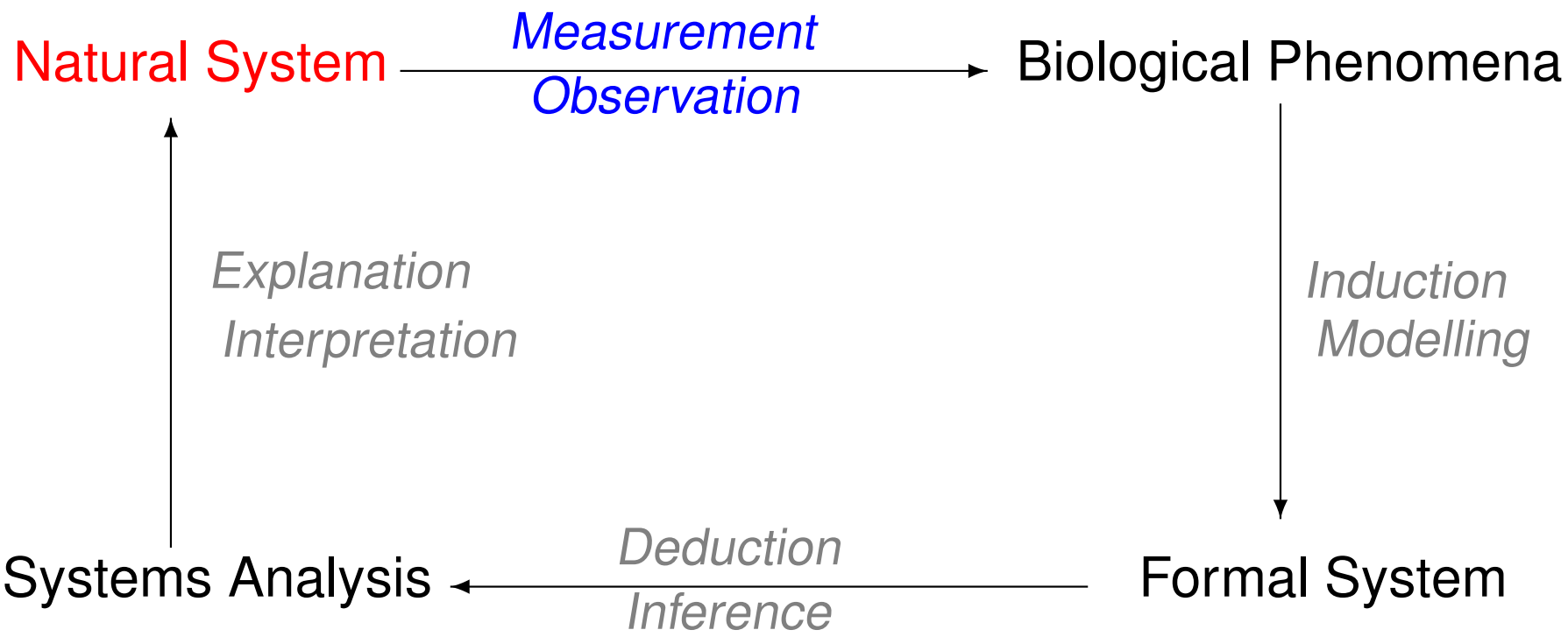

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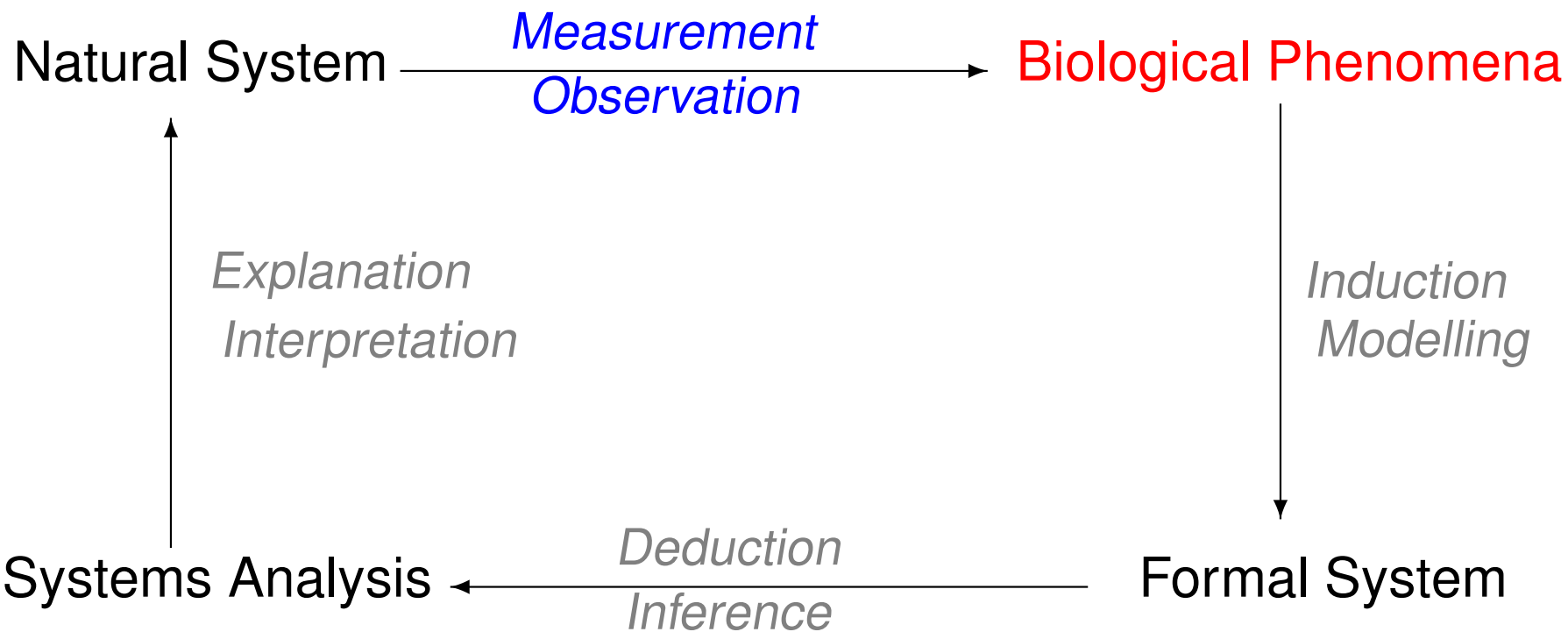

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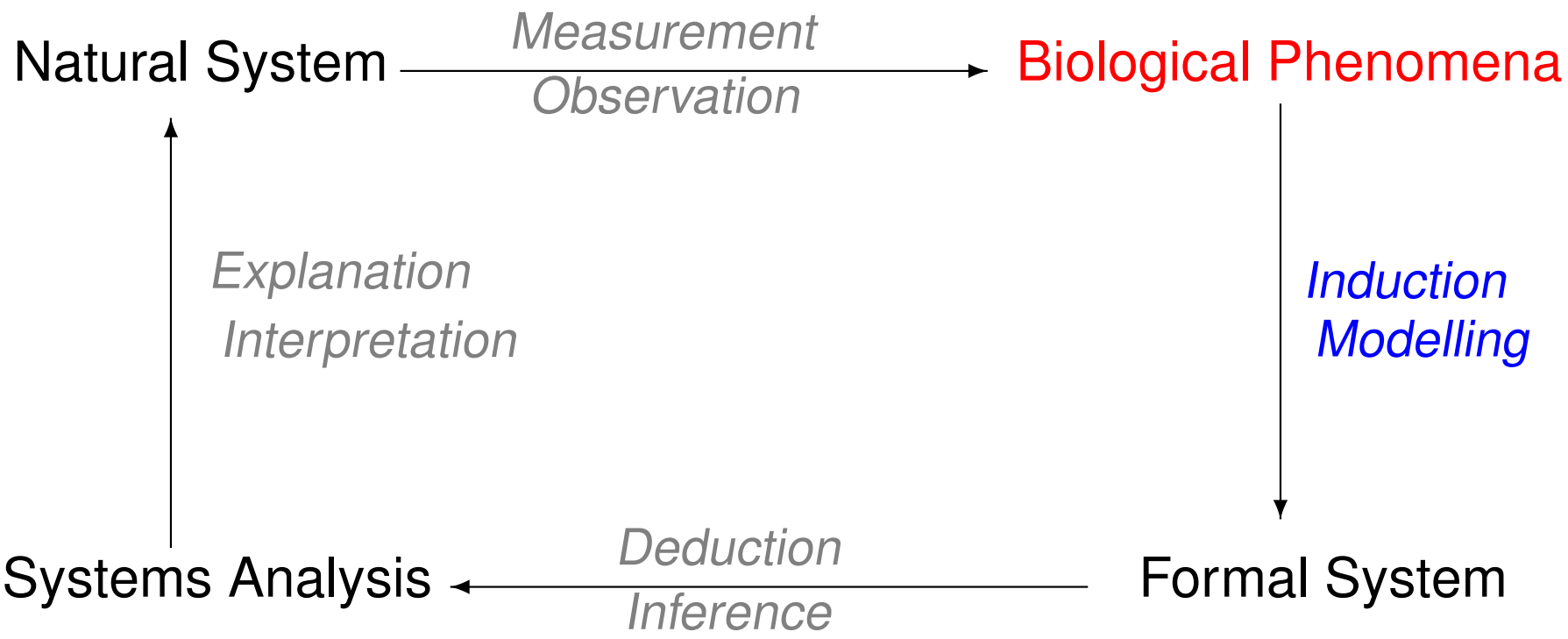

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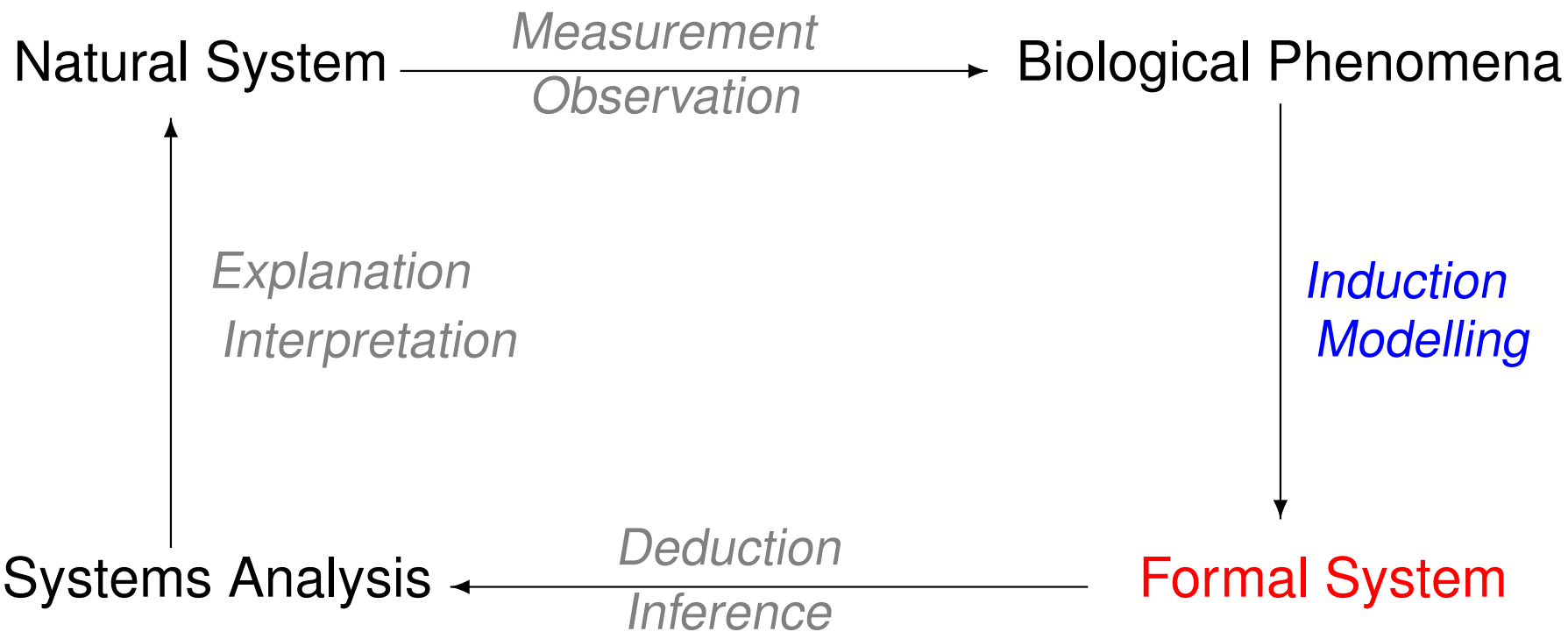

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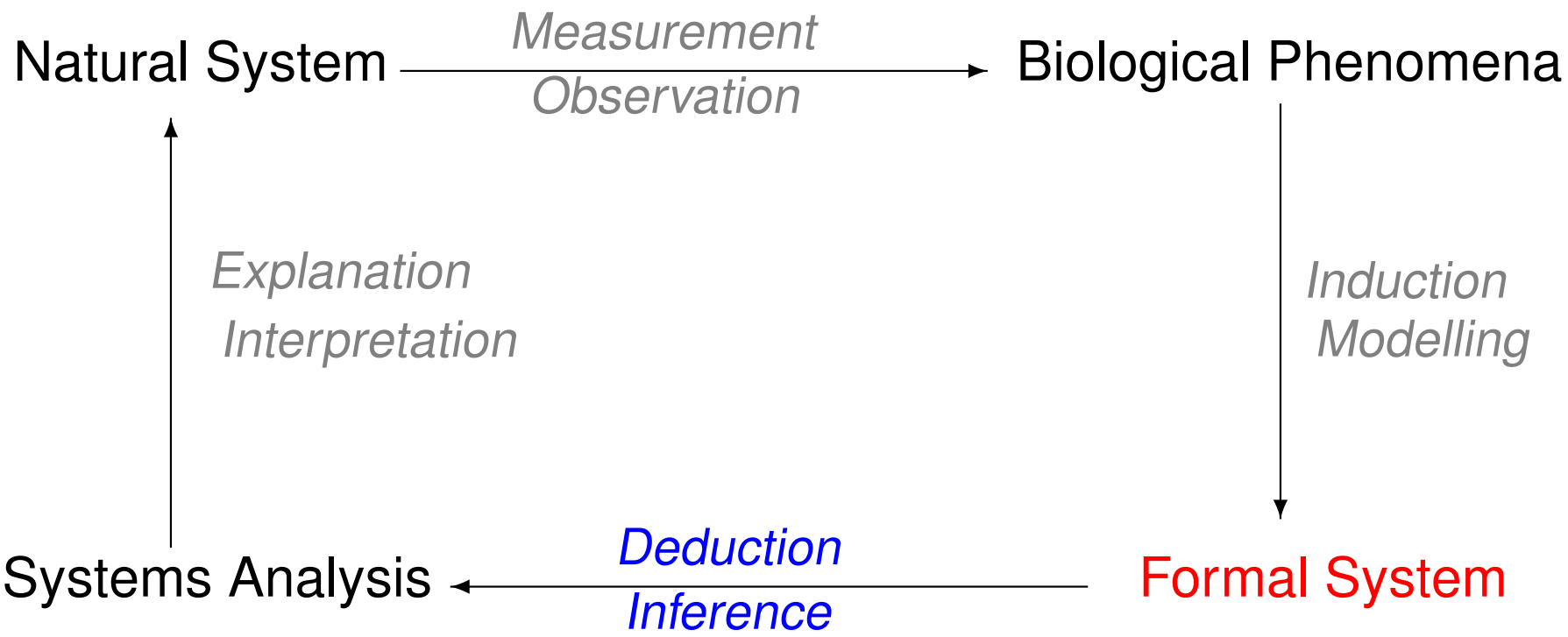

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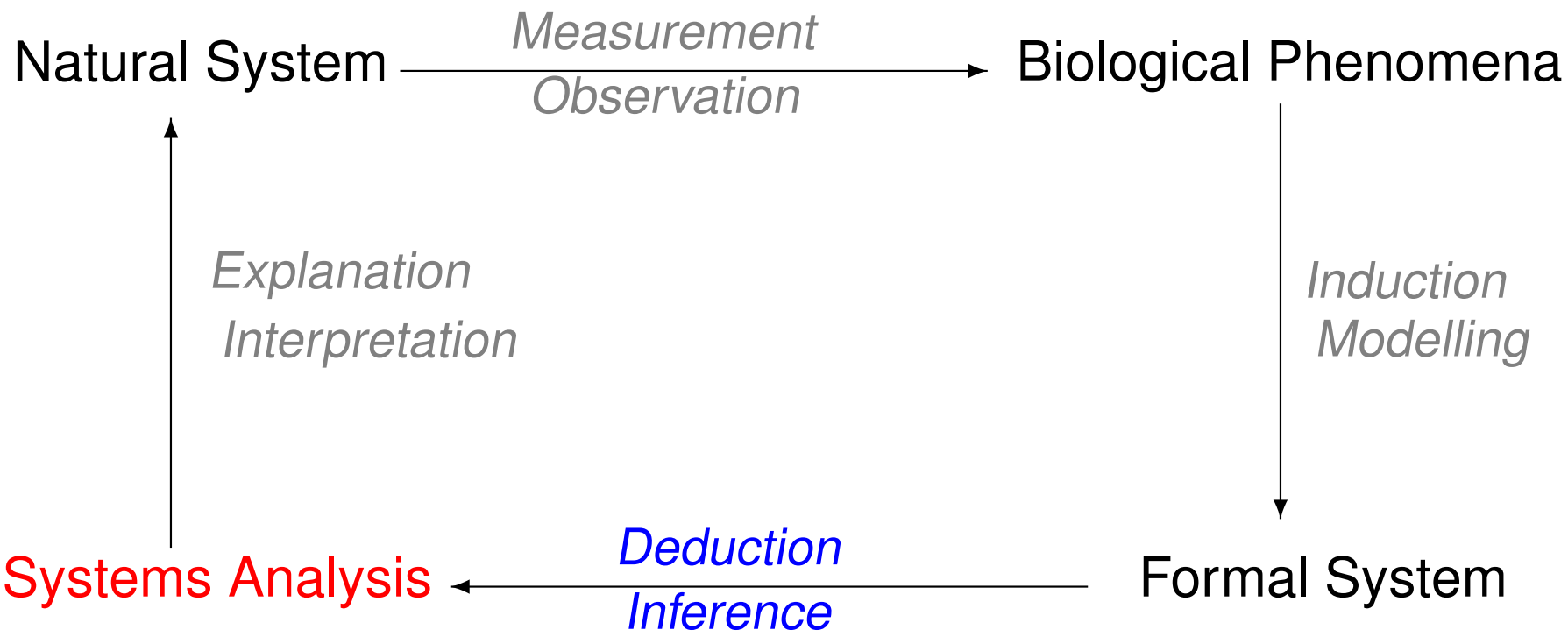

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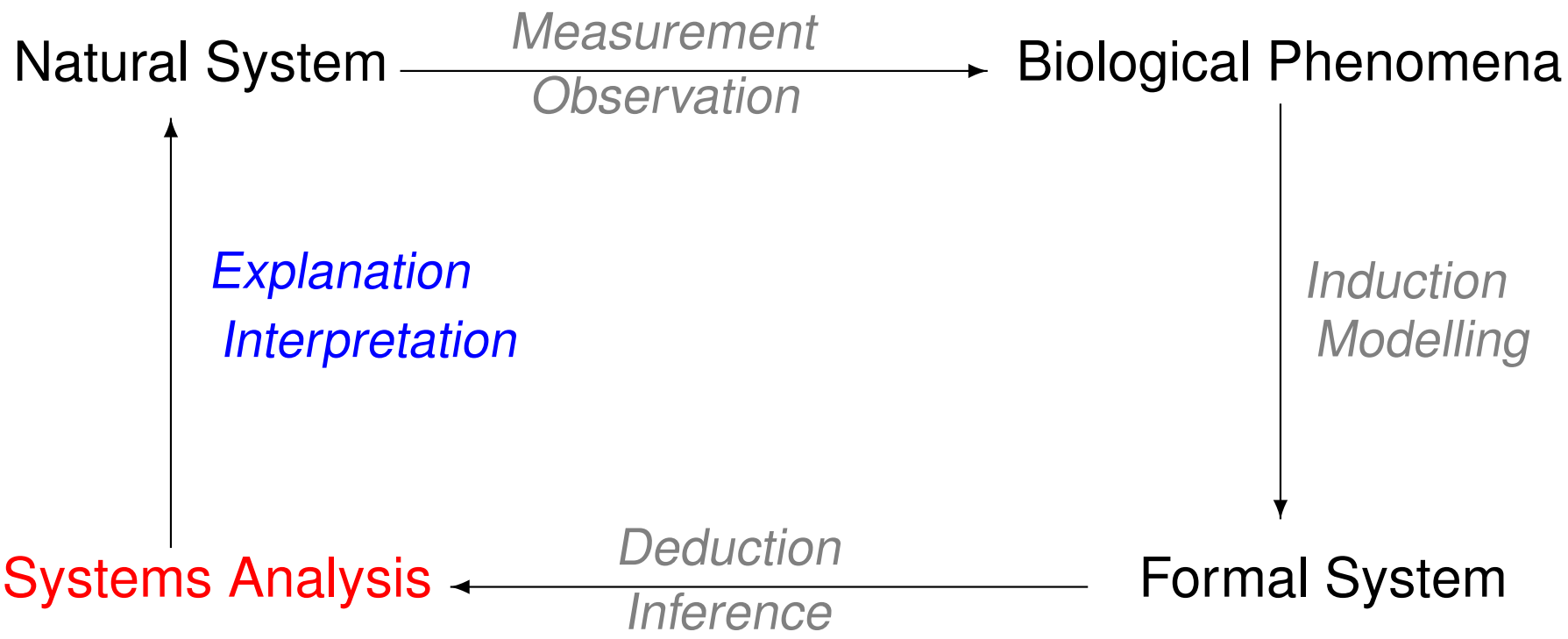

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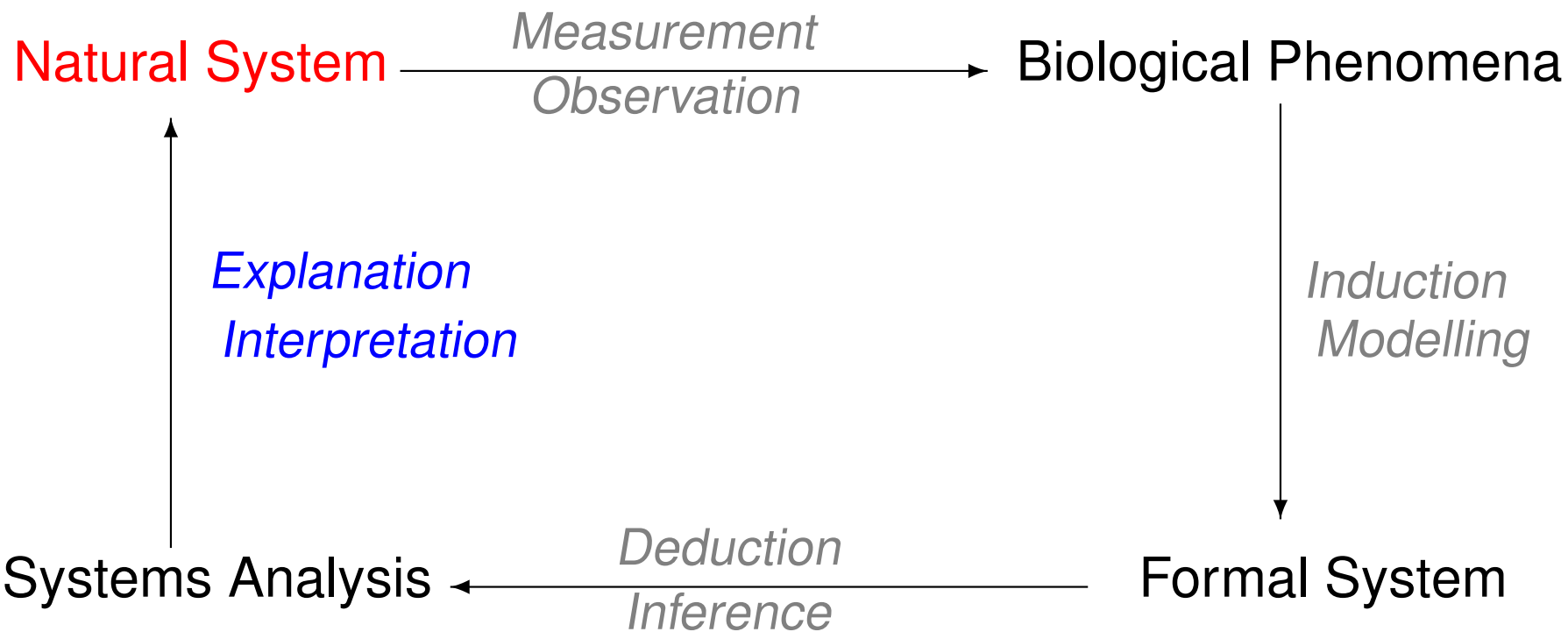

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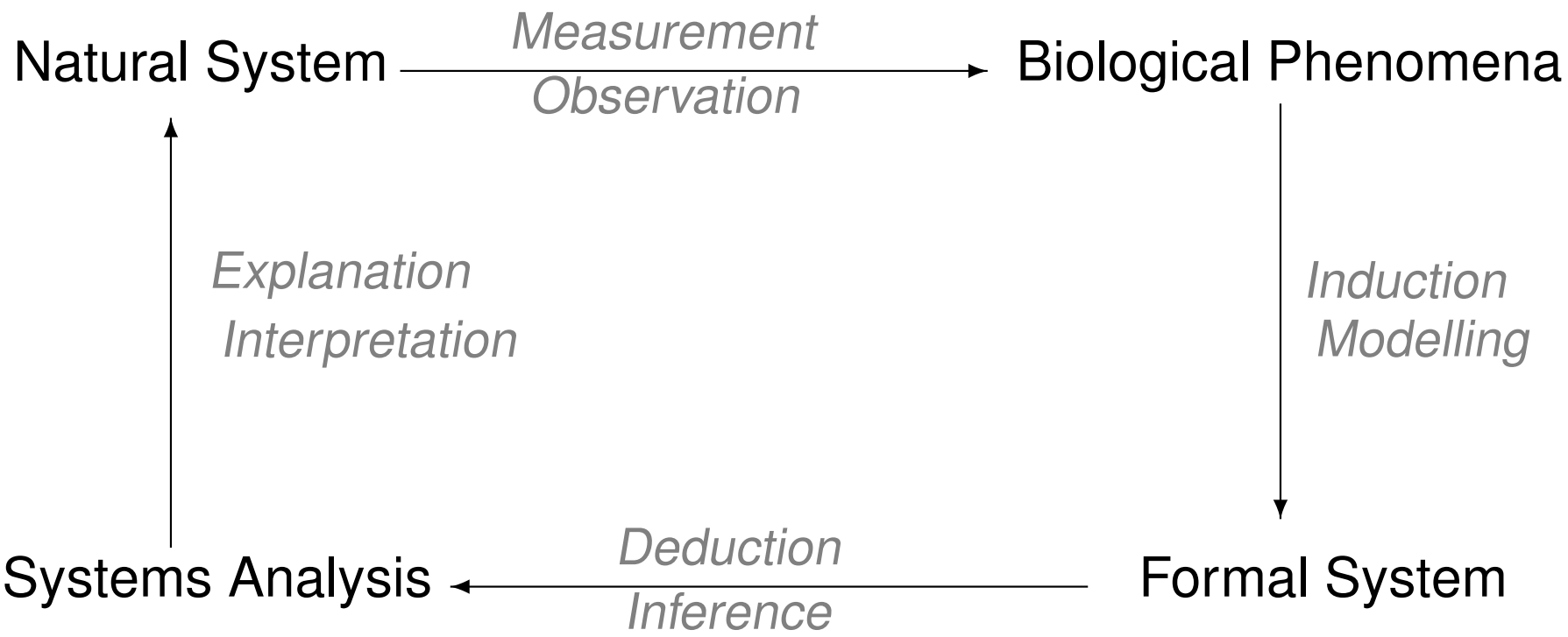

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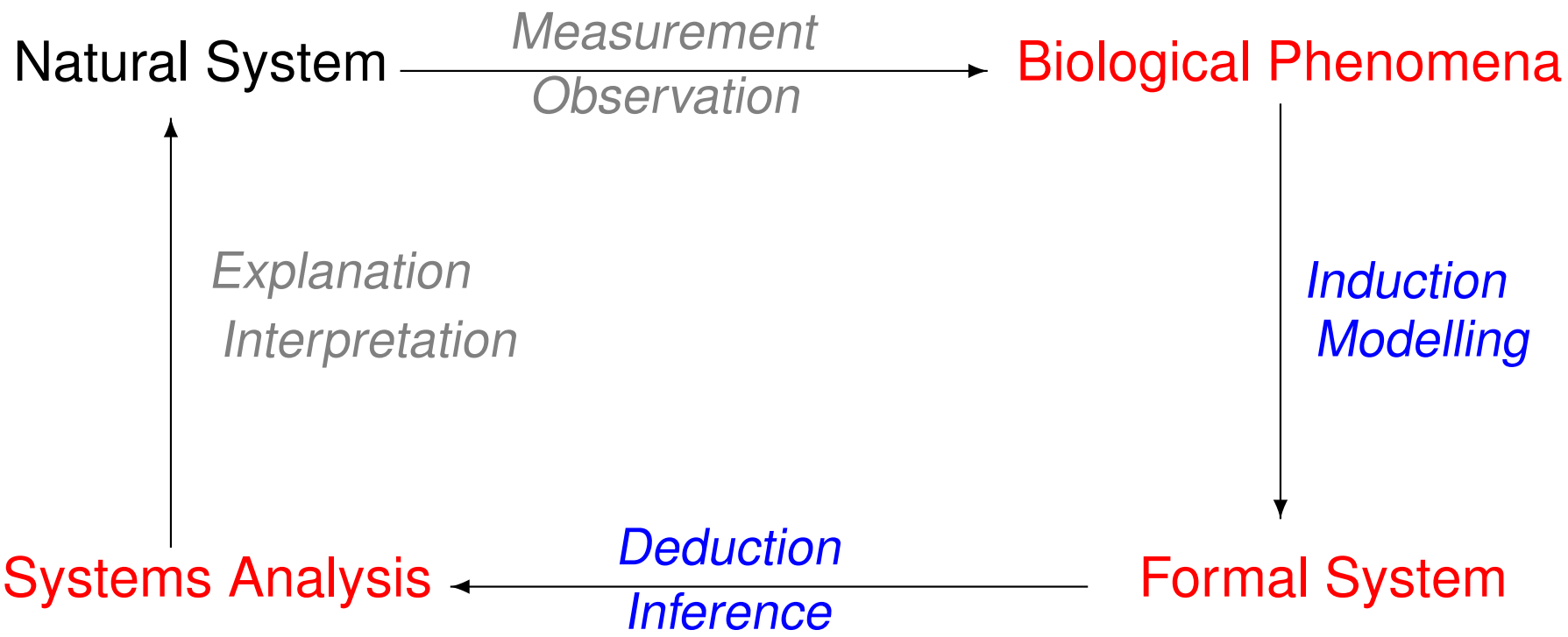

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  - continuous behaviour (concentrations),
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- Stochastic Simulation:
  - continuous time,
  - discrete behaviour (no. of molecules),
  - stochastic.

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 simulation algorithms

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Since each molecule is represented explicitly the number of generated states can be extremely large.

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- Models should match wet lab experimental data.

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- 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.

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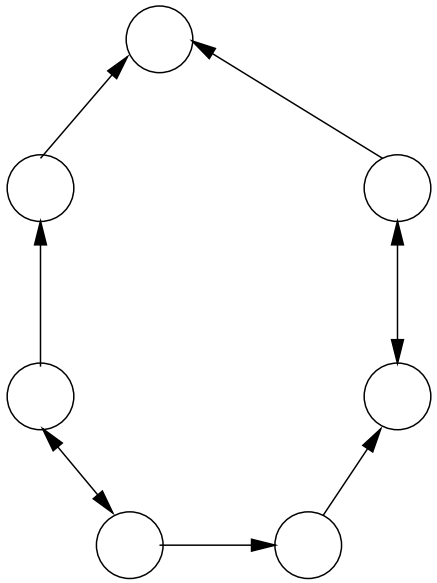
Others such as Cornish-Bowden are much more skeptical and cite the problem of infinite regress as being insurmountable.

The problem of *Infinite Regress*



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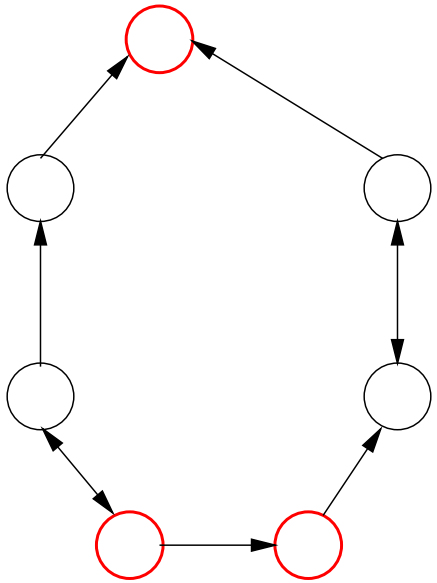

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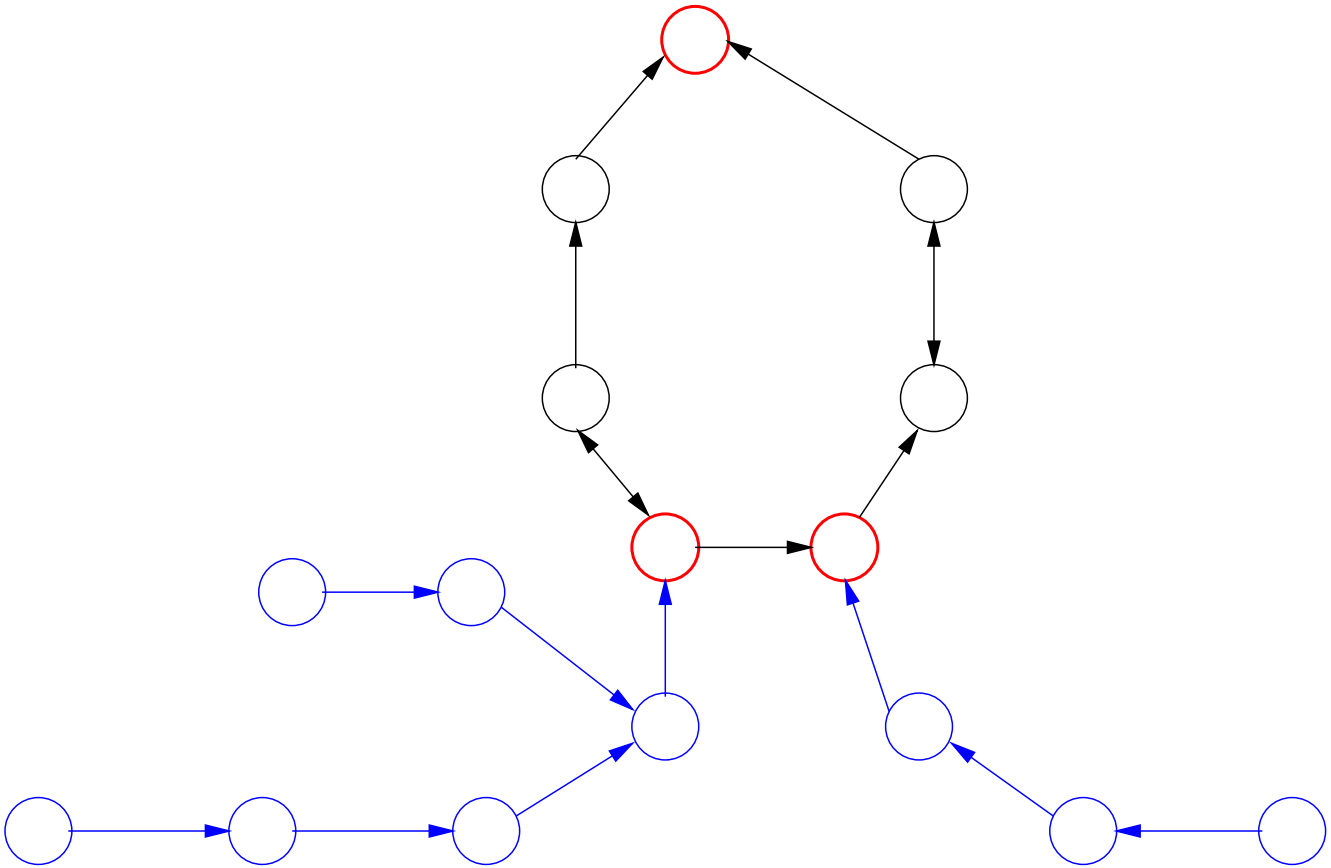

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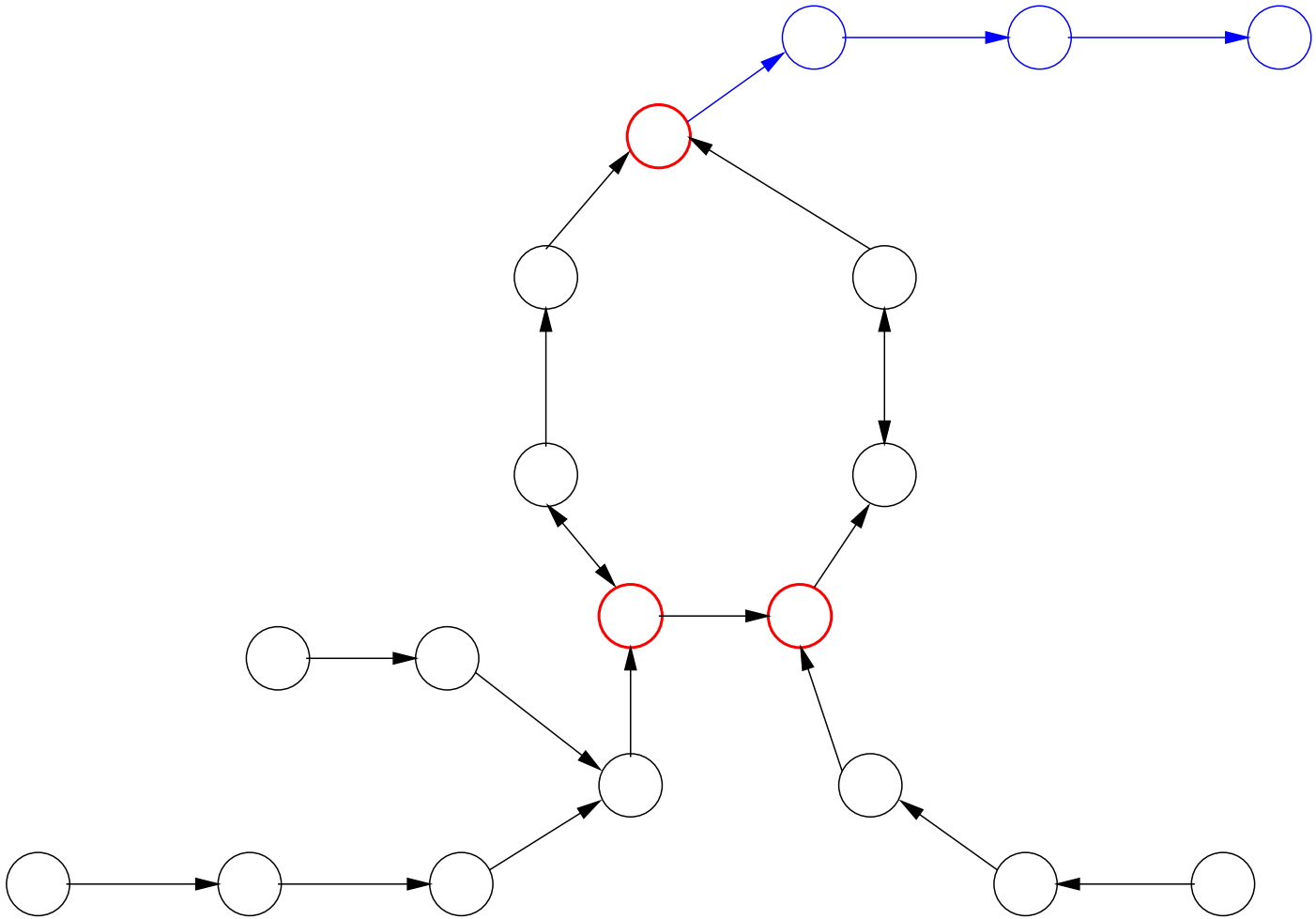

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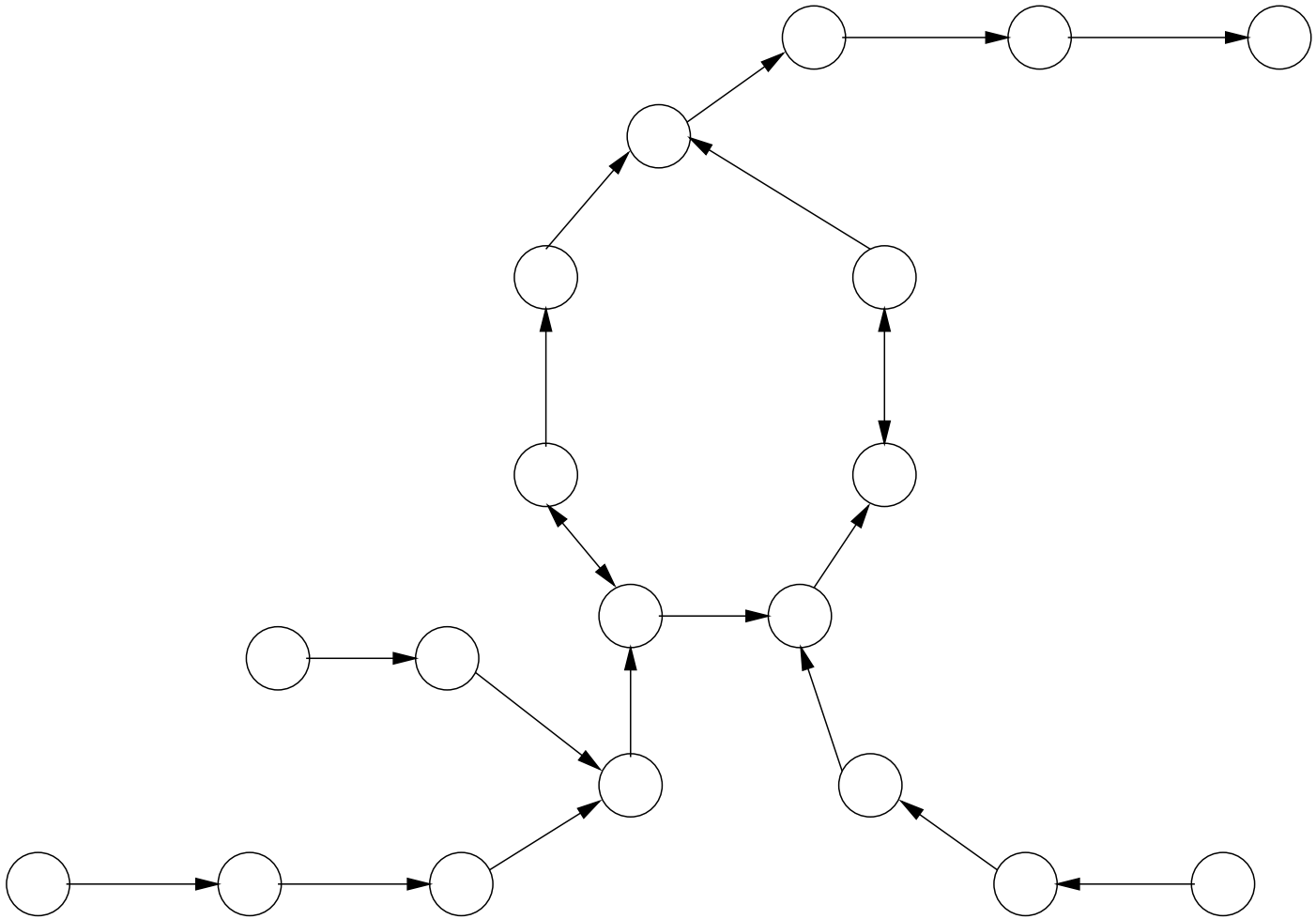

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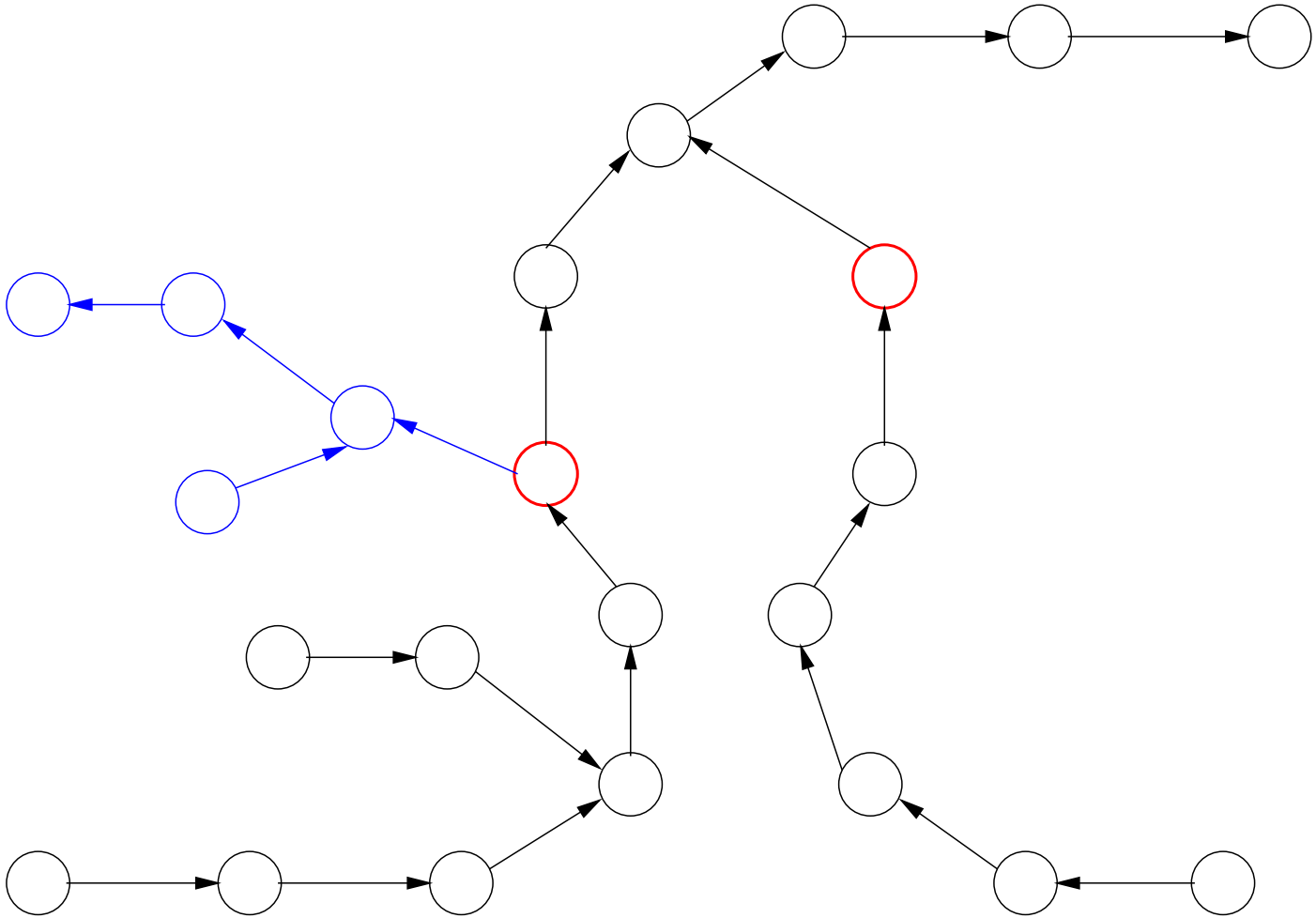

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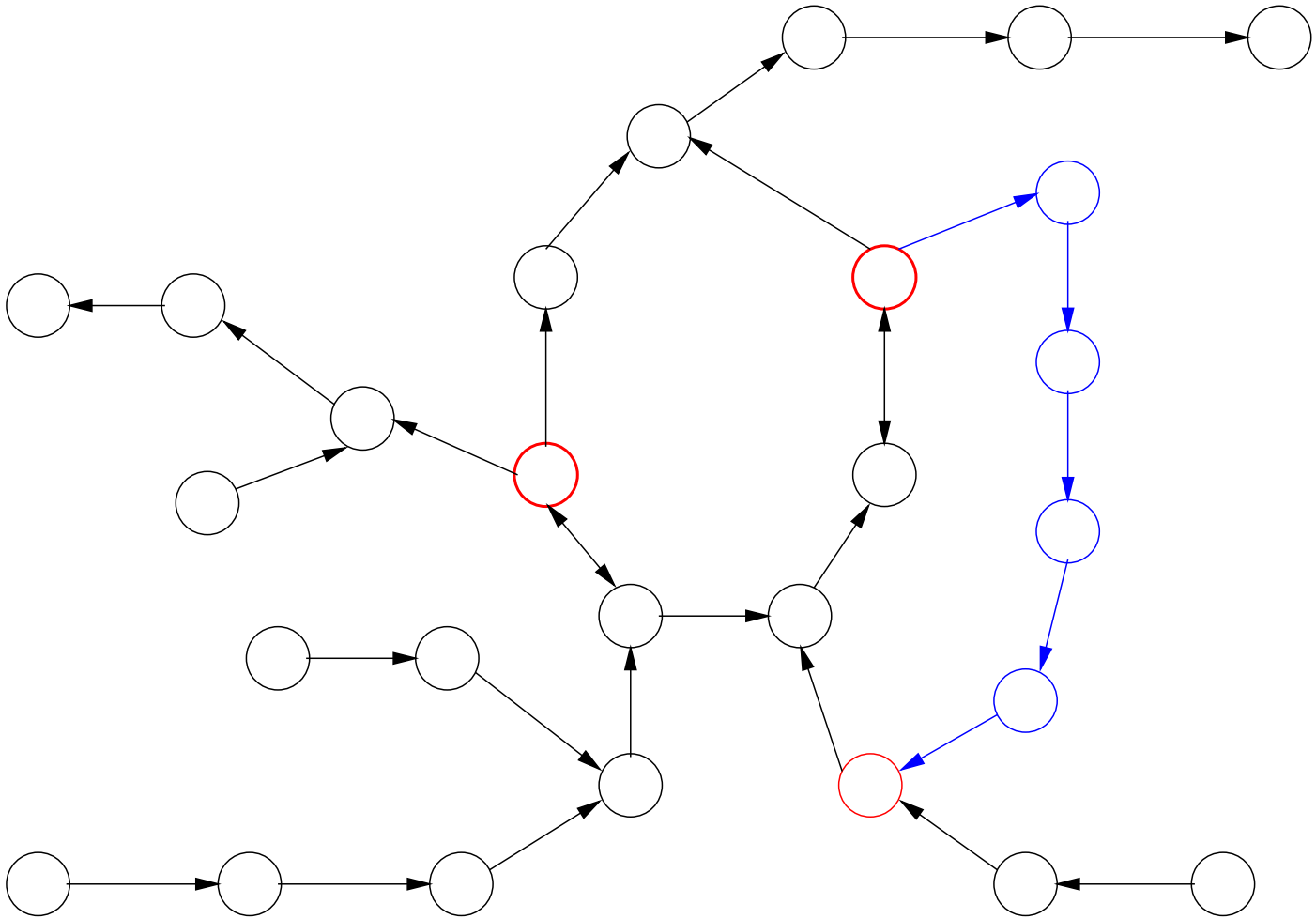

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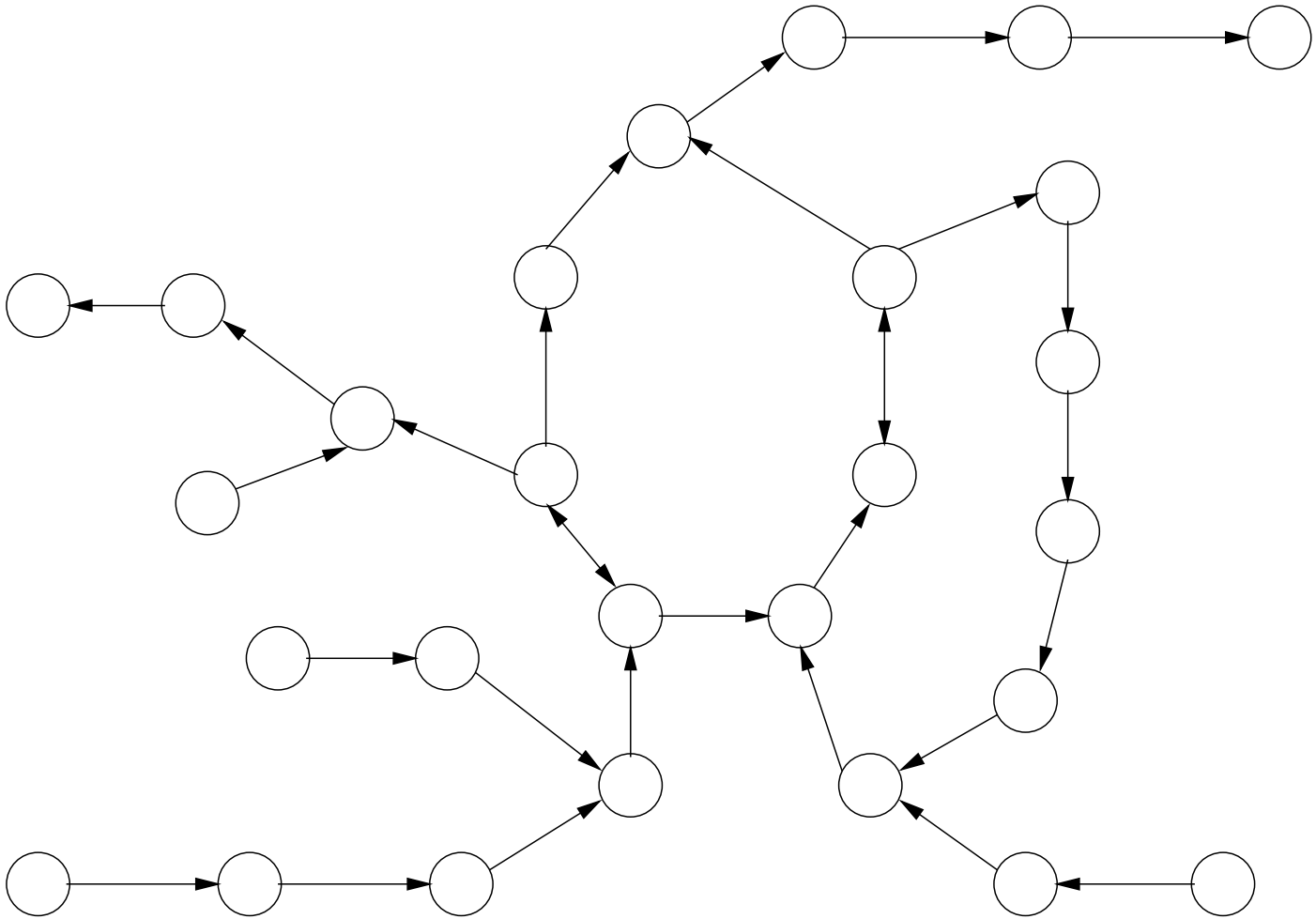

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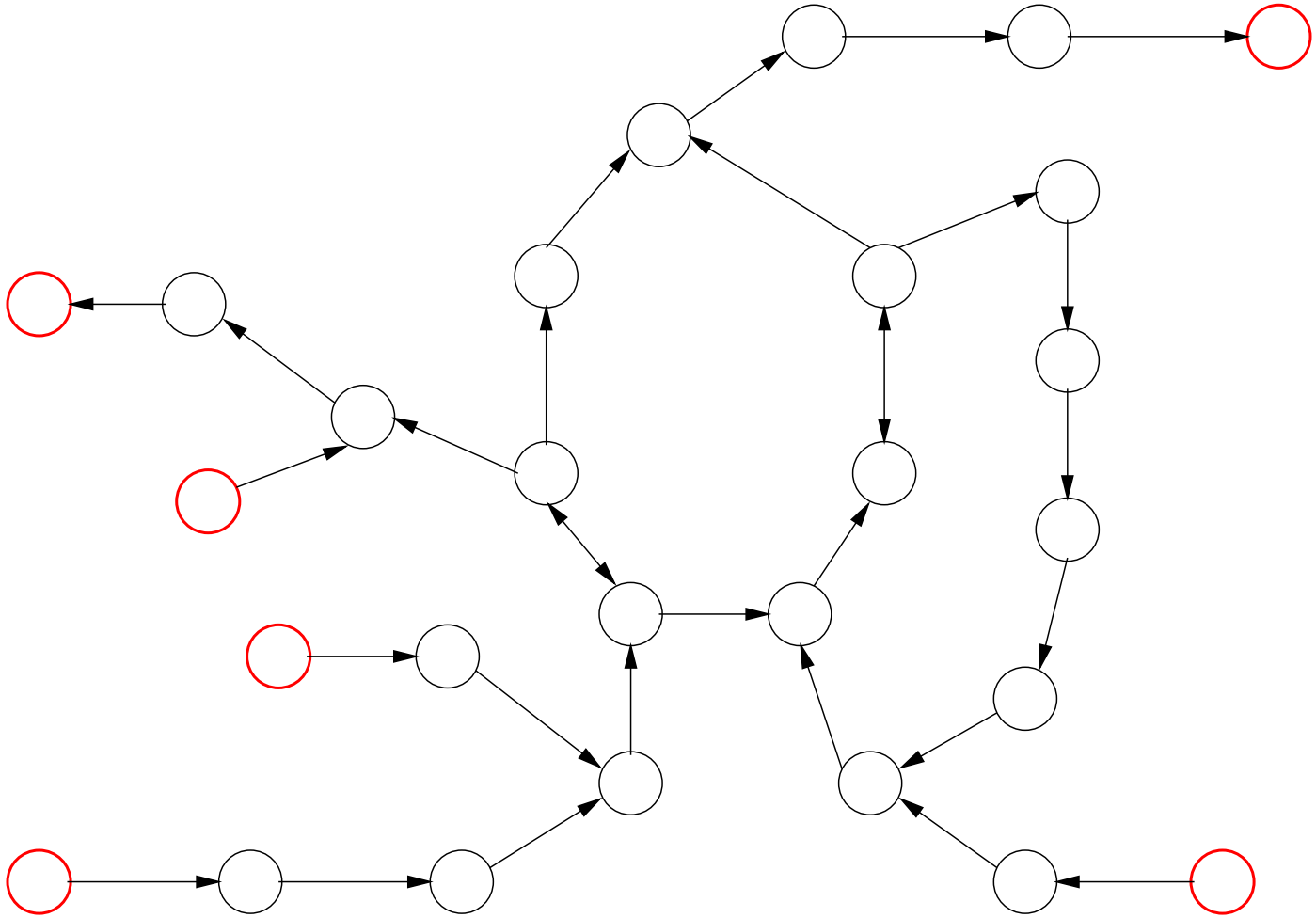

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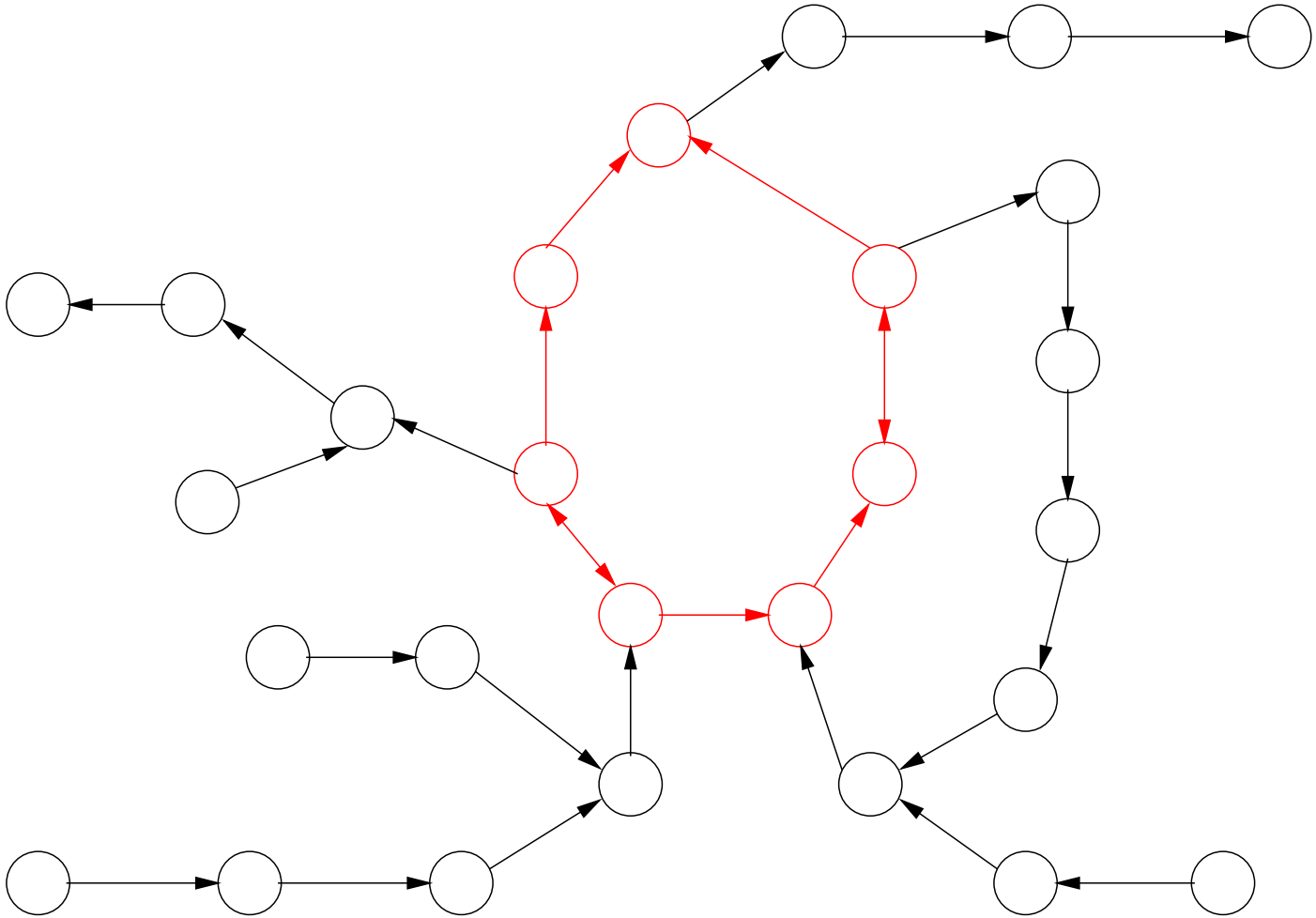

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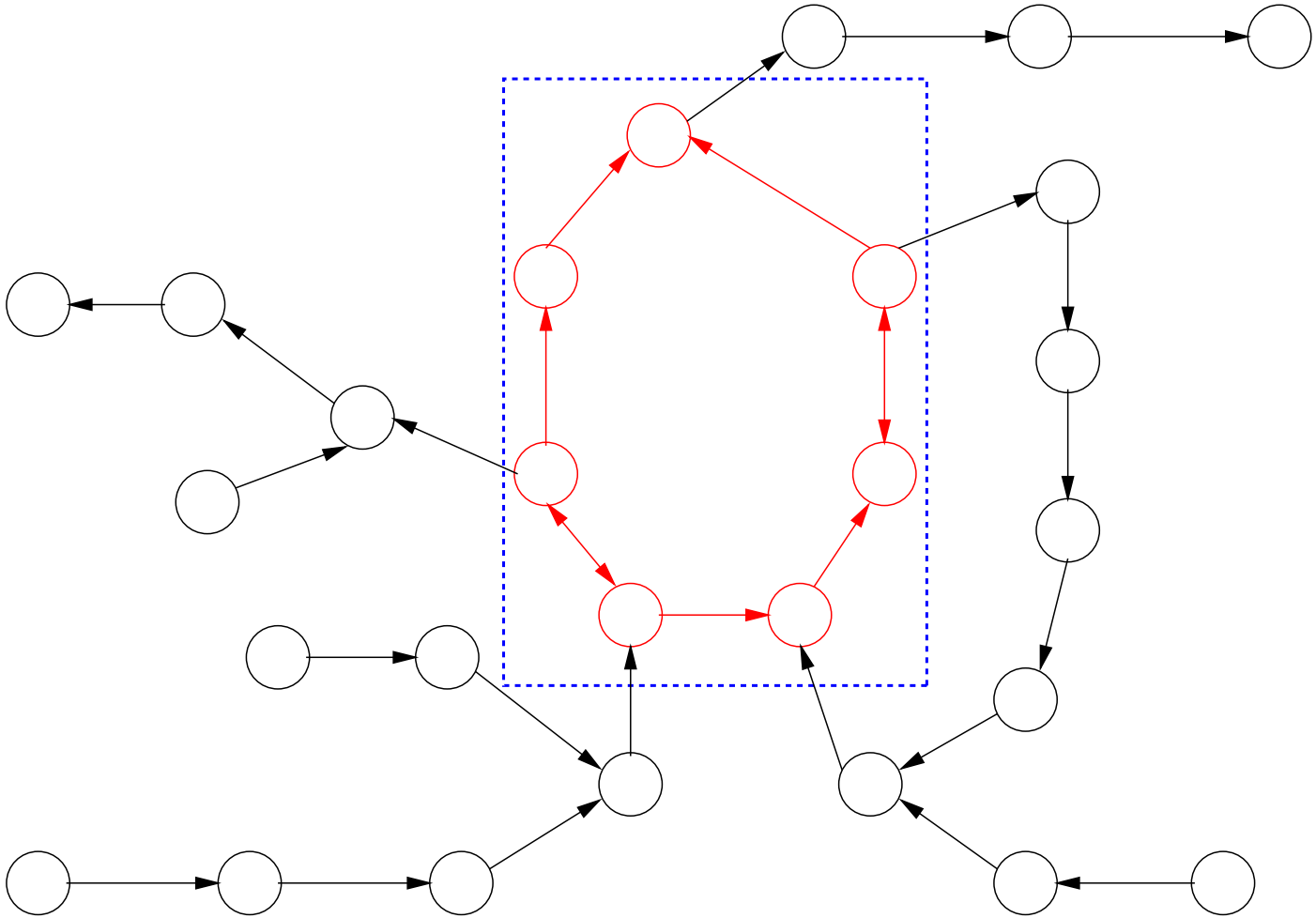

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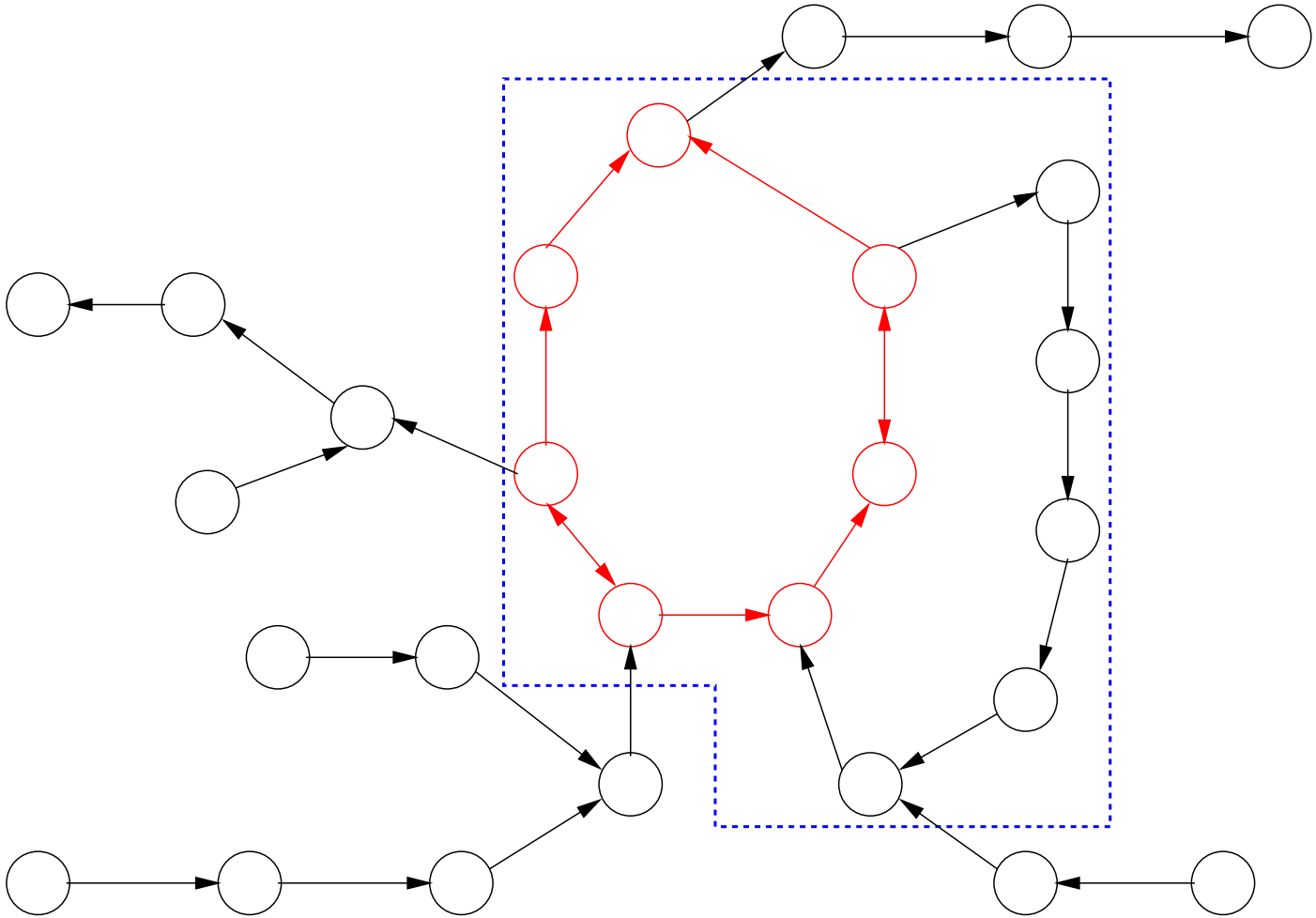

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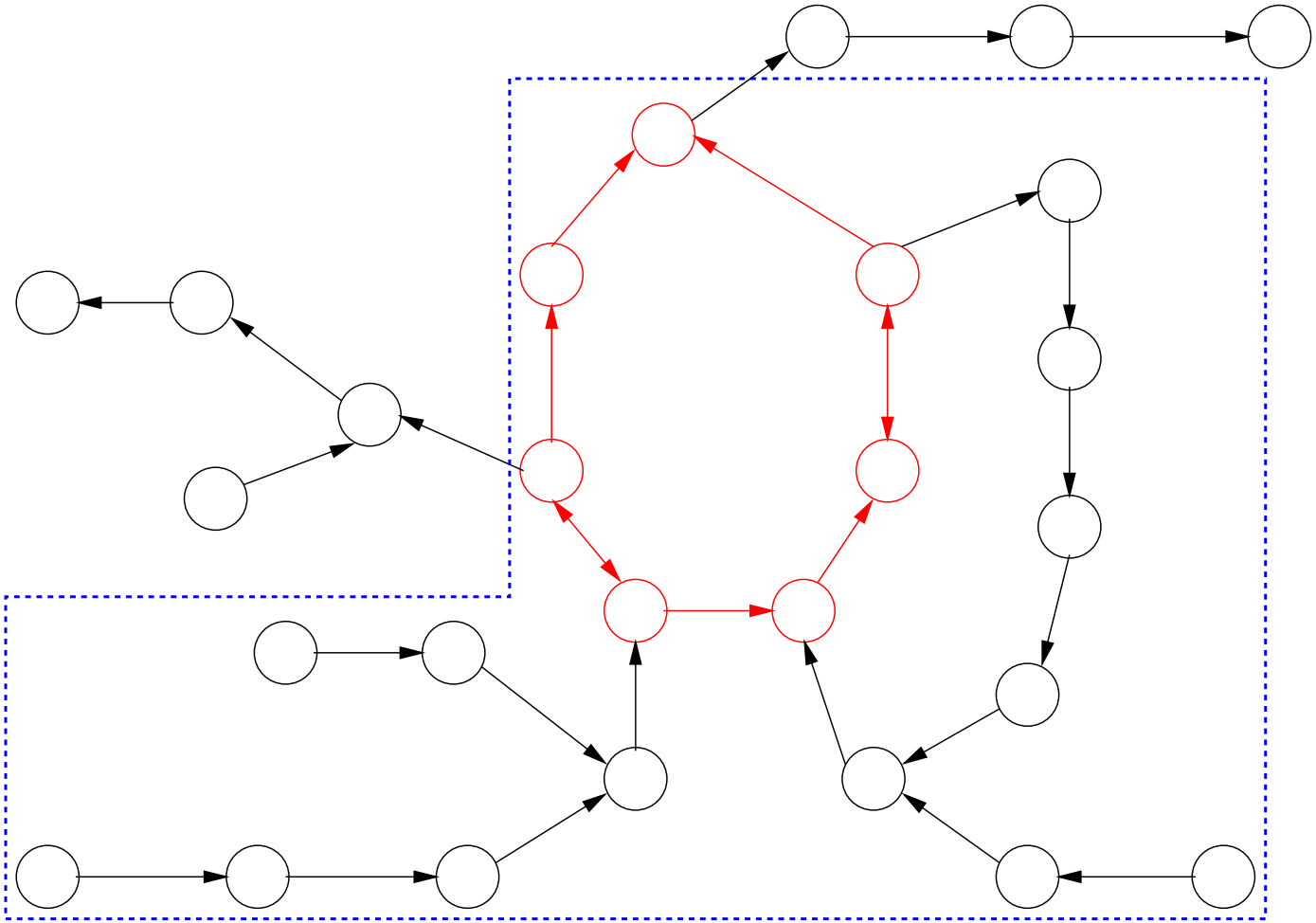

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In other cases the data is unknowable because experimental techniques do not yet exist to collect the data, or those that do involve modification to the system.

Dealing with the Unknown

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In some cases this is because no experimental data is available, or that the experimental data that is available is inconsistent.

In other cases the data is unknowable because experimental techniques do not yet exist to collect the data, or those that do involve modification to the system.

Even when data exists the quality is often very poor.

Formal Systems Revisited

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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

Using Stochastic Process Algebras

Process algebras have several attractive features which could be useful for modelling and understanding biological systems:

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- Process algebraic formulations are compositional and make interactions/constraints explicit.
- 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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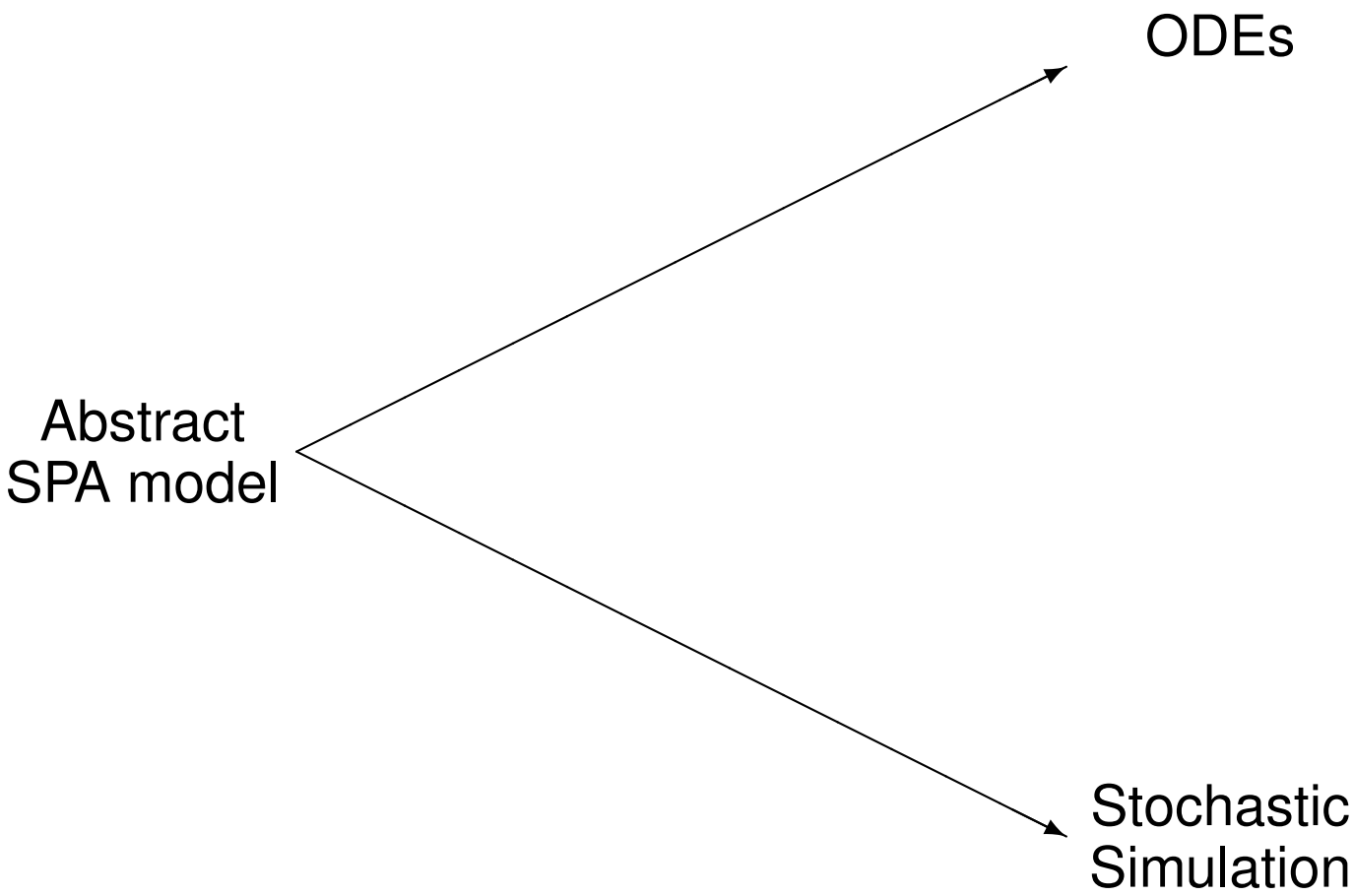
- The data that we have available to parameterise models is sometimes speculative rather than precise. This suggests that it can be useful to use semiquantitative models rather than quantitative ones.

Alternative Representations



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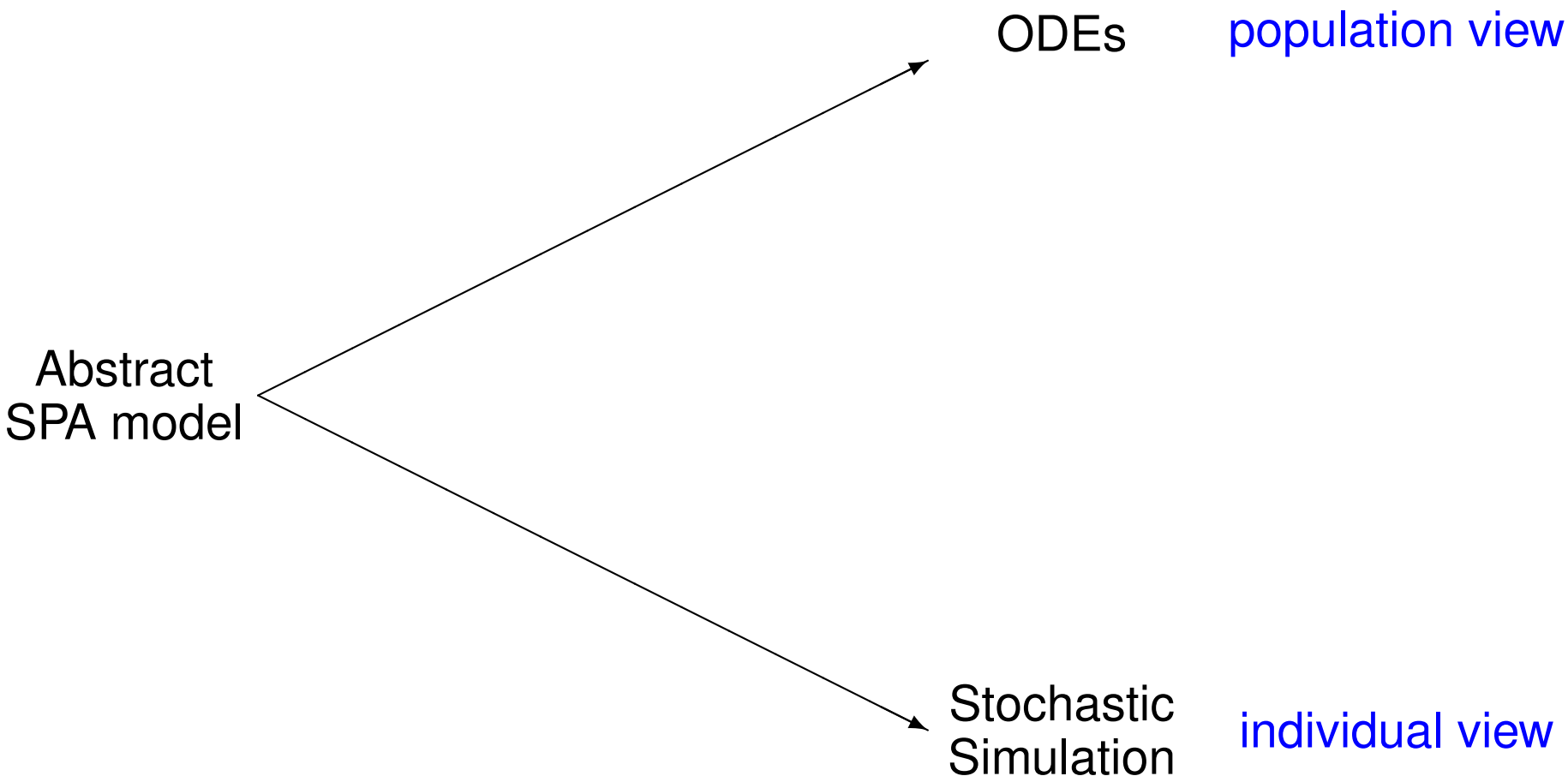

Discretising the population view

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.

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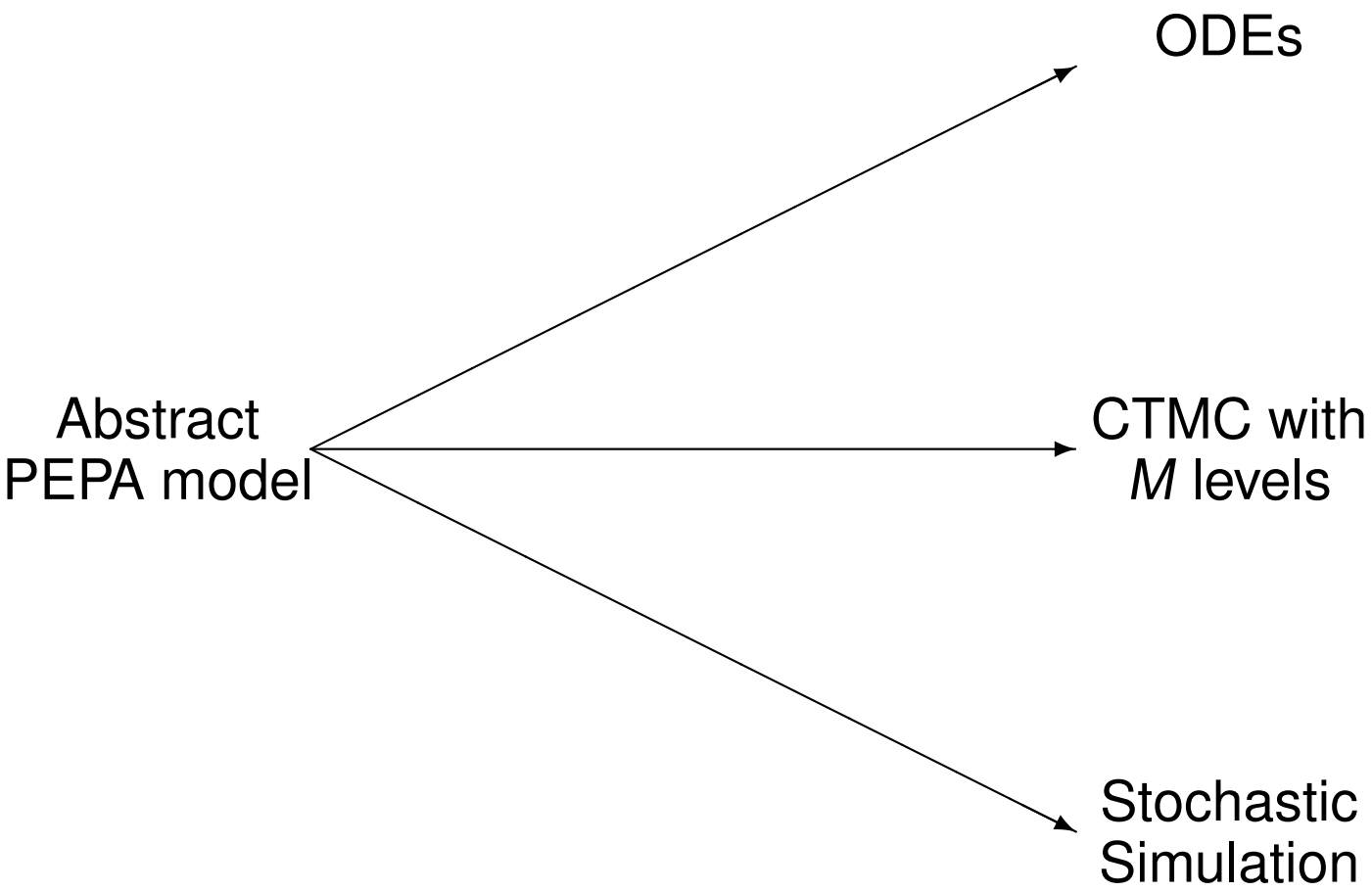

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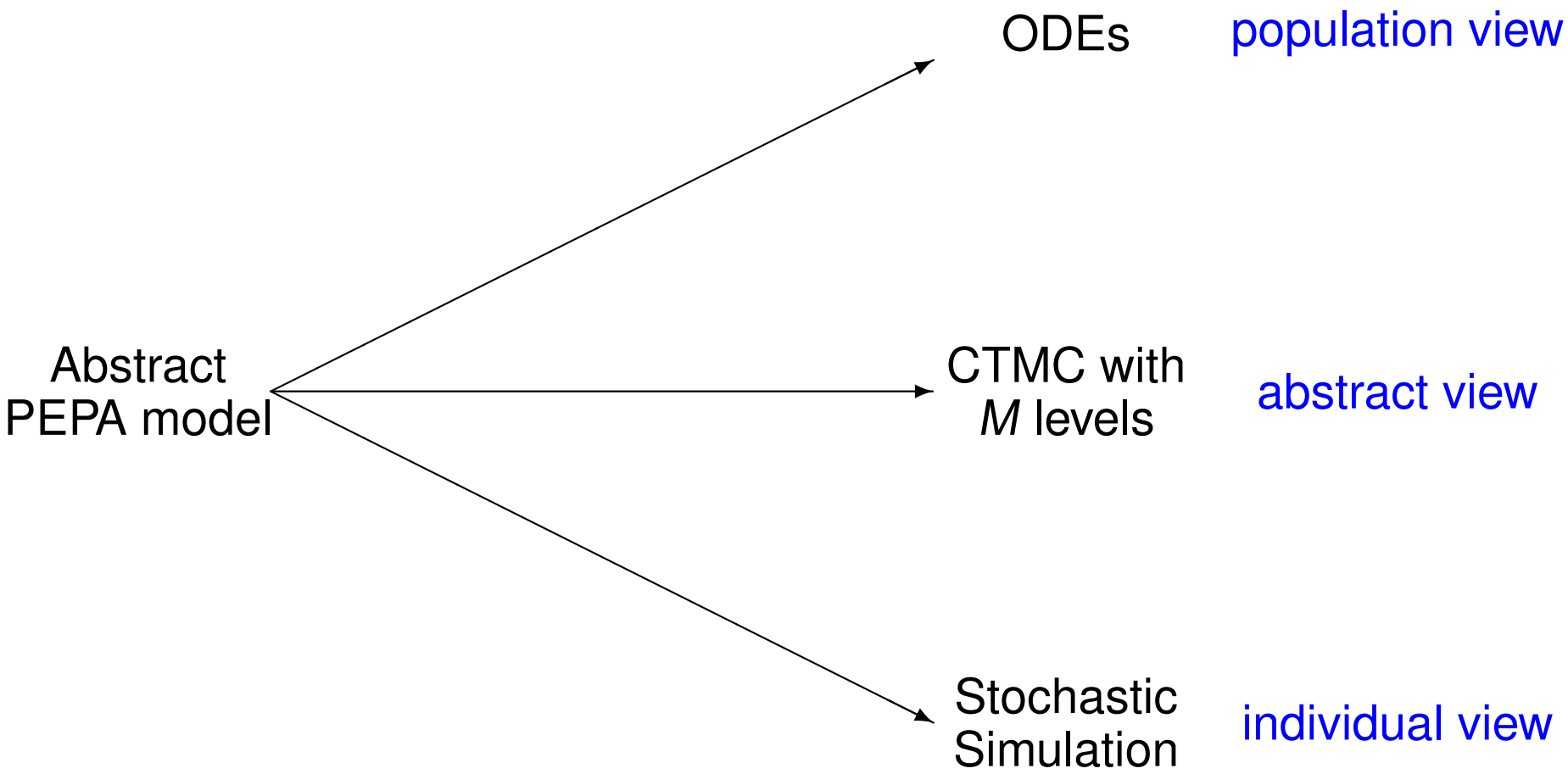

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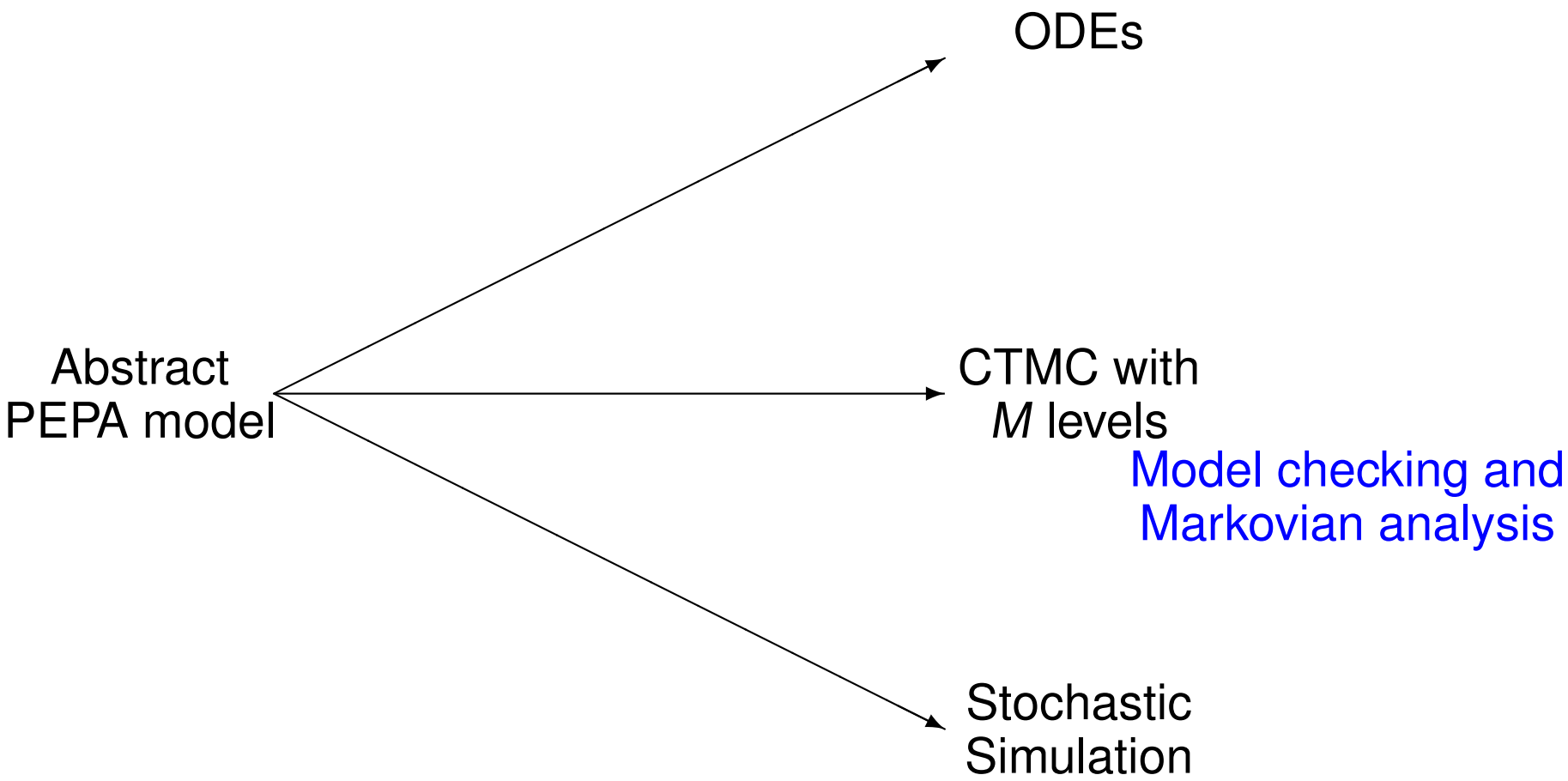

SPA Languages

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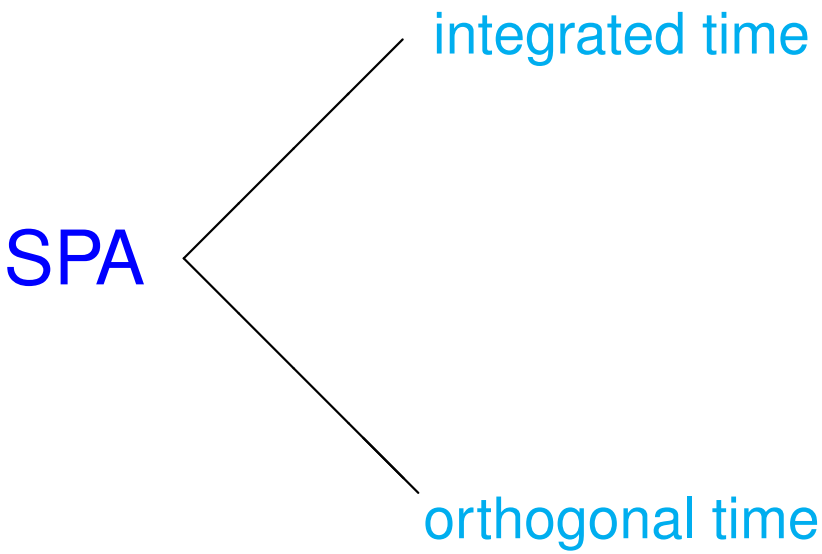

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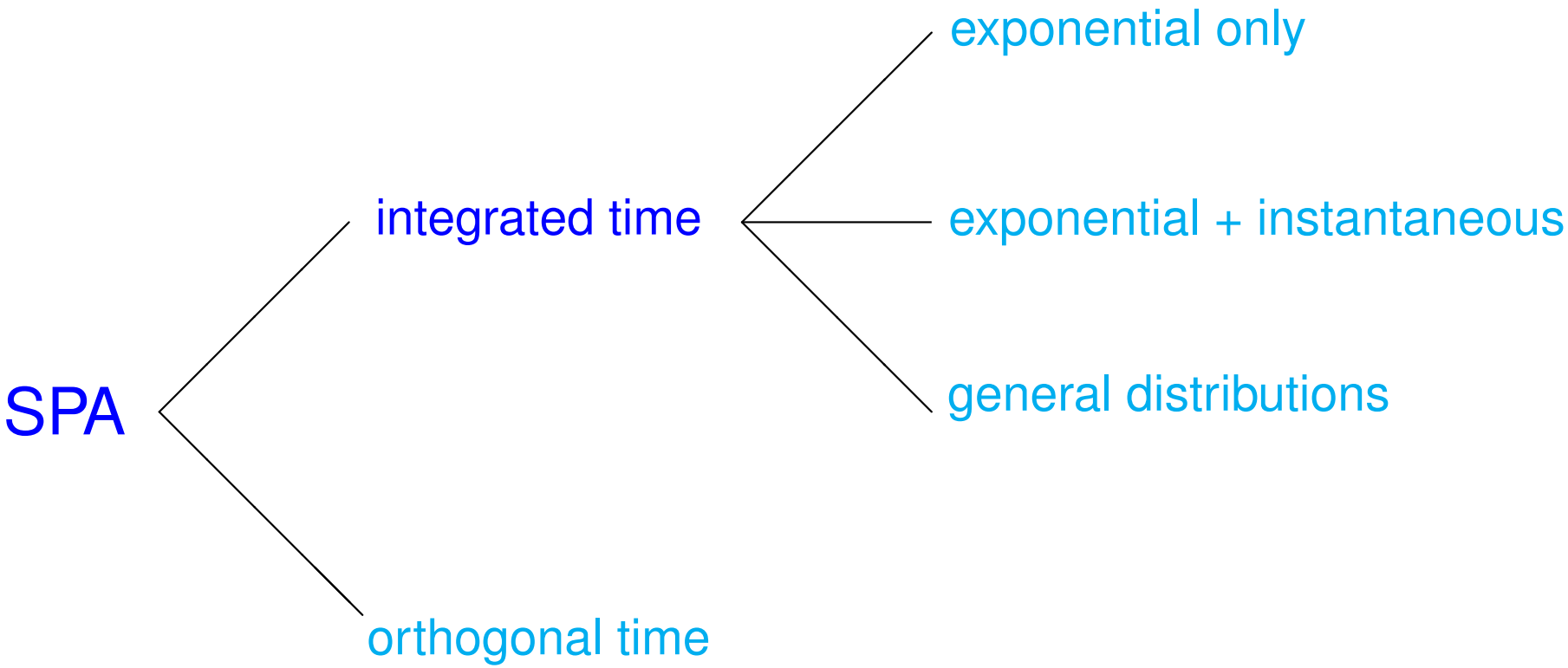

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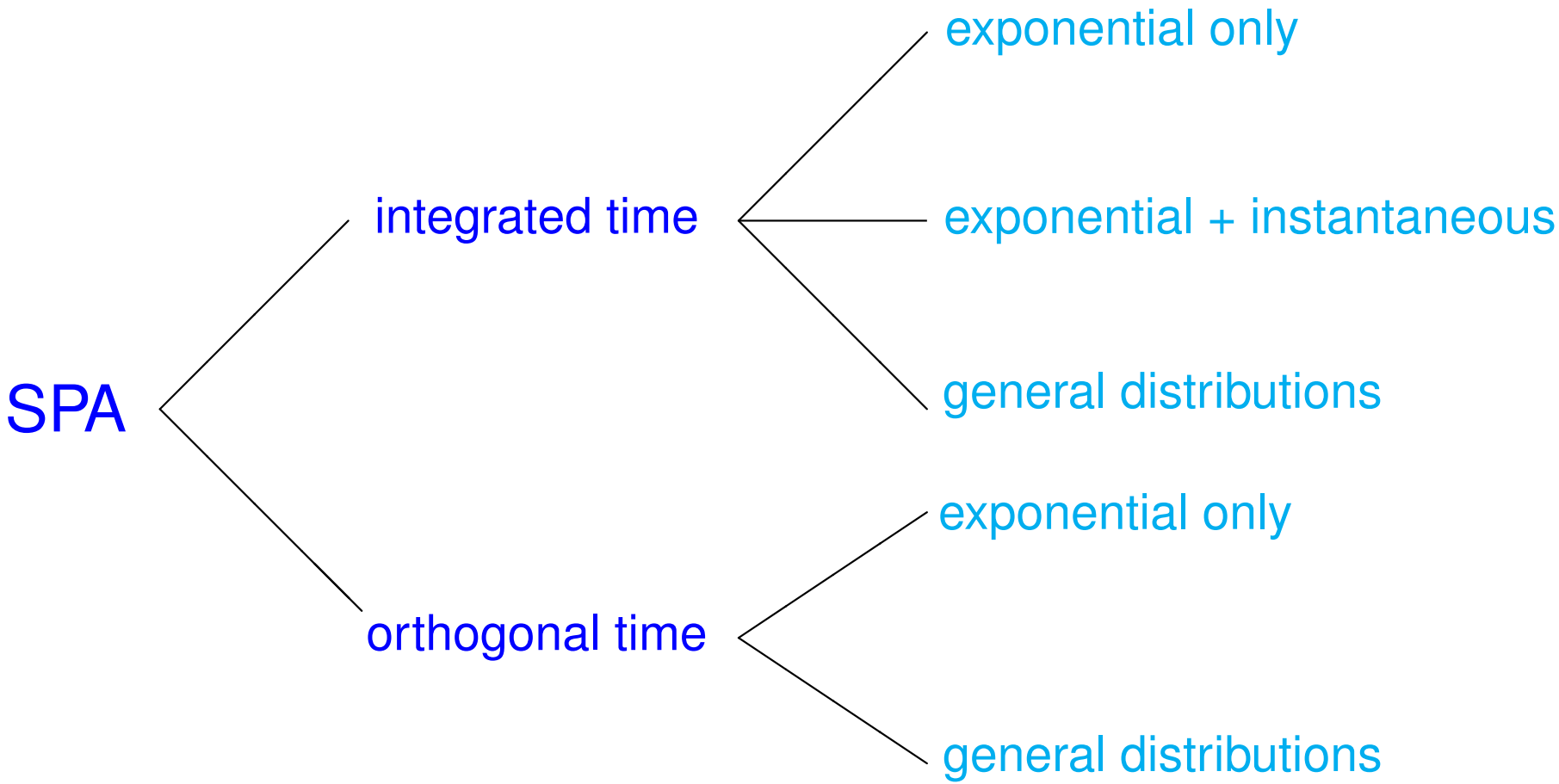

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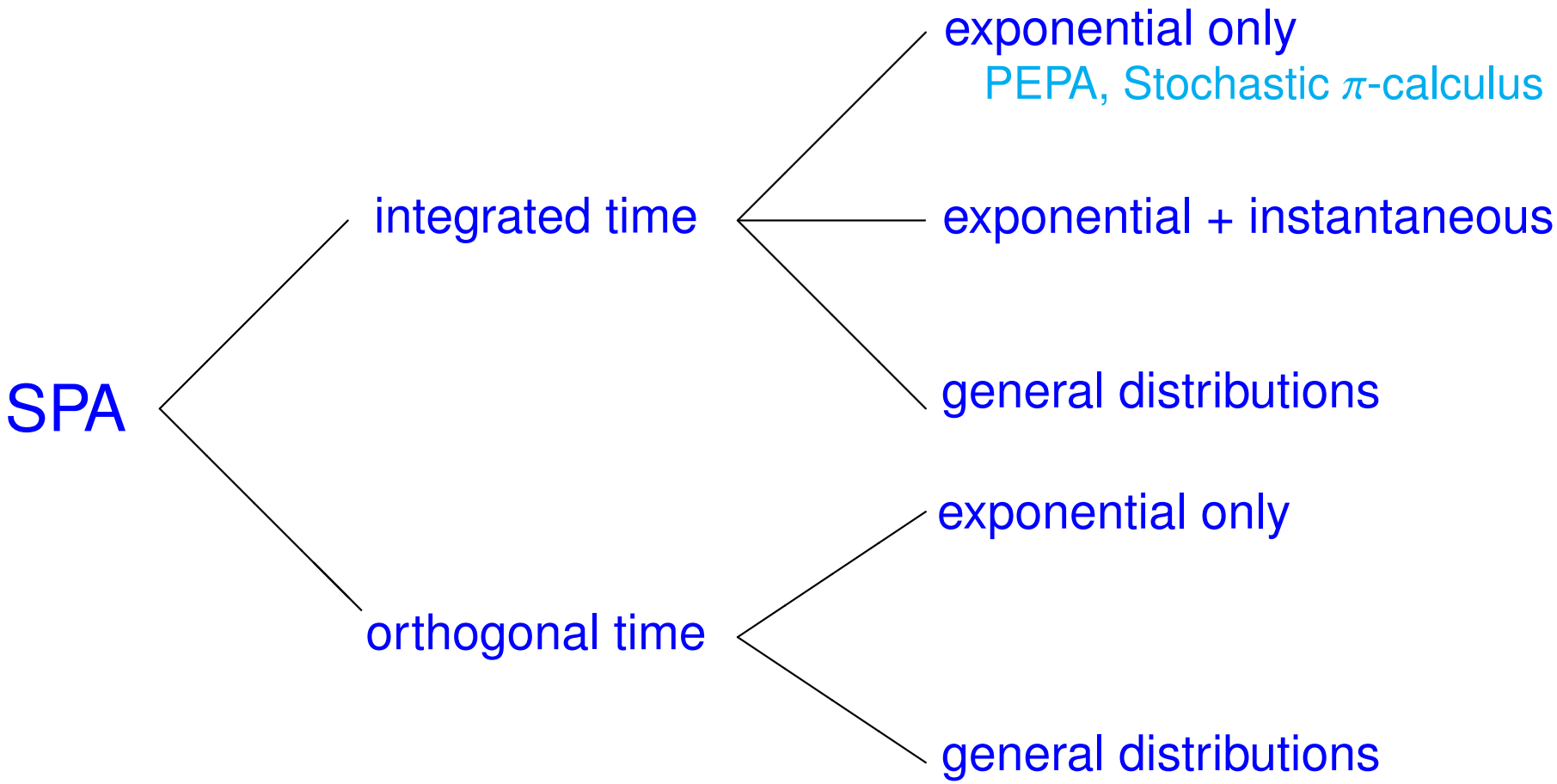

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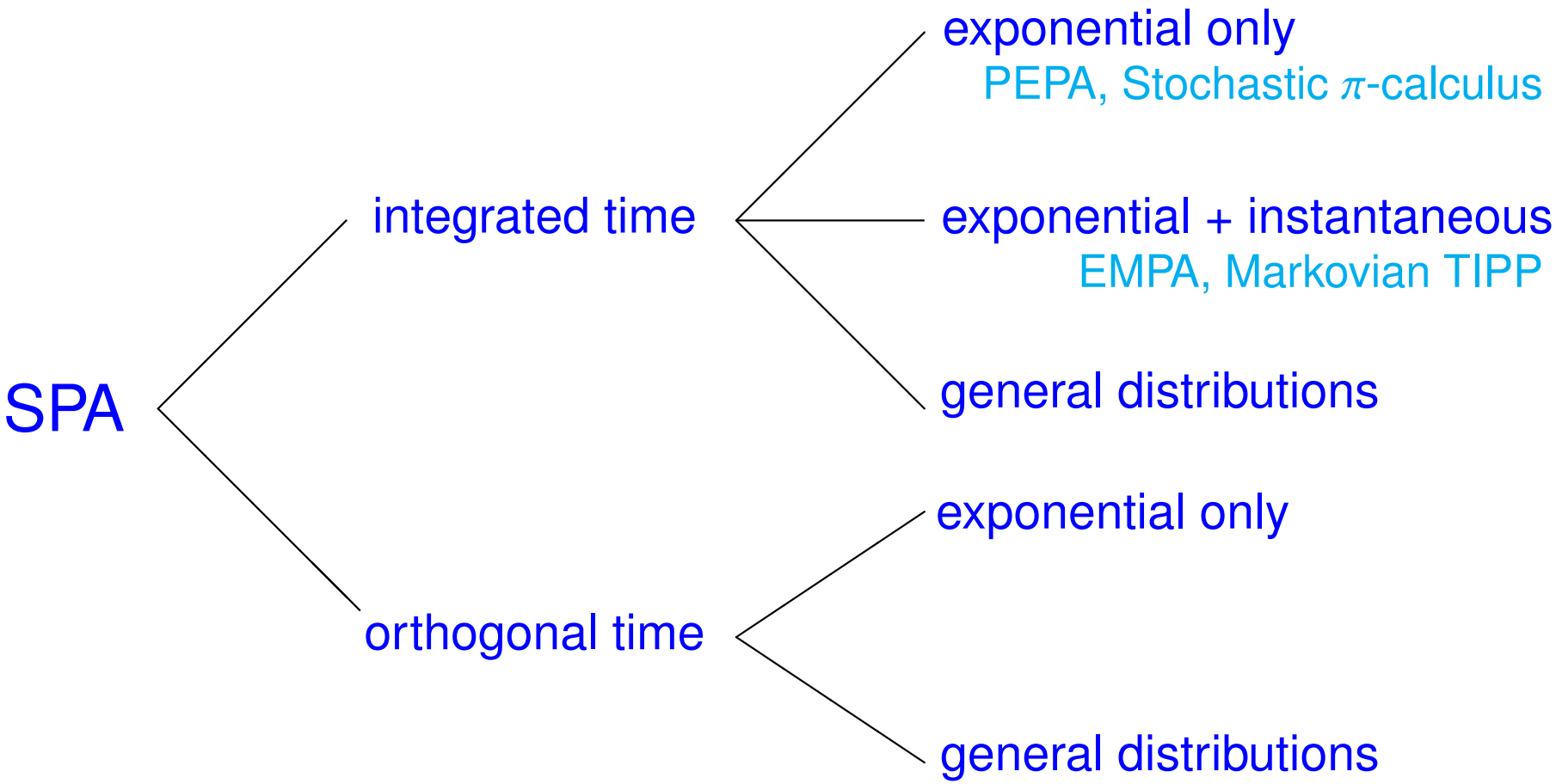

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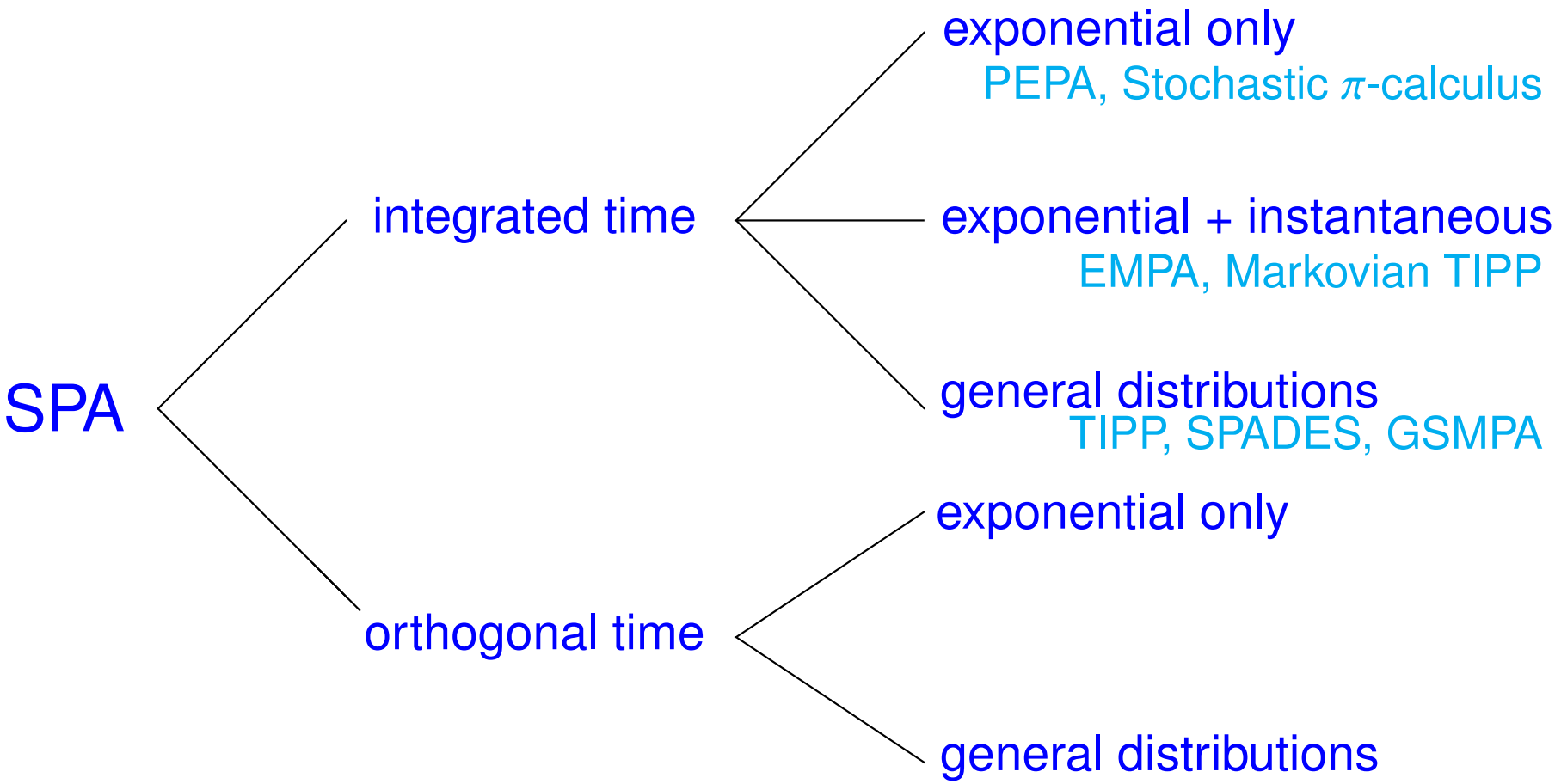

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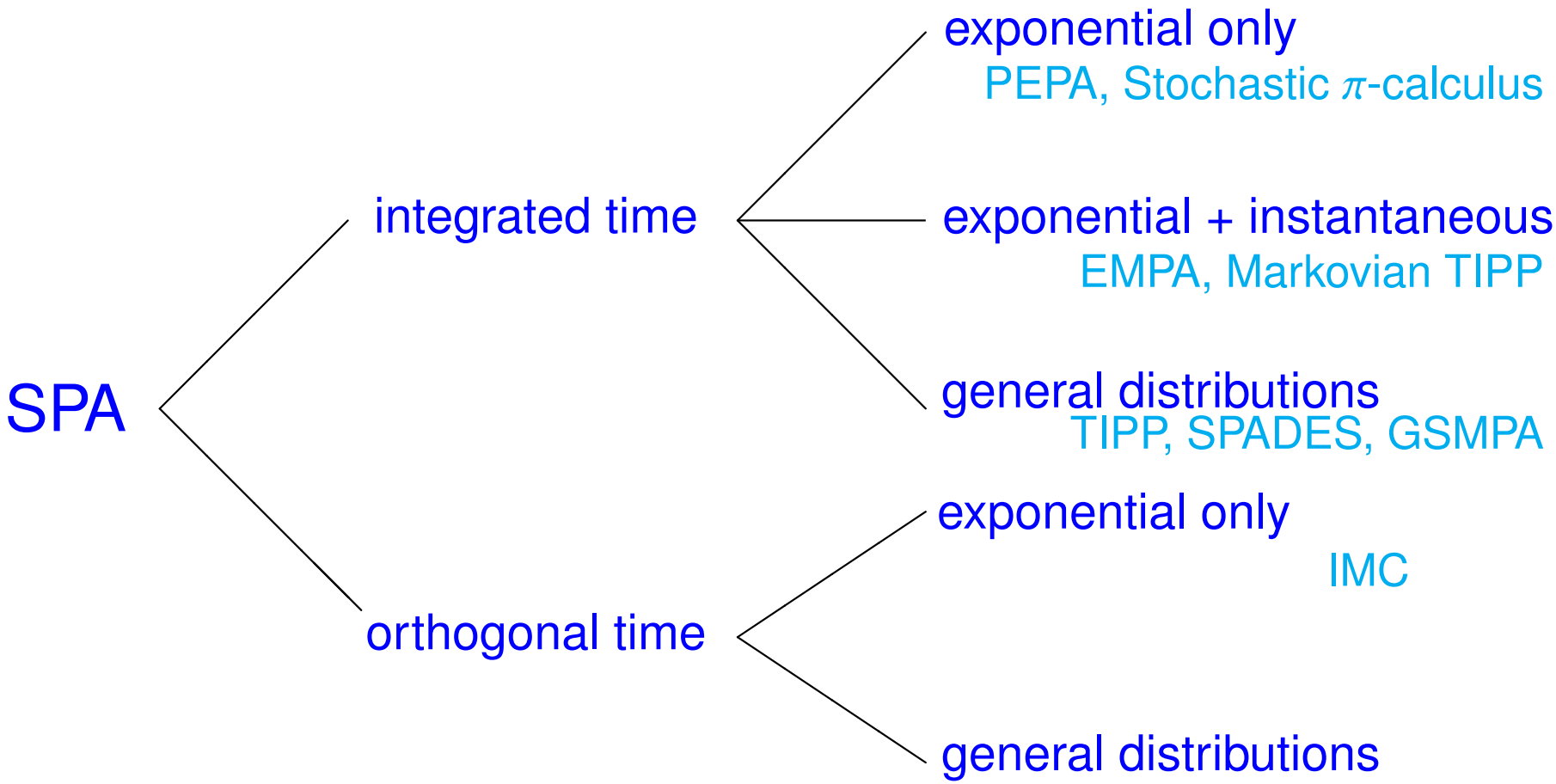

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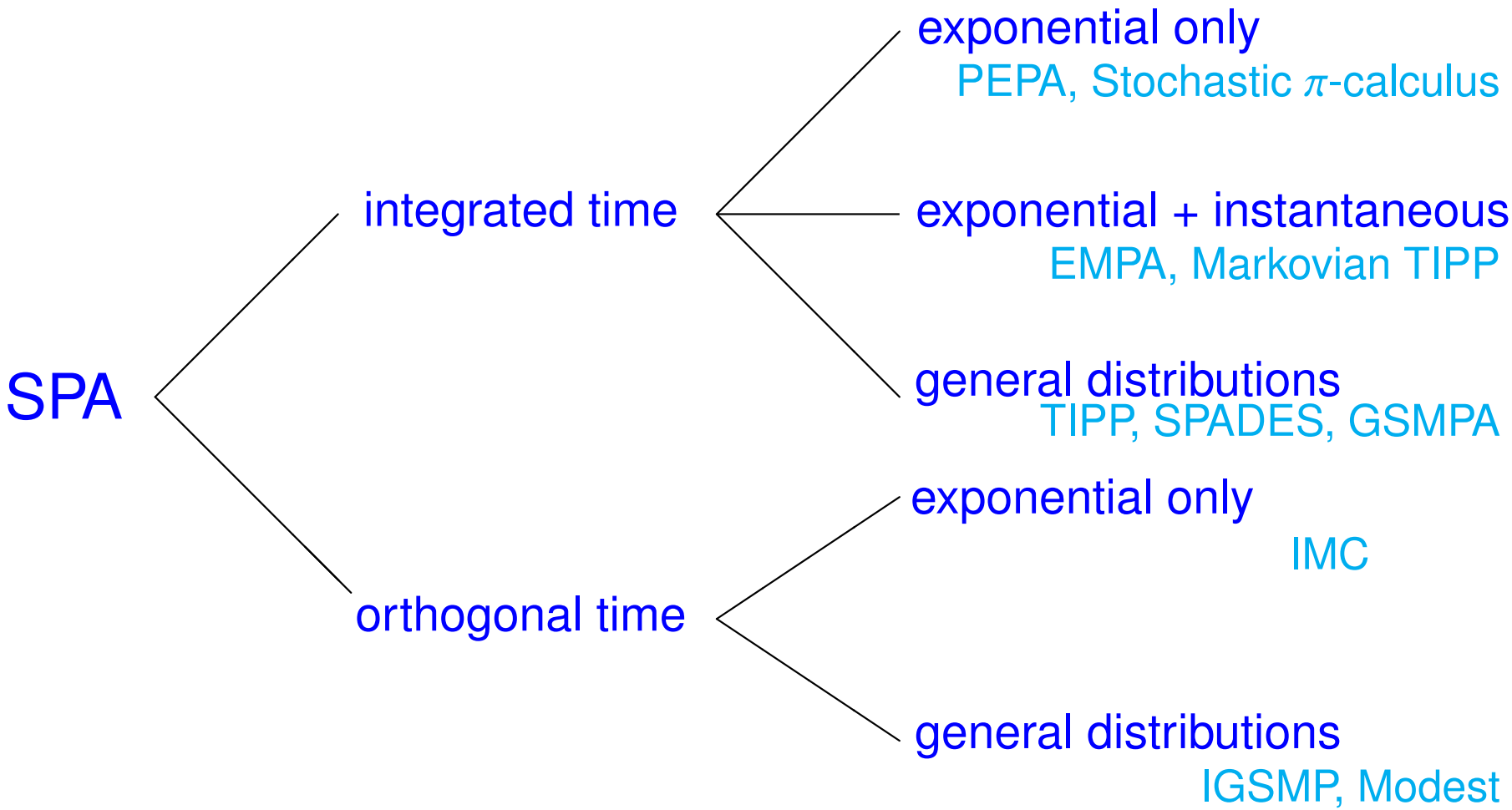

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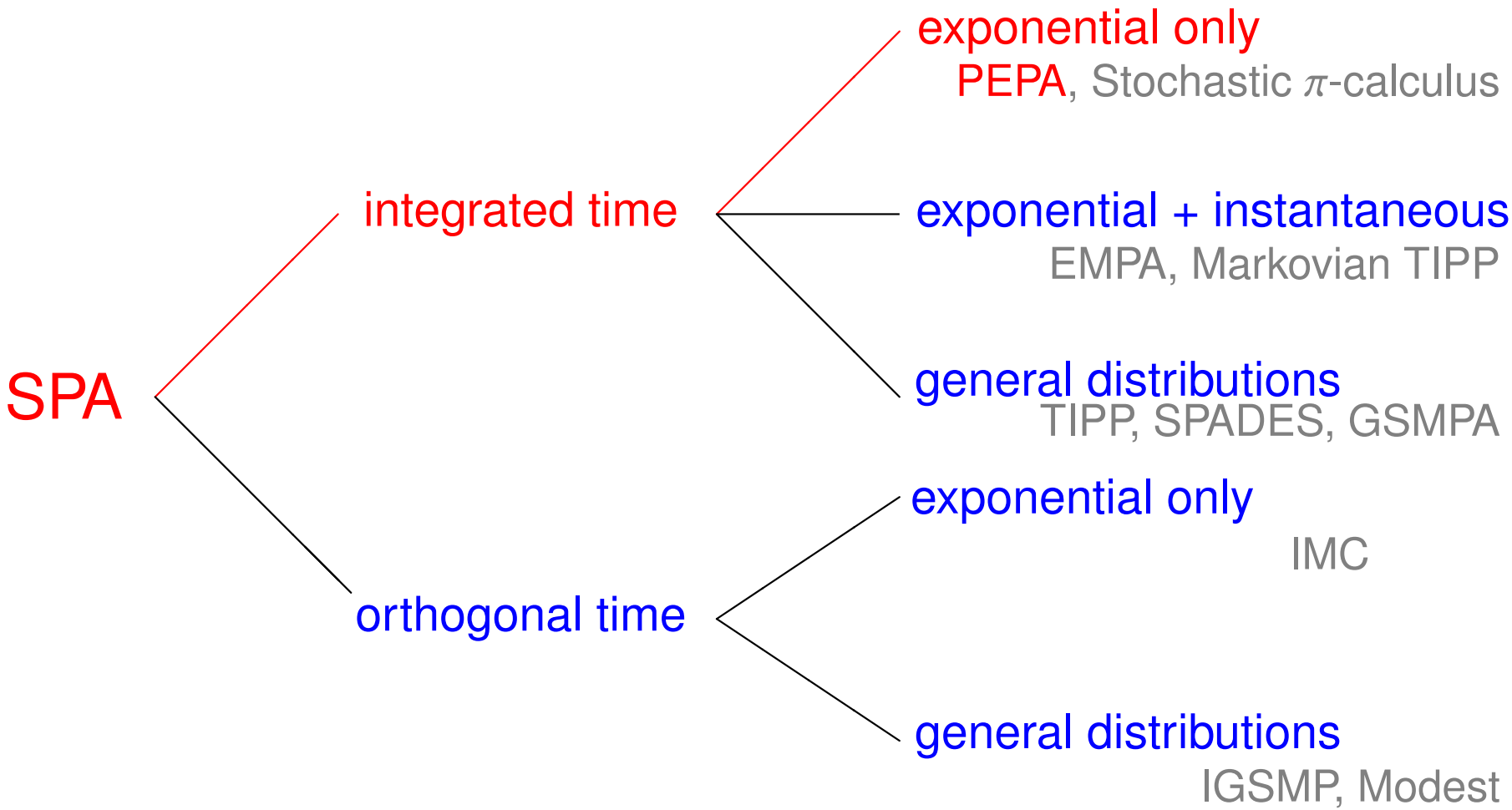

PEPA: Performance Evaluation Process Algebra

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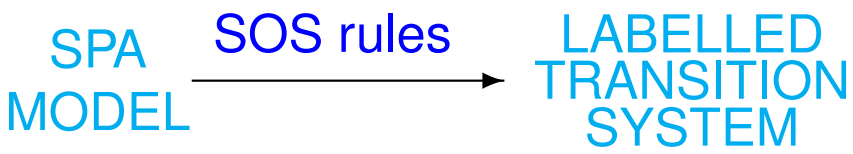

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Q is the infinitesimal generator matrix characterising the CTMC.

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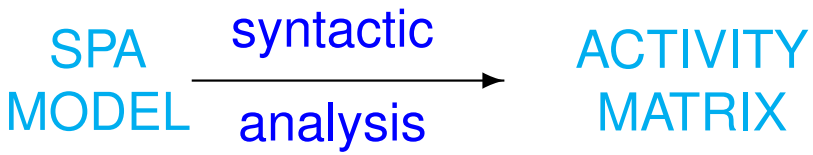

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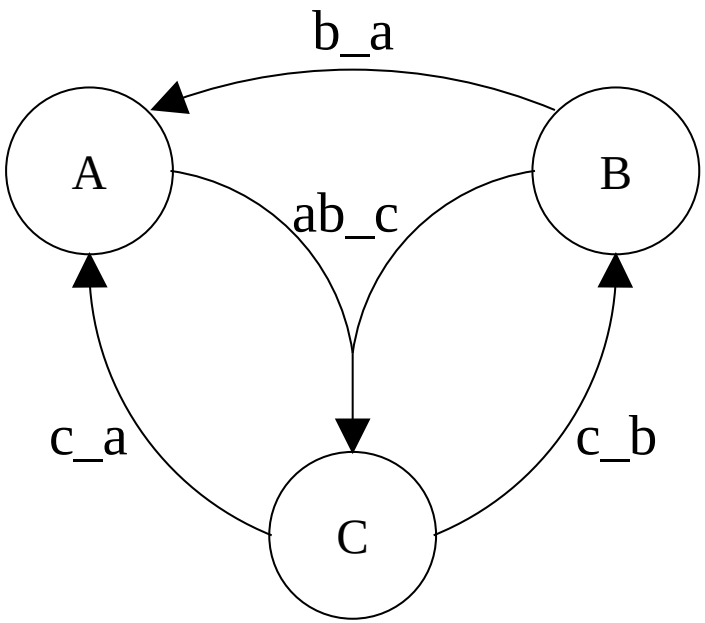
Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.

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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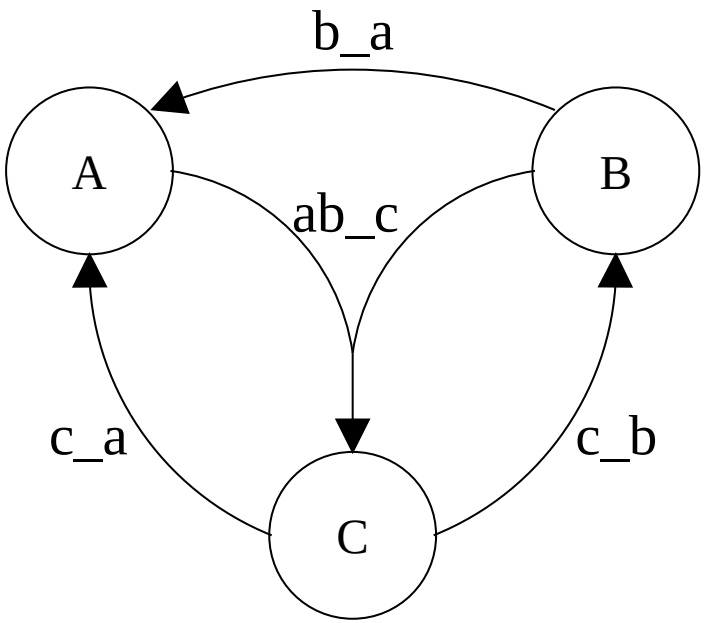

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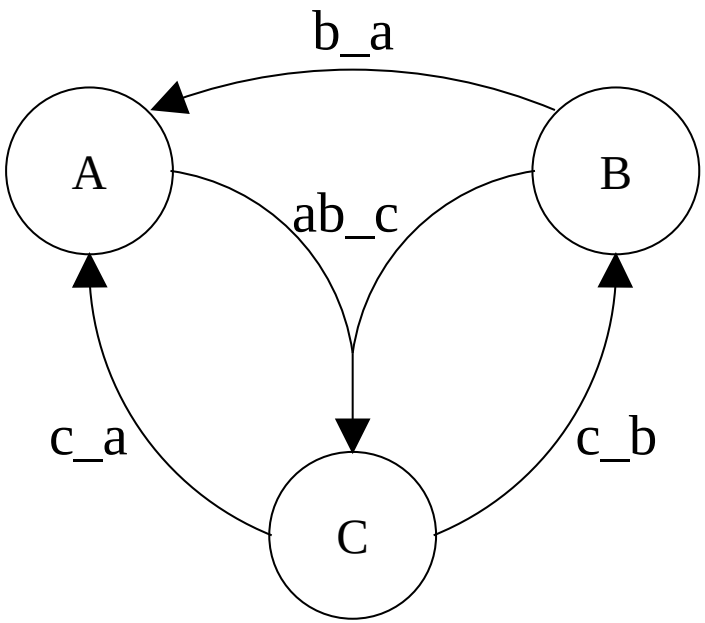

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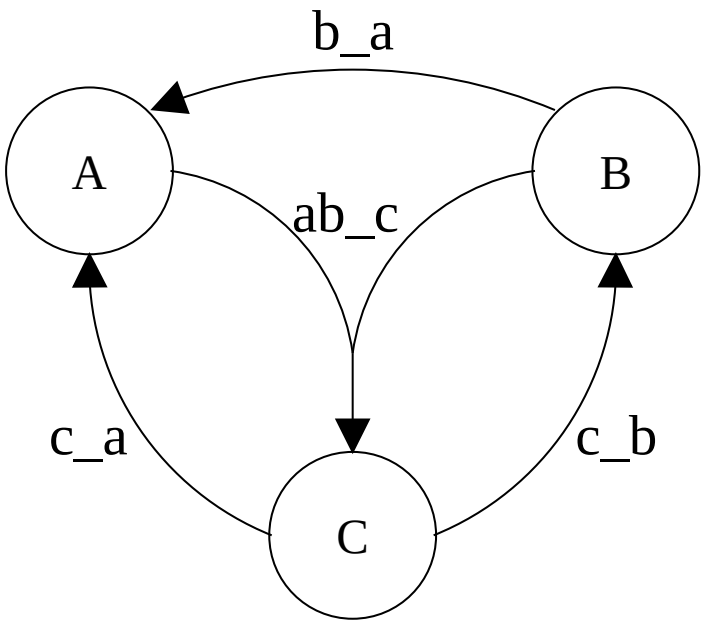

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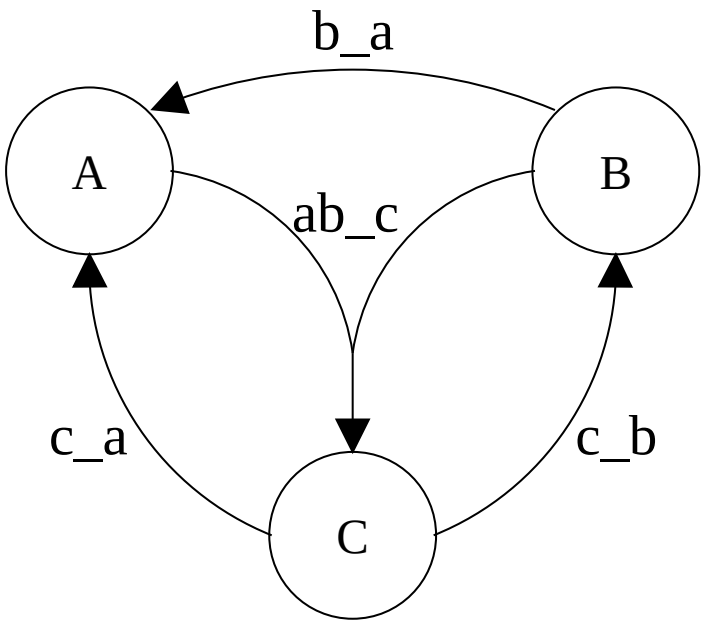

$$
\begin{aligned}
A_H &\stackrel{def}{=} (ab\_c, \alpha).A_L \\
A_L &\stackrel{def}{=} (b\_a, \beta).A_H + (c\_a, \gamma).A_H \\
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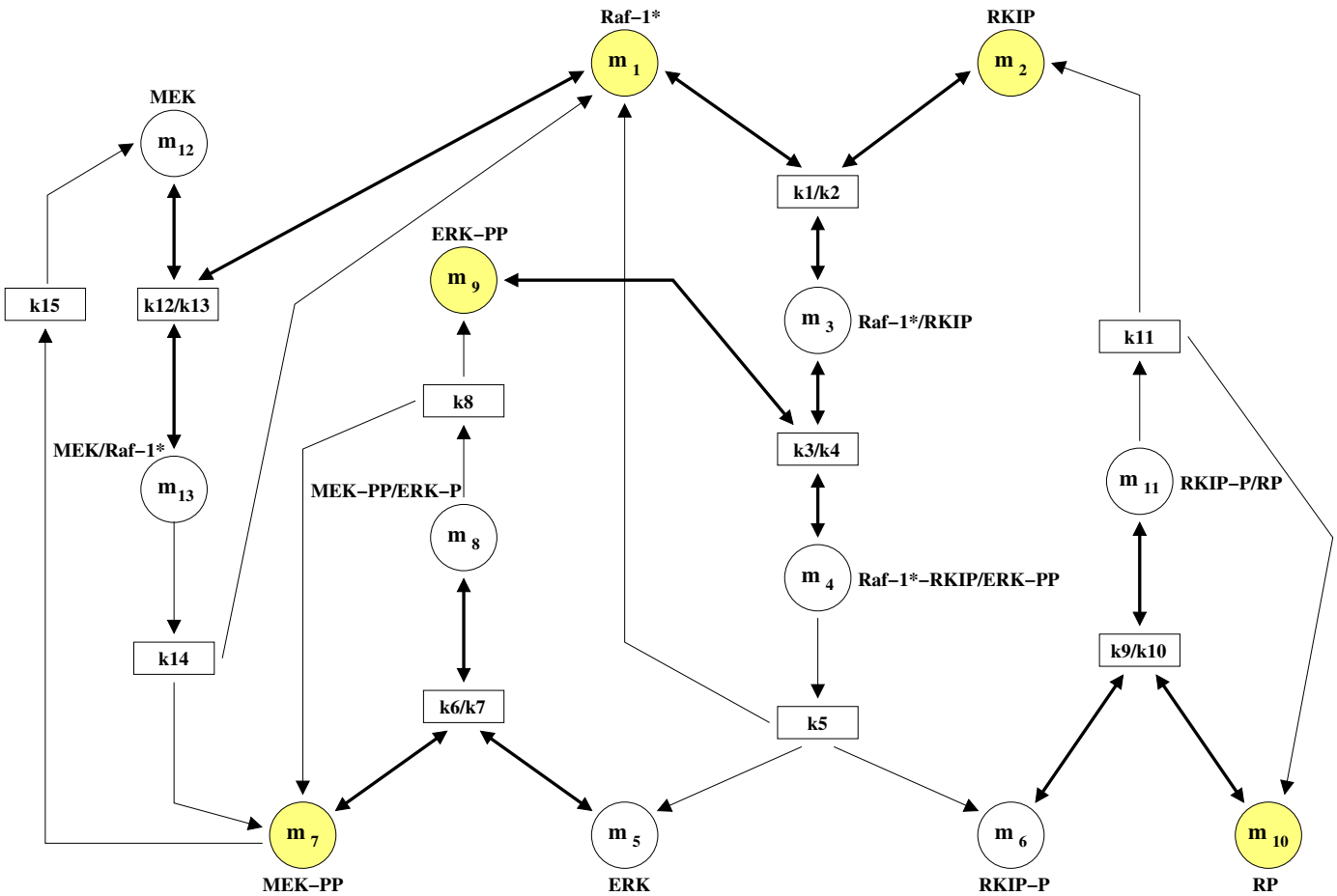
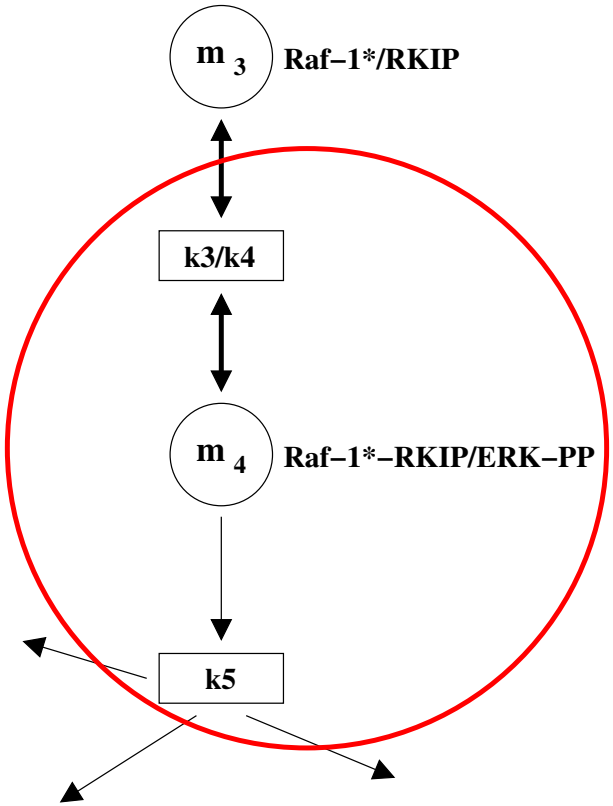
\end{aligned}
$$

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

Example: The Ras/Raf-1/MEK/ERK pathway



PEPA components of the reagent-centric model



$$\text{Raf-1}^*/\text{RKIP}/\text{ERK-PP}_\text{H} \stackrel{def}{=} (k5product, k_5).\text{Raf-1}^*/\text{RKIP}/\text{ERK-PP}_\text{L} + (k4react, k_4).\text{Raf-1}^*/\text{RKIP}/\text{ERK-PP}_\text{L}$$

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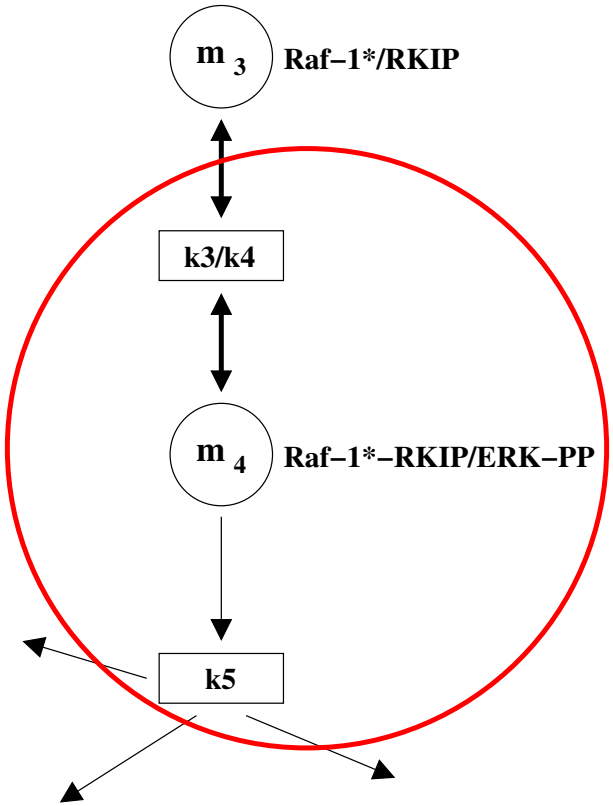

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Each reagent gives rise to a pair of PEPA definitions, one for high concentration and one for low concentration.

Commentary on the model

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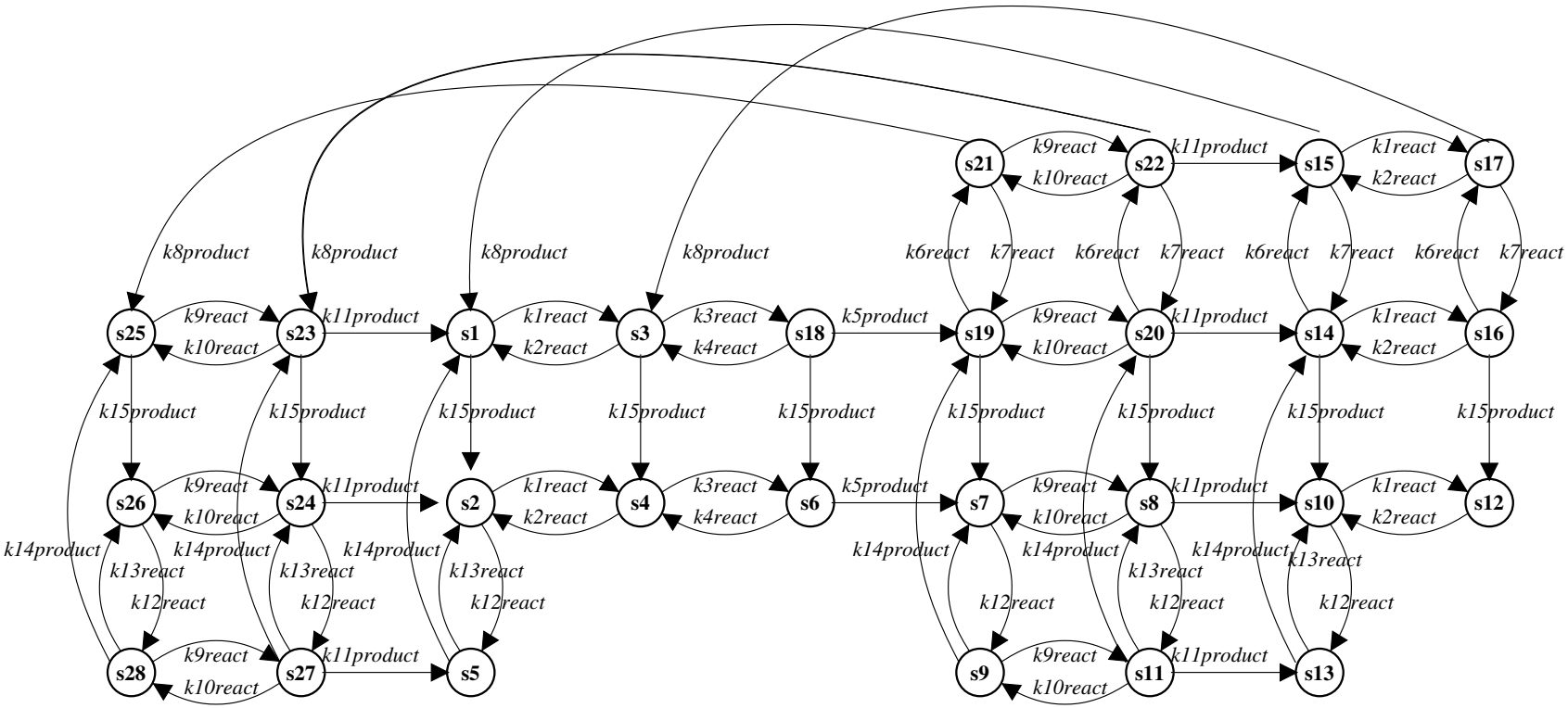
- In general we would discretise the concentration into more levels, say 6 or 7 levels. As we add levels we are capturing the concentration at finer levels of granularity.
- In fact to generate ODE and SSA models we only need two levels as this is sufficient to record the impact of each reaction on each reagent.

The state space



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- In reagent PEPA models with levels, each level of granularity gives rise to a CTMC, and the behaviour of this sequence of Markov processes converges to the behaviour of the system of ODEs.
- Some analyses which can be carried out via numerical solution of the CTMC are not readily available from ODEs or stochastic simulation.

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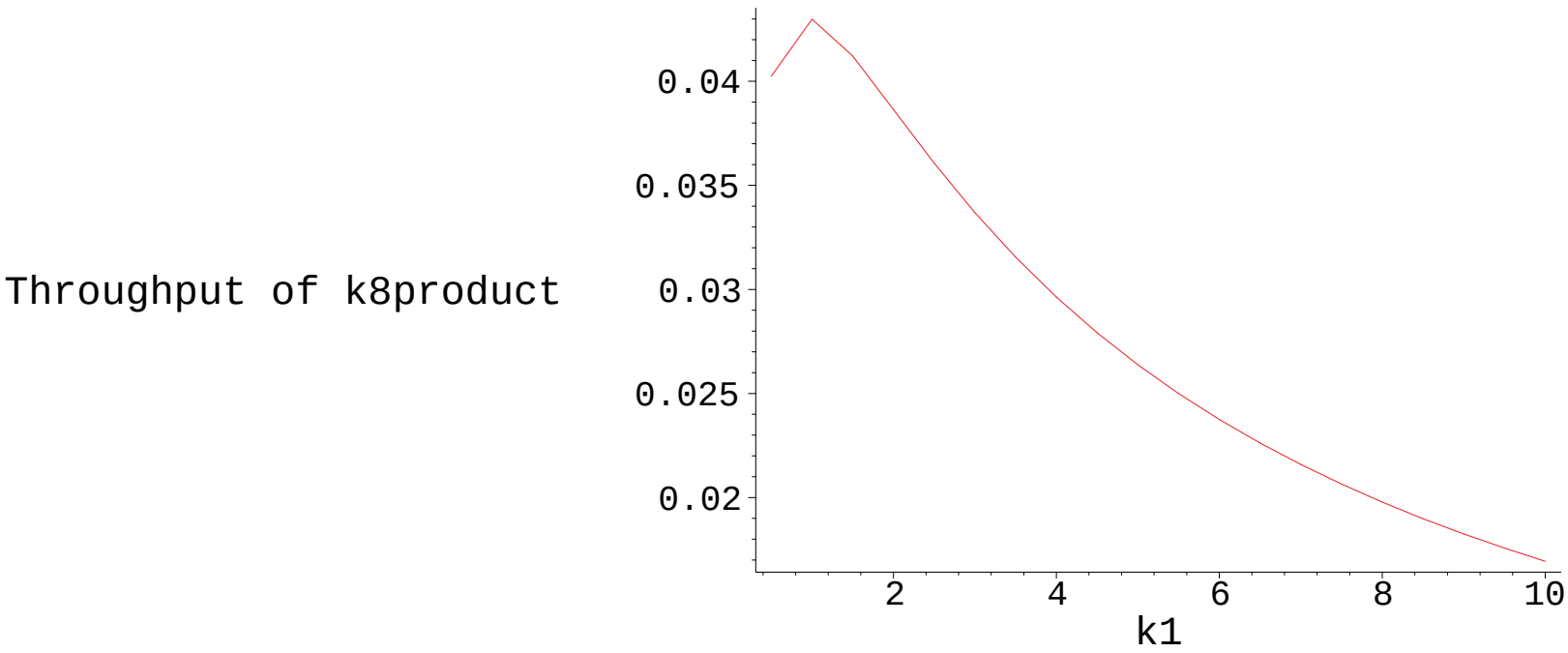
- Stochastic model checking is available via the PRISM model checker, assessing the probable validity of properties expressed in CSL (Continuous Stochastic Logic).

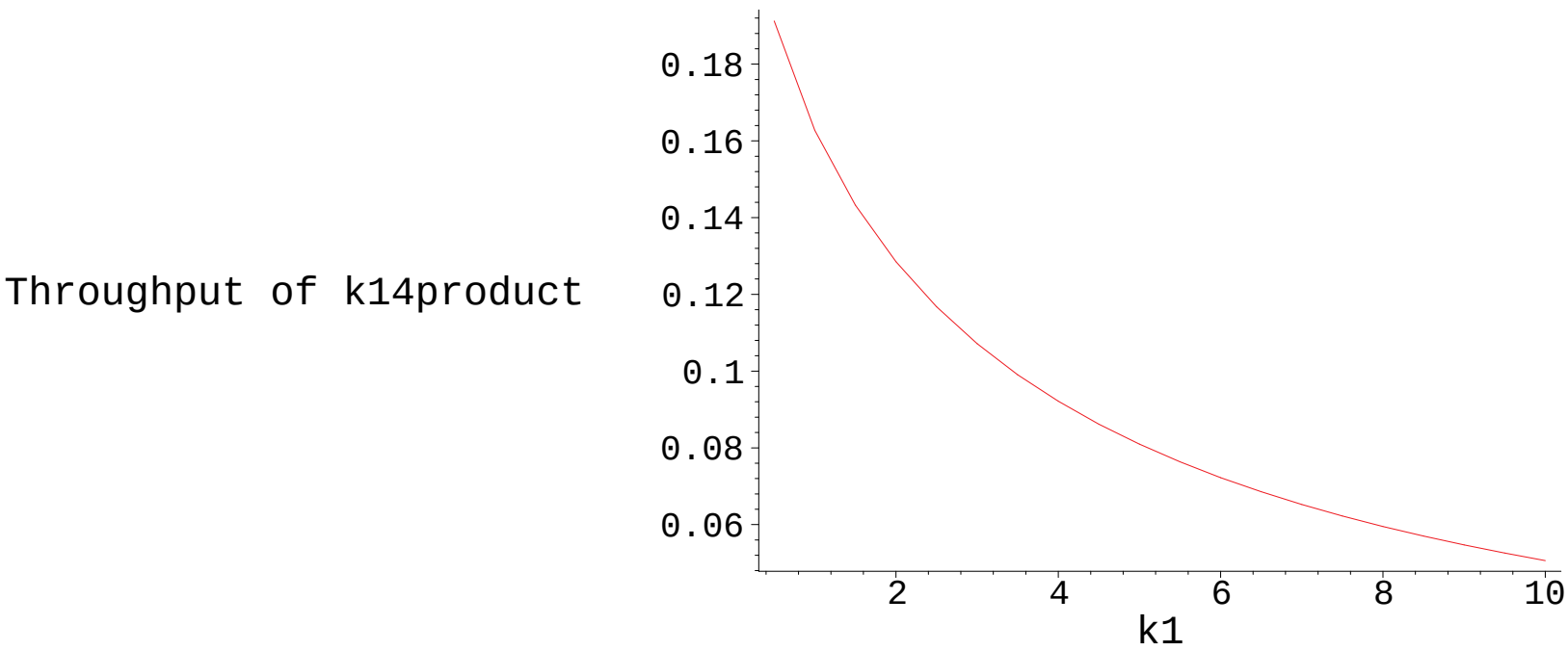
Quantified analysis – *k8product*

Approximating a variation in the initial concentration of RKIP by varying the rate constant k1, we can assess the impact on the production of ERK-PP.



Quantified analysis – *k14product*

Similarly we can assess the impact on the production of MEK-PP.



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... but no variability is captured, unlike Markovian analyses (and real systems).

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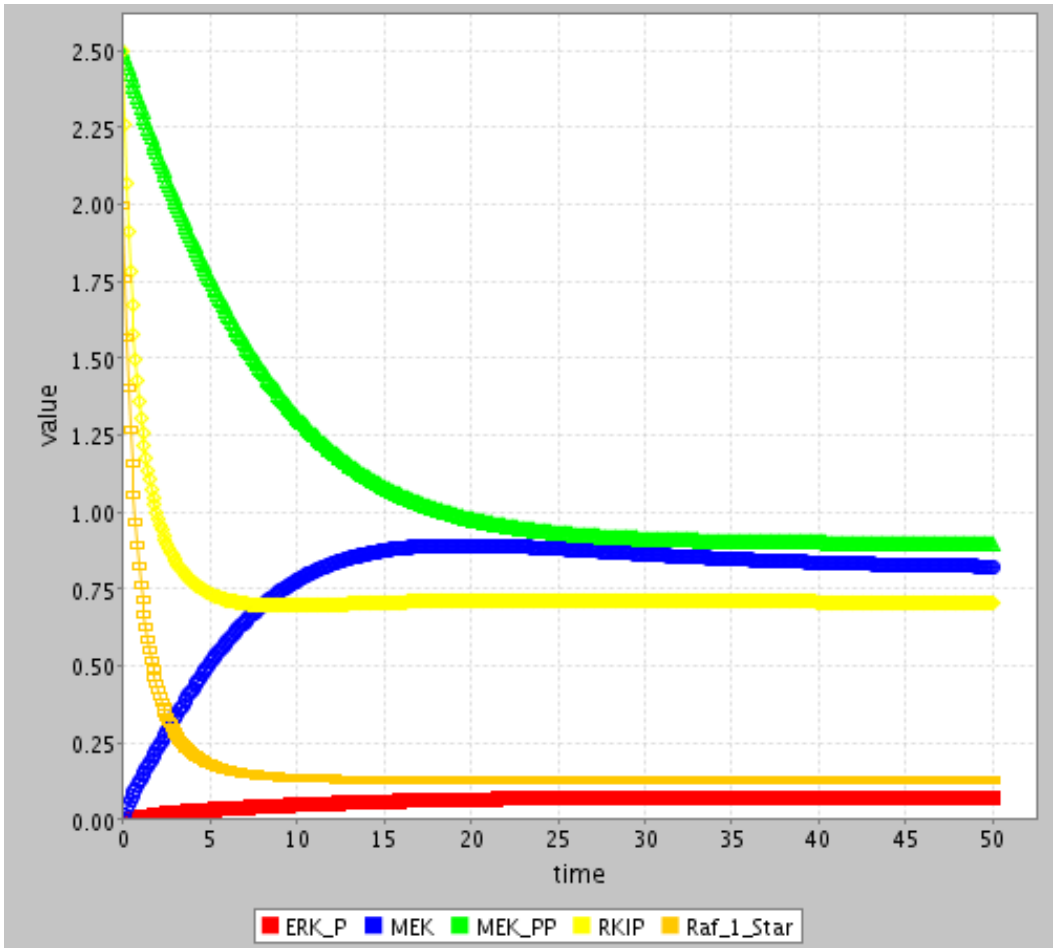

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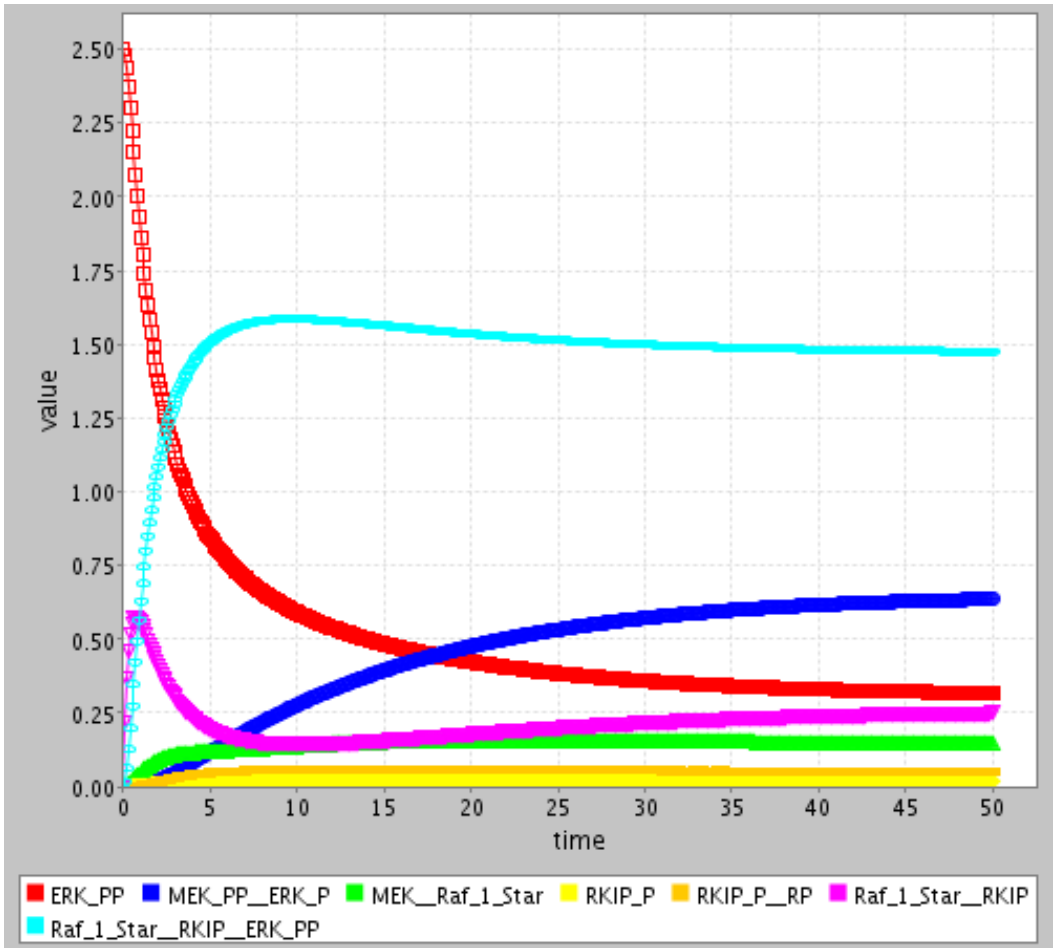

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The latter assumption is restrictive since general kinetic laws are widely-used in the models.

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Schema

Biochemical networks $\longrightarrow$ *Bio-PEPA system* $\longrightarrow$ *Analysis*

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- it can be mapped for the analysis by means of *ODEs*, *stochastic simulation*, *CTMC*, *model checking (PRISM)*

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with $op = \odot, \oplus$, or $\ominus$

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The transition system and the CTMC are defined as in PEPA.

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The species components are then composed together to describe the behaviour of the system.

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(S(l_{S0}) \underset{\{\alpha\}}{\bowtie} E(l_{E0})) \underset{\{\alpha\}}{\bowtie} P(l_{P0})
$$

Example: Competitive Inhibition

Binding of the inhibitor to the enzyme prevents binding of the substrate and vice versa.

$$S + E + I \Longleftrightarrow SE \Longrightarrow P + E$$
$$\Updownarrow$$
$$EI$$

Under QSSA (the intermediate species SE and EI are constant) we can approximate the reactions above by a unique reaction

$$S \xRightarrow{E,I:f_I} P \qquad \text{with rate } f_I = \frac{w * S * E}{S + K_M(1 + \frac{I}{K_I})}$$

where w: turnover number (catalytic constant),
K_M: Michaelis-constant and K_I: inhibition constant.

Example: Competitive Inhibition (2)

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with functional rate

$$f_\alpha = f_{CI}((w, K_M, K_I), S, E, I) = \frac{w * S * E}{S + K_M(1 + \frac{I}{K_I})}$$

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From a biological perspective we are investigating the situations in which biologists regard models or elements of models to be equivalent, particularly when this is employed for model simplification.

Bisimulation

Definition

A binary relation $\mathcal{R} \subseteq \mathcal{C} \times \mathcal{C}$ is a strong bisimulation with respect to $\mapsto$, if $(P, Q) \in \mathcal{R}$ implies for all $\alpha \in \mathcal{A}$:

- if $P \xrightarrow{\gamma_1} P'$ then, for some Q' and γ_2, $Q \xrightarrow{\gamma_2} Q'$ with $(P', Q') \in \mathcal{R}$ and
  1. $action(\gamma_1) = action(\gamma_2) = \alpha$
  2. $rate(\gamma_1) = rate(\gamma_2)$
- symmetric definition for $Q \xrightarrow{\gamma_2} Q'$

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Each of these kinds of analysis can be of help for studying different aspects of the biological model

Outline

The biological model

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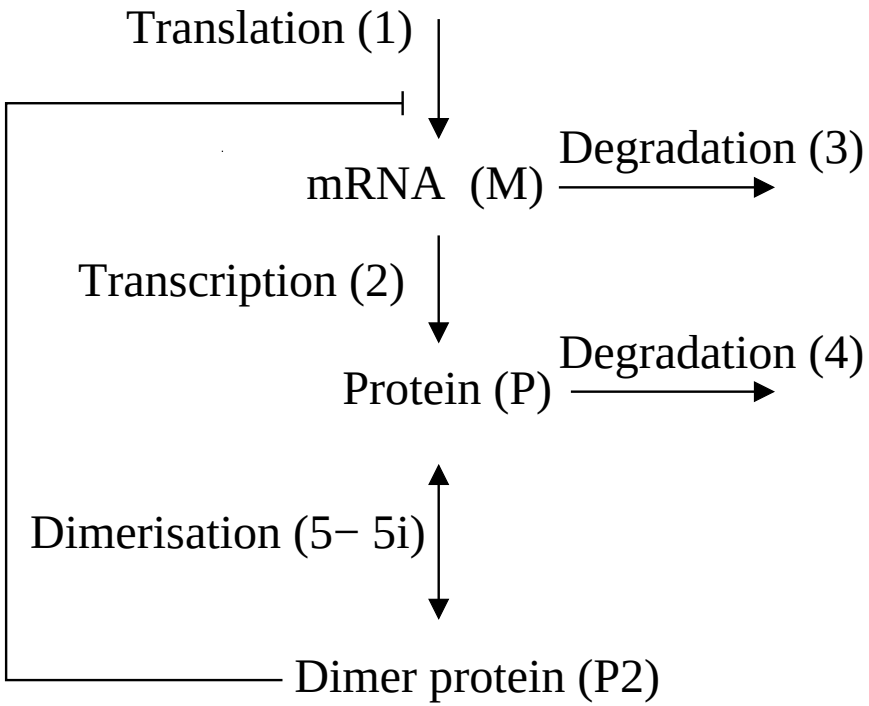

Simple genetic network model

The biological entities are:

- the *mRNA molecule* (*M*),
- the protein in monomer form (*P*) and
- the protein in dimeric form (*P2*).

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All the reactions are described by mass action kinetics with the exception of the first reaction, that has an inhibition kinetics.

Translation into Bio-PEPA

1-Definition of the list $\mathcal{N}$

$$[M : N_M, M_M;\ P : N_P, M_P;\ P2 : N_{P2}, M_{P2}]$$

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2-Definition of functional rates

$$\begin{array}{lcl} f_{\alpha_1} & = & fl((v, K_M), [P2, CF]) = \frac{v*CF}{K_M+P2}; \\ f_{\alpha_2} & = & fMA(k_2, [M]); \quad f_{\alpha_3} = fMA(k_3, [M]); \quad f_{\alpha_4} = fMA(k_4, [P]); \\ f_{\alpha_5} & = & fMA(k_5, [P]); \quad f_{\alpha_{5i}} = fMA(k_{5i}, [P2]); \end{array}$$

Translation into Bio-PEPA (cont.)

3-Definition of the system components

$$
\begin{array}{lcl}
\mathrm{M} & = & (\alpha_2,1) \oplus \mathrm{M} + (\alpha_3,1) \downarrow \mathrm{M} + (\alpha_1,1) \uparrow \mathrm{M}; \\
\mathrm{P} & = & (\alpha_4,1) \downarrow \mathrm{P} + (\alpha_5,2) \downarrow \mathrm{P} + (\alpha_{5i},2) \uparrow \mathrm{P}) + (\alpha_2,0) \uparrow \mathrm{P}; \\
\mathrm{P2} & = & (\alpha_1,1) \ominus \mathrm{P2} + (\alpha_{5i},1) \downarrow \mathrm{P2} + (\alpha_5,1) \uparrow \mathrm{P2}; \\
\mathrm{Res} & = & (\alpha_3,1) \odot \mathrm{Res} + (\alpha_4,1) \odot \mathrm{Res}; \\
\mathrm{CF} & = & (\alpha_1,1) \odot \mathrm{CF};
\end{array}
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Translation into Bio-PEPA (cont.)

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\mathrm{Res} & = & (\alpha_3,1) \odot \mathrm{Res} + (\alpha_4,1) \odot \mathrm{Res}; \\
\mathrm{CF} & = & (\alpha_1,1) \odot \mathrm{CF};
\end{array}
$$

4-Definitions of the system

$$((((CF(1) \underset{\{\alpha_1\}}{\bowtie} M(0)) \underset{\{\alpha_2\}}{\bowtie} P(0)) \underset{\{\alpha_5,\alpha_{5i}\}}{\bowtie} P2(0)) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} Res(0)$$

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For **2 levels**, the CTMC consists of **8 states** and **18 transitions**.

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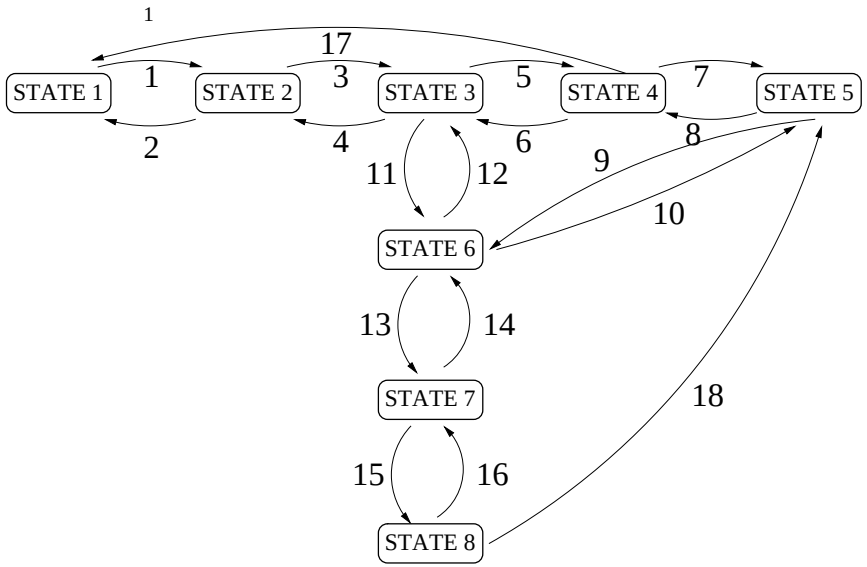

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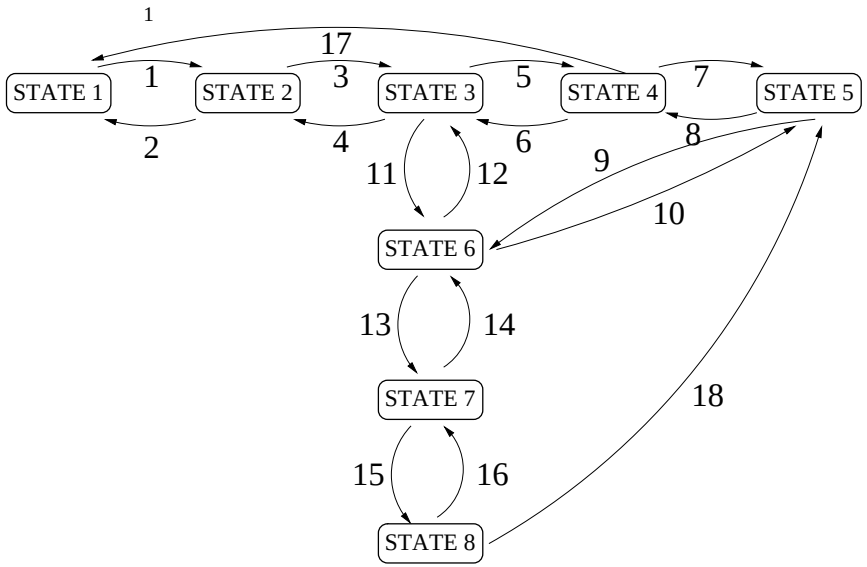

The states are $(CF(l_1), M(l_2), P(l_3), P2(l_4), RES(l_5))$,
where l_i represents the level of each species component.

Derivation of ODEs and Gillespie model

The stoichiometry matrix D associated with the system is

	R1	R2	R3	R4	R5	R6	
CF	0	0	0	0	0	0	x_{CF}
Res	0	0	0	0	0	0	x_{Res}
M	+1	0	-1	0	0	0	x_1
P	0	+1	0	-1	-2	+2	x_2
P2	0	0	0	0	+1	-1	x_3

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P2	0	0	0	0	+1	-1	x_3

The kinetic-law vector is

$$w^T = (\frac{v \times x_{CF}}{K + x_3};\ k_2 \times x_1; k3 \times x_1;\ k4 \times x_2;\ k5 \times {x_2}^2;\ ki5 \times x_3)$$

Derivation of ODEs (2)

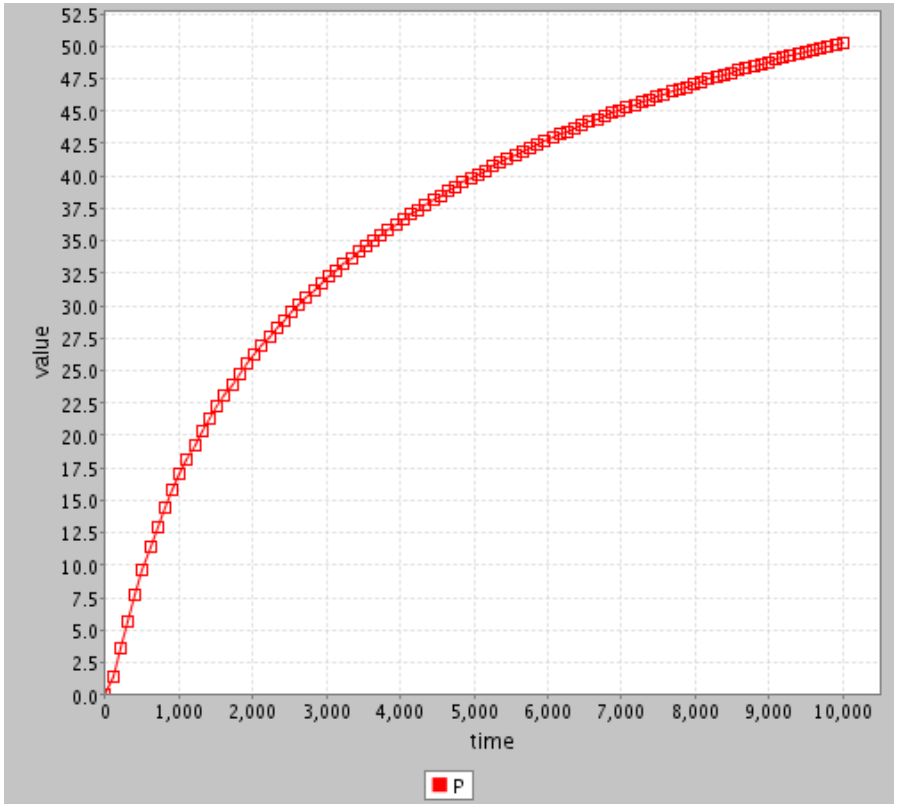
The system of ODEs is obtained as $\frac{d\bar{x}}{dt} = D \times w$:

$$\begin{aligned}
\frac{dx_1}{dt} &= \frac{v \times 1}{K + x_3} - k3 \times x_1 \\
\frac{dx_2}{dt} &= k2 \times x_1 - k4 \times x_2 - 2 \times k5 \times {x_2}^2 + 2 \times ki5 \times x_3 \\
\frac{dx_2}{dt} &= k5 \times {x_2}^2 - ki5 \times x_3
\end{aligned}$$

Derivation of Gillespie model

The derivation of the Gillespie model is made by creating molecules corresponding to each species and defining the possible reactions with appropriate adjustment of kinetic rates.

Simulation results



ODE results

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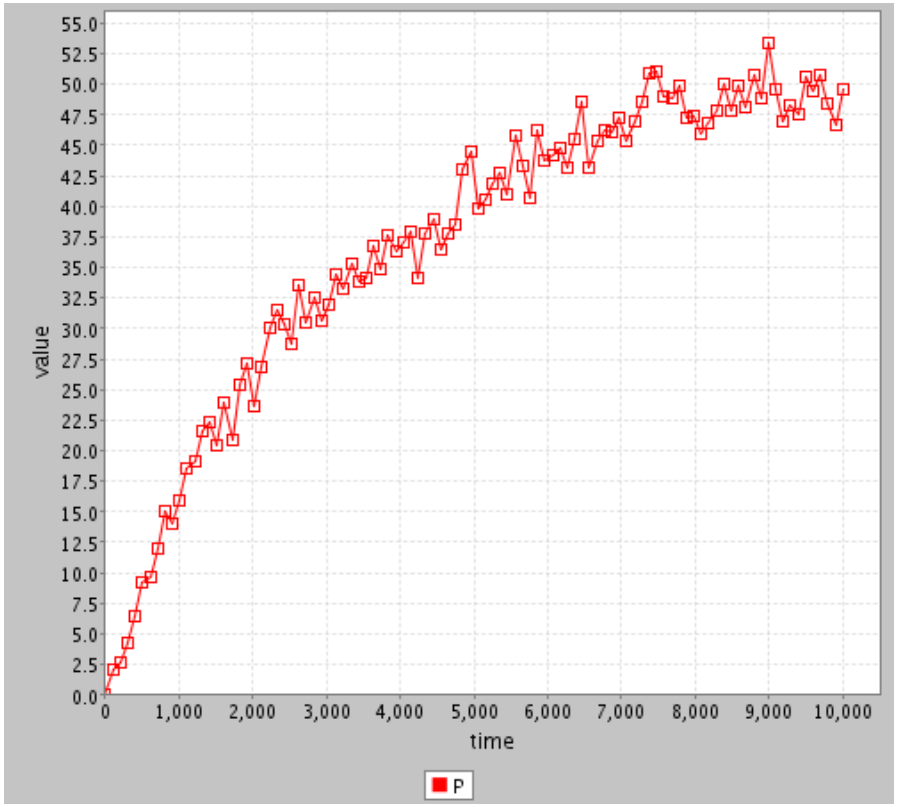

Stochastic simulation results (10 runs)

PRISM model

Each species is represented as a PRISM module.

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For example, the protein is represented as:

module p
$p : [0..Np]$ **init** 0;
$[a2]p < Np \rightarrow (p' = p + 1)$;
$[a4]p > 0 \rightarrow (p' = p - 1)$;
$[a5]p > 0 \rightarrow (p' = p - 2)$;
$[a5i]p < Np \rightarrow (p' = p + 2)$;
endmodule

PRISM model (2)

An additional (dummy) module is needed to capture the kinetic rates.

module Functional_rates
dummy: bool **init** true;
$[a1]dummy = true \rightarrow \frac{v}{(1+(pd/k))} : (dummy' = dummy);$
$[a2]dummy = true \rightarrow r2 : (dummy' = dummy);$
$[a3]dummy = true \rightarrow r3 : (dummy' = dummy);$
$[a4]dummy = true \rightarrow r4 : (dummy' = dummy);$
$[a5]dummy = true \rightarrow r5 : (dummy' = dummy);$
$[a5i]dummy = true \rightarrow r5i : (dummy' = dummy);$
endmodule

PRISM analysis

- **Frequency of monomer P over total P (in terms of levels)**.
  We need to define a reward structure in the PRISM file as:

  rewards
  $true : \frac{p}{(p+pd)};$
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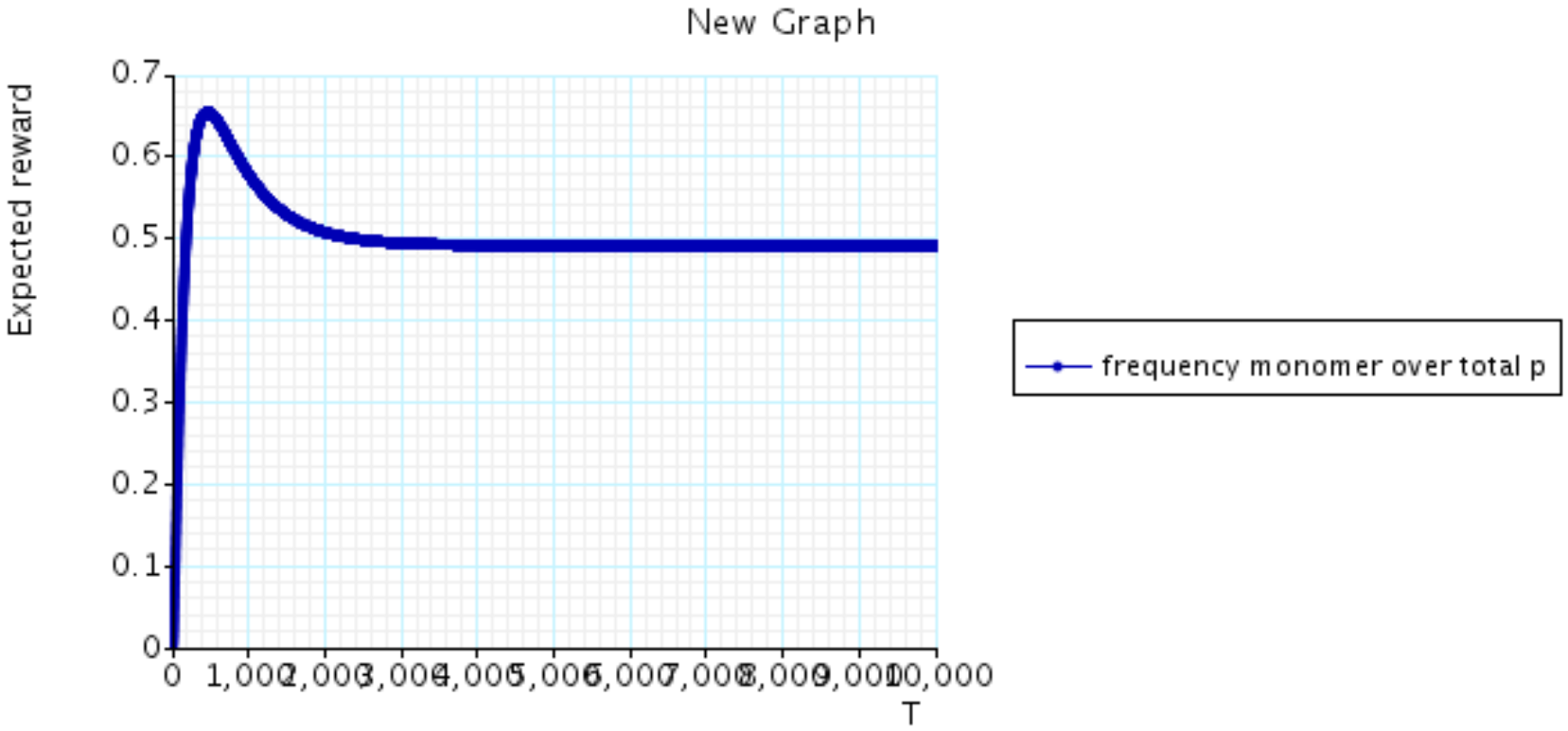
- **Probability that P is at level i at time T**

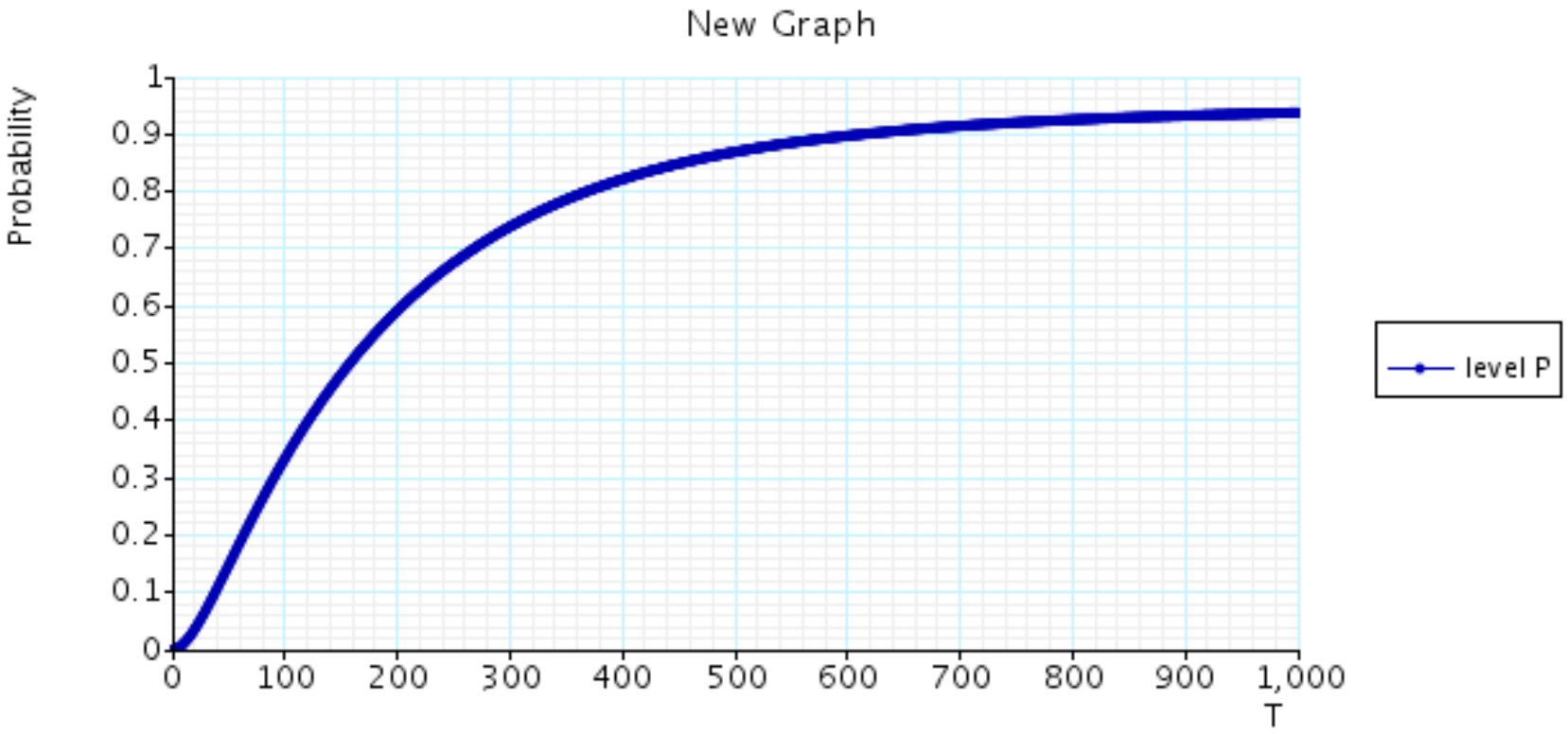
  $$P =?[trueU[T, T]p = i]$$

PRISM results



monomer frequency

PRISM results



Probability monomer protein is at high level over time

Goldbeter's model [Goldbeter 91]

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- The cyclin promotes the activation of a cdk (cdc2) which in turn activates a cyclin protease.
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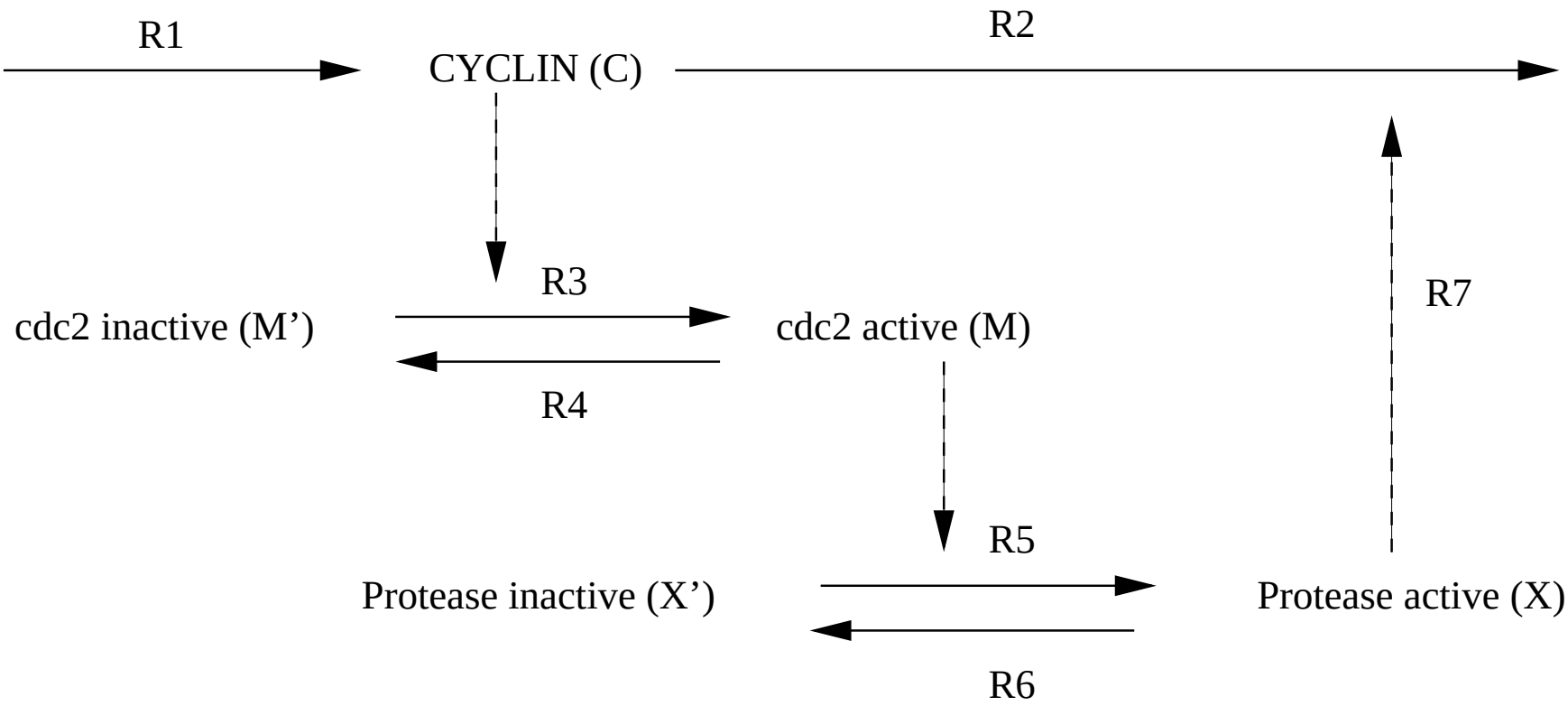
- This leads to a negative feedback loop.
- In the model most of the kinetic laws are of kind Michaelis-Menten and this can be reflected in the Bio-PEPA model

The biological model



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- cyclin protease, in both active (i.e. phosphorylated) and inactive form (i.e. phosphorylated). The variable are X and X'.

Reactions

id	name	react.	prod.	mod.	kinetic laws
R1	creation of cyclin	-	C	-	vi
R2	degradation of cyclin	C	-	-	$kd \times C$
R3	activation of cdc2 kinase	M'	M	-	$\frac{C*V_{M1}}{(K_c+C)} \frac{M'}{(K_1+M')}$
R4	deactivation of cdc2 kinase	M	M'	-	$\frac{M \times V_2}{(K_2+M)}$
R5	activation of cyclin protease	X'	X	M	$\frac{X' \times M \times V_{M3}}{(K_3+X')}$
R6	deactivation of cyclin protease	X	X'	-	$\frac{X \times V_4}{K_4+X}$
R7	X triggered degradation of cyclin	C	-	X	$\frac{C \times v_d \times X}{C+K_d}$

R1 and R2 have Mass-Action kinetics, whereas all others are Michaelis-Menten.

The Bio-PEPA model

Definition of the list $\mathcal{N}$:.

$$\mathcal{N} = [Res : 0, 1;\ CF : 1, 1;\ C : M_C, N_c;\ M : M_M, N_M;\ M' : M_{M'}, N_{M'};\ X : M_X, N_X;\ X' : M_{X'}, N_{X'}] \quad (1)$$

Res and *CF* represent degradation and synthesis respectively.

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Res and *CF* represent degradation and synthesis respectively.

Definition of functional rates ($\mathcal{F}$:)

$$f_{\alpha_1} = fMA(v_i); \qquad f_{\alpha_2} = fMA(k_d);$$

$$f_{\alpha_3} = fMM'((V_1, K_c, K_1), M', C) = \frac{v_1 * C}{K_c + C}\frac{M'}{K1 + M'};$$

$$f_{\alpha_4} = fMM(V_2, K_2); \qquad f_{\alpha_5} = fMM(V_3, K_3)$$

$$f_{\alpha_6} = fMM(V_4, K_4); \qquad f_{\alpha_7} = fMM(V_d, K_d)$$

The Bio-PEPA model (2)

Definition of species components (*Comp*):

$$
\begin{array}{lcl}
C & = & (\alpha_1,1)\uparrow C + (\alpha_2,1)\downarrow C + (\alpha_7,1)\downarrow C + (\alpha_3,1) \oplus C;\\
M' & = & (\alpha_4,1)\uparrow M' + (\alpha_3,1)\downarrow M';\\
M & = & (\alpha_3,1)\uparrow M + (\alpha_4,1)\downarrow M + (\alpha_5,1) \oplus M;\\
X' & = & (\alpha_6,1)\uparrow X' + (\alpha_5,1)\downarrow X';\\
X & = & (\alpha_5,1)\uparrow X + (\alpha_6,1)\downarrow X + (\alpha_7,1) \oplus X;\\
Res & = & (\alpha_2,1) \odot Res; \quad CF = (\alpha_1,1) \odot CF;
\end{array}
$$

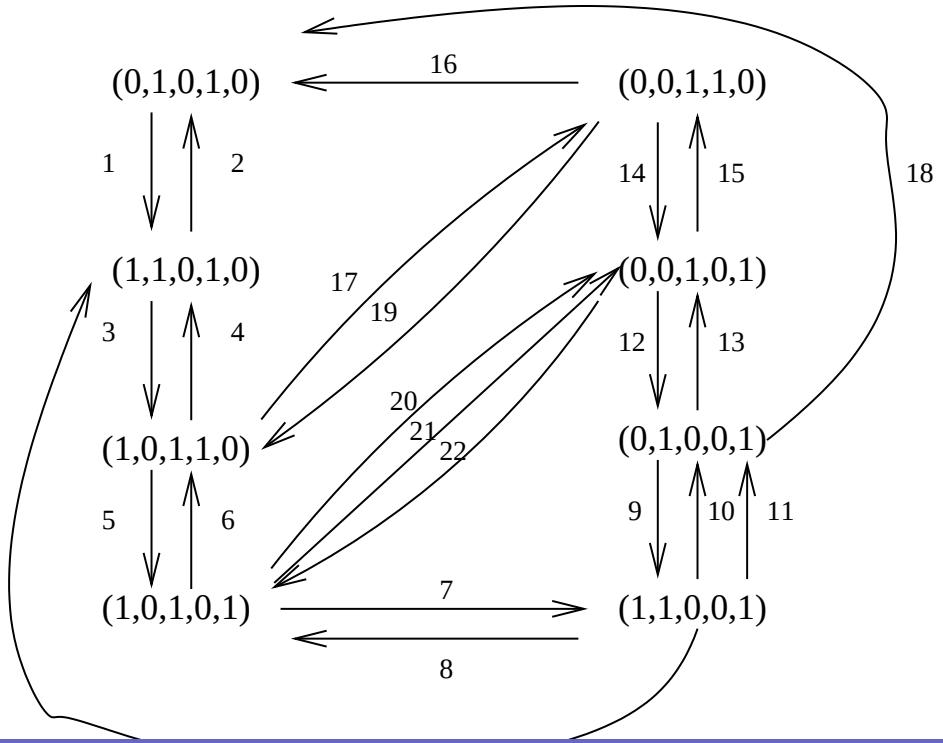
Definition of the model component (*P*):

$$
C(l_{0C}) \underset{\{\alpha_3\}}{\bowtie} M(l_{0M}) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} M'(l_{0M'}) \underset{\{\alpha_5,\alpha_7\}}{\bowtie} X(l_{0X}) \underset{\{\alpha_5,\alpha_6\}}{\bowtie} X'(l_{0X'})
$$

$$
\underset{\{\alpha_2\}}{\bowtie} Deg(0) \underset{\{\alpha_1\}}{\bowtie} CF(1)
$$

Analysis

Assume two levels for each species and initially C, M and X present (level 1) and the other elements not present (level 0).
The initial state is $(l_C(1), l_{M'}(0), l_M(1), l_{X'}(0), l_X(1))$.



ODEs

The stoichiometry matrix D:

	R1	R2	R3	R4	R5	R6	R7	
C	+1	0	0	0	0	0	-1	x_C
M'	0	0	-1	+1	0	0	0	$x_{M'}$
M	0	0	+1	-1	0	0	0	x_M
X'	0	0	0	0	-1	+1	0	$x_{X'}$
X	0	0	0	0	+1	-1	0	x_X

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M	0	0	+1	-1	0	0	0	x_M
X'	0	0	0	0	-1	+1	0	$x_{X'}$
X	0	0	0	0	+1	-1	0	x_X

The vector that contains the kinetic laws is:

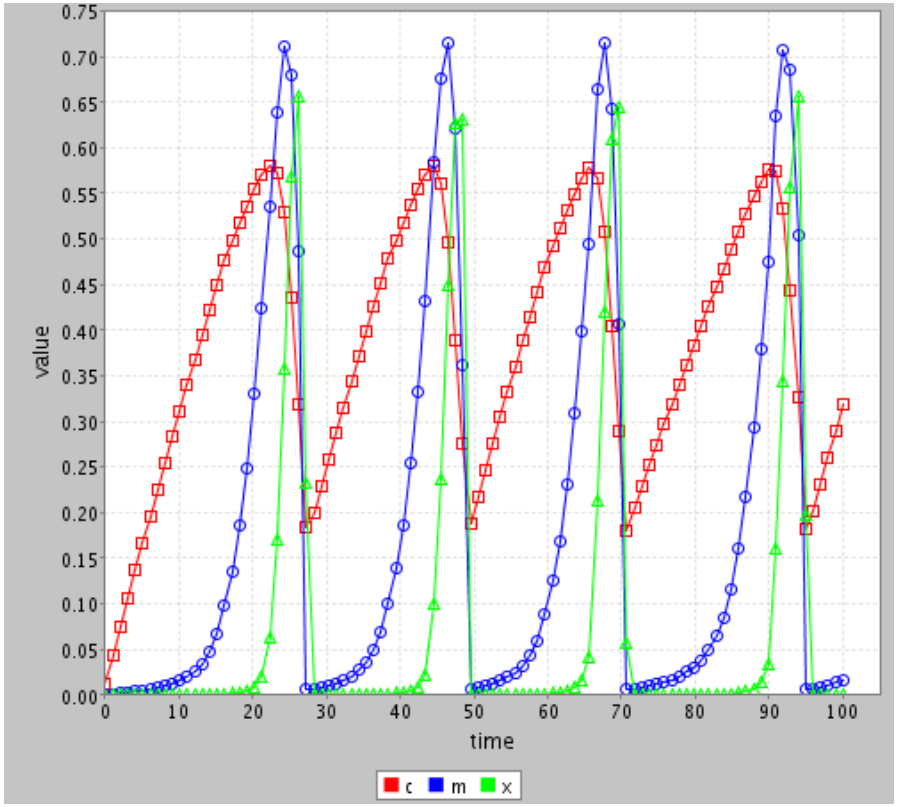
$$w = \Big(v_i * 1, k_d * x_C, \frac{V_{M1} * x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})}, \frac{V_2 * x_M}{(K_2 + x_M)}, \frac{V_{M3} * x_M * x_{X'}}{(K_3 + x_{X'})}, \frac{V_4 * x_X}{(K_4 + x_X)}, \frac{v_d * x_C * x_X}{(K_d + x_C)}\Big)$$

ODEs (2)

The system of ODEs is obtained as $\frac{d\bar{x}}{dt} = D \times w$, where $\bar{x}^T =: (x_C, x_{M'}, x_M, x_{X'}, x_X)$ is the vector of the species variables:

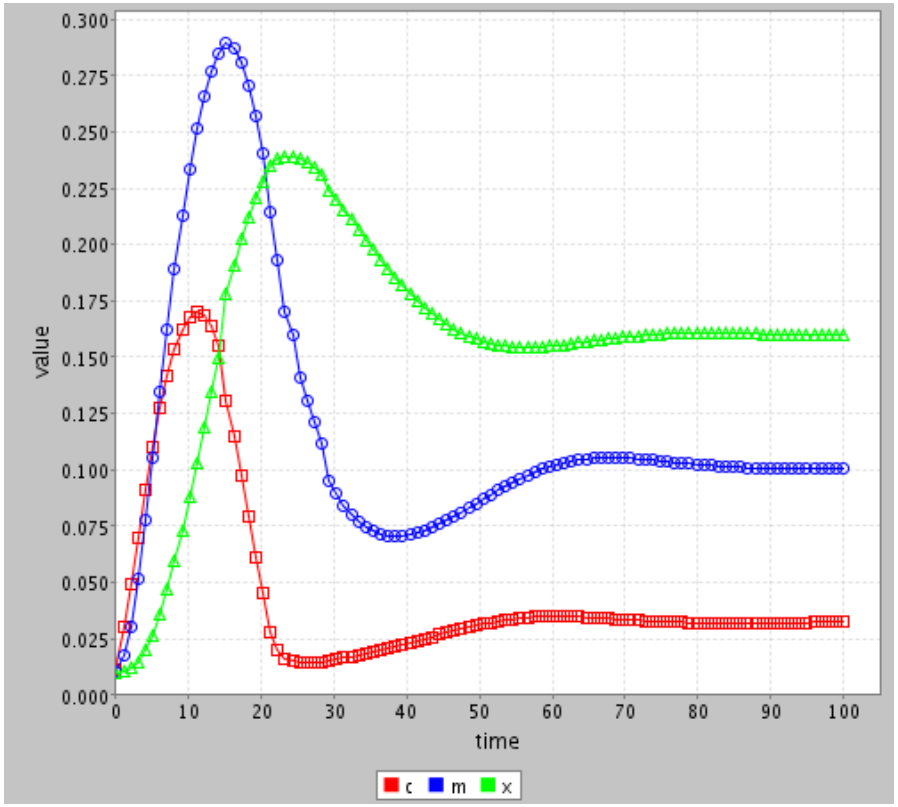
$$
\begin{aligned}
\frac{dx_C}{dt} &= v_i * 1 - k_d * x_C - \frac{v_d * x_C * x_X}{(K_d + x_C)} \\
\frac{dx_{M'}}{dt} &= -\frac{V_{M1} * x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} + \frac{V_2 * x_M}{(K_2 + x_M)} \\
\frac{dx_M}{dt} &= +\frac{V_{M1} * x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} - \frac{V_2 * x_M}{(K_2 + x_M)} \\
\frac{dx_{X'}}{dt} &= -\frac{V_{M3} * x_M * x_{X'}}{(K_3 + x_{X'})} + \frac{V_4 * x_X}{(K_4 + x_X)} \\
\frac{dx_X}{dt} &= \frac{V_{M3} * x_M * x_{X'}}{(K_3 + x_{X'})} - \frac{V_4 * x_X}{(K_4 + x_X)}
\end{aligned}
$$

ODE results



$$K_1 = K_2 = K_3 = K_4 = 0.02\mu M$$

ODE results



$$K_1 = K_2 = K_3 = K_4 = 40\mu M$$

Extended model

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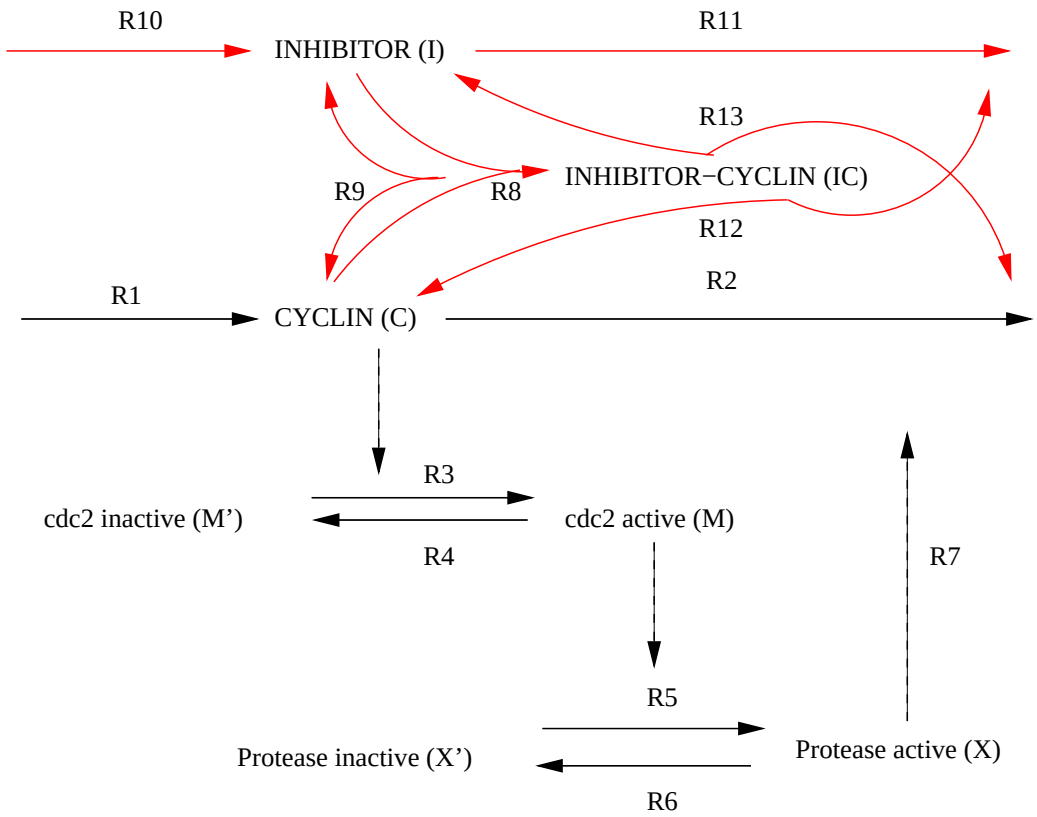
Several possible extension were presented; we consider one of them.

Extension of Goldbeter's model



Extended Bio-PEPA model

$$
\begin{aligned}
C &= \cdots + (\alpha_8, 1)\downarrow C + (\alpha_9, 1)\uparrow C + (\alpha_{12}, 1)\uparrow C; \\
&\vdots \qquad\qquad \vdots \\
Res &= \cdots + (\alpha_{11}, 1) \odot Res; \quad CF = \cdots + (\alpha_{10}, 1) \odot CF; \\
I &= (\alpha_8, 1)\downarrow I + (\alpha_9, 1)\uparrow I + (\alpha_{10}, 1)\uparrow I + (\alpha_{11}, 1)\downarrow I + (\alpha_{13}, 1)\uparrow I; \\
IC &= (\alpha_8, 1)\uparrow IC + (\alpha_9, 1)\downarrow IC + (\alpha_{12}, 1)\downarrow IC + (\alpha_{13}, 1)\downarrow IC;
\end{aligned}
$$

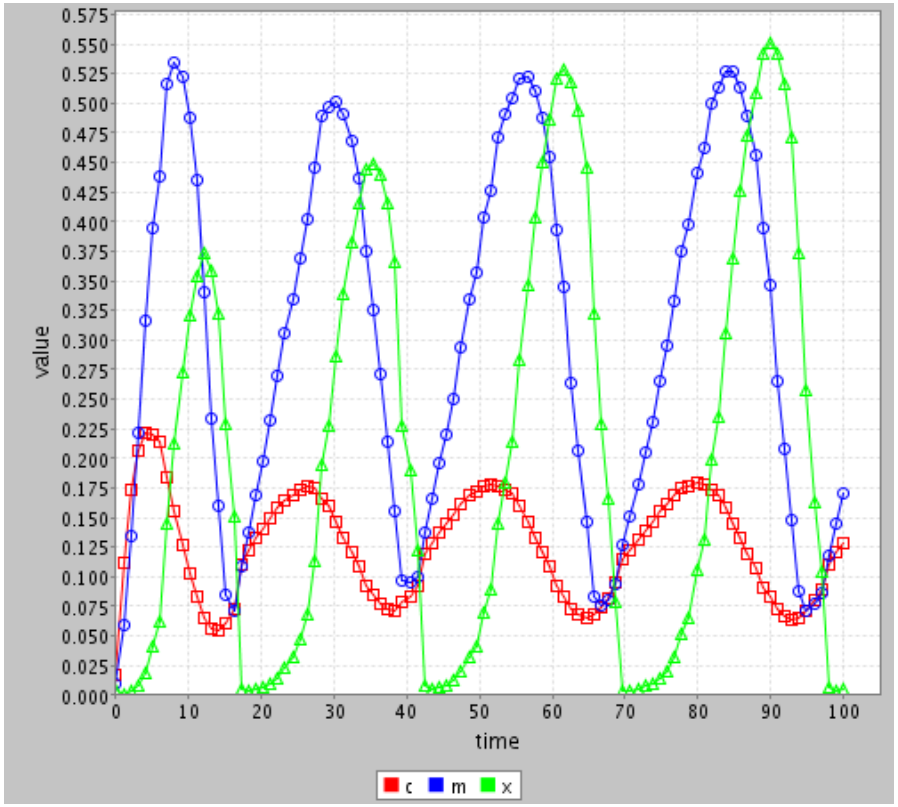
New functional rates

$$
\begin{aligned}
f_{\alpha_8} &= v_s; \\
f_{\alpha_9} &= fMA(d_1); \\
f_{\alpha_{10}} &= fMA(a_1); \\
f_{\alpha_{11}} &= fMA(a_2); \\
f_{\alpha_{12}} &= fMA(\theta * d_1); \\
f_{\alpha_{13}} &= fMA(\theta * k_d)
\end{aligned}
$$

Complete Bio-PEPA model

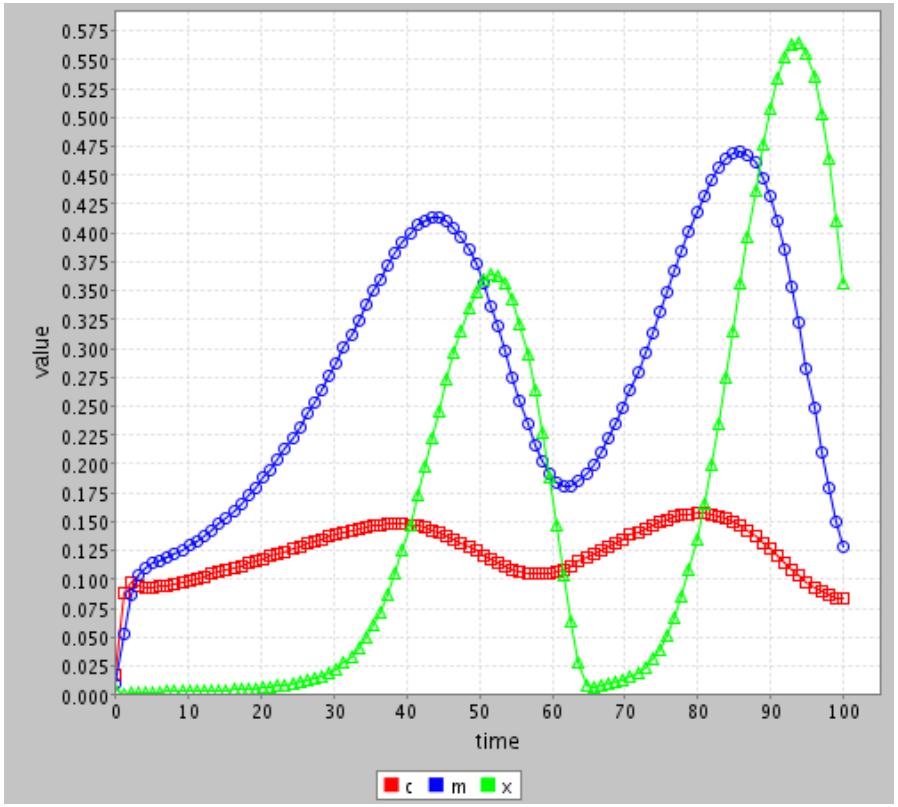
$$C(l_{0C}) \underset{\{\alpha_3\}}{\bowtie} M(l_{0M}) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} M'(l_{0M'}) \underset{\{\alpha_5,\alpha_7\}}{\bowtie} X(l_{0X}) \underset{\{\alpha_5,\alpha_6\}}{\bowtie} X'(l_{0X'}) \underset{\{\alpha_2\}}{\bowtie}$$
$$Deg(0) \underset{\{\alpha_1\}}{\bowtie} CF(1)$$
$$\underset{\{\alpha_8,\alpha_9,\alpha_{10},\alpha_{11}\}}{\bowtie} I(l_{0I}) \underset{\{\alpha_8,\alpha_9,\alpha_{12},\alpha_{13}\}}{\bowtie} IC(l_{0IC})$$

New ODE results



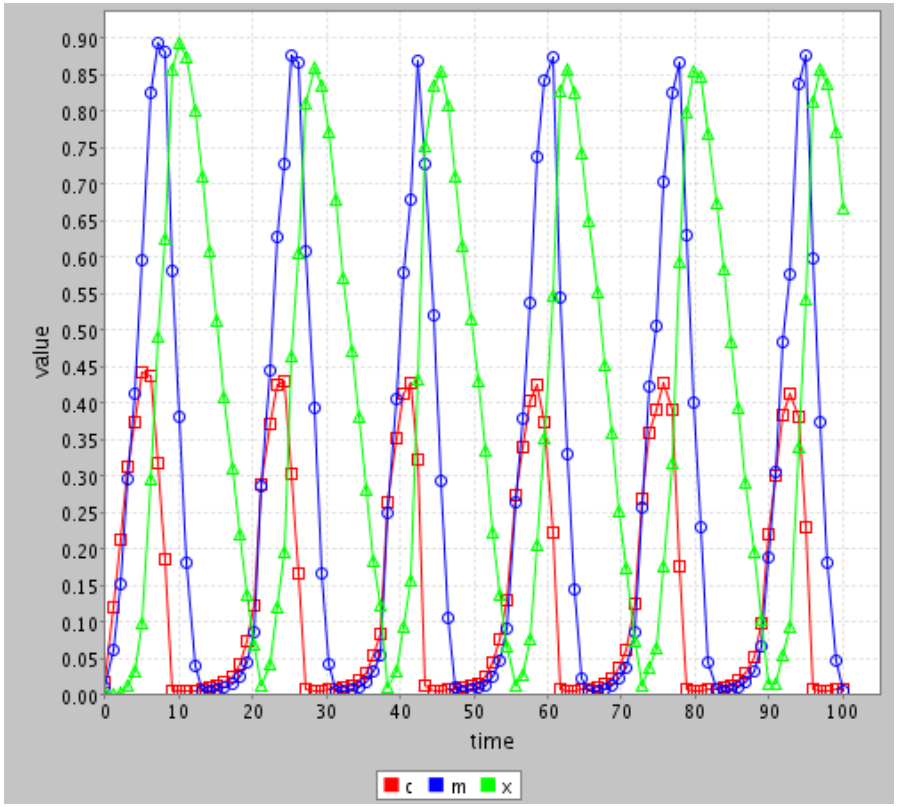
$a_1 = a_2 = 0.3$ and $v_s = 0.6$

New ODE results



$a_1 = a_2 = 0.7$ and $v_s = 1.4$

New ODE results



$a_1 = a_2 = 0.05$ and $v_s = 0.1$

Outline

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- the definition of *bisimulations* and *equivalences*;
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- the application of *model checking techniques*.

Challenges

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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.

Challenges cont.

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Challenges cont.

- The issue of unknown and uncertain data remains to be addressed.
- 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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  - Better models and simulations of living phenomena
  - New models of computations that are biologically inspired.

Thank You!

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