SPA for quantitative analysis: Lecture 6 — Modelling Biological Processes

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Outline

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Systems Biology

- Biological advances mean that much more is now known about the components of cells and the interactions between them.
- Systems biology aims to develop a better understanding of the processes involved.
- Formalisms from theoretical computer science have found a new role in developing models for systems biology, allowing biologists to test hypotheses and prioritise experiments.

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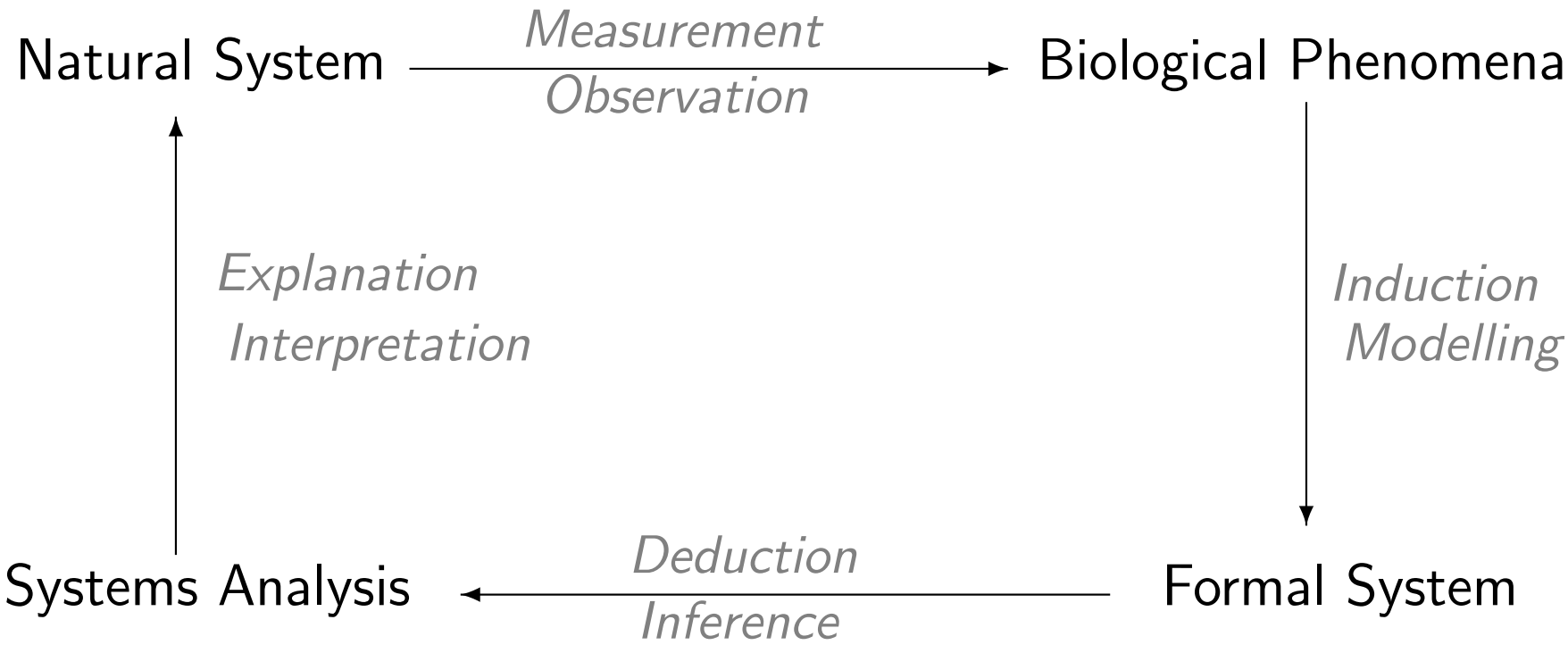

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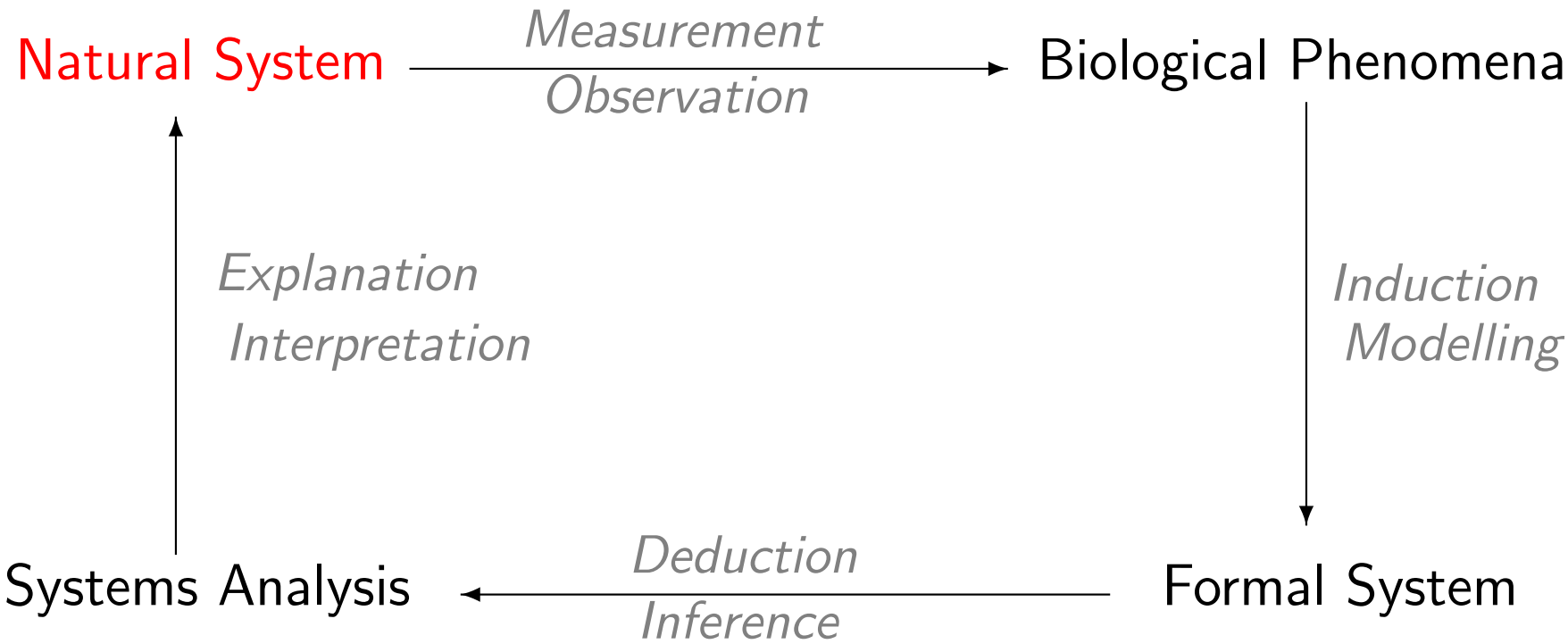

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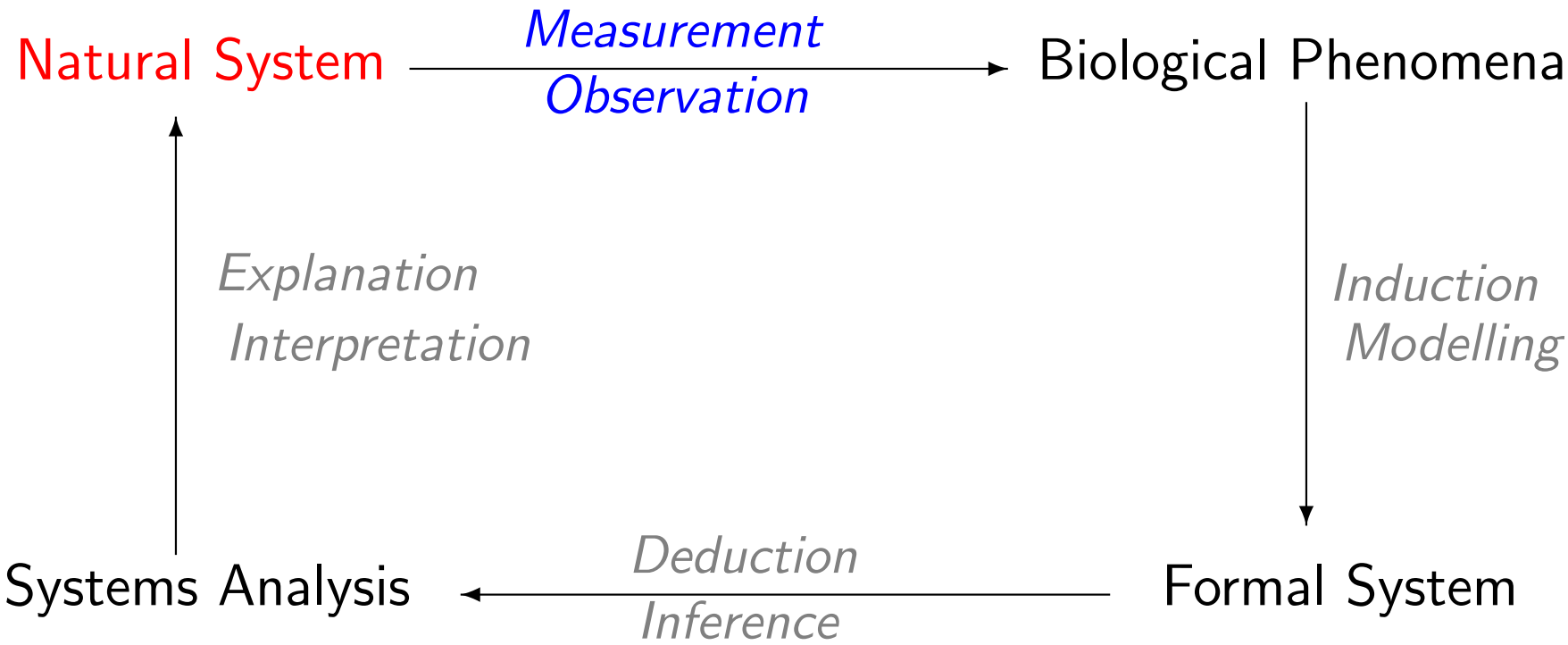

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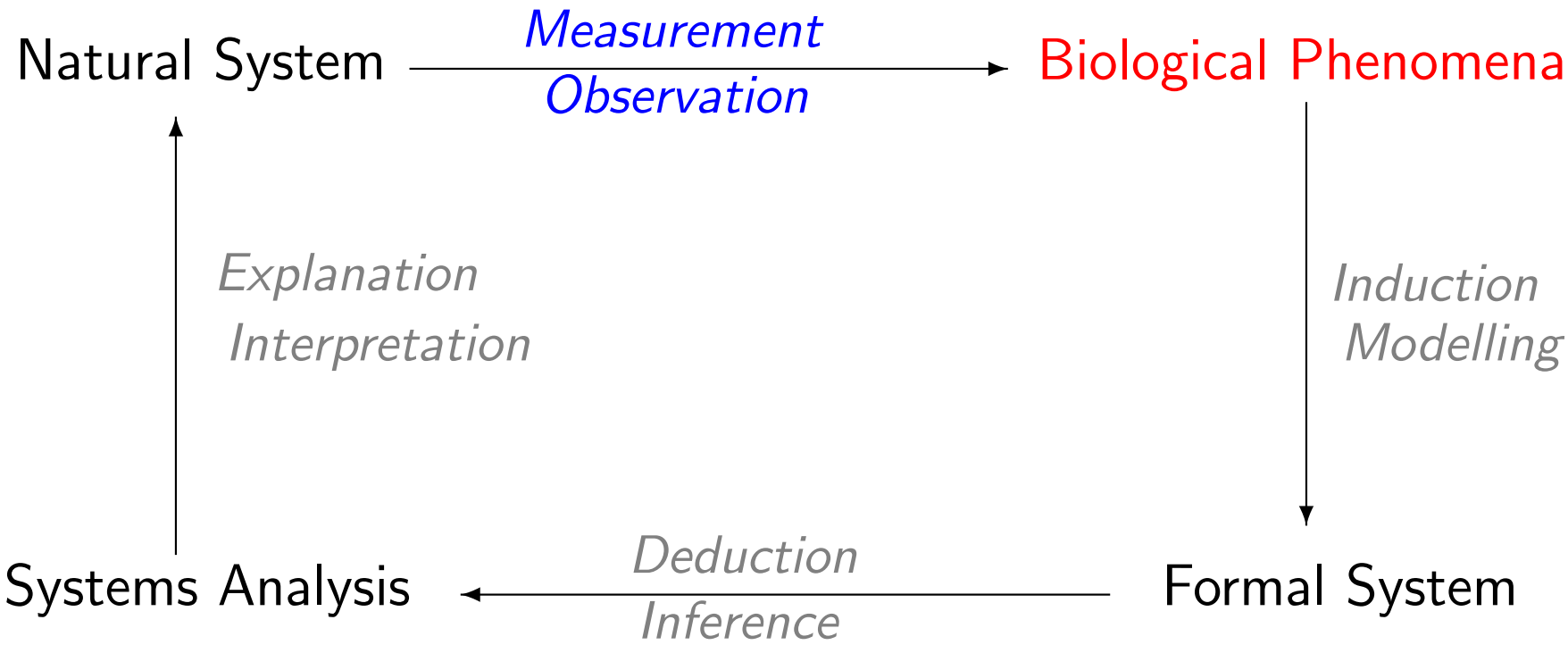

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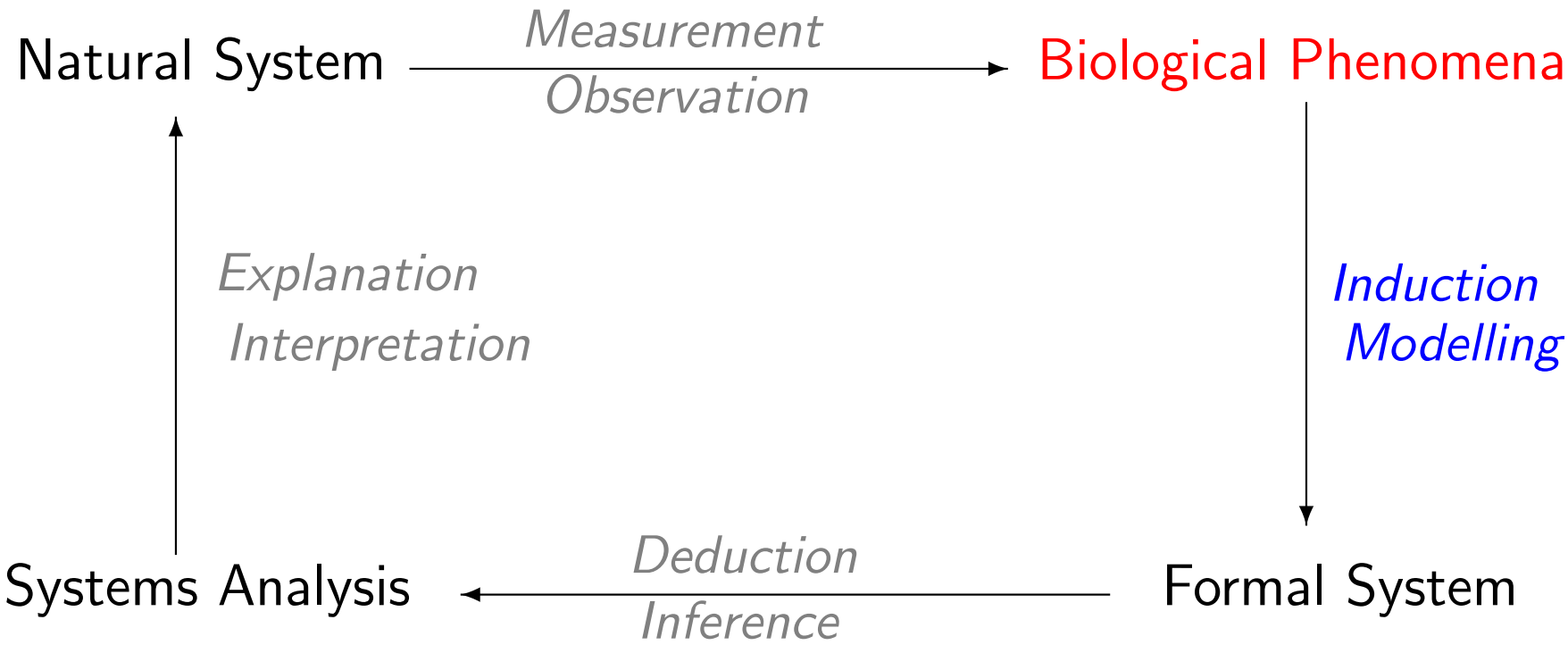

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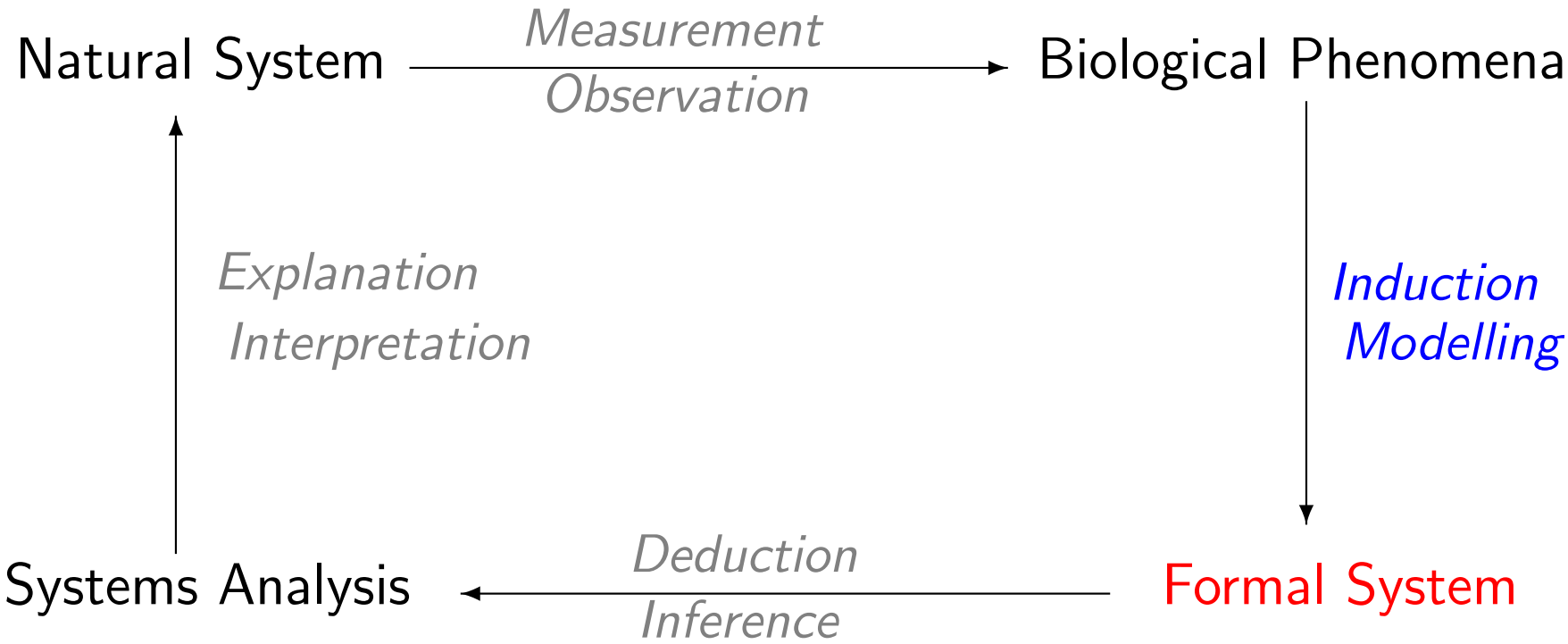

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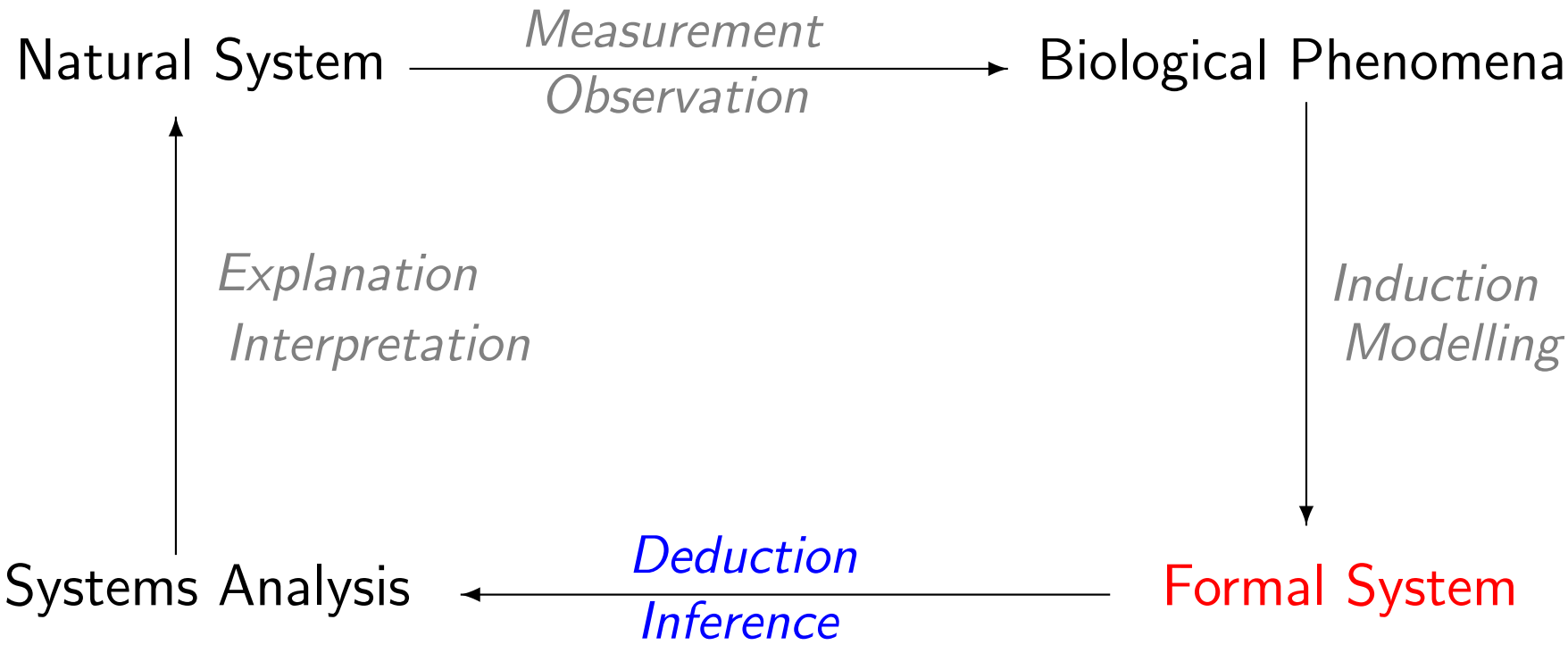

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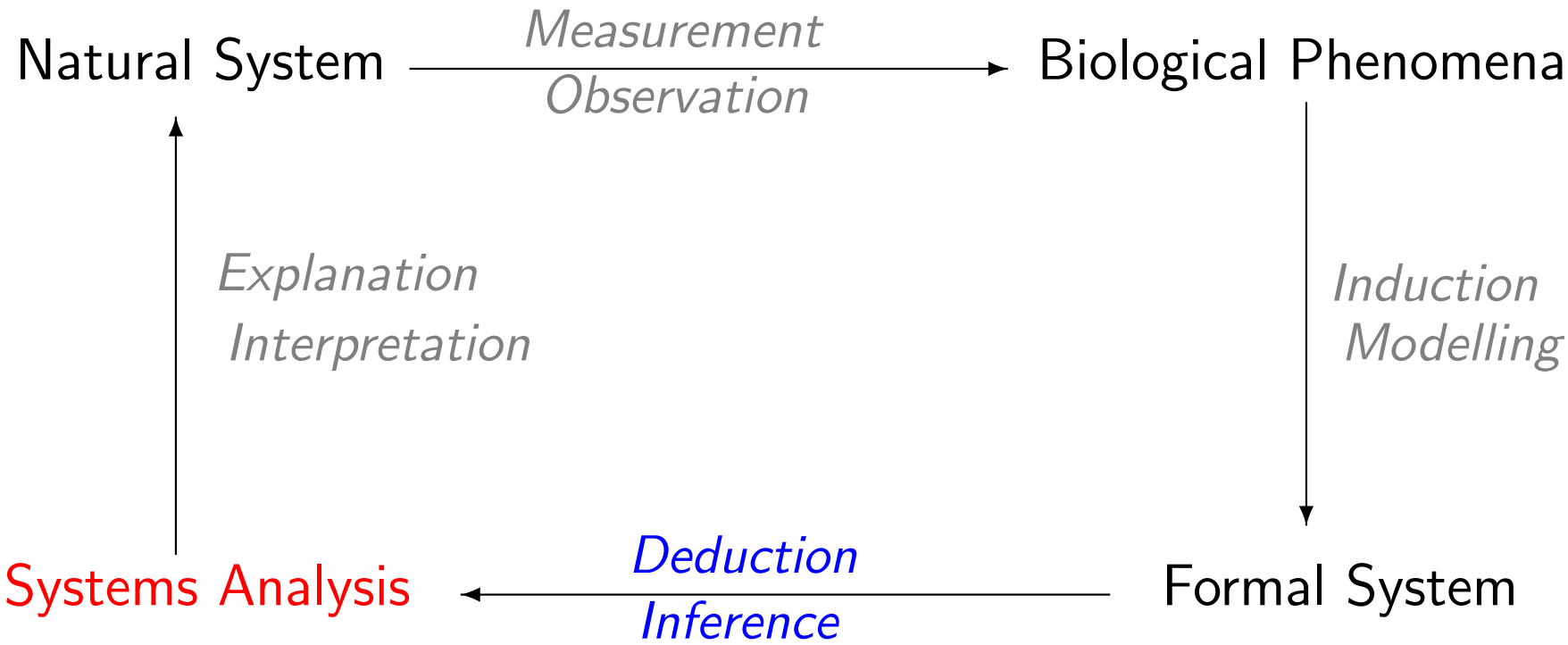

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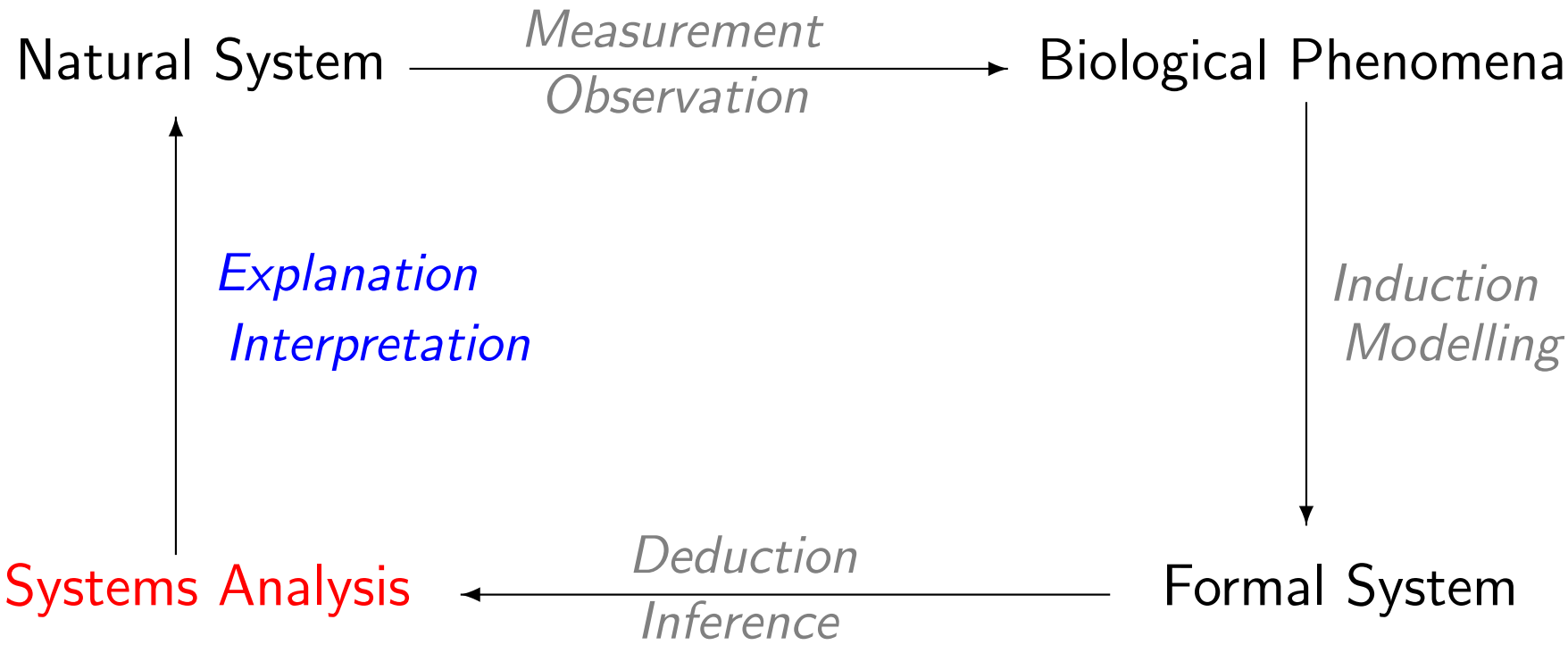

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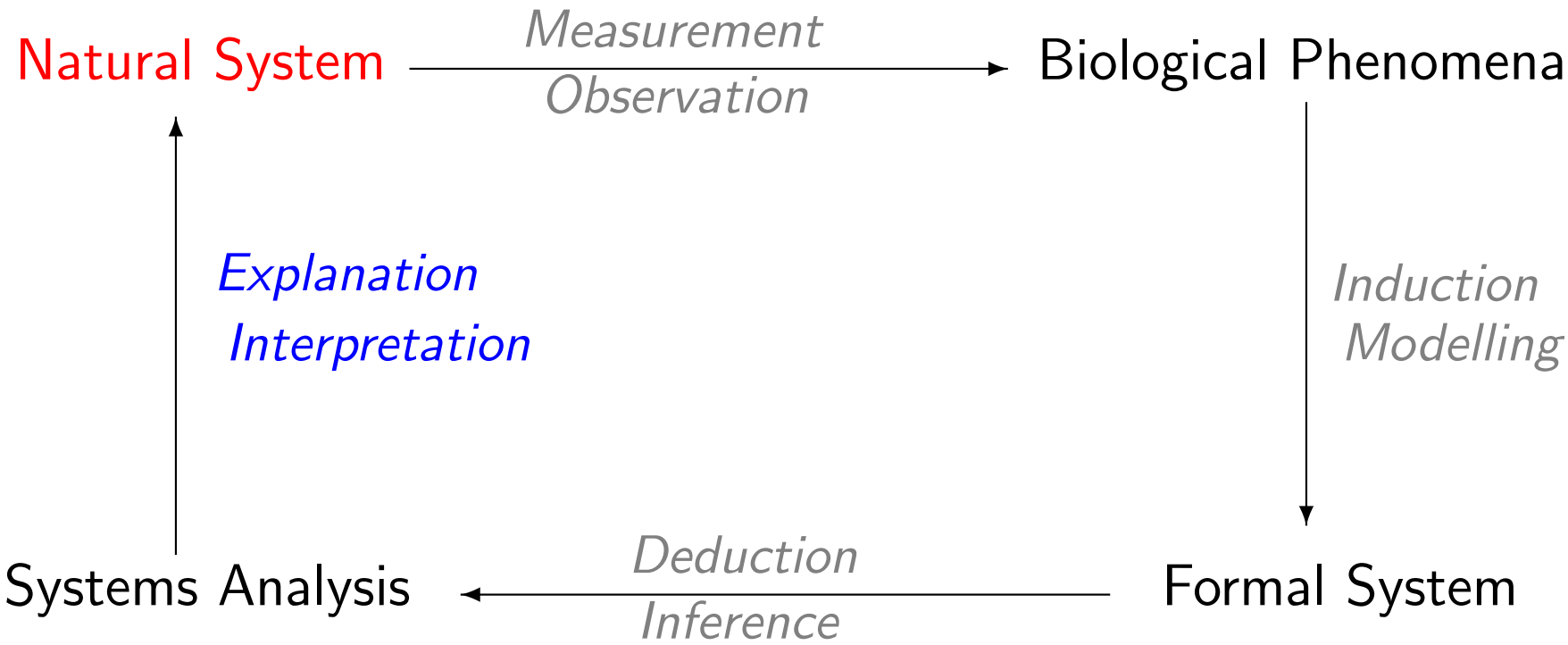

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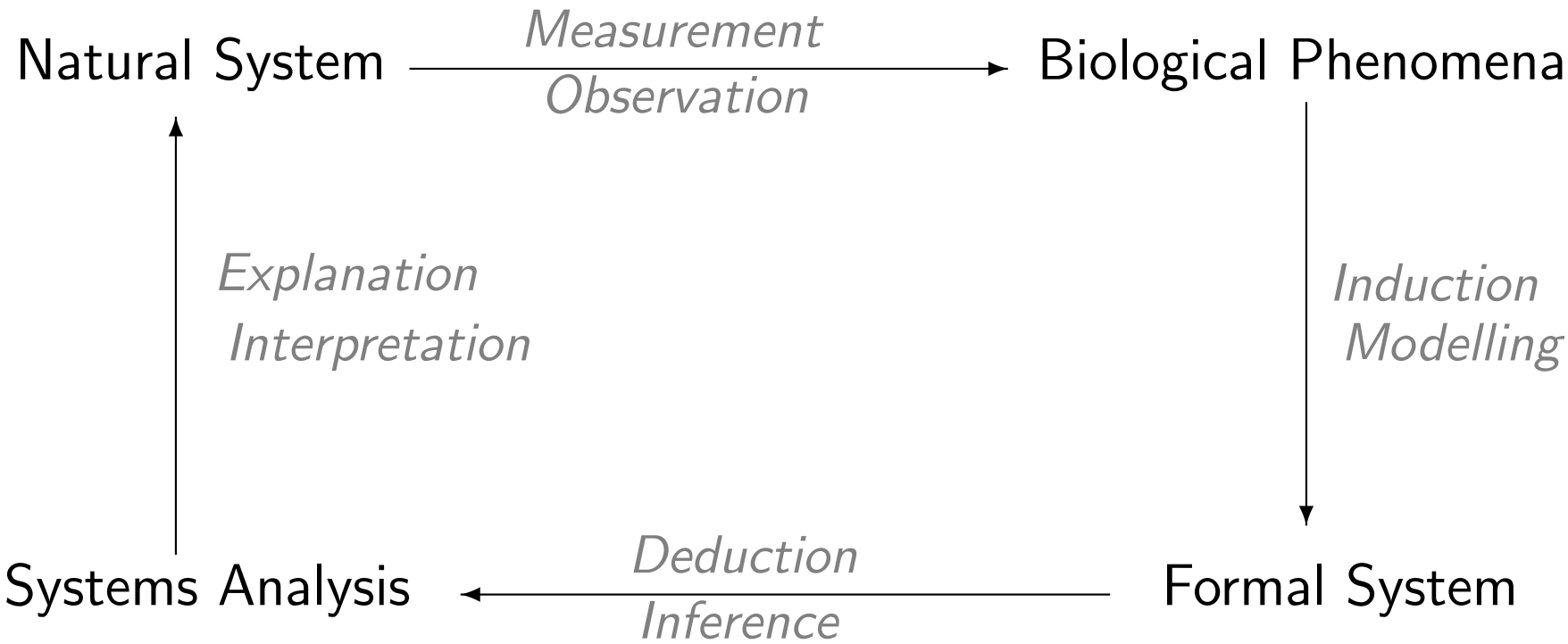

Networks in cells

We can distinguish three distinct types of links or networks in cells

Gene networks: Genes control the production of proteins but are themselves regulated by the same or different proteins.

Signal transduction networks: External stimuli initiate messages that are carried through a cell via a cascade of biochemical reactions.

Metabolic pathways: The survival of the cell depends on its ability to transform nutrients into energy.

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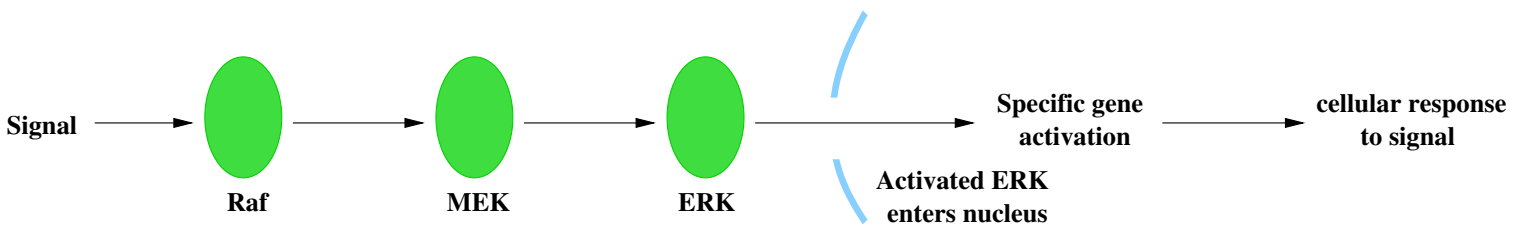
Extracellular signalling

Extracellular signalling — communication between cells.

- Signalling molecules released by one cell migrate to another;
- These molecules enter the cell and instigate a pathway, or series of reactions, which carries the information from the membrane to the nucleus;
- For example, the Ras/Raf-1/MEK/ERK pathway conveys differentiation signals to the nucleus of a cell.



Cell signalling

- All signalling is biochemical:
- Increasing protein concentration broadcasts the information about an event; for example, that a gene promoter is “on”.
- The message is “received” by a concentration dependent response at the protein signal’s site of action.
- This stimulates a response at the signalling protein’s site of action.
- Signals propagate through a series of protein accumulations.

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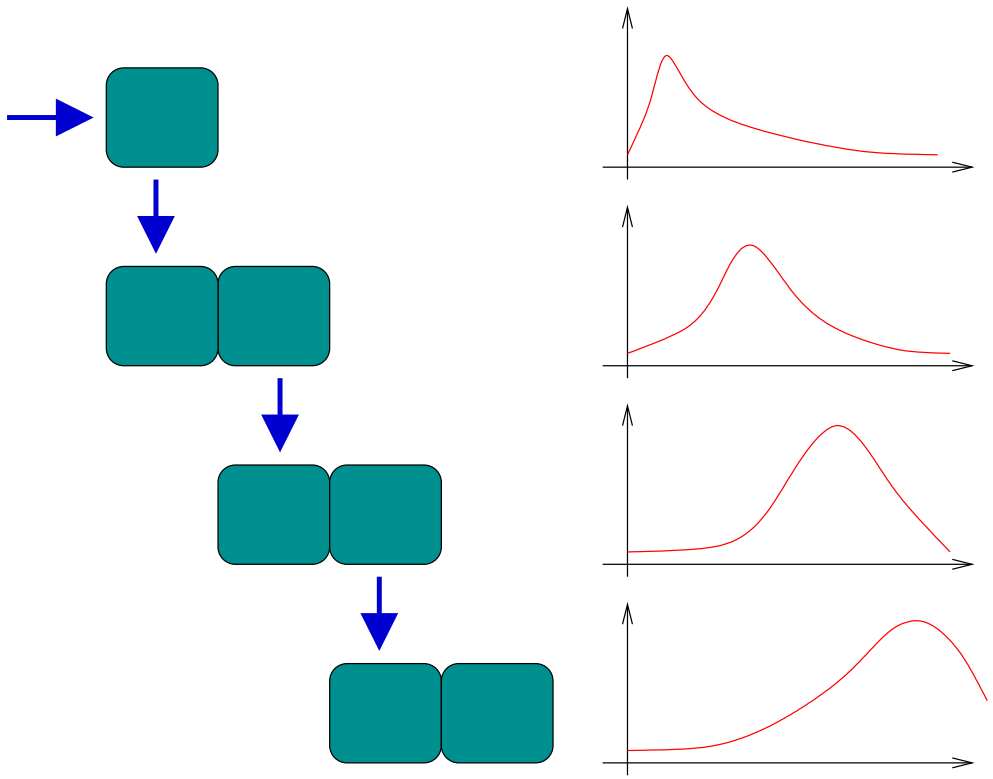
Signal transduction pathways



A series of biochemical reactions serve to pass a message from the cell membrane to the nucleus.

Gene expression pathways

- Genetic activity is controlled by molecular signals that determine when and how often a given gene is transcribed.
- The product encoded by one gene often regulates the expression of other genes.
- For appropriate combinations of input signals transcription is initiated and protein product accumulates when production exceeds degradation.
- Links are established between genes when the product of one regulates the expression of another.
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Dynamic issues

- In biochemical regulatory networks, the delay between events are determined by the delay while signal molecule concentrations accumulate or decline sufficiently.
- All reactions rely on the random process of molecules colliding with the cell.
- Thus the accumulation of protein is a stochastic process affected by several factors in the cell (temperature, pH, etc.).
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Stochastic behaviour

- The stochastic reaction rate of a chemical reaction is a function of only those molecular species involved as reactants or catalysts, and a stochastic rate constant c.
- The stochastic rate constant takes into account volume, temperature, pH and other environmental factors.
- The stoichiometry of the reaction — how many molecules of each reactant species are required — also has an impact.
- Commonly the law of mass action is used to determine the effective rate of a reaction: this is the product of the stochastic rate constant and the amount of each of the reactants.

Using Stochastic Process Algebras

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

- 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.

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Molecular processes as concurrent computations

A correspondence between cellular processes and process alebras was first highlighted by Regev and her co-authors in the early 2000s.

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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Calculi for Systems Biology

Several different process caluli have been developed or adapted for application in systems biology. Each of them has different properties able to render different aspects of biological phenomena. They may be divided into two main categories:

- Calculi defined originally in computer science and then applied in biology, such as the biochemical stochastic π-calculus, SCCP, CCS-R and PEPA;
- Calculi defined specifically by observing biological structures and phenomena, such as BioAmbients, Brane Calculi, Beta-binders, BlenX and Bio-PEPA.

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Stochastic π-calculus

- The stochastic π-calculus has been used to model and analyse a wide variety of biological systems.
- Examples include metabolic pathways, gene transcription and signal transduction.
- Analysis is mainly based on stochastic simulation (Gillespie's algorithm).
- Two tools: BioSPI and SPIM which implement slightly different versions of the language.
- There has also been some work on a graphical notation associated with the SPIM tool.

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where π is either $x(y)$ (input), $\overline{x}y$ (output) or τ (silent).

Example: The VICE project

- The aim was to construct a minimal cell in silico in order to track the dynamics of a complete metabolome.
- Thus a VIrtual CEll was defined as a stochastic π-calculus model, which seems to behave as a simplified prokaryote.
- Started from a published minimal gene set which eliminated duplicated genes and other redundancies from the smallest known bacterial genomes. This was further reduced to 180 different genes.
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This work was hugely influential and many people followed their lead in applying the stochastic π-calculus to model intracellular processes.

However the style of modelling in the π-calculus is not always ideal for representing biochemical processes.

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- The restriction to always consider actions as occurring in conjugate pairs does not always match well with biochemical reactions where you might want more than two molecules to be involved.

- The molecule-as-processes abstraction can lead to problems pragmatically. By focussing on the individual molecules the calculus forces the modeller into an individuals-based interpretation of the model. This means that simulation is often the only feasible interpretation.

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  This suggests that it can be useful to use semi-quantitative models rather than quantitative ones.

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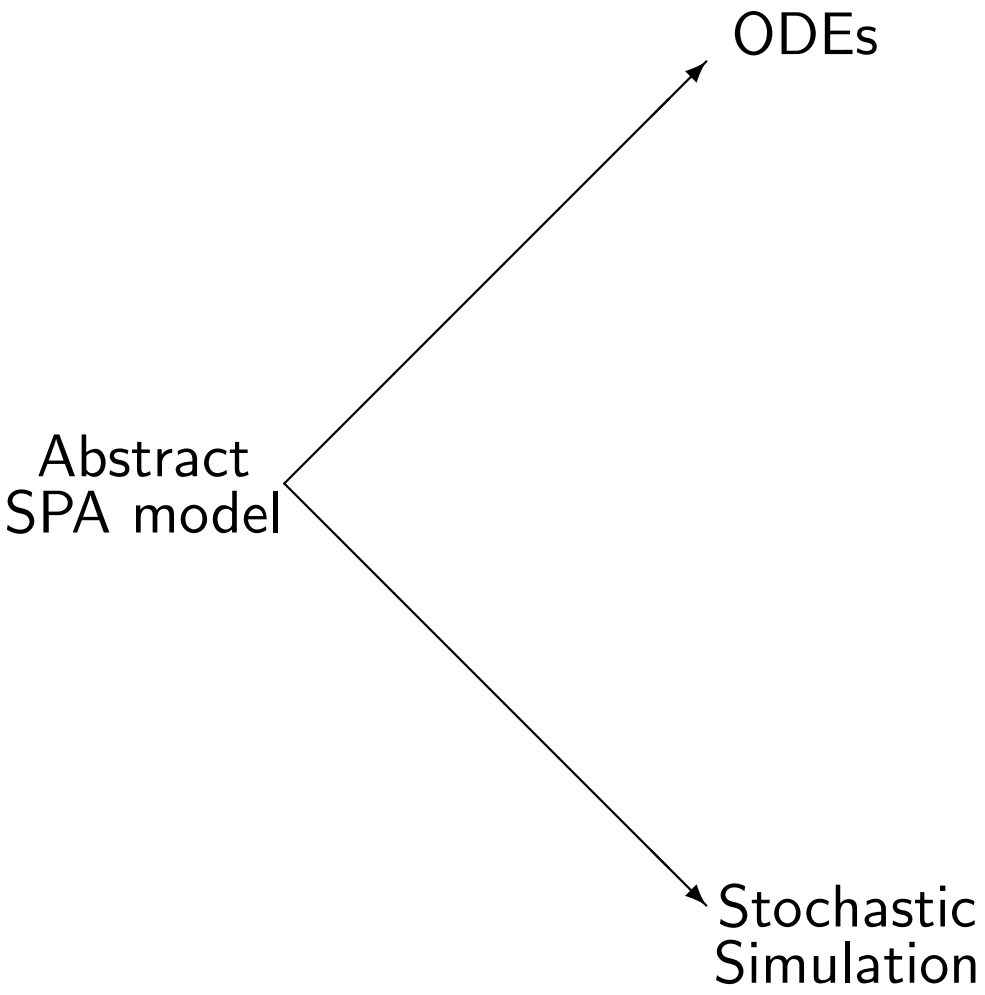

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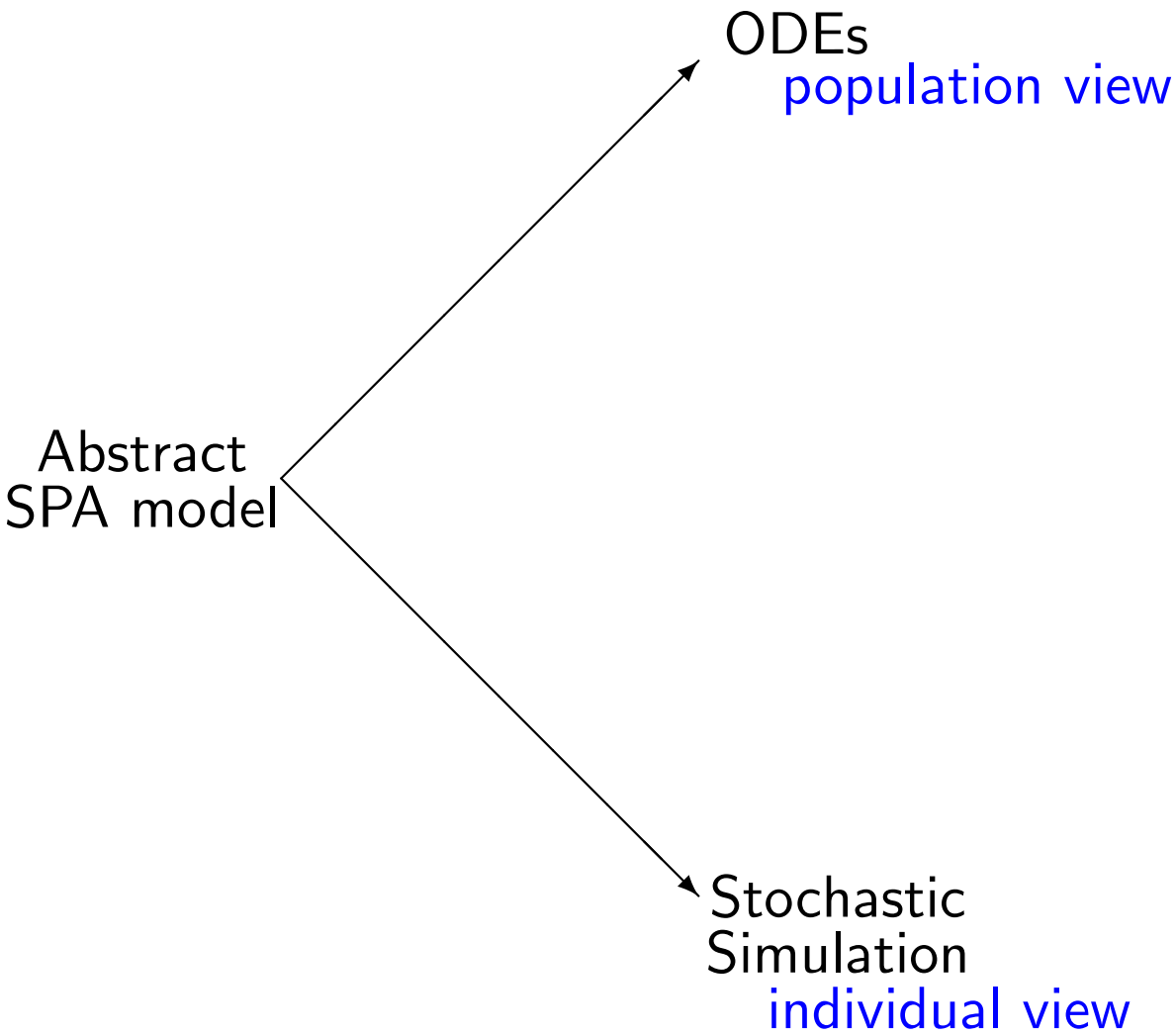

Discretising the population view

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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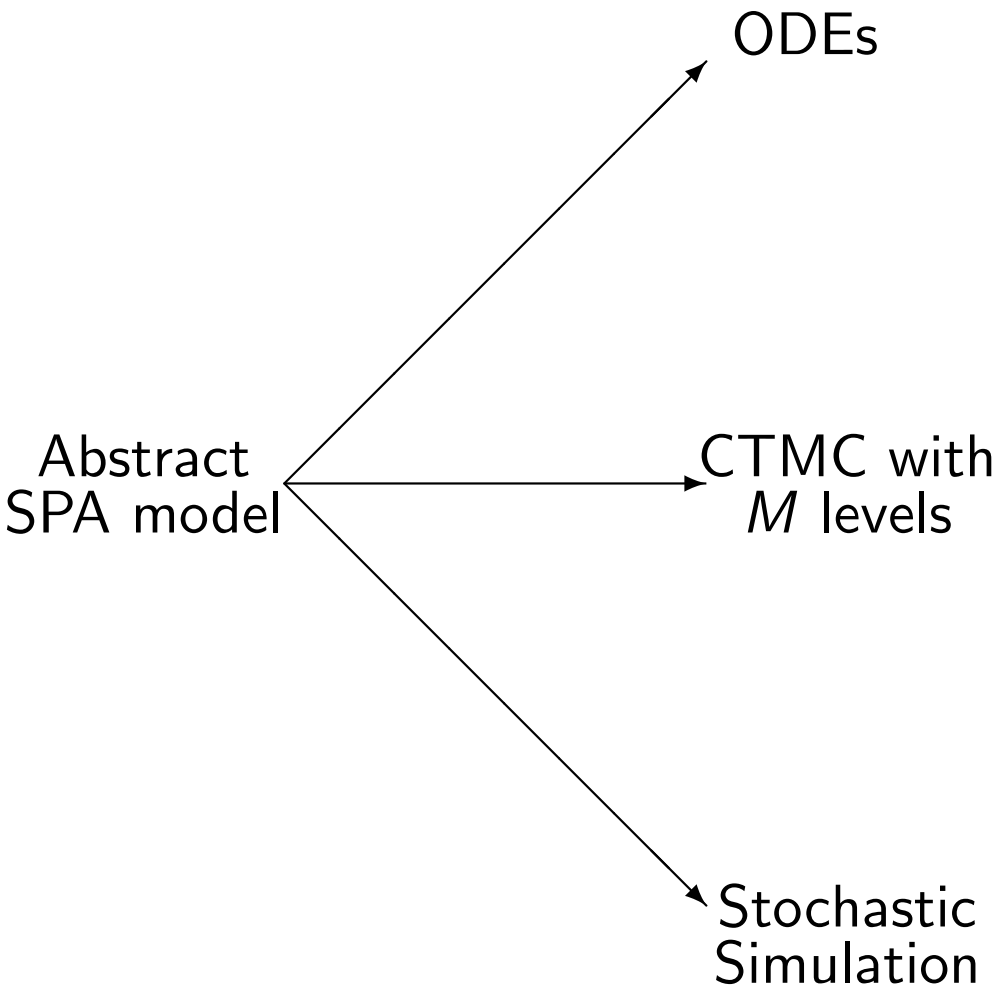

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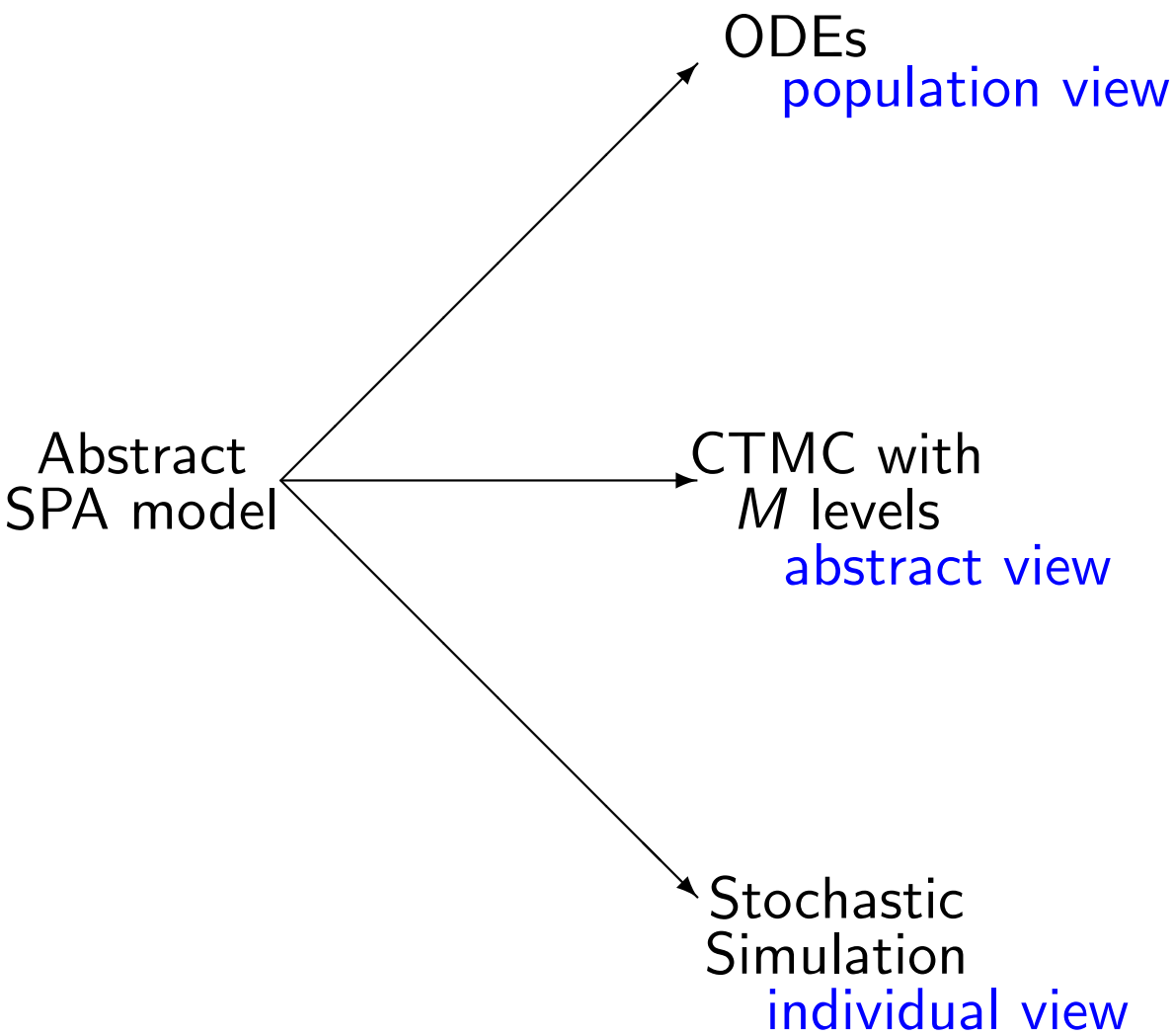

Alternative models

- The ODE model can be regarded as an approximation of a CTMC in which the number of molecules is large enough that the randomness averages out and the system is essentially deterministic.
- The full molecular view can be used for detailed study of the stochastic behaviour, usually via stochastic simulation
- In 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.
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Modelling biological features

There are some features of biochemical reaction systems which are not readily captured by π-calculus-based stochastic process algebras.

Particular problems are encountered with:

- stoichiometry — the multiplicity in which an entity participates in a reaction;
- general kinetic laws — although mass action is widely used other kinetics are also commonly employed.
- multiway reactions — although thermodynamic arguments can be made that there are never more than two reagents involved in a reaction, in practice it is often useful to model at a more abstract level.

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Consider a conversion of a substrate S, with stoichiometry 2, to a product P, under the influence of an enzyme E, i.e.

$$2 \times S \xrightarrow{E} P$$

In the stochastic π-calculus (for example) this must modelled as a sequence of unary and binary reactions:

- $S + S \longrightarrow 2S$
- $2S + E \longrightarrow 2S : E$
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$$(S(l_{S0}) \underset{\{\alpha\}}{\bowtie} E(l_{E0})) \underset{\{\alpha\}}{\bowtie} P(l_{P0})$$

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- Unique rates are associated with each reaction (action) type, separately from the specification of the logical behaviour. These rates may be specified by functions.
- The representation of an action within a component (species) records the stoichiometry of that entity with respect to that reaction. The role of the entity is also distinguished.
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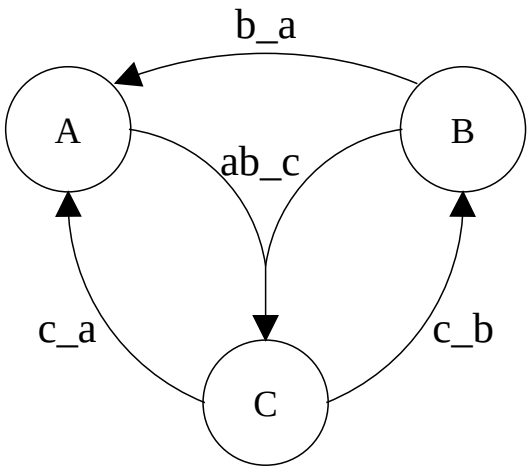
Bio-PEPA reagent-centric example



$$
\begin{aligned}
A &\stackrel{def}{=} (ab\_c, 1)\downarrow A + (b\_a, 1)\uparrow A \\
&\quad + (c\_a, 1)\uparrow A \\
B &\stackrel{def}{=} (ab\_c, 1)\downarrow B + (b\_a, 1)\downarrow B \\
&\quad + (c\_b, 1)\uparrow B \\
C &\stackrel{def}{=} (c\_a, 1)\downarrow C + (c\_b, 1)\downarrow C \\
&\quad + (ab\_c, 1)\uparrow C
\end{aligned}
$$

$$
\left(A(l_{A0}) \underset{\{ab\_c, b\_a\}}{\bowtie} B(l_{B0})\right) \underset{\{ab\_c, c\_a, c\_b\}}{\bowtie} C(l_{C0})
$$

Reagent-centric view

Role	*Impact on reaction rate*	*Impact on reagent*
Reactant	positive impact, e.g. proportional to current concentration	decreases level
Product	no impact, except at saturation	increases level
Enzyme	positive impact, e.g. proportional to current concentration	level unchanged
Inhibitor	negative impact, e.g. inversely proportional to current concentration	level unchanged

Outline

The syntax

Sequential component (species component)

$$S ::= (\alpha, \kappa)\ \mathtt{op}\ S \mid S + S \mid C \qquad \text{where } \mathtt{op} = \downarrow \mid \uparrow \mid \oplus \mid \ominus \mid \odot$$

Model component

$$P ::= P \underset{\mathcal{L}}{\bowtie} P \mid S(I)$$

The parameter I is abstract, recording quantitative information about the species.

Depending on the interpretation, this quantity may be:

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The Bio-PEPA system

A Bio-PEPA system $\mathcal{P}$ is a 6-tuple $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \mathit{Comp}, P \rangle$, where:

- $\mathcal{V}$ is the set of compartments;
- $\mathcal{N}$ is the set of quantities describing each species (step size, number of levels, location, ...);
- $\mathcal{K}$ is the set of parameter definitions;
- $\mathcal{F}_R$ is the set of functional rate definitions;
- *Comp* is the set of definitions of sequential components;
- P is the model component describing the system.

Outline

Semantics

The semantics of Bio-PEPA is given as a small-step operational semantics, intended for deriving the CTMC with levels.

We define two relations over the processes:

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

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$$\texttt{coopFinal} \quad \frac{P_1 \xrightarrow{(\alpha,v_1)}_c P_1' \quad P_2 \xrightarrow{(\alpha,v_2)}_c P_2'}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha,v_1::v_2)}_c P_1' \underset{\mathcal{L}}{\bowtie} P_2'} \quad \text{with } \alpha \in \mathcal{L}$$

Semantics: rates and transition system

In order to derive the rates we consider the stochastic relation $\rightarrow_s \subseteq \mathcal{P} \times \Gamma \times \mathcal{P}$, with $\gamma \in \Gamma := (\alpha, r)$ and $r \in \mathbb{R}^+$.

The relation is defined in terms of the previous one:

$$\frac{P \xrightarrow{(\alpha_j, v)}_c P'}{\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, Comp, P \rangle \xrightarrow{(\alpha_j, r_{\alpha_j})}_s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, Comp, P' \rangle}$$

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Example: Michaelis-Menten

The reaction $S \xrightarrow{E} P$ represents the enzymatic reaction from the substrate S to the product P with enzyme E.

The dynamics is described by the law $\frac{v \times E \times S}{(K+S)}$.

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Outline

Analysis

A Bio-PEPA system is a formal, intermediate and compositional representation of the system.

From it we can obtain

- a CTMC (with levels)
- a ODE system for simulation and other kinds of analysis
- a Gillespie model for stochastic simulation
- a PRISM model for model checking

Each of these kinds of analysis can be of help for studying different aspects of the biological model. Moreover they can be used in conjunction.

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The abstraction

When modelling in Bio-PEPA we use the following abstraction:

- Each species i is described by a Bio-PEPA component C_i.
- Each reaction j is associated with an action type α_j and its dynamics is described by a specific function f_{α_j}.

Given a reaction j, all the species/components cooperate on the action type α_j and consequently, reactants decrease their levels, while products increase them.

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

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State representation

- The state of the system at any time consists of the local states of each of its sequential/species components.
- The local states of components are quantitative rather than functional, i.e. distinct states of the species are represented as distinct components, not derivatives of a single component.
- A component varying its state corresponds to it varying its quantity or level.
- This is captured by an integer parameter associated with the species and the effect of a reaction is to vary that parameter by a number of levels corresponding to the stoichiometry of this species in the reaction as we saw in the formal semantics.

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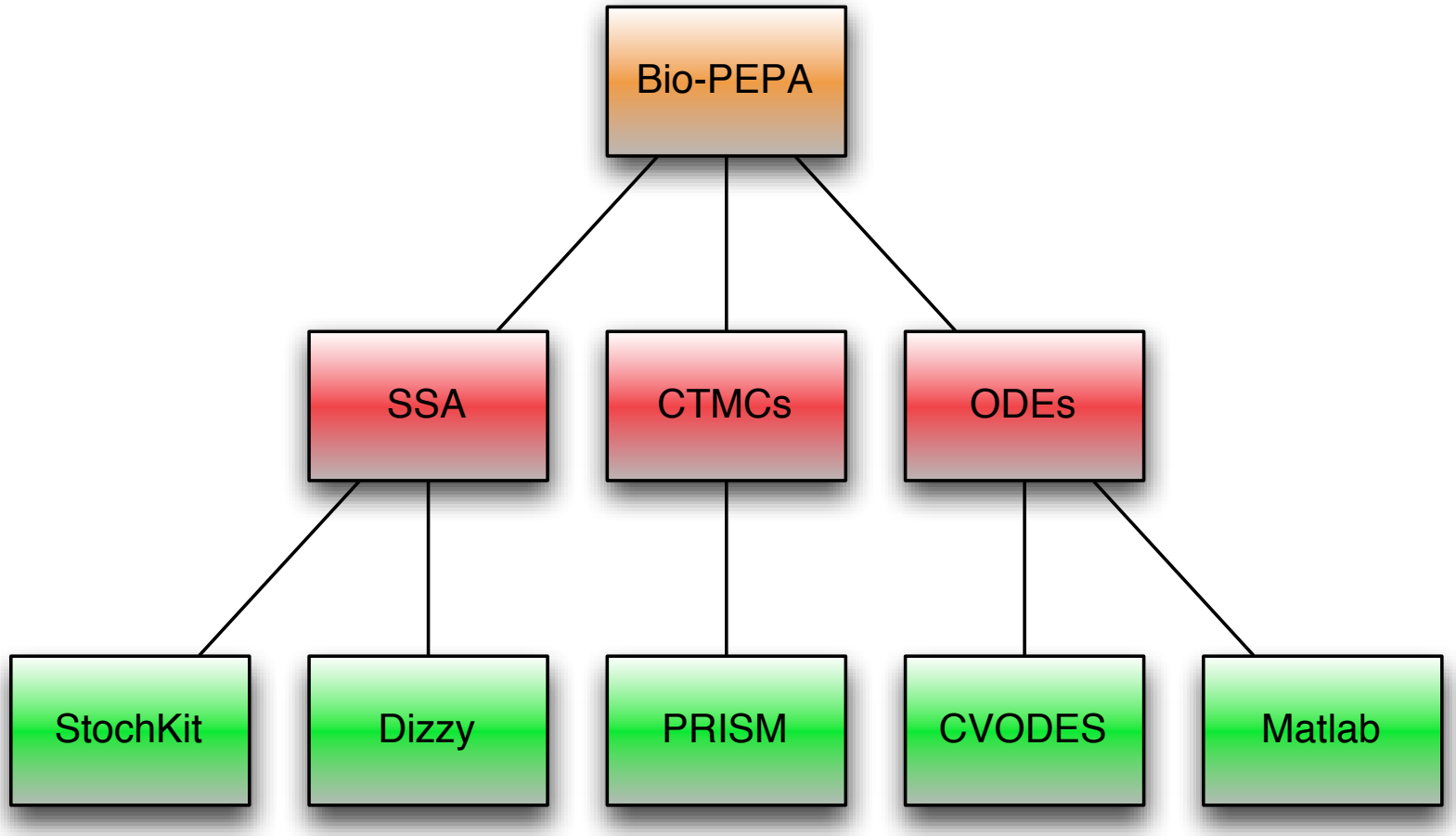
Analysis with Bio-PEPA



Outline

CTMC

- Analysis of the Markov process can yield quite detailed information about the dynamic behaviour of the model.
- A steady state analysis provides statistics for average behaviour over a long run of the system.
- A transient analysis provides statistics relating to the evolution of the model over a fixed period. This will be dependent on the starting state.

In the biological context transient analysis is appropriate much more frequently than steady state analysis.

If molecule counts are kept in states then either analysis rapidly becomes infeasible.

Bio-PEPA models can also be simulated using the Gillespie Stochastic Simulation Algorithm for CTMCs that we considered for PEPA.

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- Models are based on discrete levels of concentration within a species.
- The granularity of the system is defined in terms of the step size h of the concentration intervals.
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- The rate of a transition is set to be consistent with the granularity.
- The granularity must be specified by the modeller as the expected range of concentration values and the number of levels considered.
- The structure of the CTMC derived from Bio-PEPA, which we term the CTMC with levels, will depend on the granularity of the model.
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ODE system

The derivation of the ODEs from the Bio-PEPA is straightforward, based on the definitions of the species components.

1. definition of the $(N \times M)$ stoichiometry matrix D, where N is the number of species and M is the number of reactions;
2. definition of the kinetic law vector v_{KL} containing the kinetic law of each reaction;
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There are advantages to be gained by using a process algebra model as an intermediary to the derivation of the ODEs.

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- The cyclin promotes the activation of a cdk (cdc2) which in turn activates a cyclin protease.
- This protease promotes cyclin degradation.
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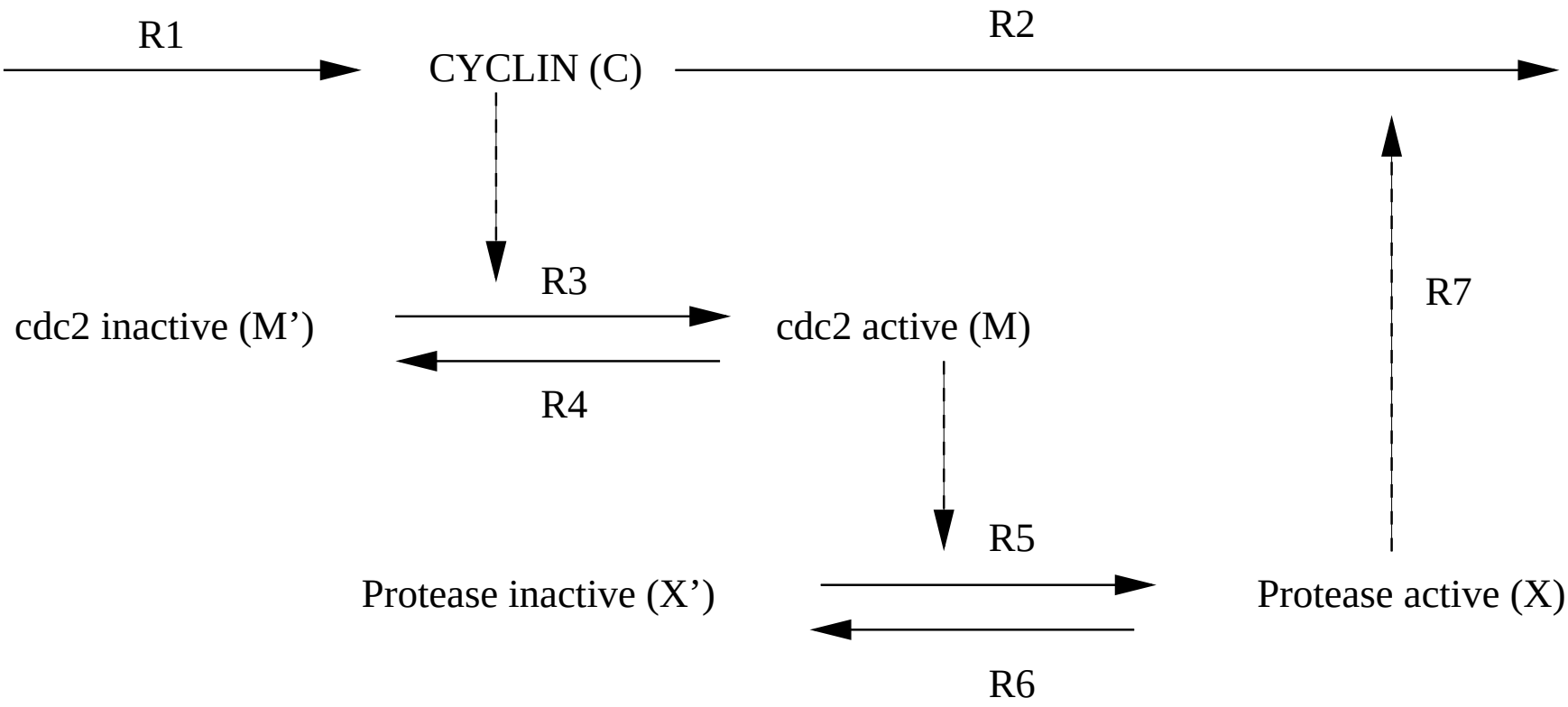
The biological model



The biological model (2)

There are three different biological species involved:

- cyclin, the protein protagonist of the cycle, represented as C;
- cdc2 kinase, in both active and inactive form. The variables used to represent them are M and M', respectively;
- cyclin protease, in both active and inactive form. The variable are X and X'.

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Reactions

id	reaction	react.	prod.	mod.	kinetic laws
α_1	creation of cyclin	-	C	-	v_i
α_2	degradation of cyclin	C	-	-	$kd \times C$
α_3	activation of *cdc*2 kinase	M'	M	C	$\frac{C \times V_{M1}}{(K_c + C)} \frac{M'}{(K_1 + M')}$
α_4	deactivation of *cdc*2 kinase	M	M'	-	$\frac{M \times V_2}{(K_2 + M)}$
α_5	activation of cyclin protease	X'	X	M	$\frac{X' \times M \times V_{M3}}{(K_3 + X')}$
α_6	deactivation of cyclin protease	X	X'	-	$\frac{X \times V_4}{K_4 + X}$
α_7	X triggered degradation of cyclin	C	-	X	$\frac{C \times v_d \times X}{C + K_d}$

α_1, α_2 have mass-action kinetics; others are Michaelis-Menten.

Translation into Bio-PEPA

Definition of the set $\mathcal{N}$:

$$\mathcal{N} = [C : h_C, N_c;\ M : h_M, N_M;\ M' : h_{M'}, N_{M'};\ X : h_X, N_X, ;\ X' : h_{X'}, N_{X'}]$$

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

$$f_{\alpha_1} = fMA(v_i); \qquad f_{\alpha_2} = fMA(k_d);$$
$$f_{\alpha_4} = fMM(V_2, K_2); \qquad f_{\alpha_5} = fMM(V_3, K_3);$$
$$f_{\alpha_6} = fMM(V_4, K_4); \qquad f_{\alpha_7} = fMM(V_d, K_d);$$

$$f_{\alpha_3} = \frac{v_1 \times C}{K_c + C} \frac{M'}{K1 + M'}$$

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The Bio-PEPA model

Definition of species components (*Comp*):

$$
\begin{aligned}
C &\stackrel{def}{=} (\alpha_1, 1)\uparrow C + (\alpha_2, 1)\downarrow C + (\alpha_7, 1)\downarrow C + (\alpha_3, 1) \oplus C \\
M' &\stackrel{def}{=} (\alpha_4, 1)\uparrow M' + (\alpha_3, 1)\downarrow M' \\
M &\stackrel{def}{=} (\alpha_3, 1)\uparrow M + (\alpha_4, 1)\downarrow M + (\alpha_5, 1) \oplus M \\
X' &\stackrel{def}{=} (\alpha_6, 1)\uparrow X' + (\alpha_5, 1)\downarrow X' \\
X &\stackrel{def}{=} (\alpha_5, 1)\uparrow X + (\alpha_6, 1)\downarrow X + (\alpha_7, 1) \oplus X
\end{aligned}
$$

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'})
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ODEs

The stoichiometry matrix D:

	α_1	α_2	α_3	α_4	α_5	α_6	α_7	
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

The vector that contains the kinetic laws is:

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

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M	0	0	$+1$	-1	0	0	0	x_M
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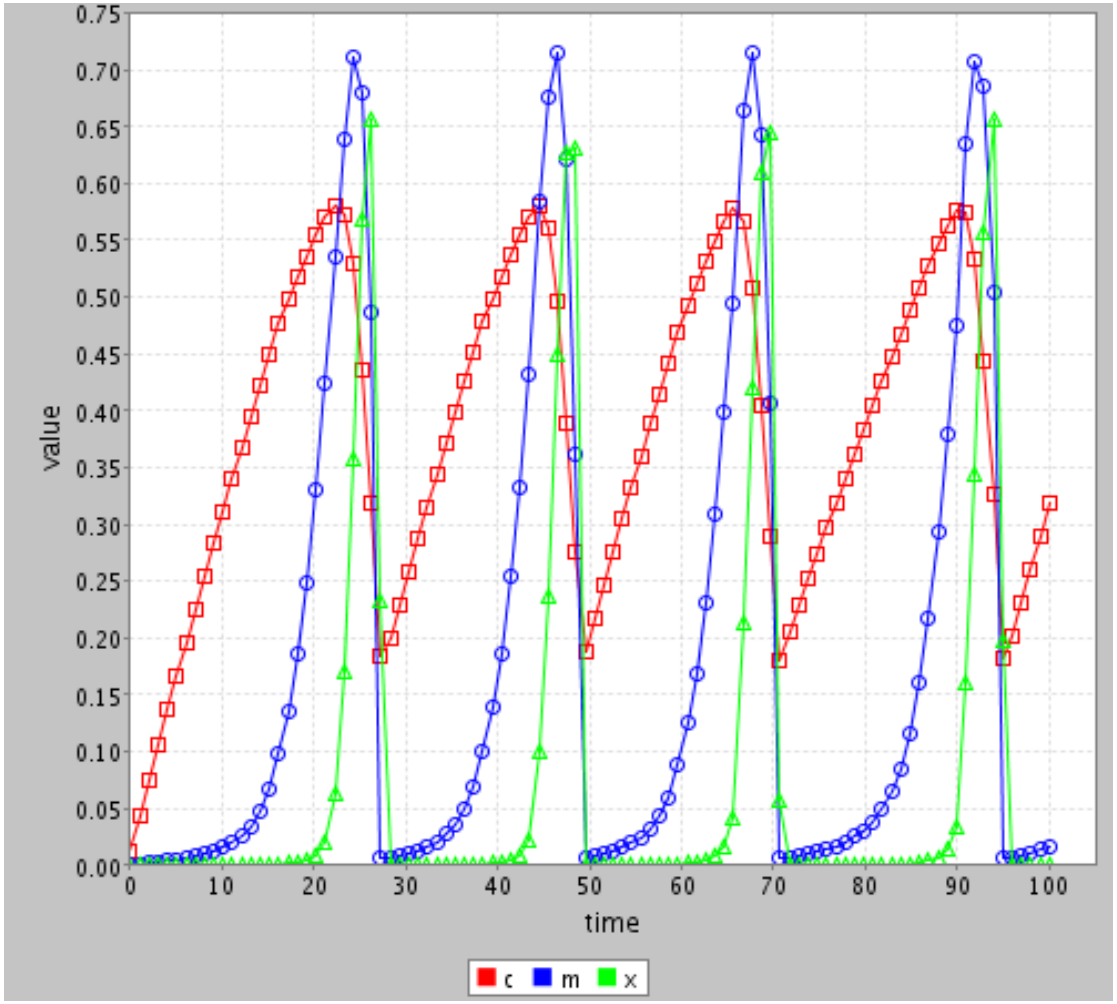
ODEs (2)

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:

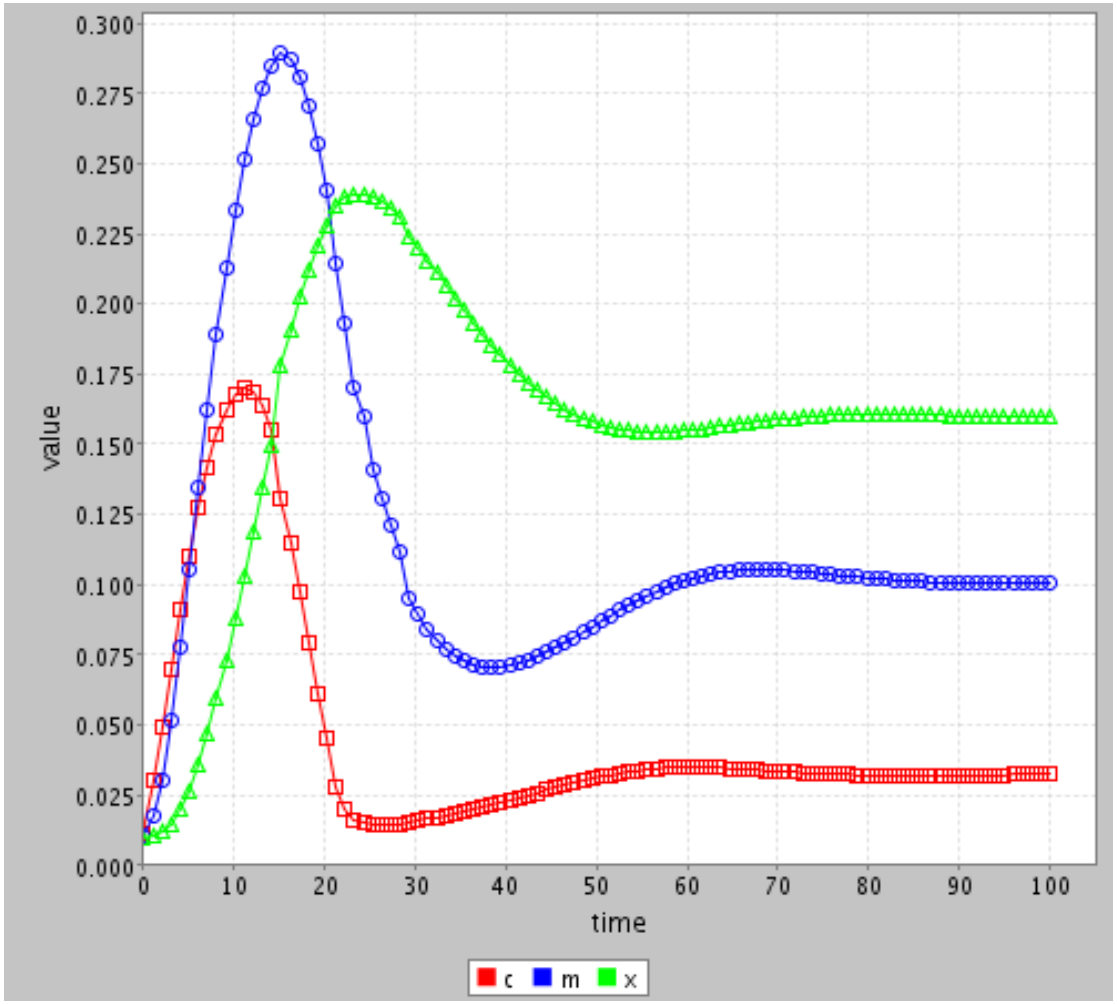
$$
\begin{aligned}
\frac{dx_C}{dt} &= v_i \times 1 - k_d \times x_C - \frac{v_d \times x_C \times x_X}{(K_d + x_C)} \\
\frac{dx_{M'}}{dt} &= -\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} + \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_M}{dt} &= +\frac{V_{M1} \times x_C}{K_c + x_C}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

ODE results



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

ODE results



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

PRISM model

Each species is represented as a PRISM module.

For example, the cyclin is represented as:

module c
$c : [0..Nc]$ **init** 0;
$[a1]c < Nc \rightarrow (c' = c + 1)$;
$[a2]c > 0 \rightarrow (c' = c - 1)$;
$[a3]c > 0 \rightarrow (c' = c)$;
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endmodule

We assume that there are 12 levels of C and 20 levels of the other species. This results in 5733 and 31744 transitions.

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PRISM model (2)

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

module Functional_rates
dummy: bool **init** true;
$[a1]dummy = true \rightarrow r1 : (dummy' = dummy);$
$[a2]dummy = true \rightarrow r2 : (dummy' = dummy);$
$[a3]dummy = true \rightarrow r3 : (dummy' = dummy);$
$[a4]dummy = true \rightarrow r4 : (dummy' = dummy);$
$[a5]dummy = true \rightarrow r5 : (dummy' = dummy);$
$[a6]dummy = true \rightarrow r6 : (dummy' = dummy);$
$[a7]dummy = true \rightarrow r7 : (dummy' = dummy);$
endmodule

PRISM analysis

- **Probability that cyclin is exhausted in the cell.**

$$P =?[trueU[T, T]cyclin = 0]$$

- **Expected number of degradation reactions (both standard and by means of X)**

$$R\alpha_2 =?[C <= T] \quad \text{and} \quad R\alpha_7 =?[C <= T]$$

- **Probability that the level of active kinase (M) is greater than the level of inactive kinase (M') at time T**

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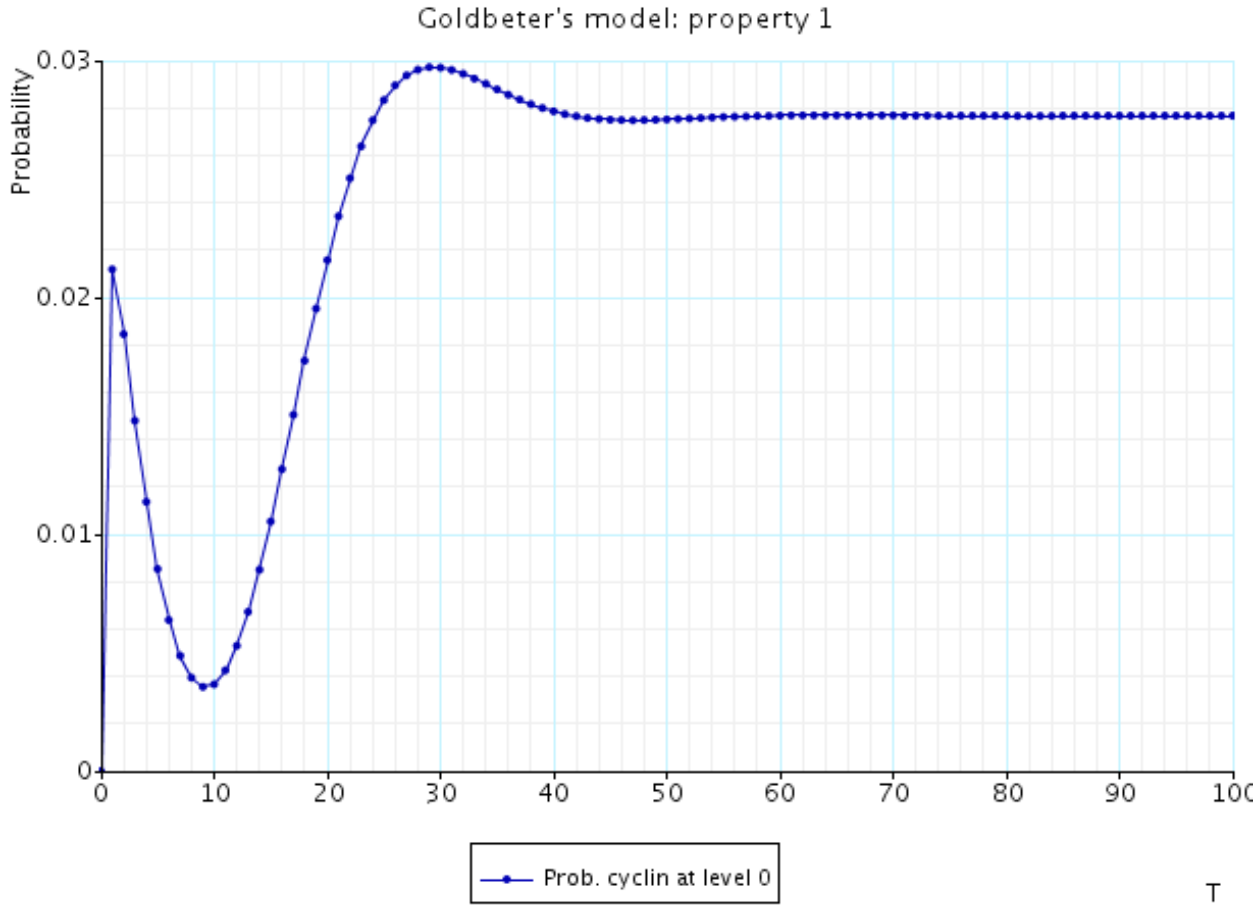

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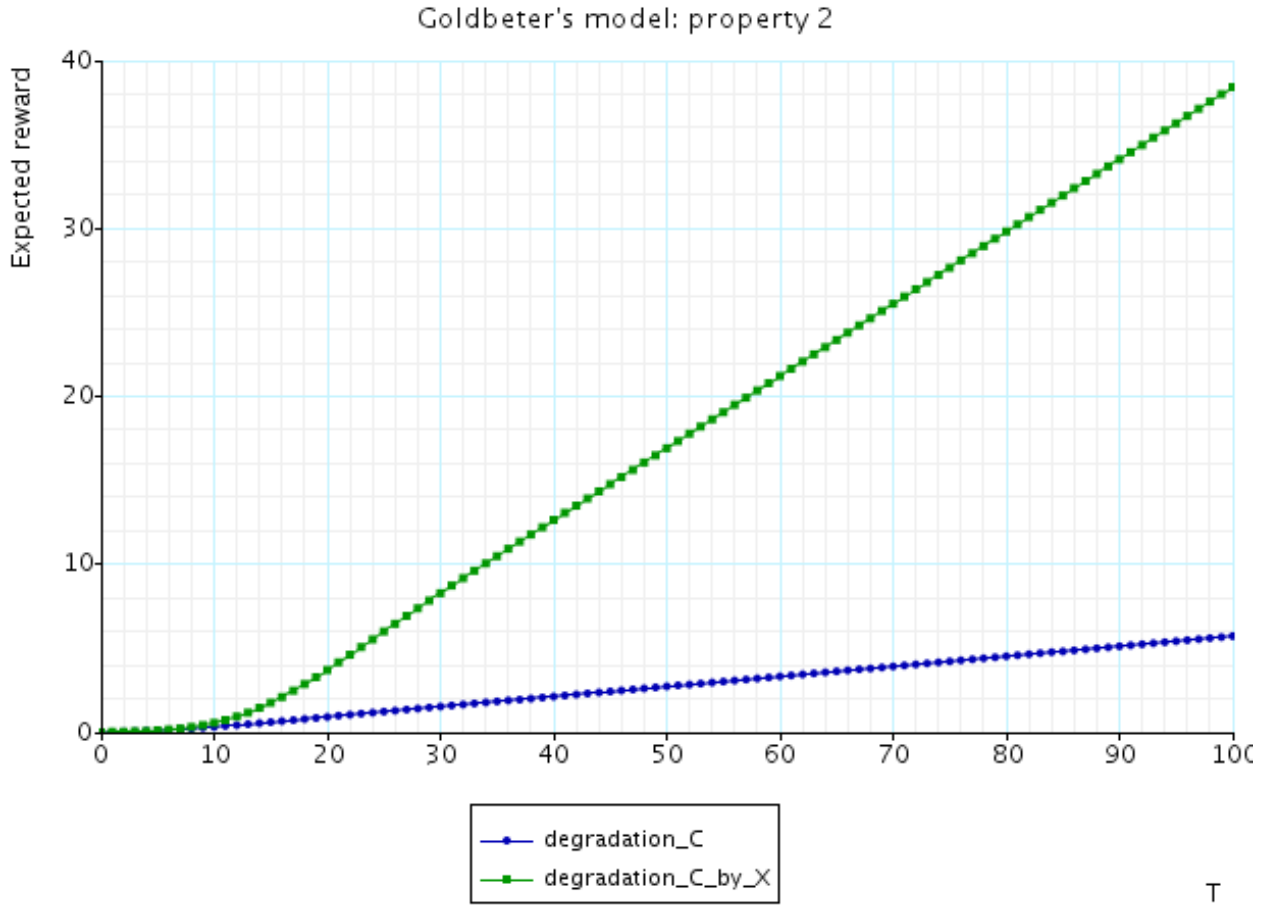
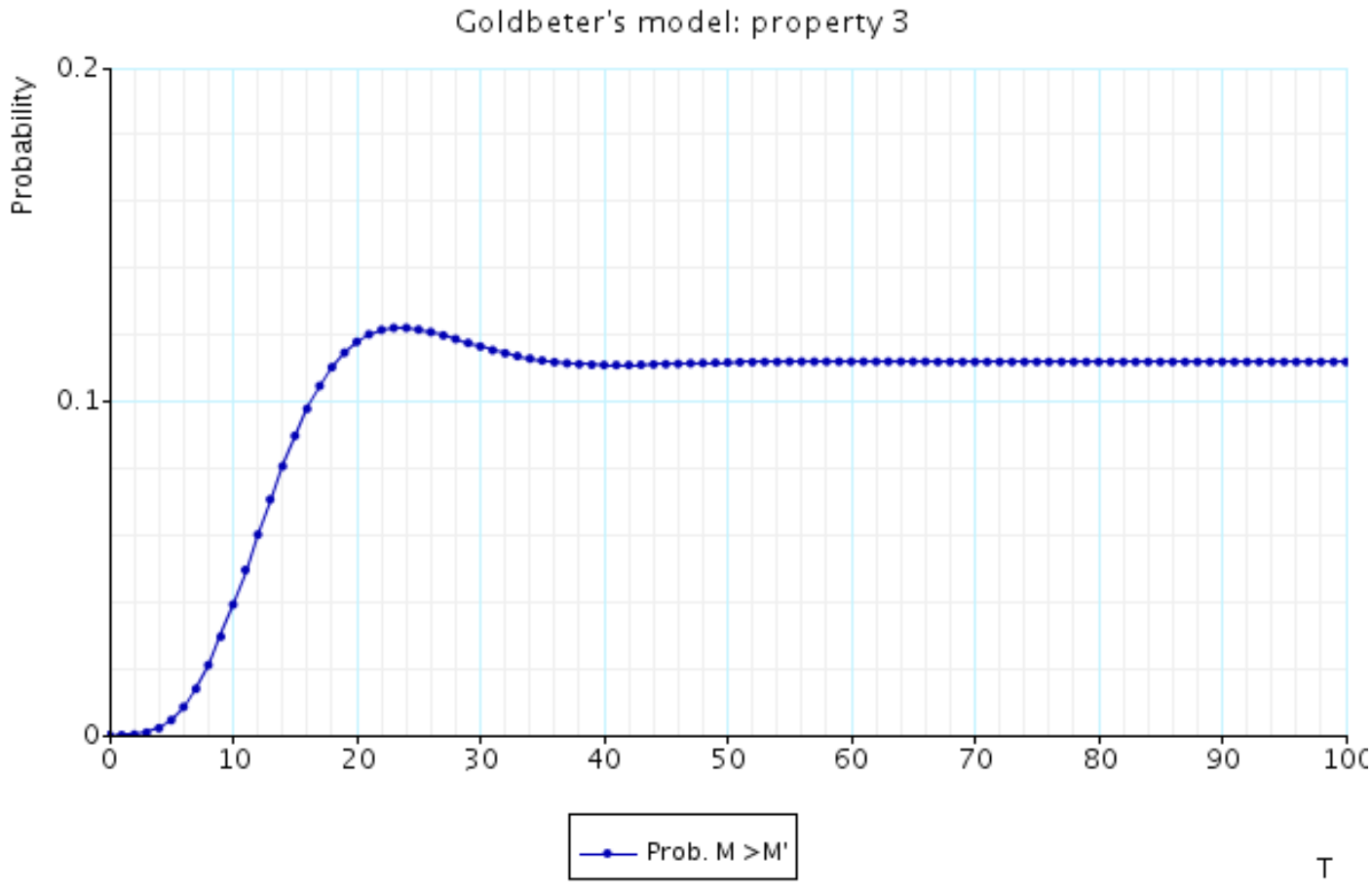


$R\alpha_2 =?[C <= T]$ and $R\alpha_7 =?[C <= T]$

PRISM results



$$P =?[trueU[T, T]M > M']$$

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