Inductive Process Modeling for Learning the Dynamics of Biological Systems

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Inductive Process Modeling for Systems Biosciences

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Systems Sciences: What do they study?

Systems sciences

study complex systems in nature and society

- Behavior/Dynamics: State of system changes
- Structure: Components & interconnections
- Environment: Inputs & outputs
- The system is more than the sum of its parts

Systems biosciences: Study biological systems

- Systems ecology (macro-scale; populations)
- Systems biology (micro- to meso-scale; molecular to organismal)

Systems Sciences: How do they do it?

A key concept/tool in systems sciences:

Model of the system:
Simplified (formal) representation of the system

The use of models

Understanding the system studied

- Structure (components, connections)
- Behavior

Predicting the behavior of the system

Achieving desired behavior

Systems Sciences: The tasks

The central task in systems sciences:

Modeling: Constructing a model of the studied system, in a given formalism, including structure and parameters

Typically done manually by an expert or a team thereof

Related tasks in systems sciences:

Analysis: Given model; examine possible behaviors

How model parameters/structure influence behavior

Identification: Given observed behavior; generate model

Control: Given model, desired outputs; generate inputs

Design: Given desired behavior, generate model

The diversity of Systems Sciences: System representation and modeling formalisms

The model of a system describes how the **system state changes/evolves** over some **context**

Context space: **time**/space/space-time (discr./cont.)

State space: System variables (discrete vs. **continuous**)

Evolution rules:

- **Deterministic** (one possible evolution in time, approximates avg. behavior of system)
- Stochastic (closer correspondence with nature, e.g. discrete/small number of molecules and stoch. react.))

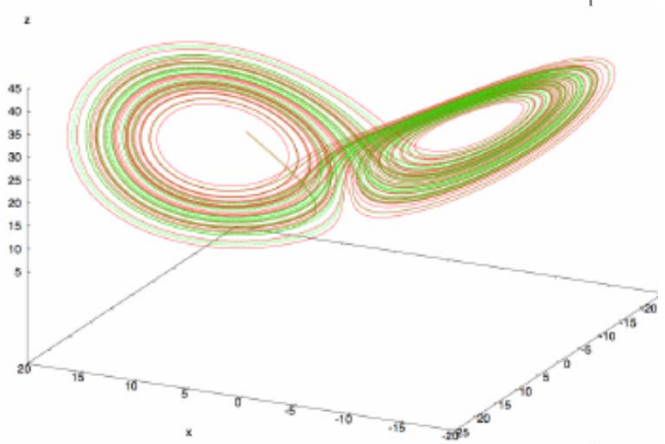
The prototypical case: **systems of ODEs**

Two Models of Dynamic Systems: An abstract and a real-world example

- The Lorenz system: Atmospheric convection

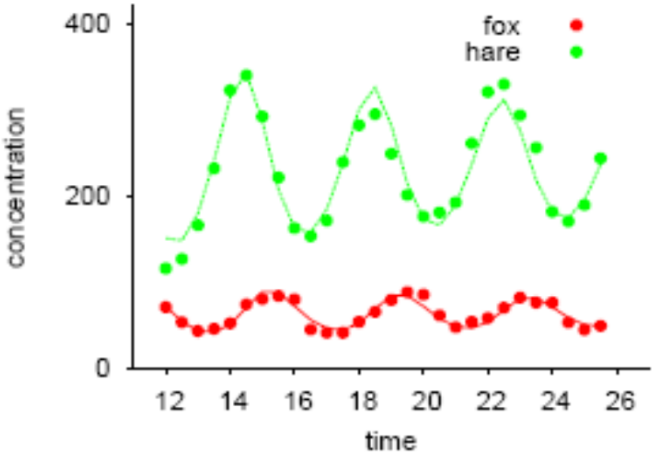
$$\frac{dx}{dt} = \sigma(y - x)$$
$$\frac{dy}{dt} = x(\rho - z) - y$$
$$\frac{dz}{dt} = xy - \beta z$$

σ	ρ	β
10	28	8/3



- Lotka-Volterra: Predator-prey interaction in ecology

$$\frac{d}{dt} hare = 2.5 \cdot hare - 0.3 \cdot hare \cdot fox$$
$$\frac{d}{dt} fox = 0.1 \cdot 0.3 \cdot hare \cdot fox - 1.2 \cdot fox$$



Systems Sciences: The challenge

Complexity of systems studied **increases**

The **models** that are used in systems sciences are mostly **constructed manually**

Manual modeling is a knowledge-intensive, time-consuming (and thus **expensive**) task

This represents a **bottleneck** in the further development of systems sciences

The Knowledge-Driven Modeling Paradigm

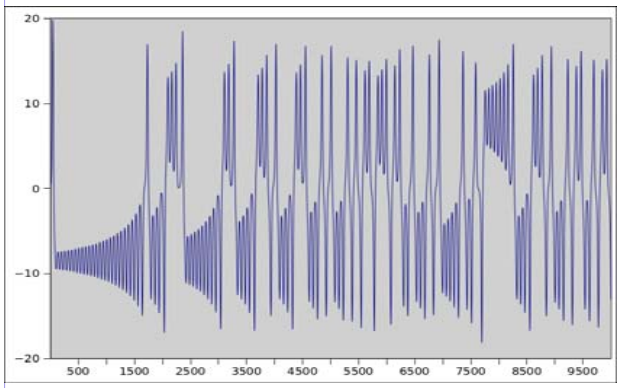
In knowledge-driven (theoretical) modeling:

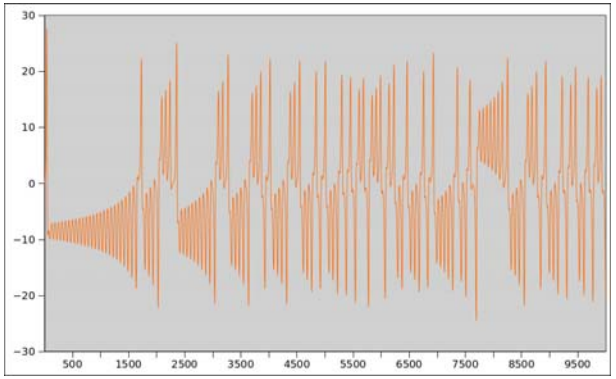
1. Expert derives a proper model (structure)
   - Based on domain-specific knowledge and
   - Knowledge of modeling formalism

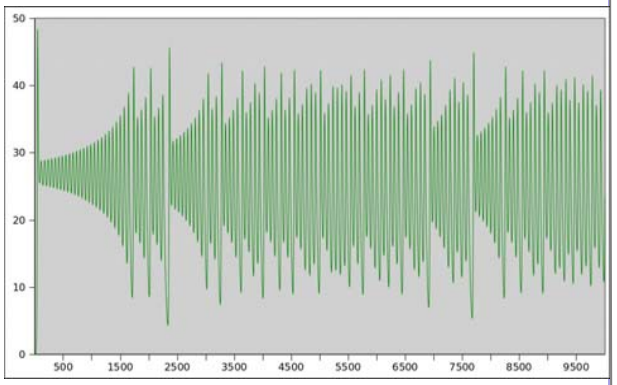
2. Typically, both the structure and parameters of the models are derived by the expert from
   - Knowledge about processes (e.g., bear reproduction)
   - Knowledge about process rates/parameters (e.g., birth rates = average number of cubs/litter)

Data-Driven Modeling: An Example

- Input: Observed behavior of dynamic system







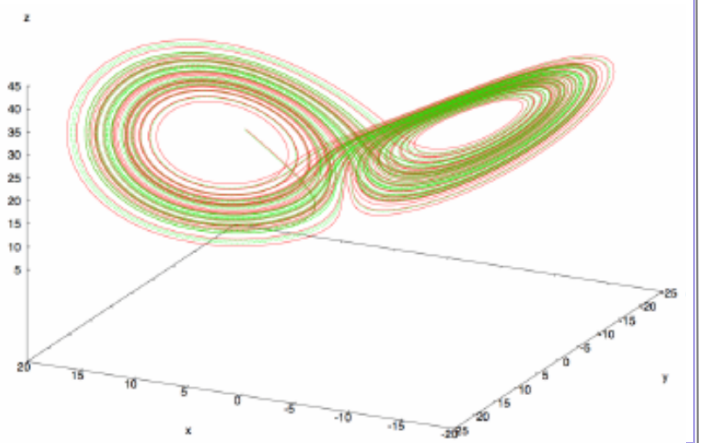
- Output: Set of ordinary differential equations(ODEs)

$$\frac{dx}{dt} = \sigma(y - x)$$

$$\frac{dy}{dt} = x(\rho - z) - y$$

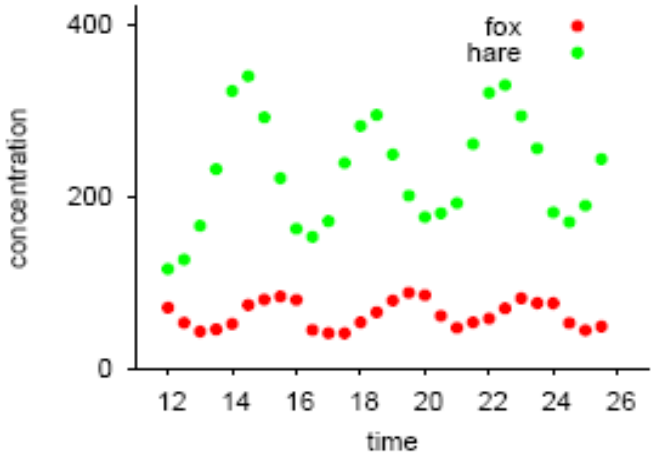
$$\frac{dz}{dt} = xy - \beta z$$

σ	ρ	β
10	28	8/3



Learning Models of Dynamic Systems: A Real-world Example from Ecology

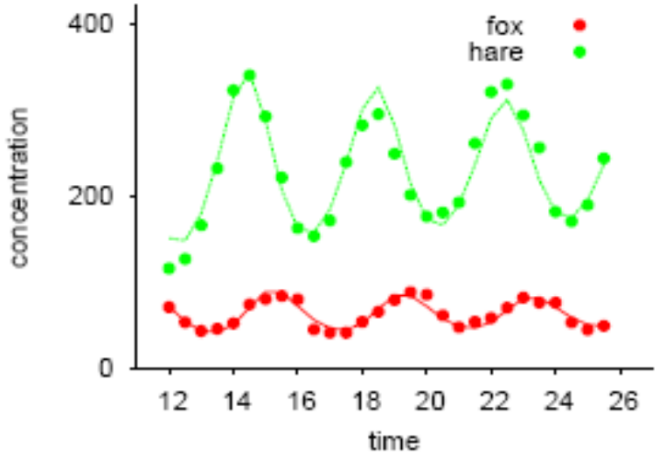
- Input: Observed behavior of dynamic system



- Output: Set of ordinary differential equations(ODEs)

$$\frac{d}{dt} hare = 2.5 \cdot hare - 0.3 \cdot hare \cdot fox$$

$$\frac{d}{dt} fox = 0.1 \cdot 0.3 \cdot hare \cdot fox - 1.2 \cdot fox$$



Learning Models of Dynamic Systems: The task

- Given example behavior(s) of a dynamic system
  - Measurements of system variables
  - Over the course of time

Time	System variables			
	v_1	v_2	$\ldots$	v_n
t_0	$v_{1,0}$	$v_{2,0}$	$\ldots$	$v_{n,0}$
t_1	$v_{1,1}$	$v_{2,1}$	$\ldots$	$v_{n,1}$
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
t_m	$v_{1,m}$	$v_{2,m}$	$\ldots$	$v_{n,m}$

- Find a set of ODEs (structure and parameters)
- That describe the dynamics of the system (fit the observed behavior(s))

The Data-Driven Modeling Paradigm

In data-driven (empirical) modeling:

1. (Many) Different model structures (from a given class) are considered in a trial& error fashion

2. A model = structure + parameter values that fits the data best is returned

System identification typically

- Fixes the models structure, finds the parameters (parameter identification)
- Considers linear model structures

Data-Driven or Knowledge-Driven Modeling?

In knowledge-driven (theoretical) modeling:

- A lot of domain knowledge is needed, but
- Little (if any) data are needed and
- The result is an understandable model that makes sense from the domain point of view

In data-driven (empirical) modeling:

- A lot of data of good quality are needed, but
- Little (if any) domain knowledge is needed
- However, the result is most often a model that makes no sense from the domain point of view (or is even not understandable)

Data-and-Knowledge-Driven Modeling!

- We would like to have the best of both worlds and integrate knowledge- and data-driven modeling
- We would like to flexibly trade-off between data and domain knowledge and handle
  - Lots of knowledge and little data or
  - Lots of data and little knowledge, as the case may be
- We would like to have models that fit the data well
- But are also understandable and make sense from the domain point of view

Data-and-Knowledge-Driven Modeling!

To integrate knowledge-driven and data-driven modeling, we will need

- A formalism for representing models and domain knowledge
  - The formalism has to be powerful and allow precise modeling and simulation of dynamic system
  - It has to be understandable
- Methods for learning models from domain knowledge and data
  - That will take data and domain knowledge as input
  - Will produce accurate models in the formalism, and fast

Knowledge Representation: Dynamic Systems

Dynamic systems consist of

- **Entities** and
- **Processes**

These are very general notions and key concepts in ontological representations of the world

E.g., the Basic Formal Ontology is a framework that consists of a number of ontologies that describe

- **Continuants**, i.e., entities
- **Occurents**, i.e., processes

Our formalism: Process-Based Models

Process-based models have two major components

- **Entities** and
- **Processes**

Entities participate in **processes**

Each process-based model, consisting of completely specified processes, corresponds to a system of ODEs

The Es and Ps specify the qualitative aspect of the model

The ODEs specify the quantitative aspect of the model

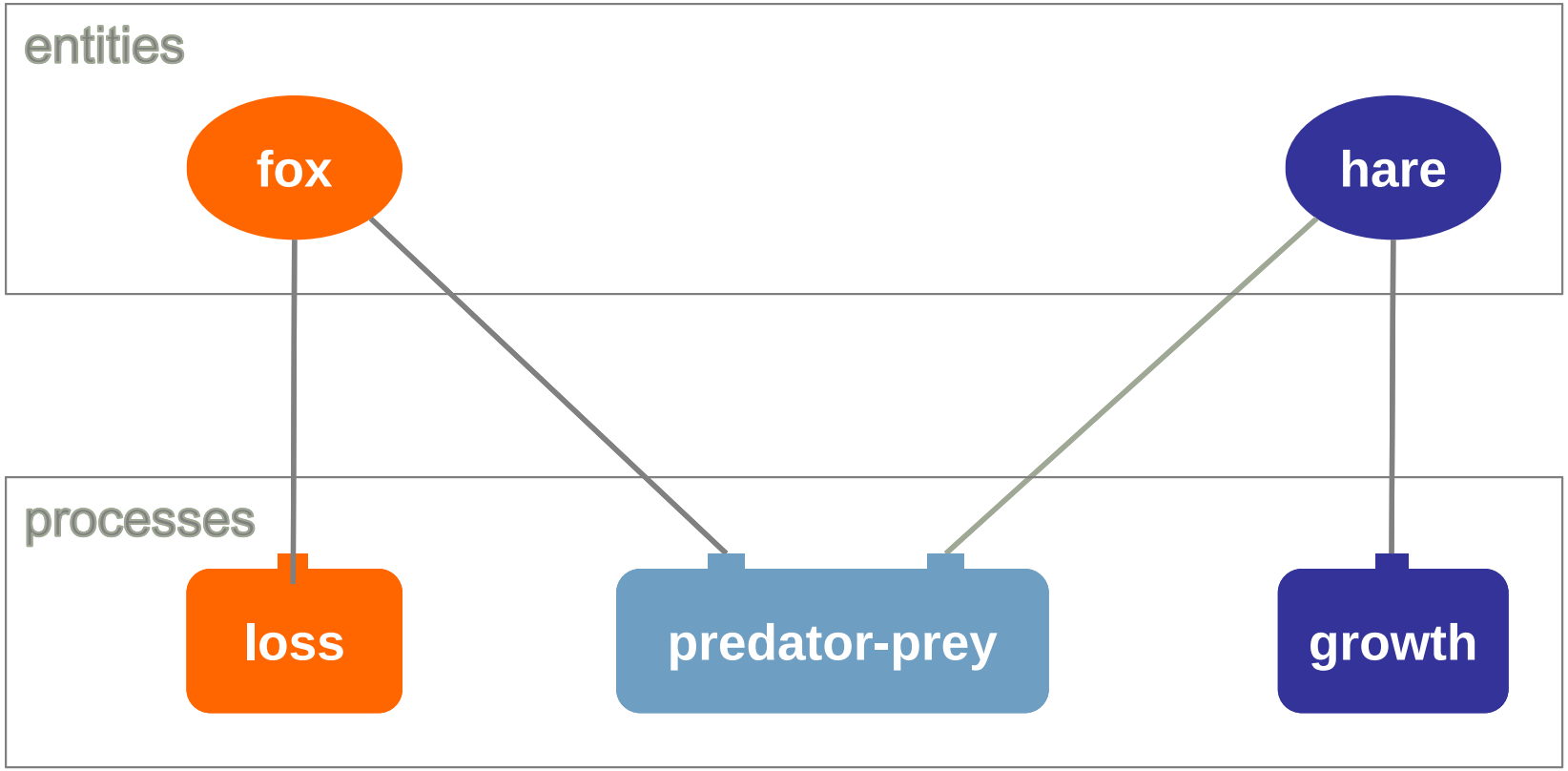
Process-based Models (PBM)

- Integrate two aspects of equation-based models
  - Quantitative aspect: ODEs with given structure and parameter values that allow simulation

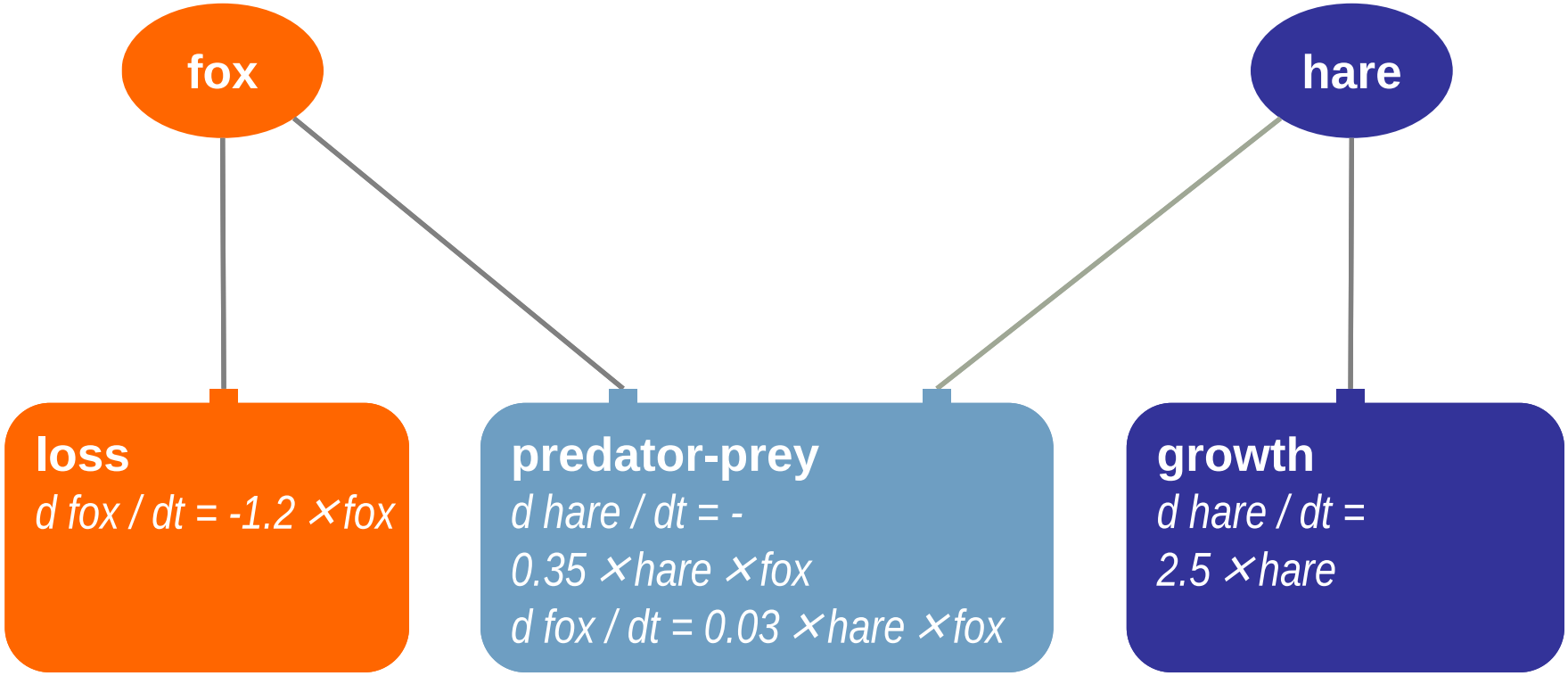
$$\frac{d}{dt} hare = 2.5 \cdot hare - 0.3 \cdot hare \cdot fox$$
$$\frac{d}{dt} fox = 0.1 \cdot 0.3 \cdot hare \cdot fox - 1.2 \cdot fox$$

  - Qualitative aspect: explanation of the structure of the modeled systems in terms of entities and processes
- In equations: Variables correspond to **entities**, terms correspond to **processes**
  - Exponential growth of hare population
  - Exponential loss of fox population
  - Predator-prey interaction between the two species

PBM: Qualitative Aspect



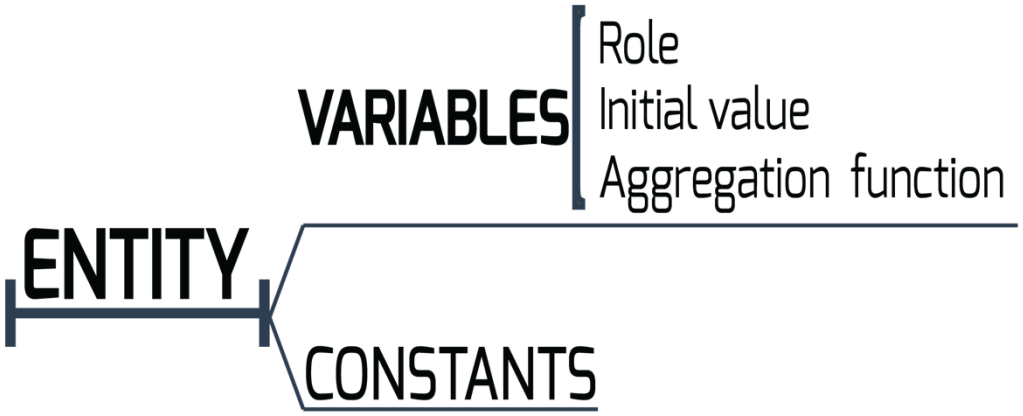
PBM: Quantitative Aspect



Entities in Process-Based Models

Entities (e.g., person) have as properties **constants** (e.g., gender) and **variables** (e.g., weight or height)

The latter have an *initial value* that changes over time



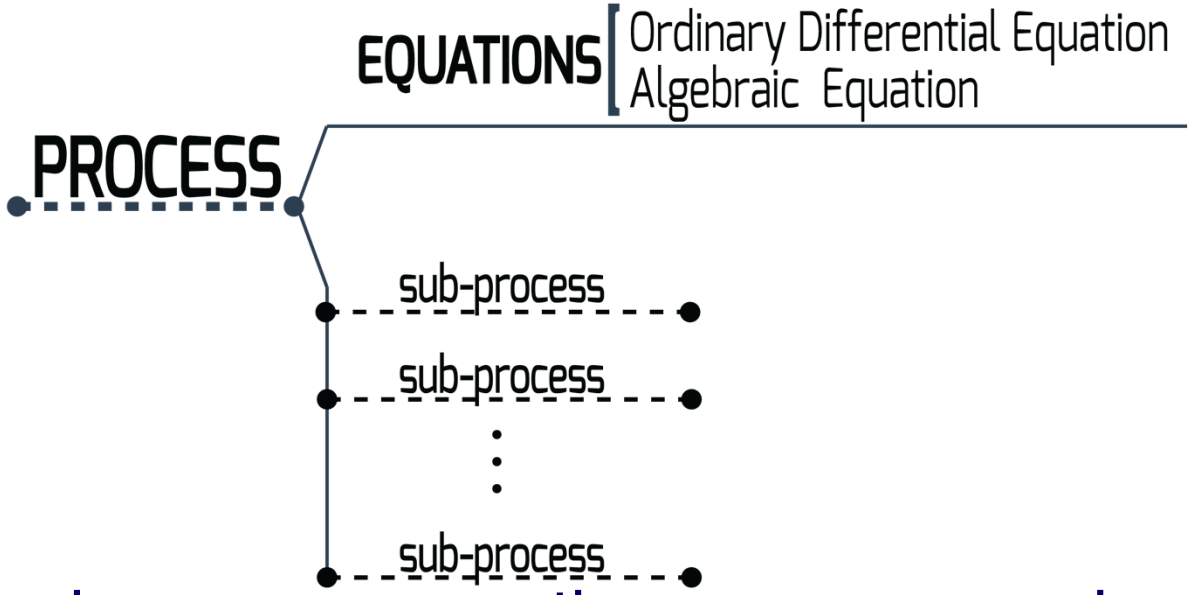
The variables appear in (OD) equations: Their *role* determines whether they are endogenous (system) vars. or exogenous (input) variables

Entities participate in processes and are influenced by them. *Agg. Function* = How influences are combined

Processes in Process-Based Models

Processes have entities as participants, which they influence

Besides participants, **processes** have equations, which specify their kinetic rates, and **sub-processes**



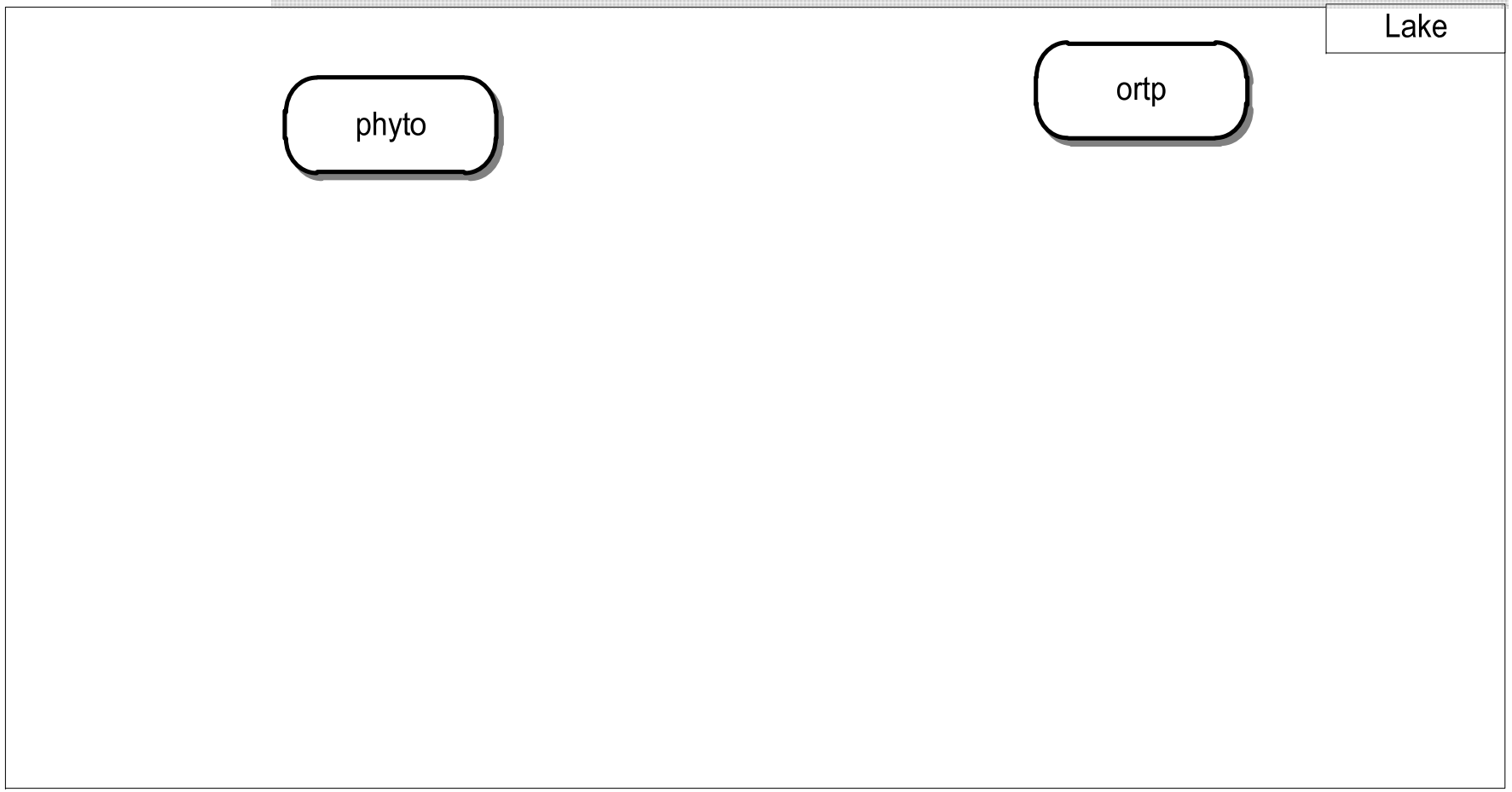
Each process contributes a term to the (OD) equations for the variables of each participating entity

Process-based models

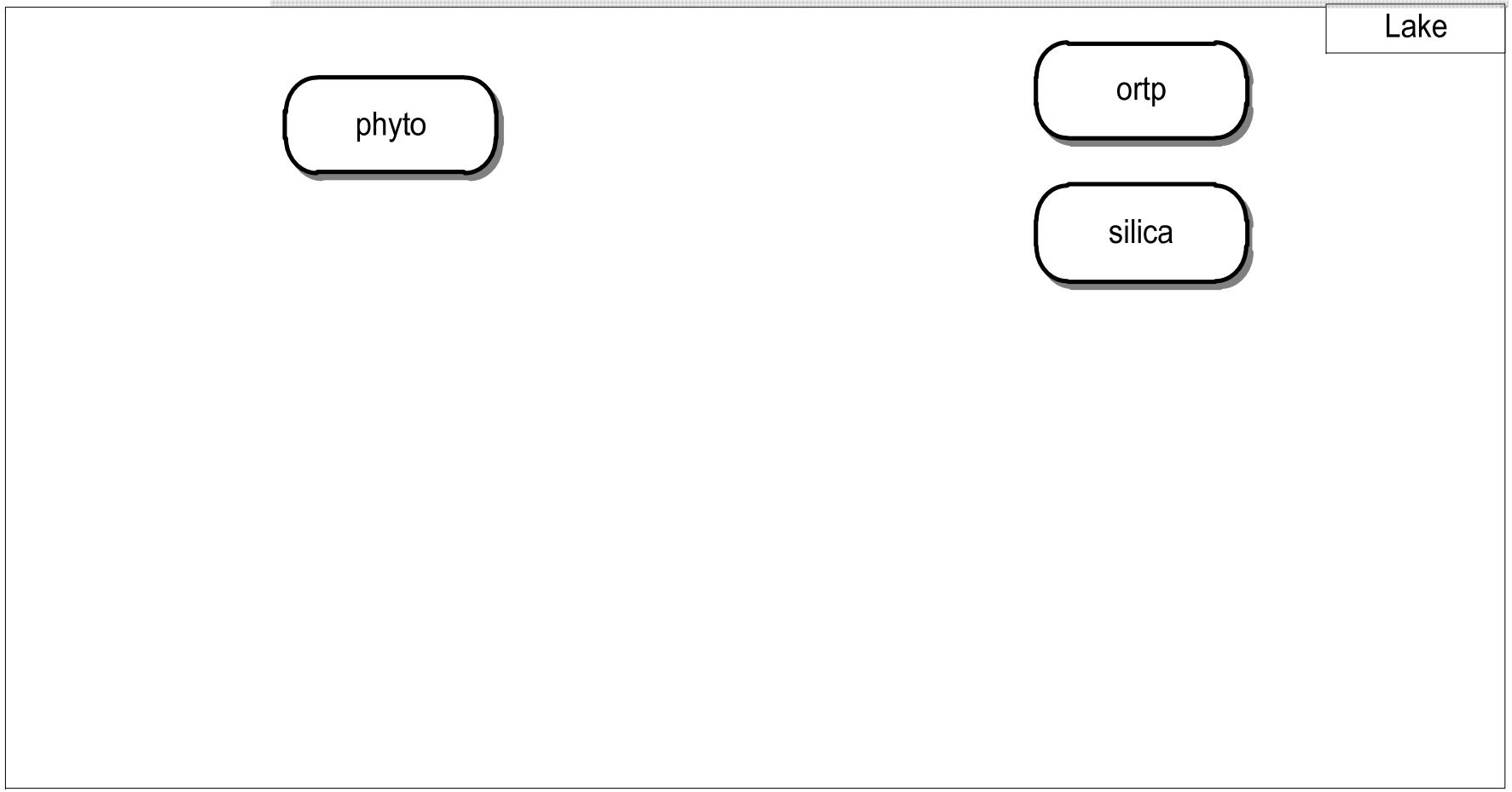
Lake

Process-based models

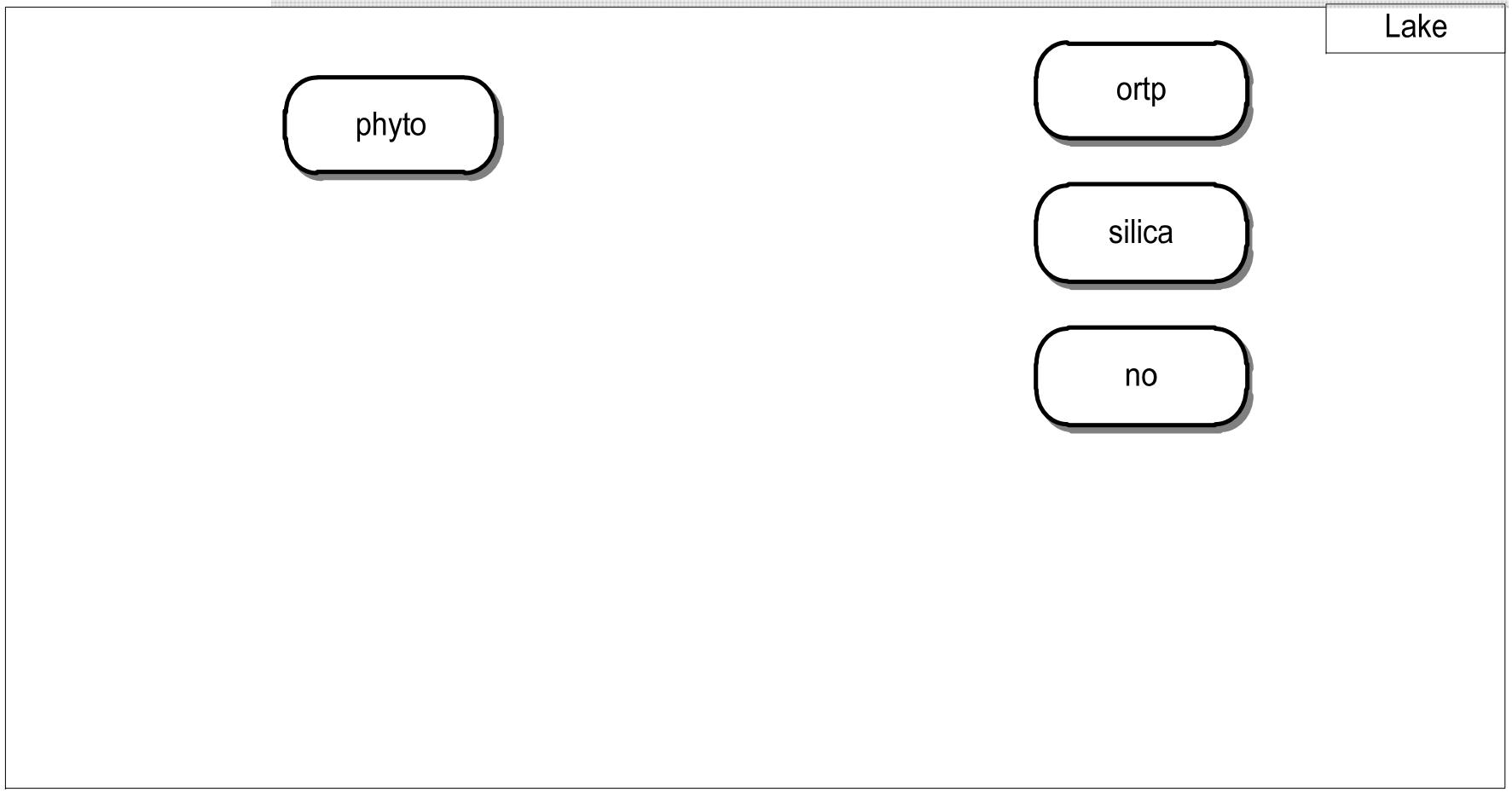
Process-based models



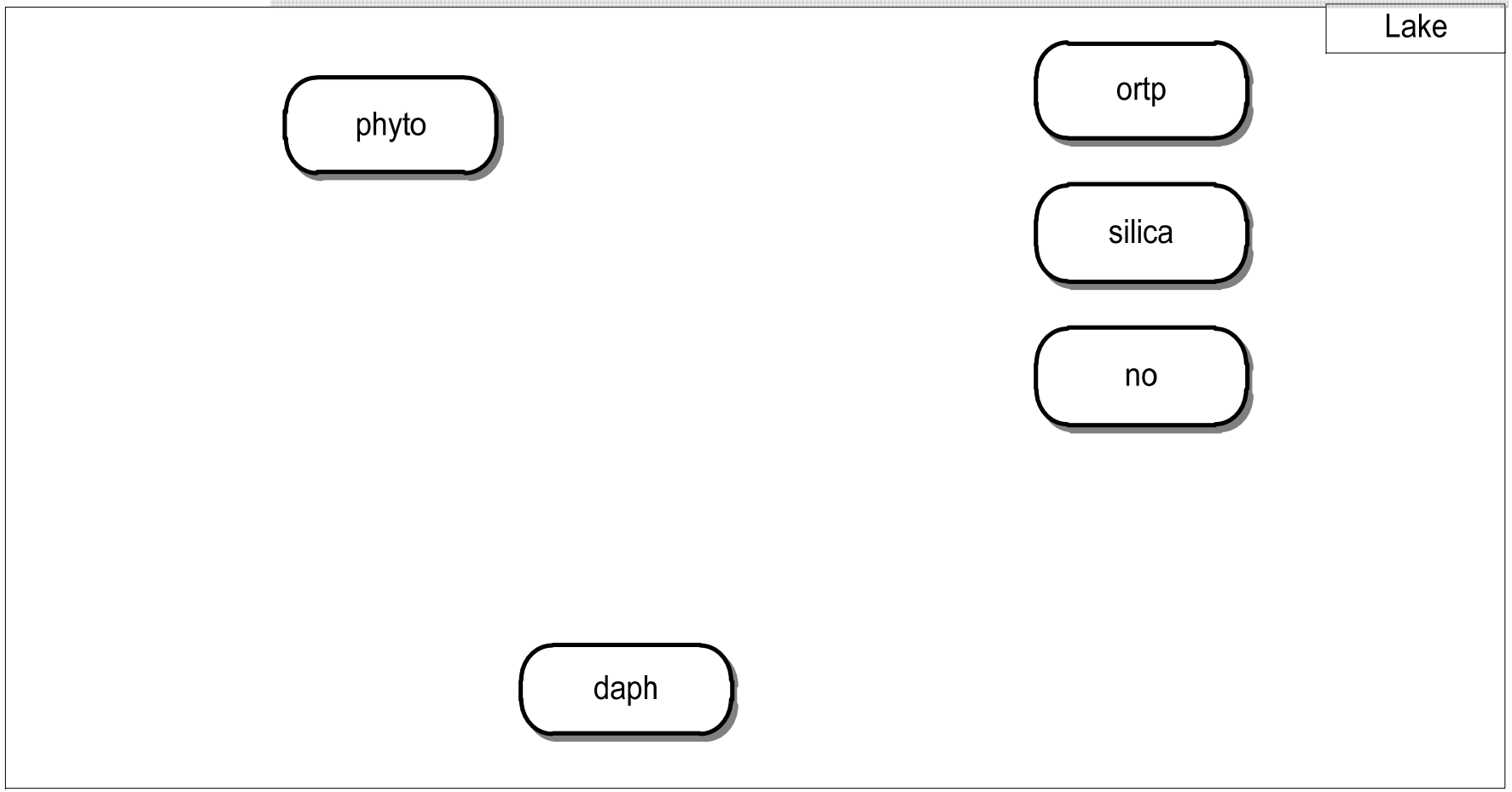
Process-based models



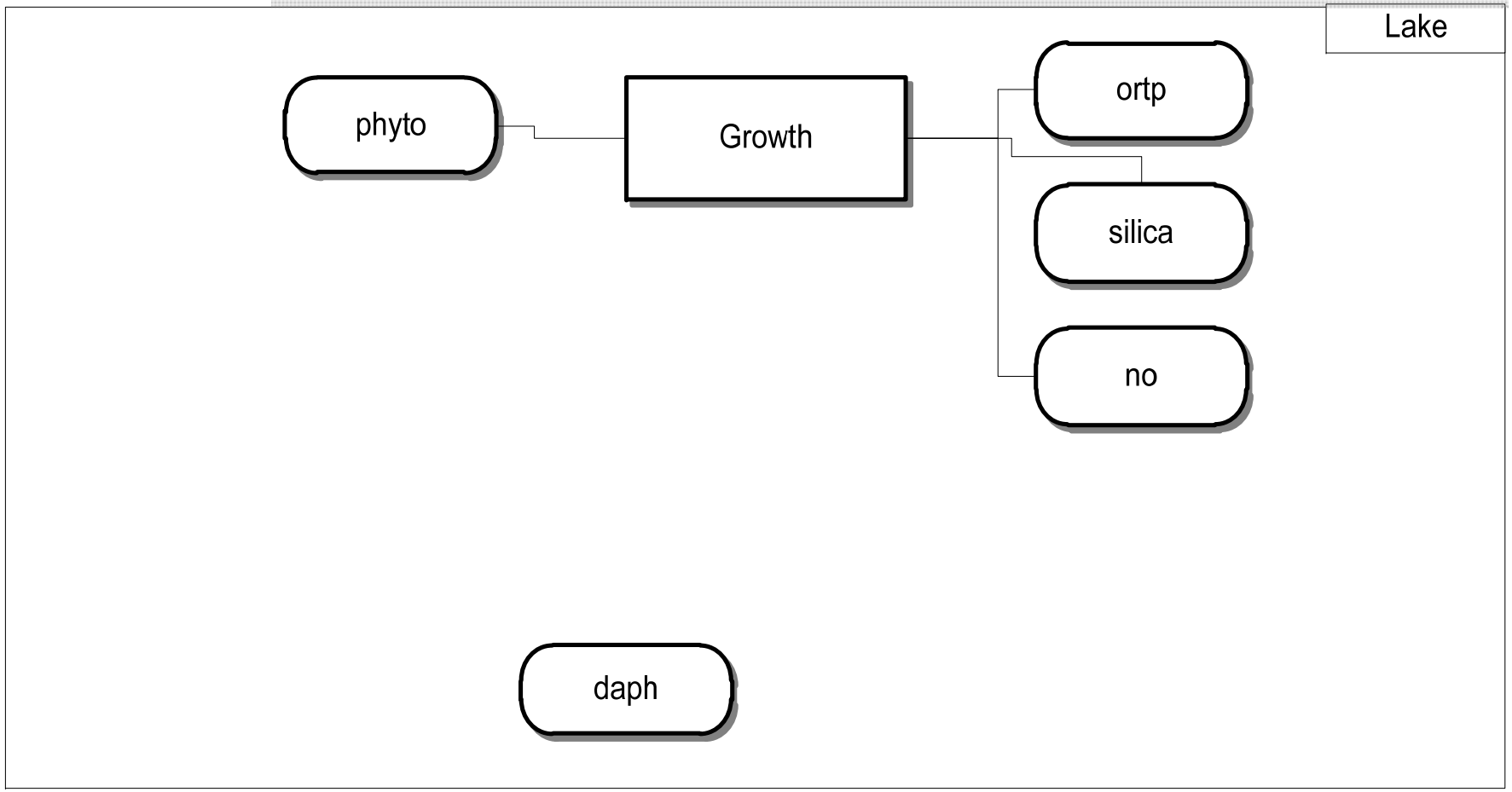
Process-based models



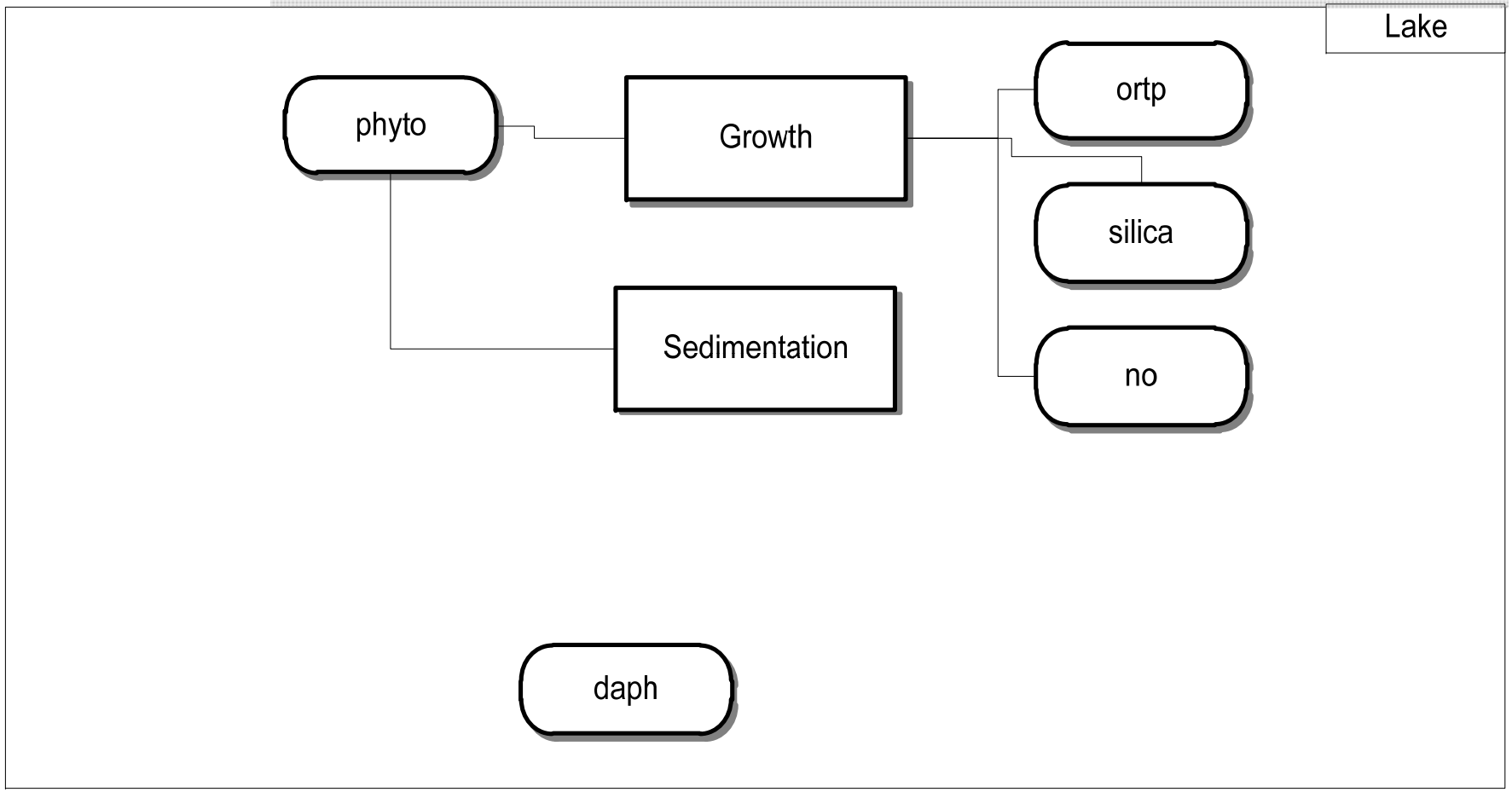
Process-based models



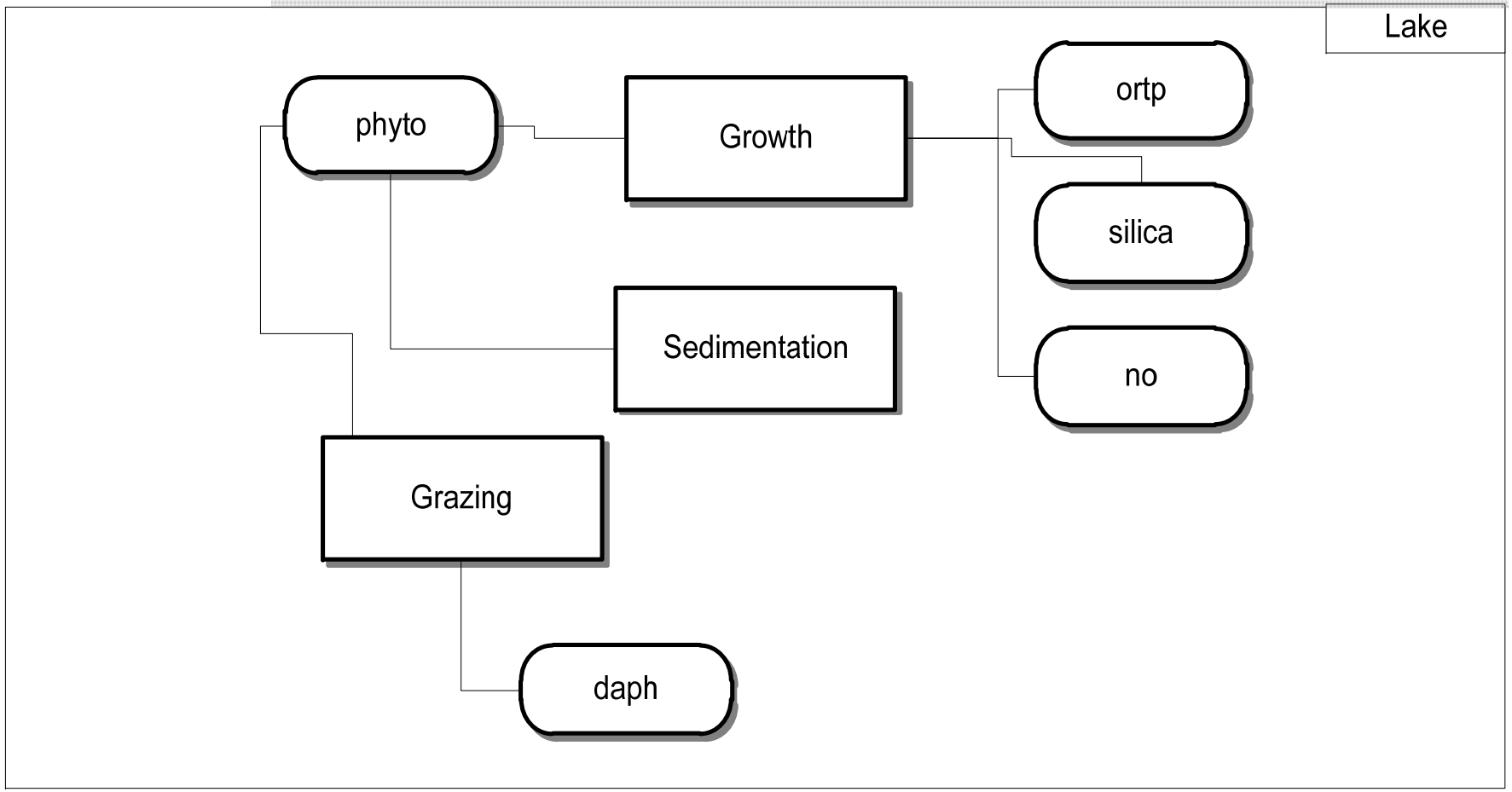
Process-based models



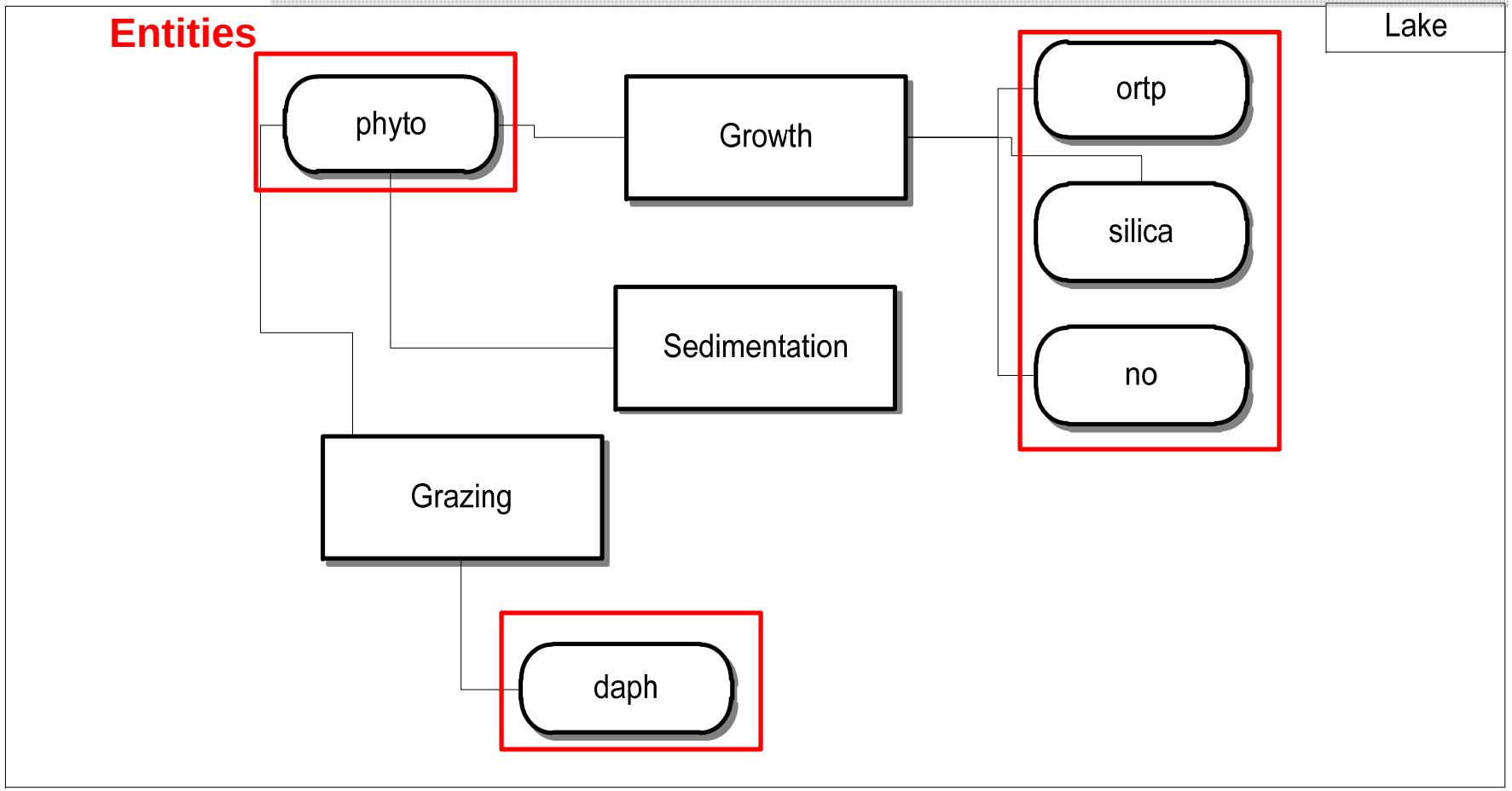
Process-based models



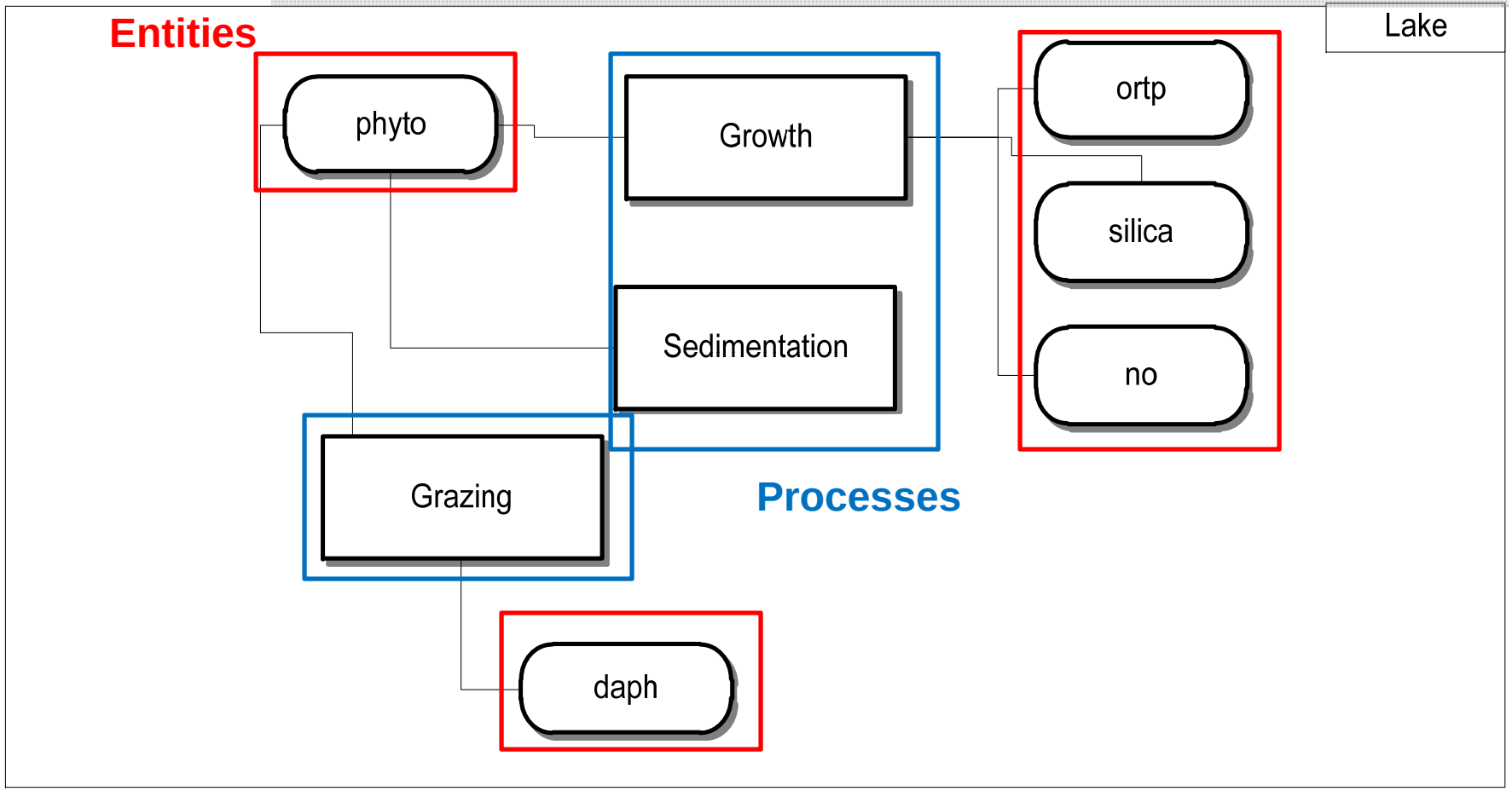
Process-based models



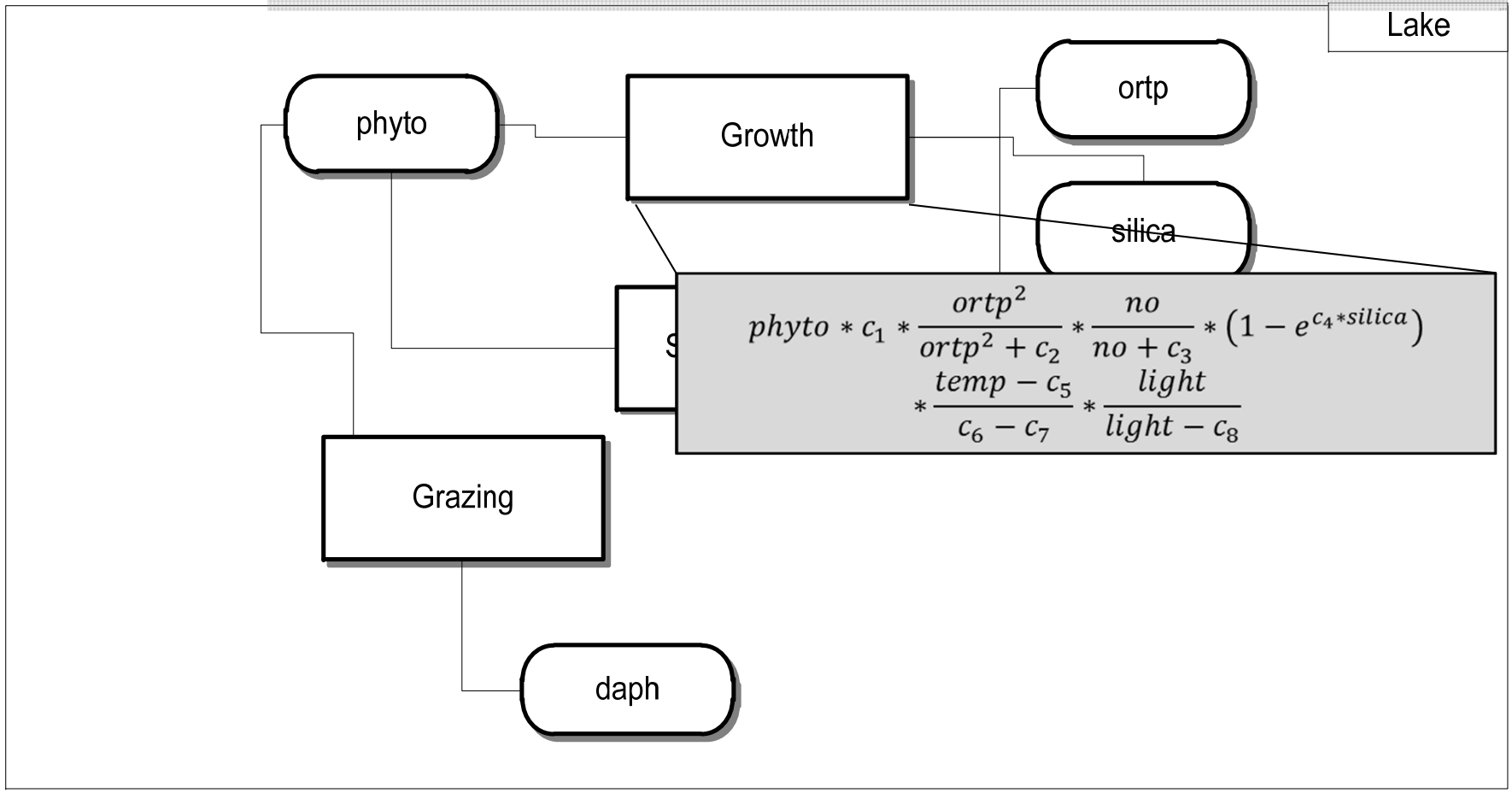
Process-based models



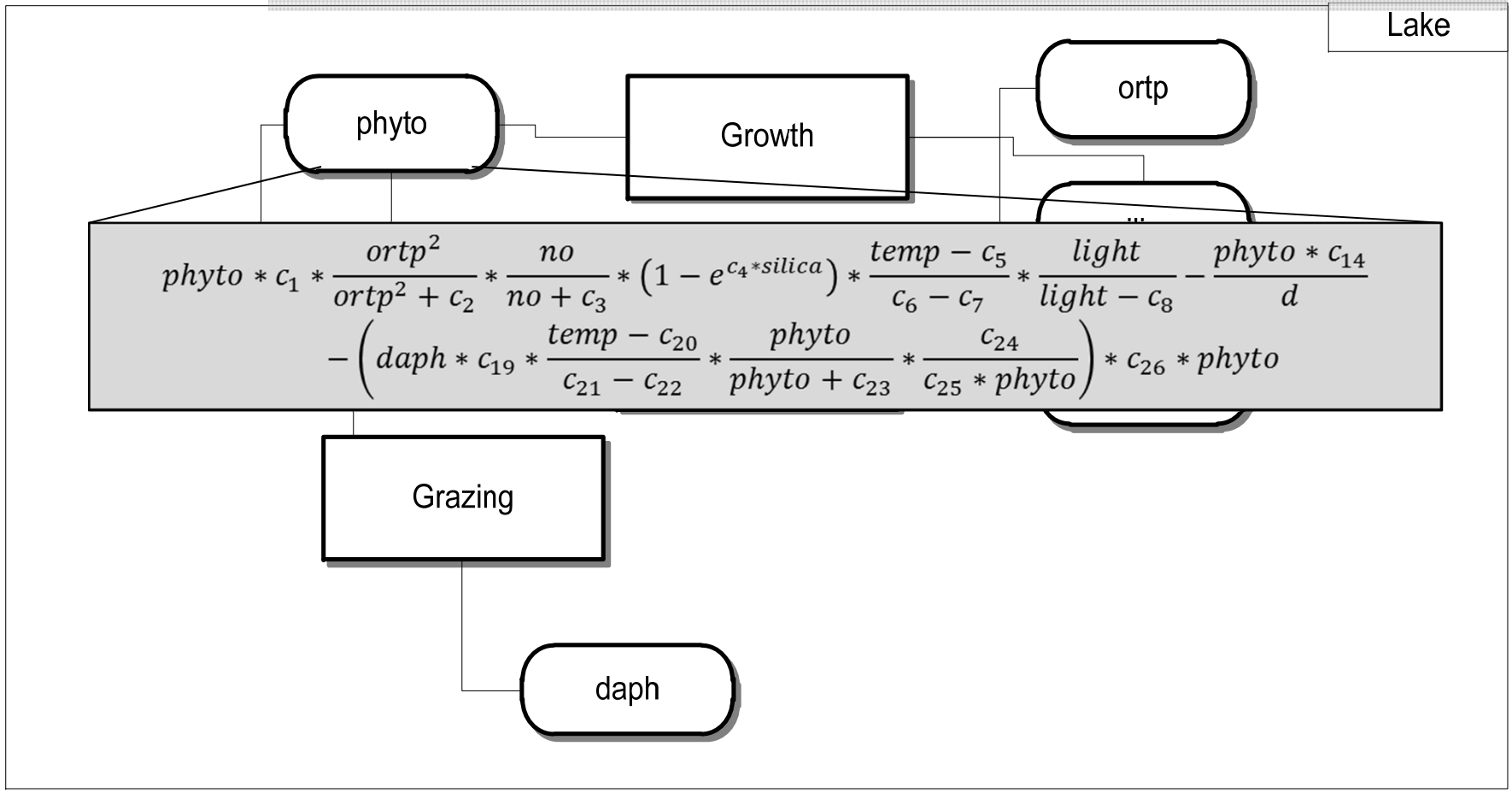
Process-based models



Process-based models



Process-based models



The Syntax of Process-Based Models: Entities

- Three entities in an aquatic ecosystem

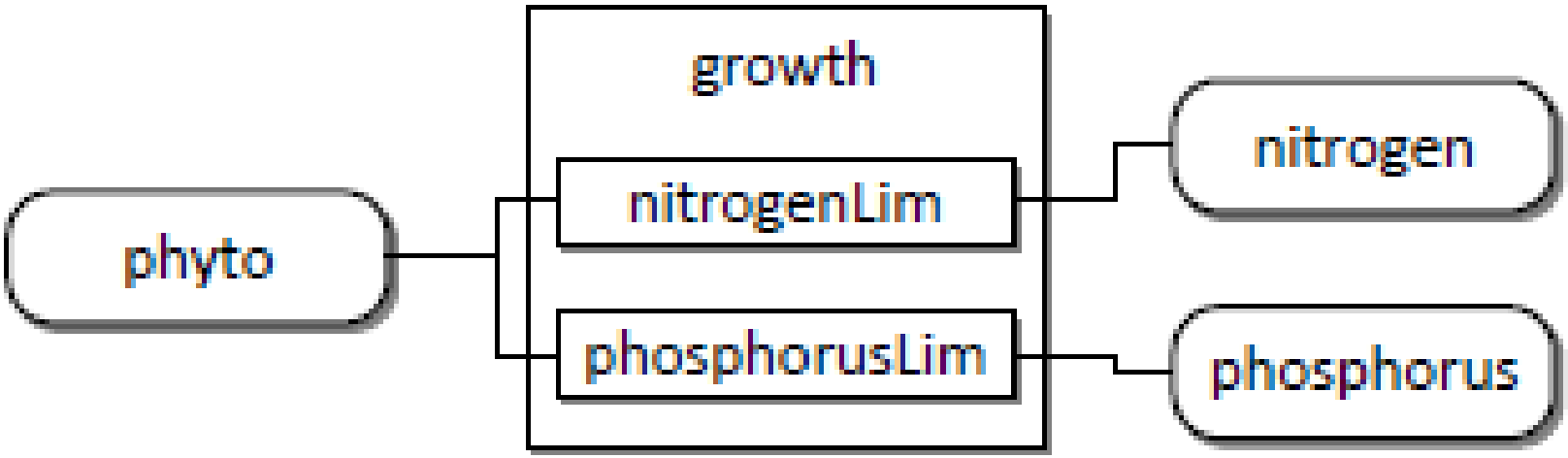
```
entity phyto {
    vars:
        conc{role: endogenous; aggregation: sum; initial: 10},
        nutrientLim{aggregation: product};
    consts:
        maxGrowthRate = 0.5,
}
entity phosphorus {
    vars:
        conc{role: endogenous; initial: 3};
    consts:
        halfSaturation = 0.02,
        alpha = 0.1;
}
entity nitrogen {
    vars:
        conc{role: exogenous};
    consts:
        halfSaturation = 0.2,
        alpha = 0.7;
}
```

The Syntax of Process-Based Models: Processes

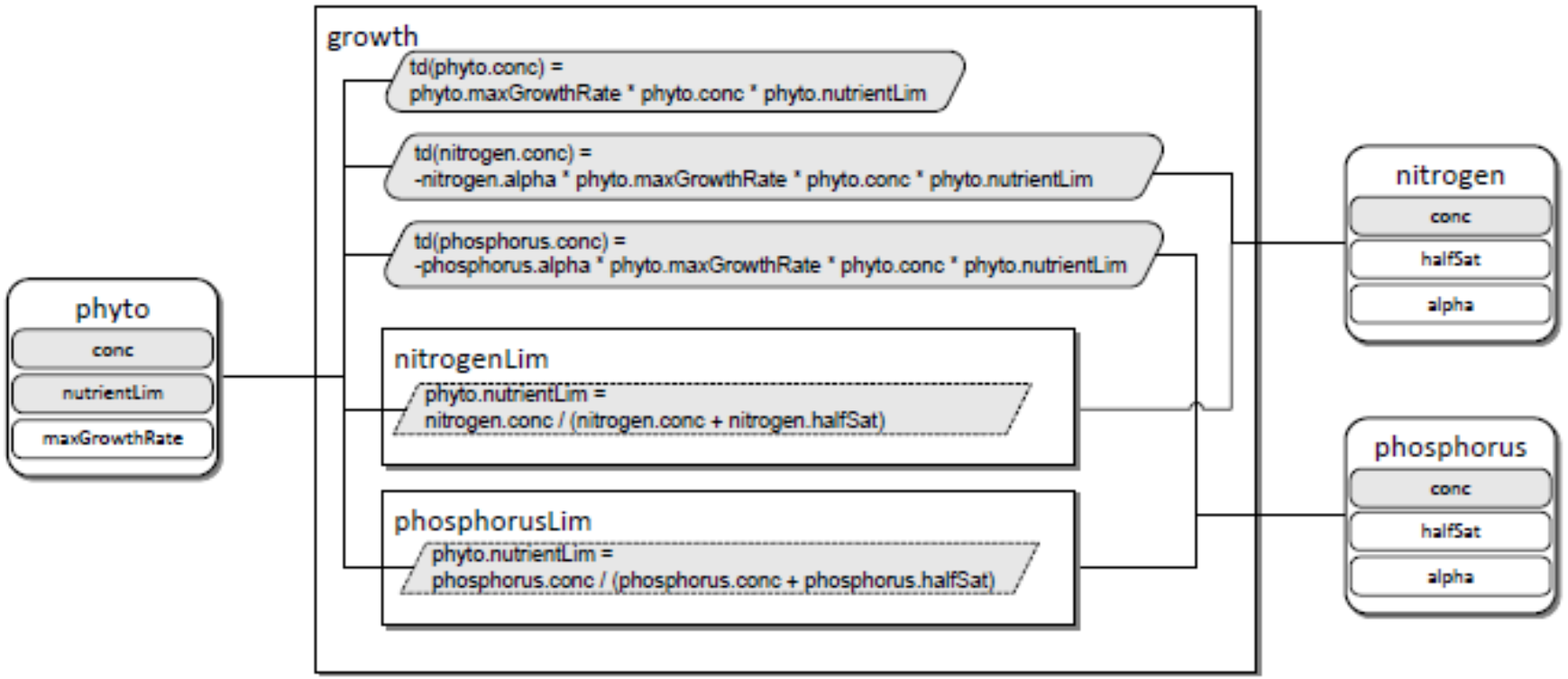
- A process with two sub-processes connecting the three entities in an aquatic ecosystem

process *growth*(*phyto*, [*phosphorus*, *nitrogen*]) {
  processes:
    phosphorusLim, *nitrogenLim*;
  equations :
    td(*phyto.conc*) = *phyto.maxGrowthRate* ∗ *phyto.conc* ∗ *phyto.nutrientLim*,
    td(*phosphorus.conc*) = *phosphorus.alpha* ∗ *phyto.maxGrowthRate* ∗ *phyto.conc* ∗
      phyto.nutrientLim;
}
process *phosphorusLim*(*phyto*, *phosphorus*) {
  equations:
    phyto.nutrientLim = *phosphorus.conc* / (*phosphorus.conc* + *phosphorus.*
      halfSaturation);
}
process *nitrogenLim*(*phyto*, *nitrogen*) {
  equations:
    phyto.nutrientLim = *nitrogen.conc* / (*nitrogen.conc* + *nitrogen.halfSaturation*);
}

The Qualitative Structure of the PMB



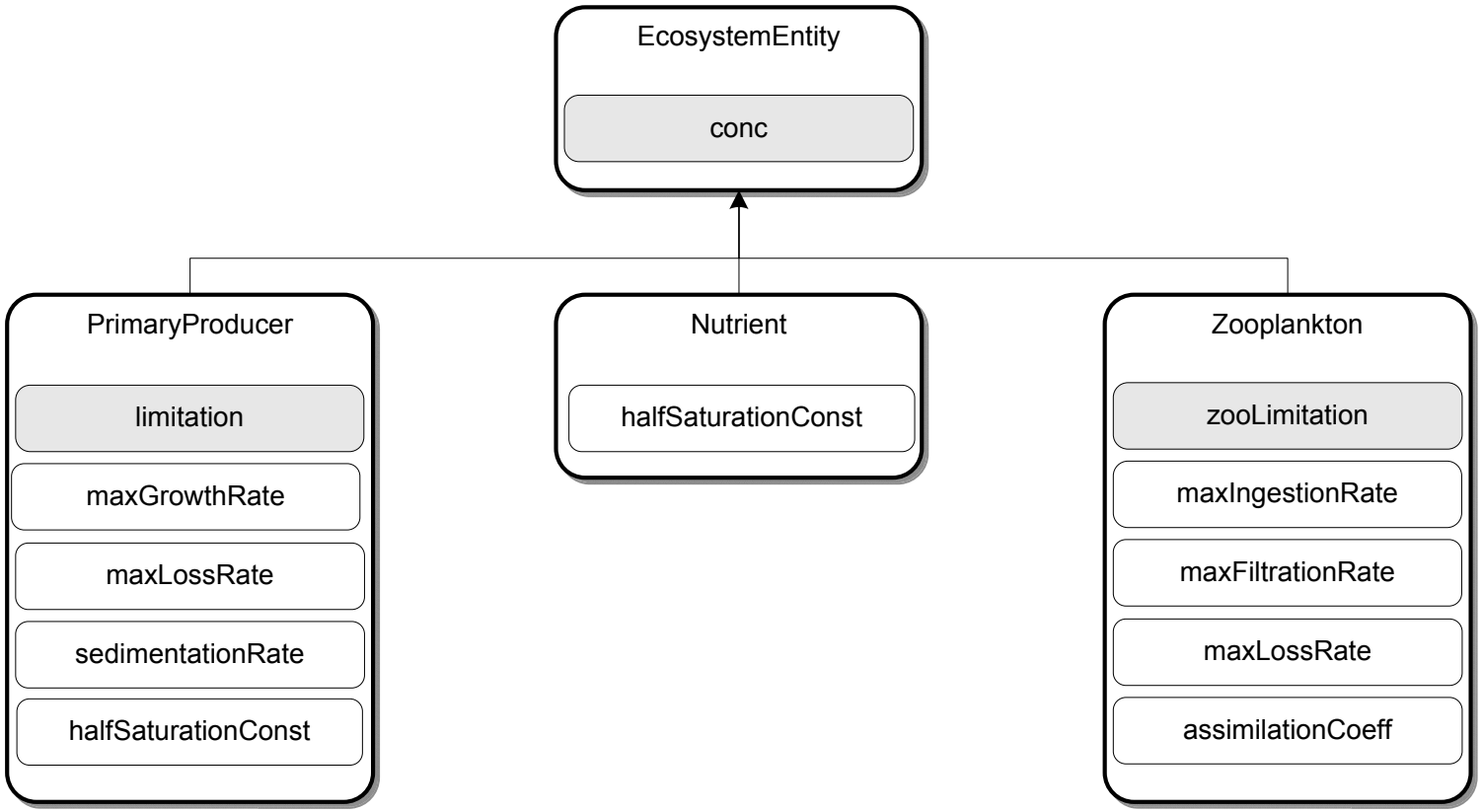
The Quantitative Structure of the PMB



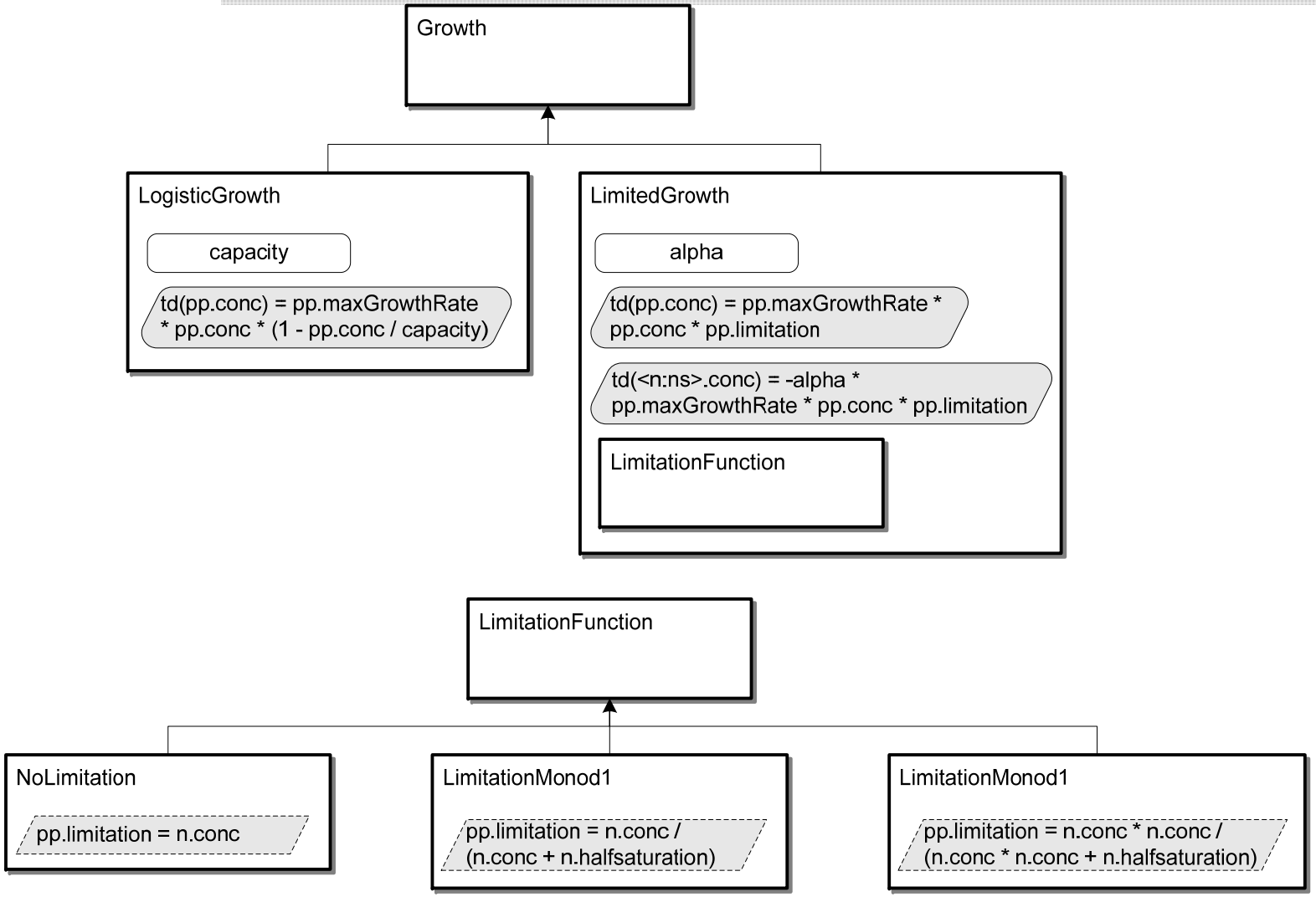
Domain Knowledge for Process-Based Modeling

- Some entities (and processes) are very similar
  - have the same properties
  - have properties that have the same pattern
- Extract these common properties into higher level concepts, called **templates**
- Templates
  - are partial/incomplete specifications that capture common information
  - Entity Templates
  - Process Templates
- Templates are organized into hierarchies

Entity Templates Hierarchy



Process Templates Hierarchy

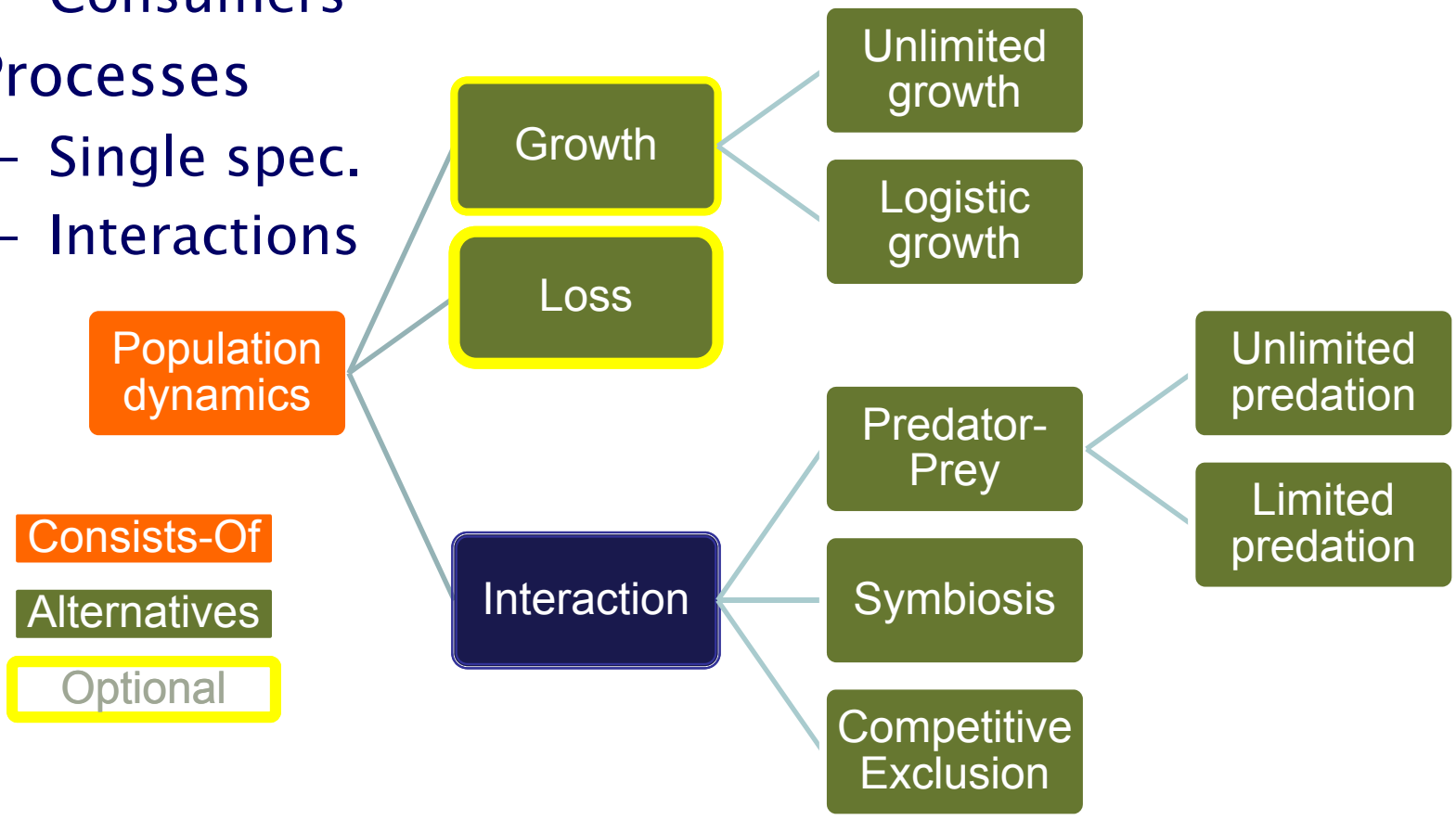


Libraries of Domain Knowledge

- A catalogue of kinds of entities and processes encountered in the domain of discourse
- Template entities/ processes
- Hierarchies of entities and processes
- Mathematical formulations of processes
  - Equation fragments
  - Alternative formulations allowed

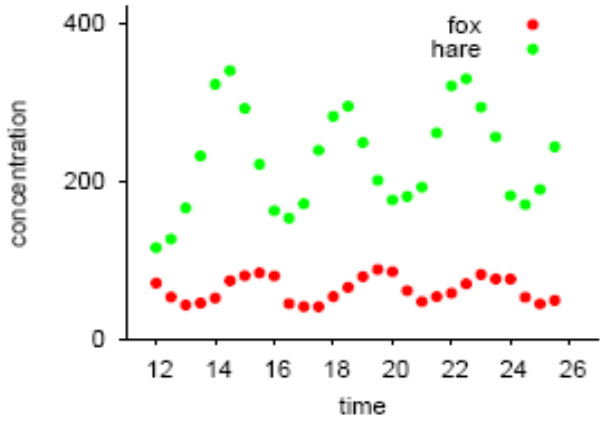
Hierarchies of Species and Processes

- Taxa (Species, Genera, …)
  - Primary producers
  - Consumers
- Processes
  - Single spec.
  - Interactions



Learning PBMs: Inductive Process Modelling

- Input: Observed behavior+ Task+ Template processes



process predator_prey_interaction
variables $Prey\{species\}, Pred\{species\}$
parameters $r[0, \inf], e[0, \inf]$
equations
$\frac{d}{dt} Prey = -1 \cdot r \cdot Prey \cdot Pred$
$\frac{d}{dt} Pred = e \cdot r \cdot Prey \cdot Pred$

- Output: Instance processes + ODEs

process exponential_growth
$\frac{d}{dt} hare = 2.5 \cdot hare$

process exponential_loss
$\frac{d}{dt} fox = -1.2 \cdot fox$

process predator_prey_interaction
$\frac{d}{dt} hare = -0.3 \cdot hare \cdot fox$
$\frac{d}{dt} fox = 0.1 \cdot 0.3 \cdot hare \cdot fox$

$\frac{d}{dt} hare = 2.5 \cdot hare - 0.3 \cdot hare \cdot fox$
$\frac{d}{dt} fox = 0.1 \cdot 0.3 \cdot hare \cdot fox - 1.2 \cdot fox$

Modeling Task Specification

- Specifies the entities present in the system, as well as the measurements available and their relation to the entities
- Specifies high-level processes expected to take place
- Allows for flexible use of the domain knowledge in the library

- For example, we can have quite a complete task specification, leaving only constant parameters to fit
- Or, we can have very high-level processes, requiring the search through a large set of combinations of alternative formulations for each of these

A Machine Learning Approach to Learning Models of Dynamic Systems

- Heuristically search the space of possible **model structures**
  - What is the space?
    - The space of structures considered is defined by the **task specification** and **library of domain knowledge** (template entities and processes)
  - What is the heuristic?
    - Takes error/degree of fit to the **observed behavior(s)** into account, possibly additional factors (such as model complexity)

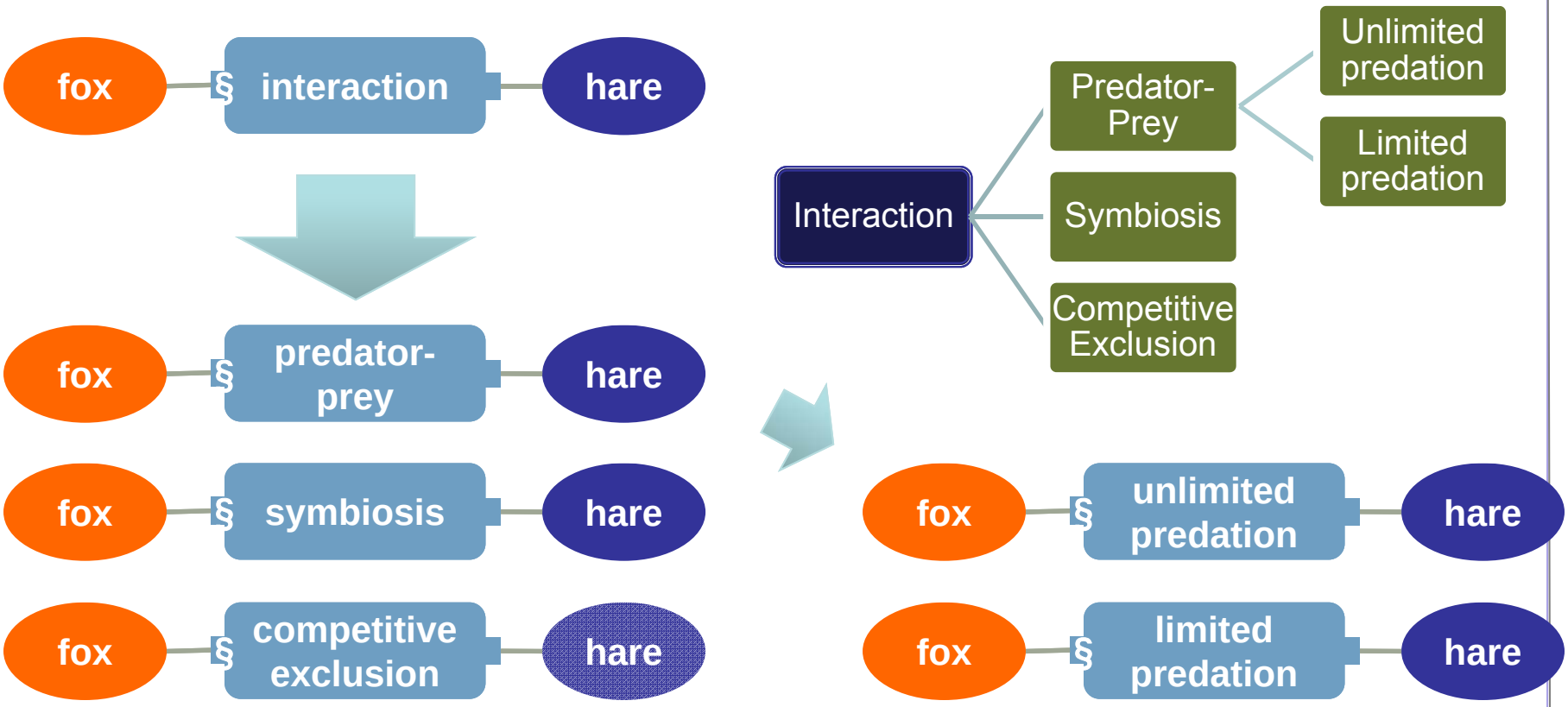
A machine learning approach to IPM

- Consider different sets of (high-level) processes
- Consider different sub-processes and alternative model formulations for each process:
  These correspond to different ODE structures
- To evaluate candidate model structures
  - Parameters are calibrated (nonlinear optimization)
  - Goodness of fit between measured and simulated values is considered

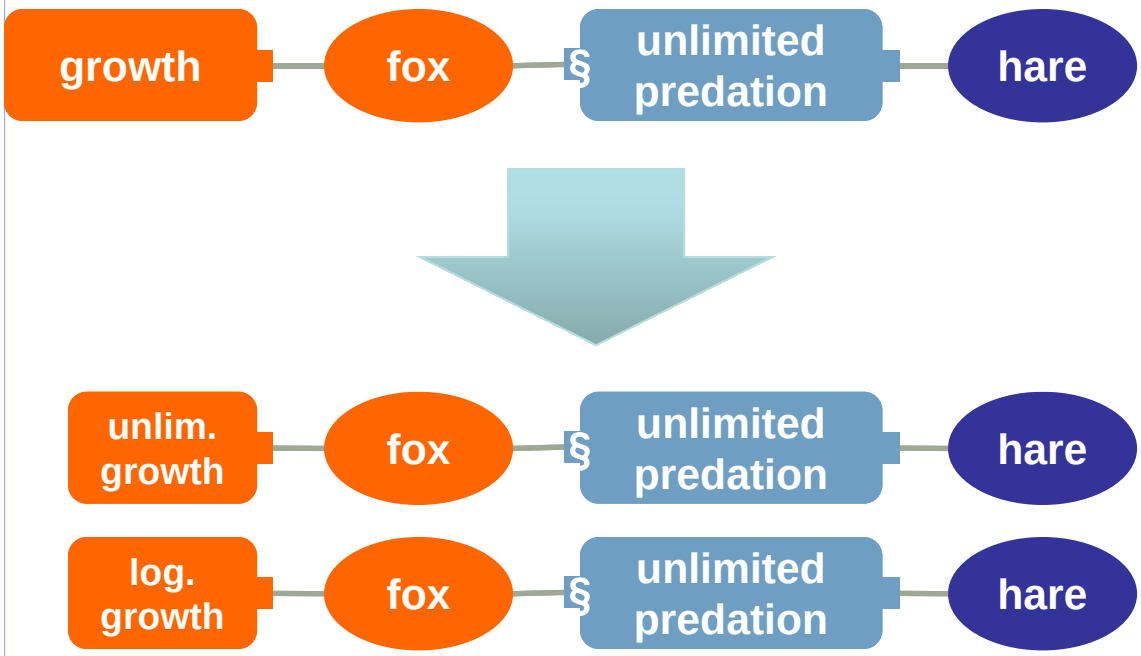
IPM: Direct Search for Process Models

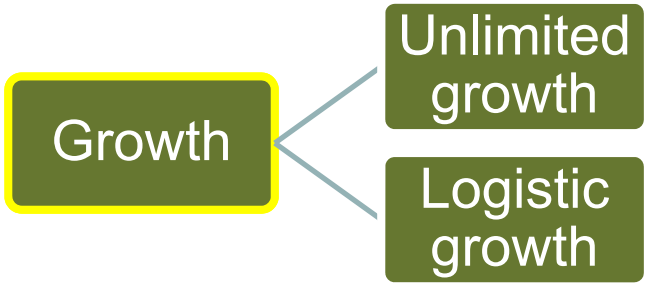
- Consider different sets of (high-level) processes
- Consider different sub-processes and alternative model formulations for each process:
  These correspond to different ODE structures
- To evaluate candidate model structures
  - Parameters are calibrated (nonlinear optimization)
  - Goodness of fit between measured and simulated values is considered

IPM: Generate Models



IPM: Generate Models (2)

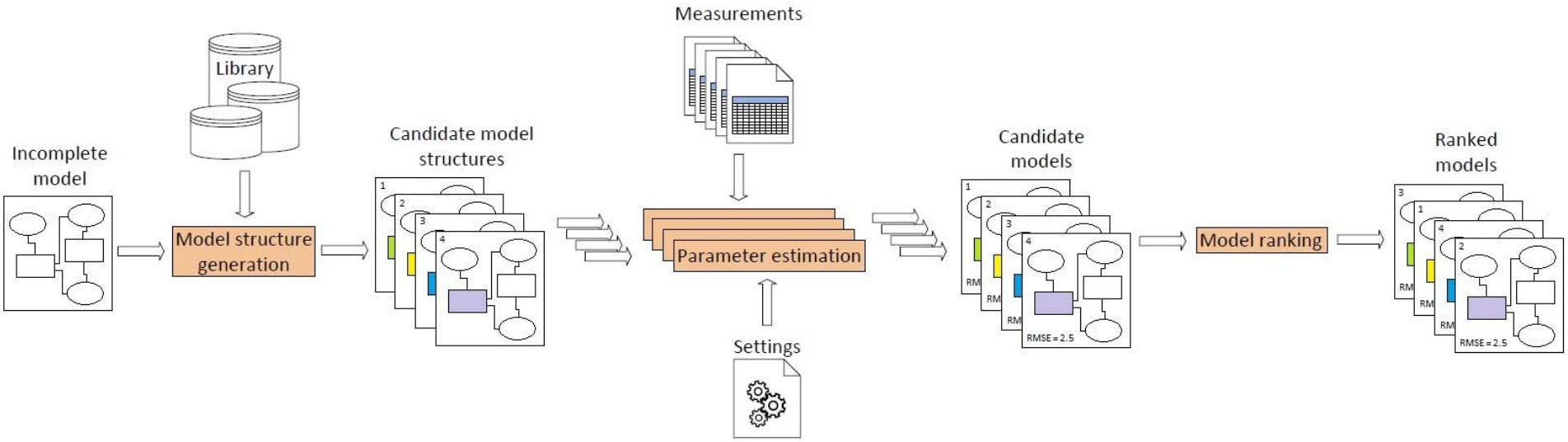




etc.

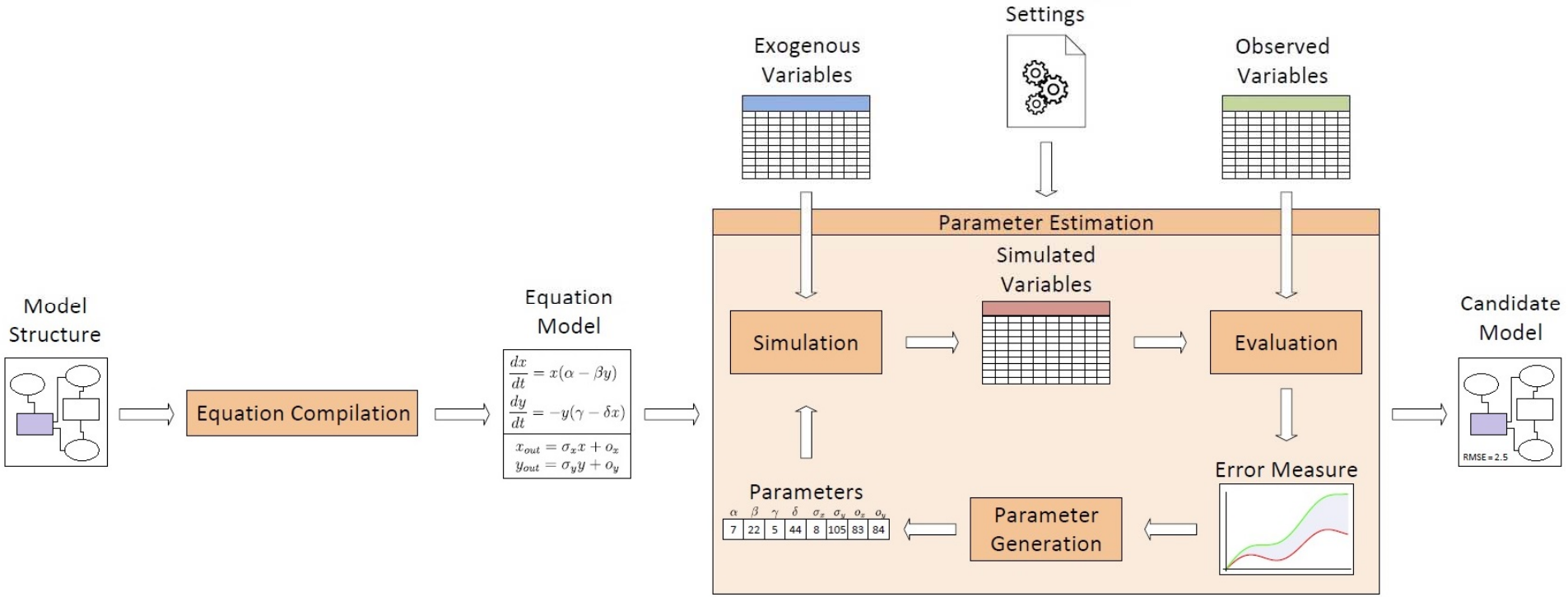
ProBMoT: A SW Platform for IPM

- Process-Based Modeling Tool (D. Čerepnalkoski)
- Given library of domain knowledge, conceptual model (task specification), measured data
- Generates (exhaustively) model structures
- Fits model parameters and
- Finds best candidate (process-based) model(s)

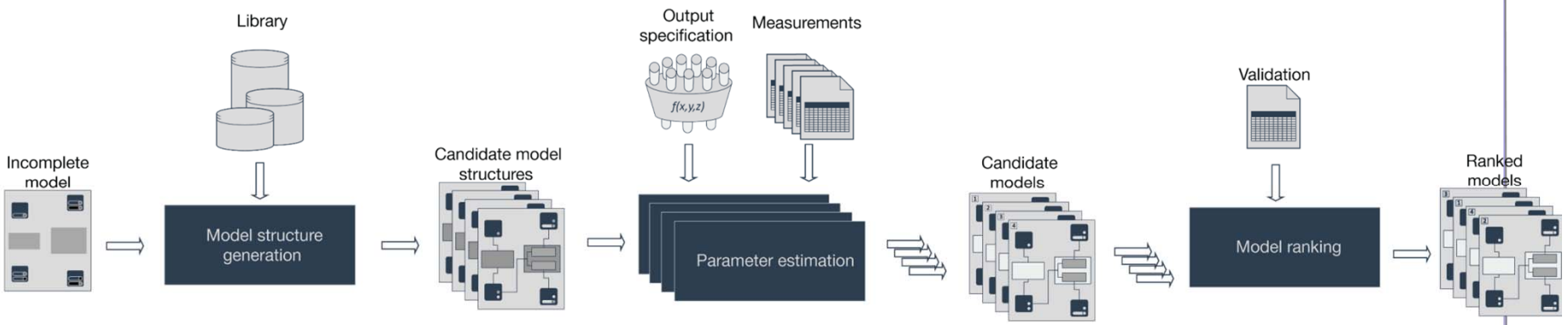


Parameter Estimation in ProBMoT

- Supports the use of different optimization methods for parameter fitting (incl. gradient descent with RRRs)
  - ACO/DASA, Differential Evolution, Multi-objective DE
- Supports the use of different fitness functions (and not just sum of squared errors)



ProBMoT: More accurate workflow



PROCESS-BASED MODELING TOOL
PROBMOT
WWW.PROBMOT.IJS.SI

Recent Advances in IPM Methods

Meta-heuristic optimization for parameter estimation:

- Different and **multiple** objective functions
- Different optimization methods from a general library

Formalism(s) for representing domain knowledge:
Stochastic reaction models

Search model structures: Heuristic (evolutionary) search

Learning ensemble ODE models: Bagging/Boosting IPMs

Meta-learning about IPM: Learning constraints on models

Applications of Inductive Process Modeling

Application areas

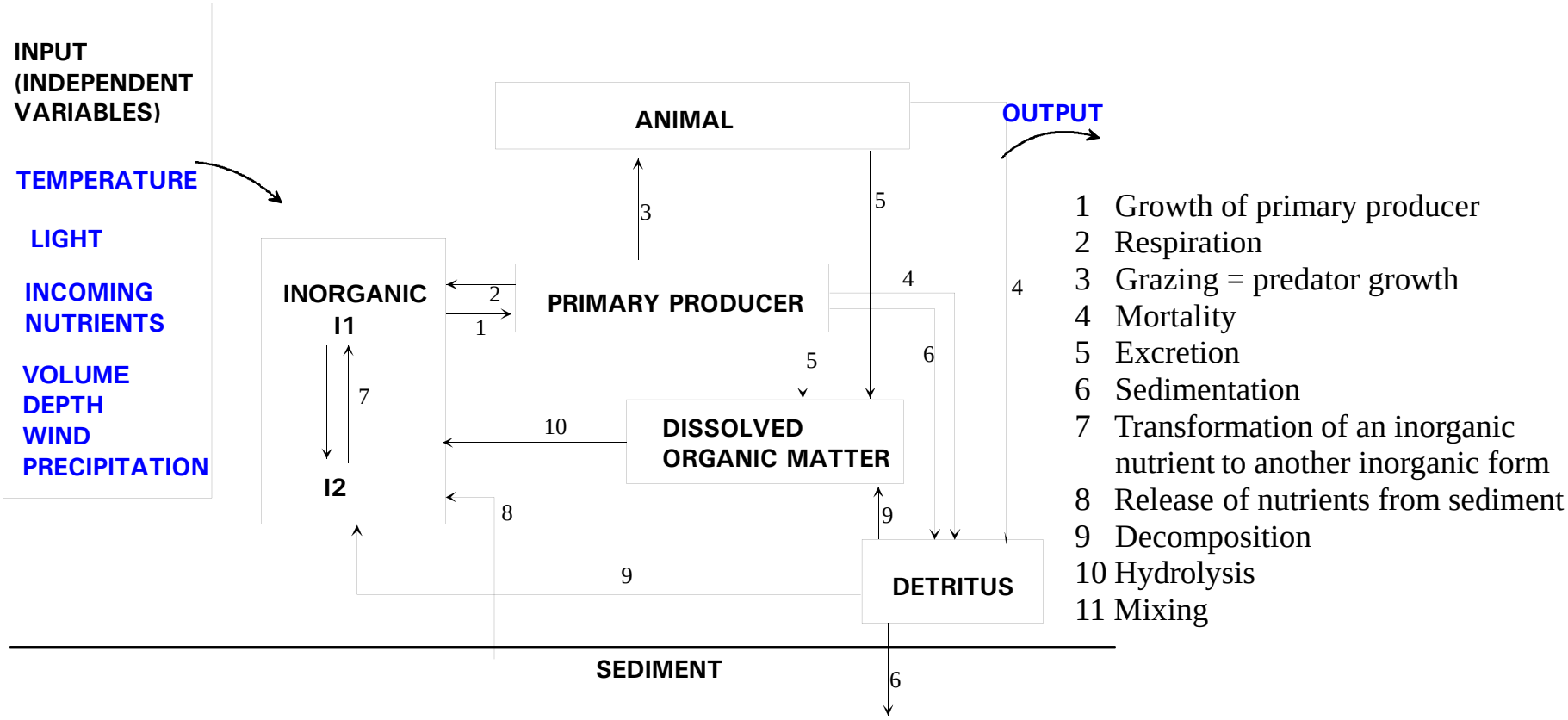
- Systems Ecology
- Systems Biology
- Synthetic Biology

Systems Ecology

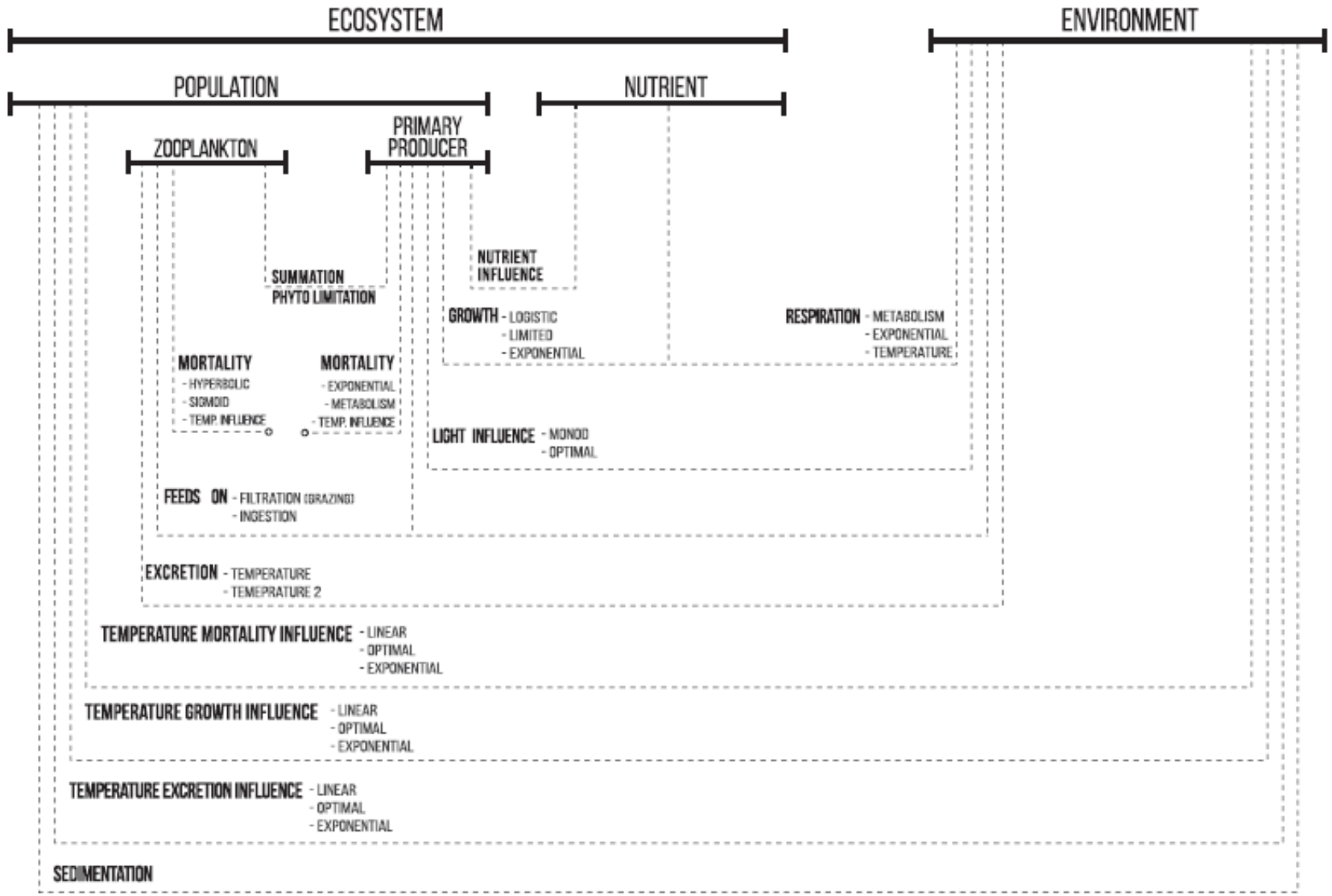
- Population ecology, esp. population dynamics
- Mostly for aquatic ecosystems
- Library of domain knowledge (Atanasova et al. 2006)
- Used for modeling many different aquatic ecosystems
  - Lakes
  - Lagoon
  - Sea

Knowledge for Modeling Aquatic Ecosystems

- An overview of entities and processes in the library



Knowledge for Modeling Aquatic Ecosystems



Modeling Aquatic Ecosystems

Venice lagoon

$$\dot{\texttt{biomass}} = 4.79 \cdot 10^{-5} \cdot \texttt{biomass} \cdot (1 - \frac{\texttt{biomass}}{0.844}) + 0.406 \cdot \texttt{biomass} \cdot (1 - e^{-0.216 \cdot \texttt{temp}}) \cdot (1 - e^{-0.413 \cdot \texttt{DO}}) \cdot \frac{\texttt{NH3}}{\texttt{NH3} + 1} - 0.0343 \cdot \texttt{biomass}$$

Ross sea, Antarctica

Lake Glumsoe, Denmark

$$\dot{\texttt{phyto}} = 0.553 \cdot \texttt{temp} \cdot \frac{\texttt{phosp}}{0.0264 + \texttt{phosp}} - 4.35 \cdot \texttt{phyto} - 8.67 \cdot \texttt{phyto} \cdot \texttt{zoo}$$

Automated Modeling of Lake EcoSystems

Lake ecosystems

- Lake Bled

- Lake Kasumigaura

- Lake Greifensee, Switzerland
- Lake Kinneret, Israel
- Lake Zurich, Switzerland

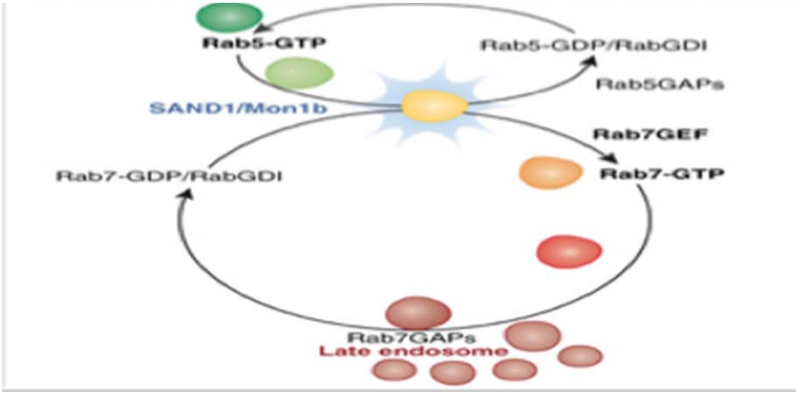
Systems Biology: 'Reconstructing' Biological Networks

- Reconstructing networks is of central interest in SB
  - Formulating network models
  - That capture the dynamics of the studied systems
  - From time course data
- Need to determine structure and dynamics of the net
  - Structure (nodes/species, arcs/reactions)
  - Dynamics: behavior in time, captured by ODEs
    - Functional form of ODEs, including reaction rates (e.g., Michaelis-Menten vs. Hill kinetics)
    - Constant parameters in the ODE (e.g., kinetic or reaction rates constants, e.g.,

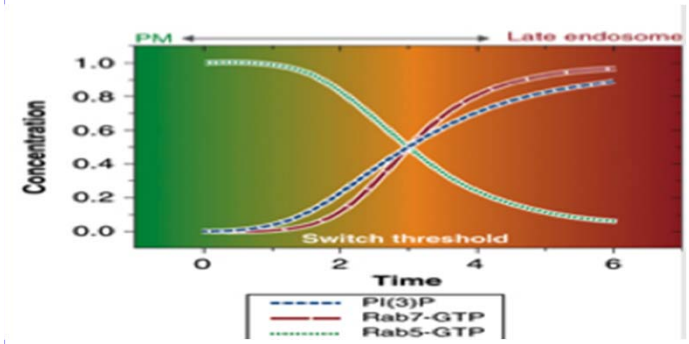
      $dP / st = reaction\_rate \times S \times S / (S + modulation\_rate)$

‘Reconstructing’ Biological Networks

- Structure



- Dynamics



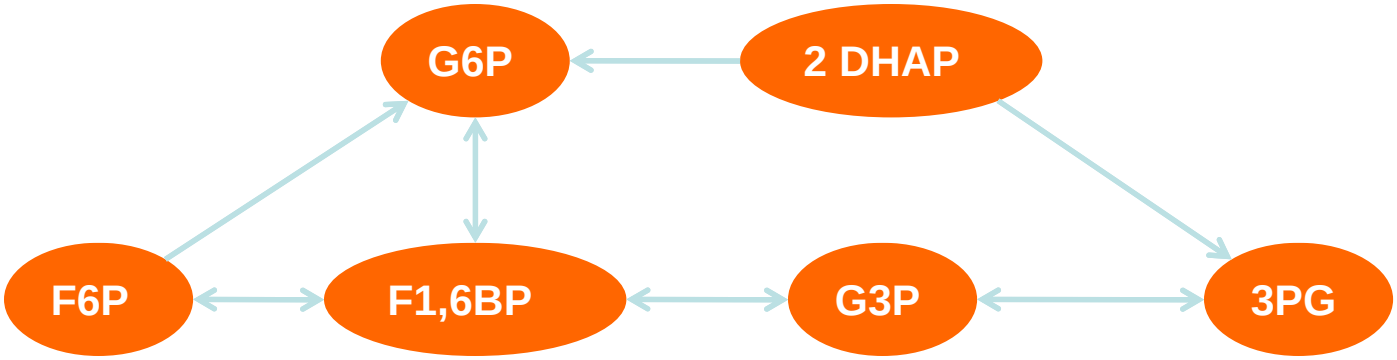
$$\frac{d}{dt}r_5 = v_1 + v_7 + v_9 - v_2 - v_3$$
$$\frac{d}{dt}R_5 = v_2 - v_7 - v_9$$
$$\frac{d}{dt}r_7 = v_4 + v_{10} - v_5 - v_6 - v_8$$
$$\frac{d}{dt}R_7 = v_5 + v_6 - v_{10}.$$

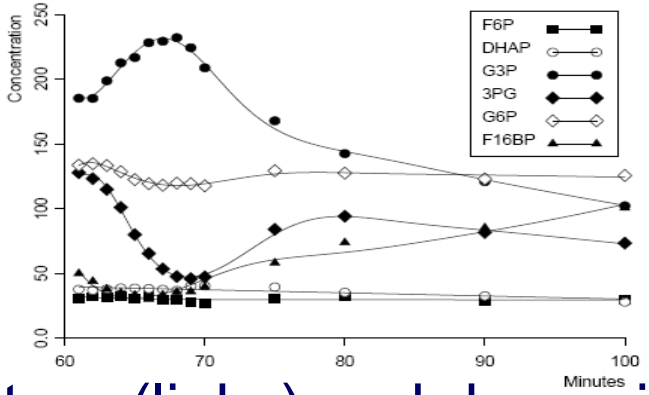
$$v_1 = c_1$$
$$v_2 = \frac{c_2 r_5(t)}{1 + e^{(c_3 - R_5(t))c_4}} \frac{t}{100 + t}$$
$$v_3 = c_5 r_5(t)$$
$$v_4 = c_6$$
$$v_5 = \frac{c_7 r_7(t) R_7(t)^{c_8}}{c_9 + R_7(t)^{c_8}}$$
$$v_6 = \frac{c_{10} r_7(t)}{1 + e^{(c_{11} - R_5(t))c_{12}}}$$
$$v_7 = \frac{c_{13} R_5(t)}{1 + e^{(c_{14} - R_7(t))c_{15}}}$$
$$v_8 = c_{16} r_7(t)$$
$$v_9 = c_{17} R_5(t)$$
$$v_{10} = c_{18} R_7(t).$$

‘Reconstructing’ Networks is an IPM task

Input

- Domain knowledge (partial models, basic processes)
- Time course data



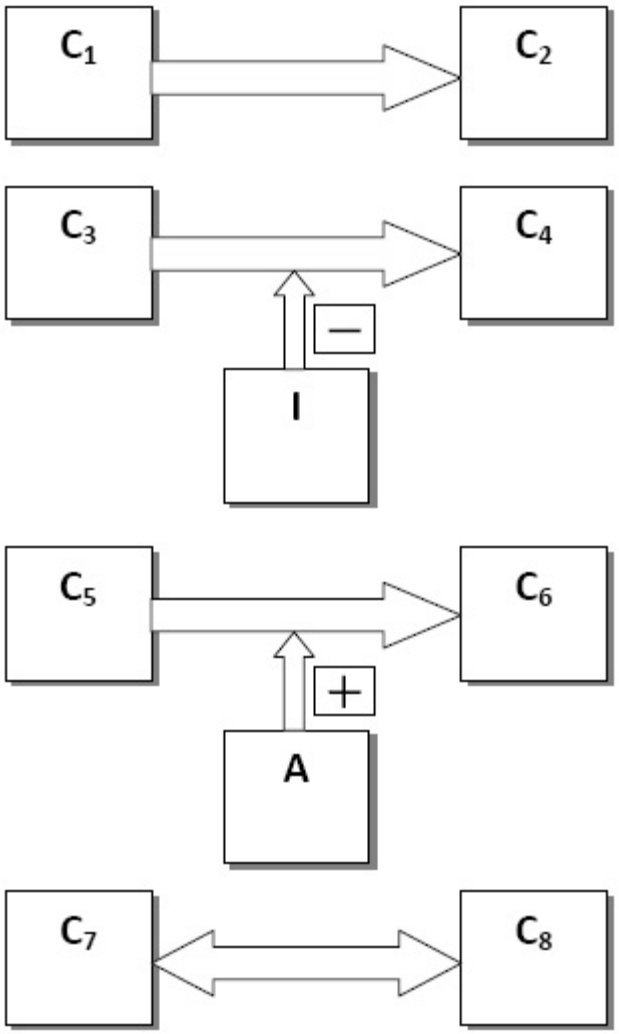


Output: Network structure (links) and dynamics (ODEs)

Metabolic Networks: Library for IPM

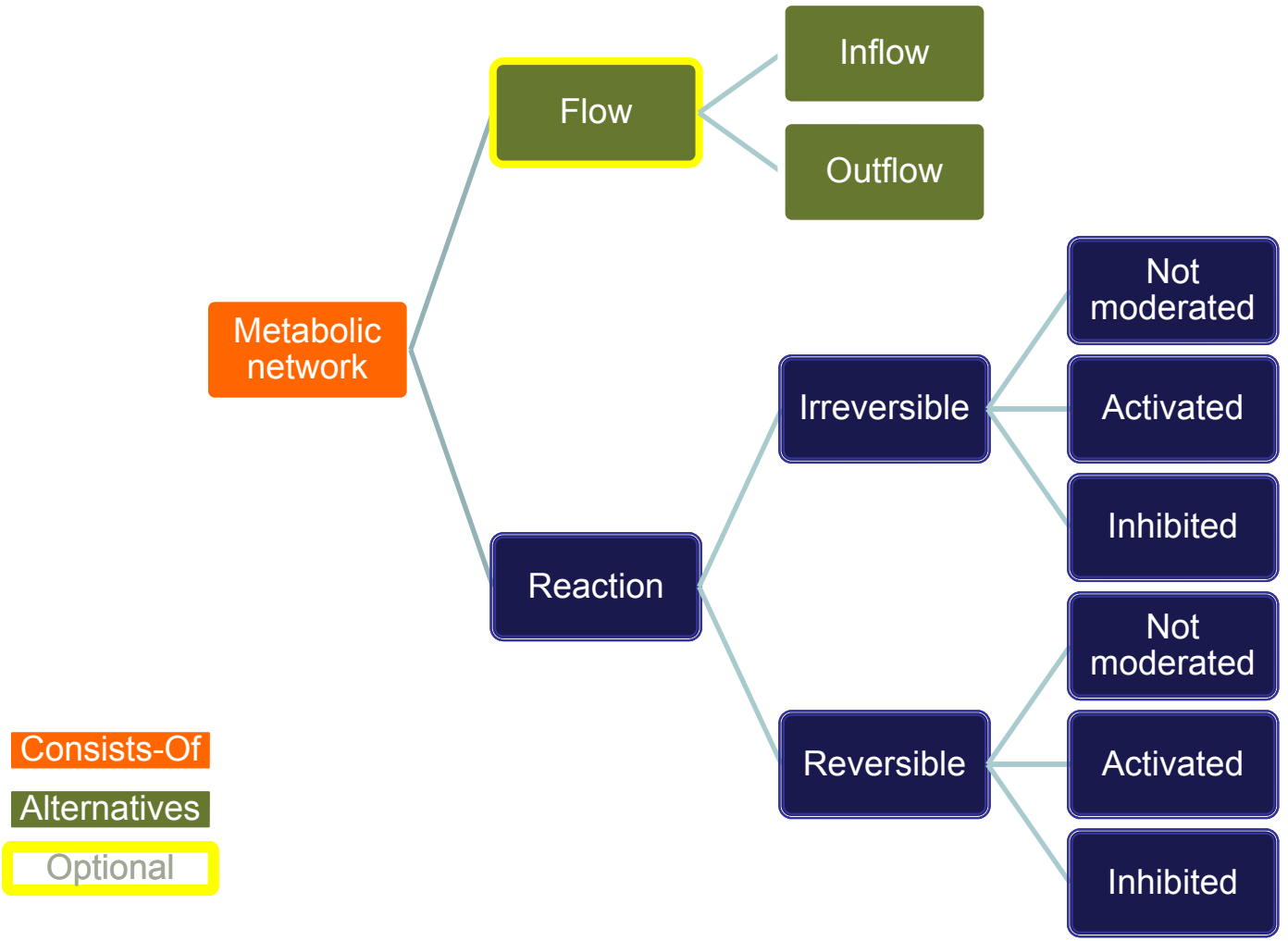
- Entities = chemical compounds
- Processes = chemical reactions
- Entities can have different roles in reactions
  - Substrates are input compounds
  - Products are output compounds
  - Modulates are enzymes that activate/inhibit the reaction

Types of Reactions in Reaction Networks



- Irreversible
- Inhibition
- Activation
- Reversible

Modeling Knowledge for Metabolic Networks



Template Processes: Irreversible

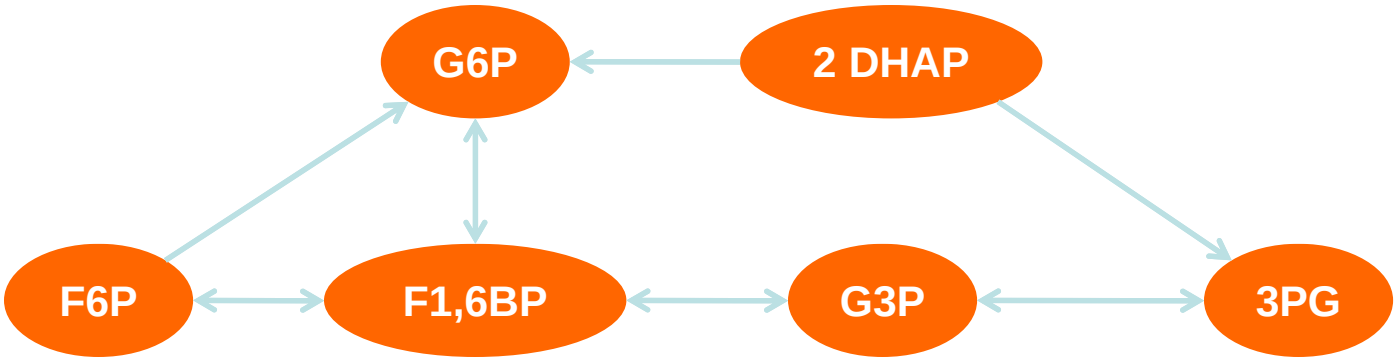
- template process Irreversible_not_modulated
  - variables *S{compound}, P{compound}*
  - constants *reaction_rate(0, Inf)*
  - equations
    - *dS / dt = –1 × reaction_rate × S*
    - *dP / st = reaction_rate × S*

- template process Irreversible_activated
  - variables *S{compound}, P{compound}, M{compound}*
  - constants *reaction_rate(0, Inf), modulation_rate(0, Inf)*
  - equations
    - *dS / dt = –1 × reaction_rate × S × S / (S + modulation_rate)*
    - *dP / st = reaction_rate × S × S / (S + modulation_rate)*

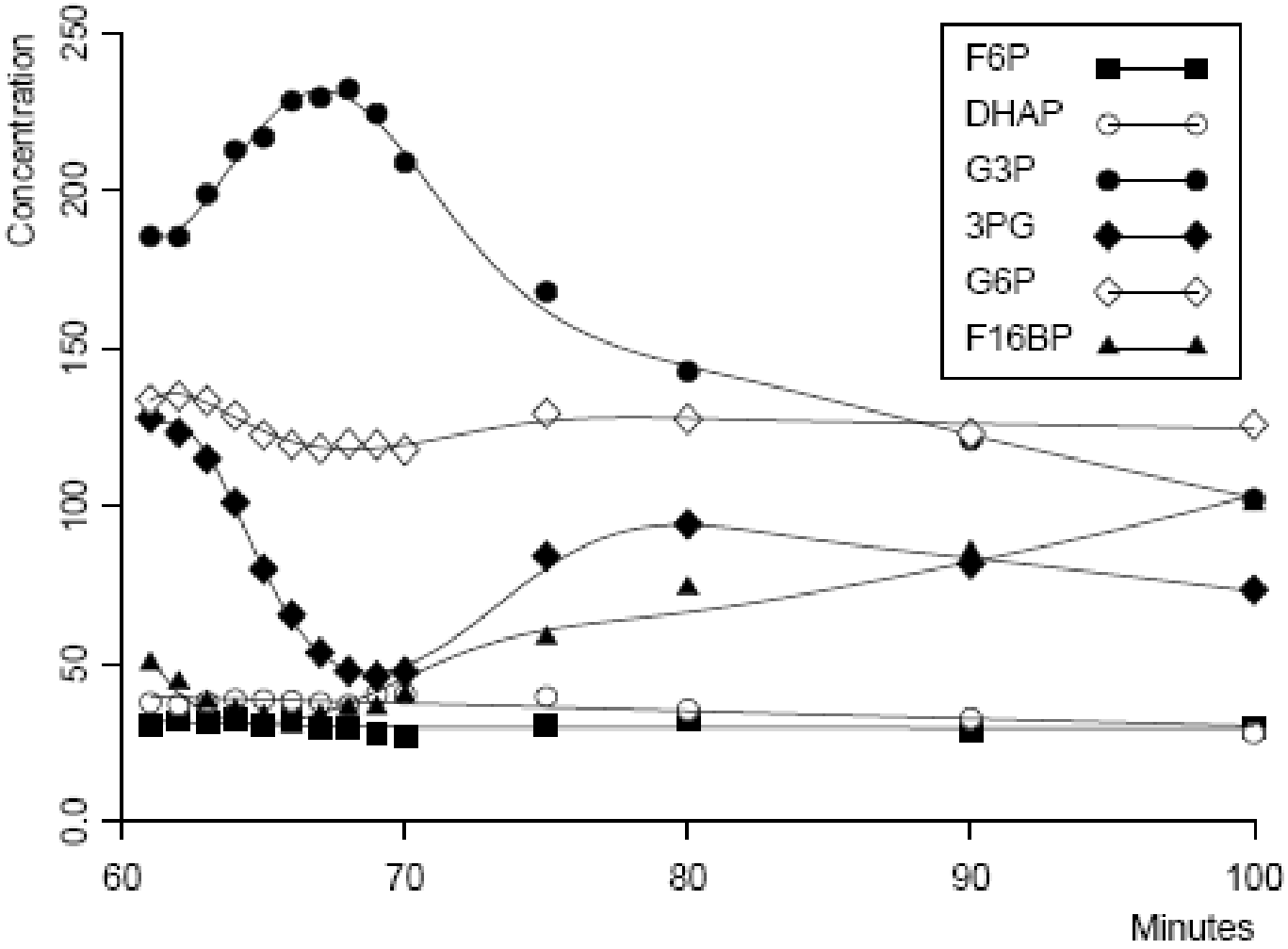
Example Application: Glycolisys

- Inducing (partial) chemical network of glycolisys
  - Data: temporal responses of species to pulse changes (14 time points)
  - From: Torralba et al. (2003) PNAS 100(4): 1494-1498
- Responses of six chemical compounds:
  - G6P (glucose 6-phosphate)
  - F6P (fructose 6-phosphate)
  - F1,6BP (fructose 1,6-bisphosphate)
  - G3P (glycerol 3-phosphate)
  - 3PG (3-phosphoglycerate)
  - DHAP (dihydroxyacetone 3-phosphate)
- Library of domain knowledge as above

Induced Glycosis Network

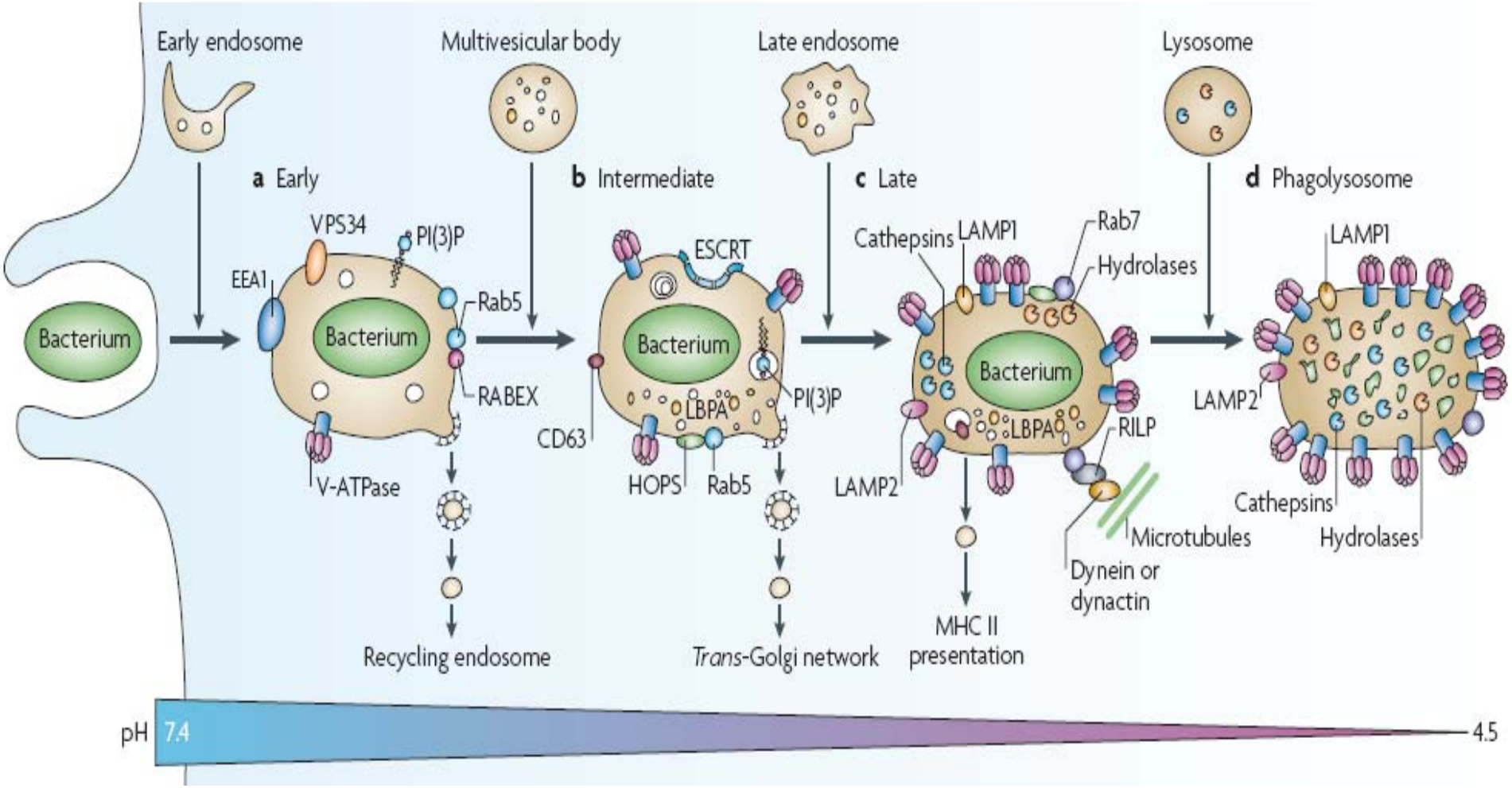


Apps in SB/Glycolisys: Measured and predicted



Systems Biology: Modelling phagocytosis

- The endocytic/phagocytic pathway

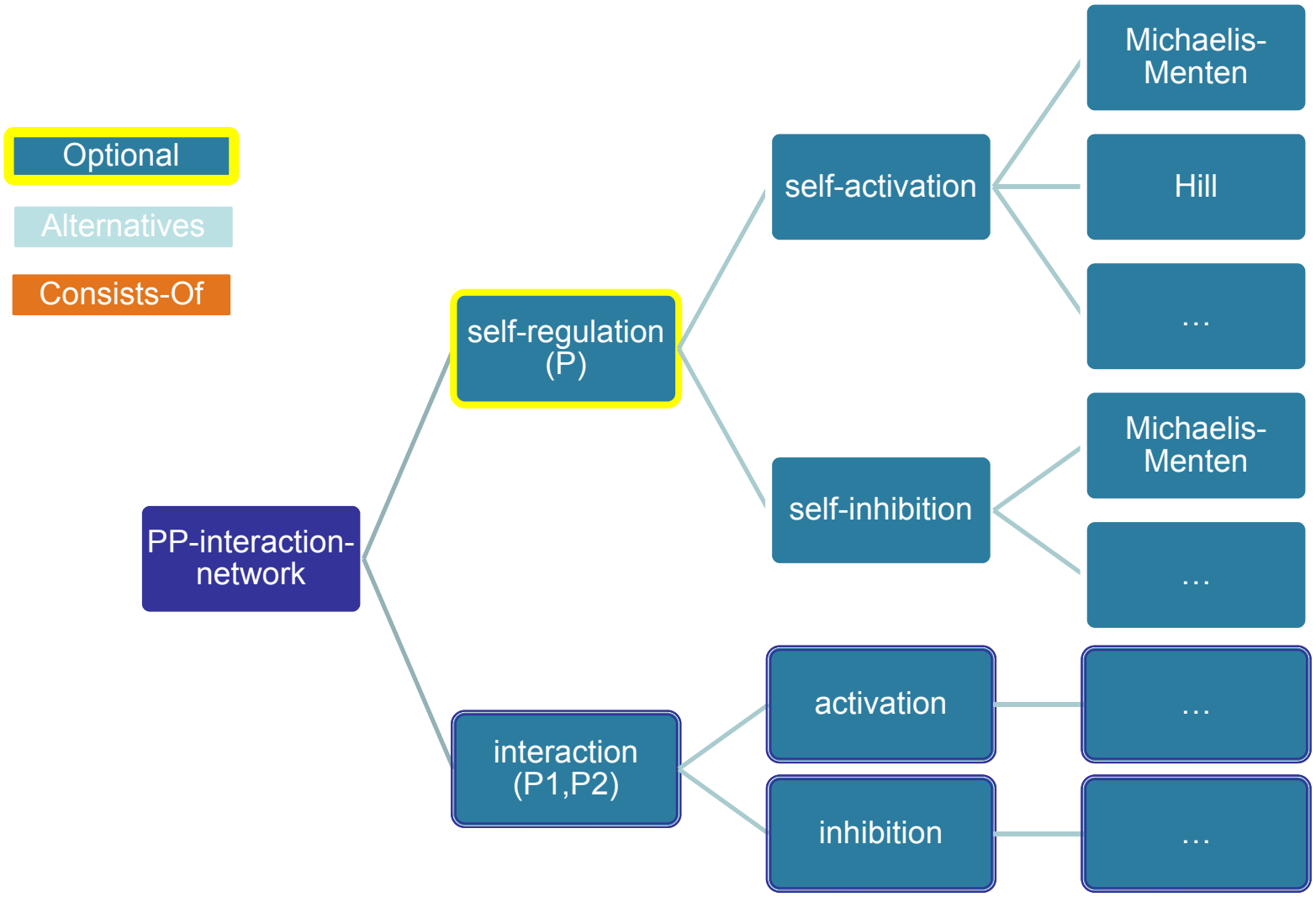


Endosome maturation

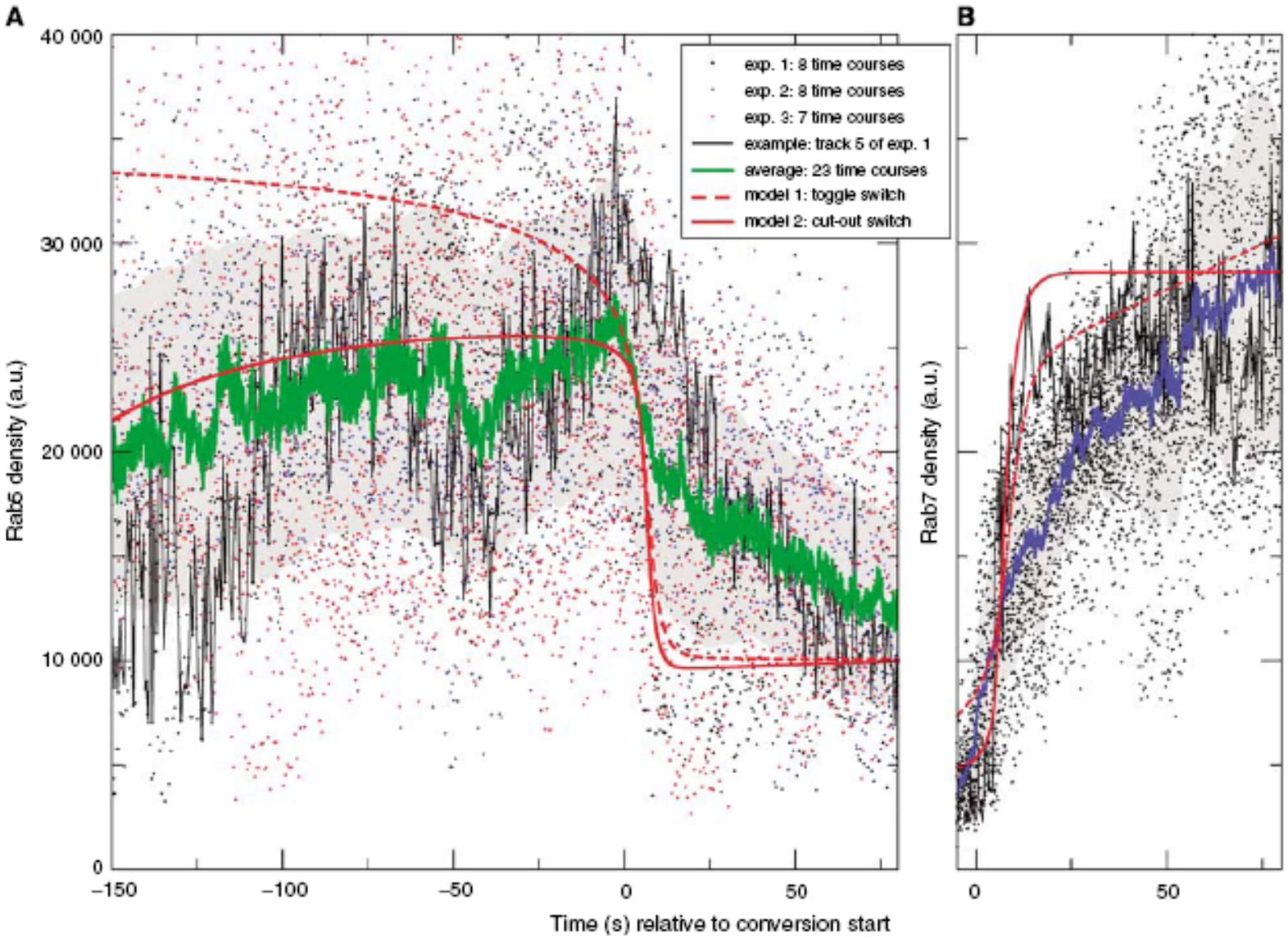
- Early endosomes: pH 6.0-6.5, **rich in Rab5**, EEA1, syntaxin 13, endobrevin, PI(3)P
- Late endosomes: pH 5.0-6.0, **rich in Rab 7**, M6PR, VAMP7, syntaxin 7, vATPase, LAMP-1/-2, lusosbisphospatidic acid

- Endosome maturation: early -> late endosome
  - Rab conversion crucial in the process (Rab5 to Rab7)
  - Expected behavior: switch from high Rab5/low Rab7 to low Rab5/high Rab7
- Different possible switches: toggle vs. cut-out

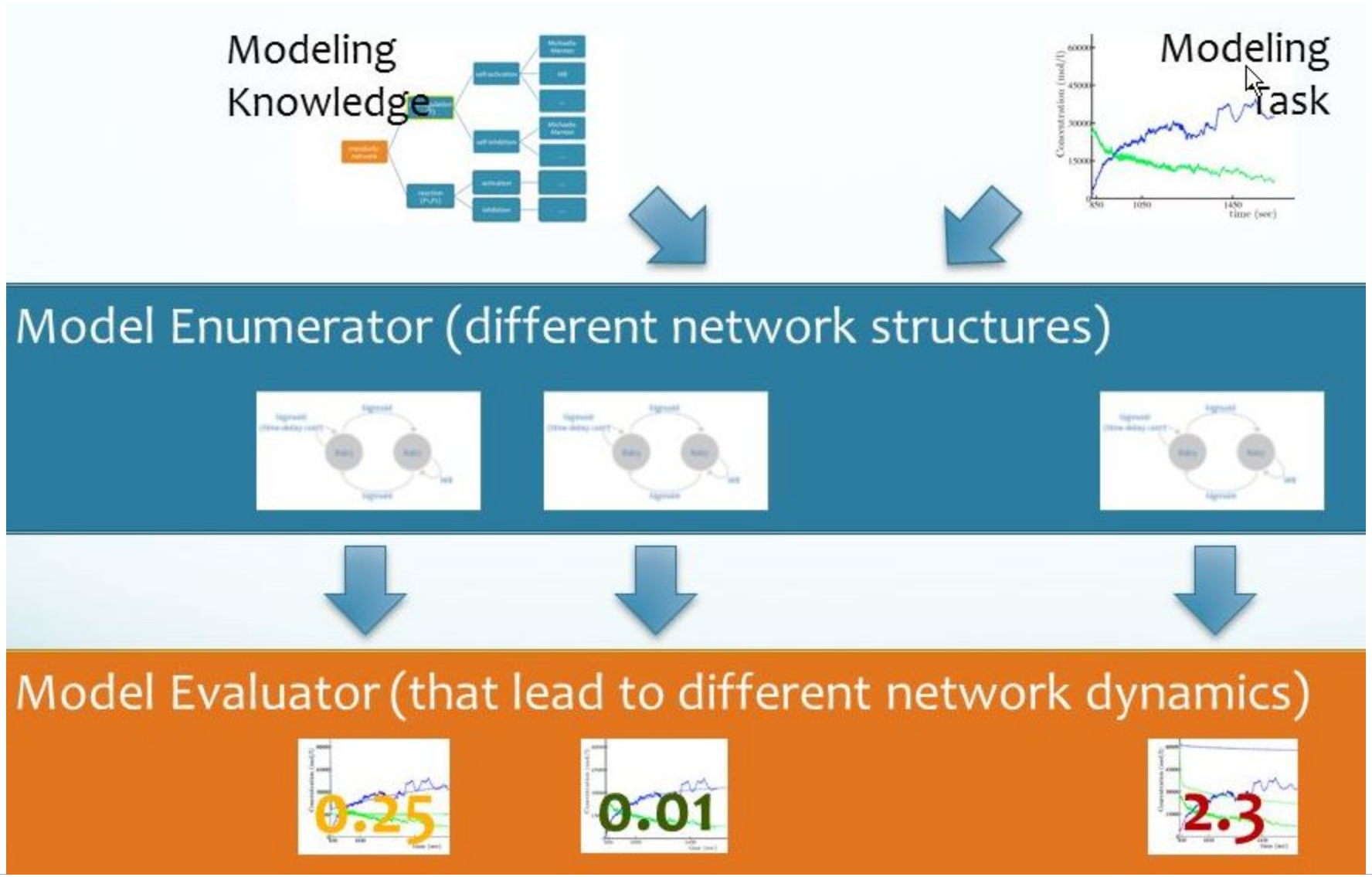
The GTPase modeling library: Processes



The Data


A
B
40 000
30 000
20 000
10 000
0
Rab5 density (a.u.)
Rab7 density (a.u.)
exp. 1: 8 time courses
exp. 2: 8 time courses
exp. 3: 7 time courses
example: track 5 of exp. 1
average: 23 time courses
model 1: toggle switch
model 2: cut-out switch
–150
–100
–50
0
50
0
50
Time (s) relative to conversion start

Modeling endosome maturation

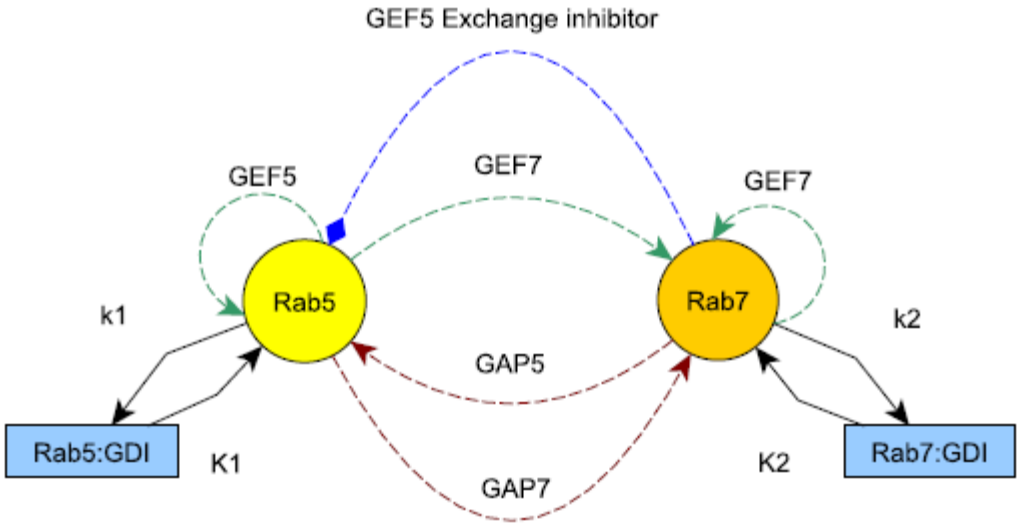


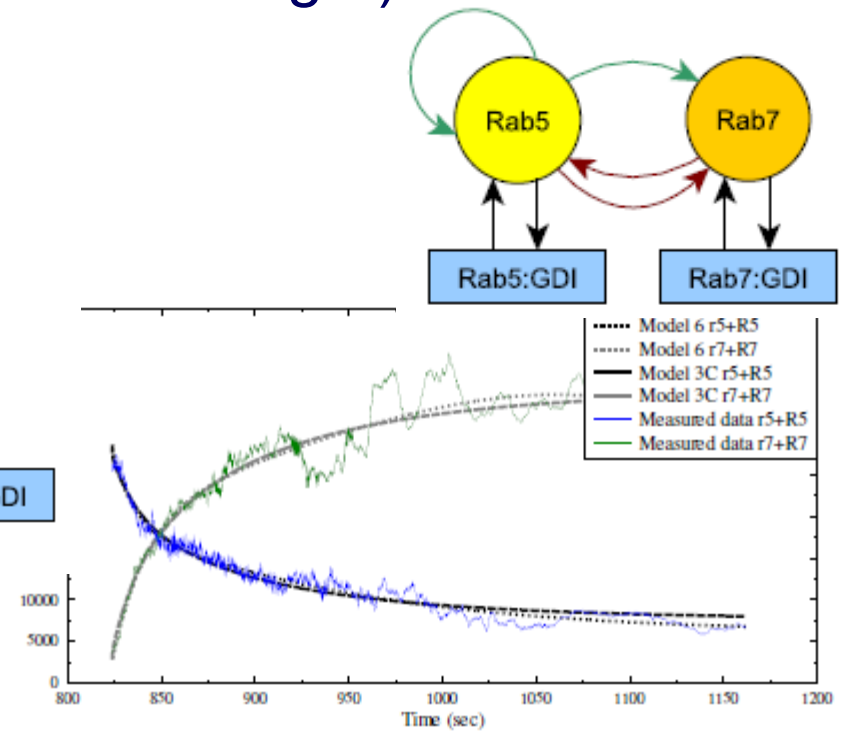
Model by del Conte Zerial et al. and alternative proposed by ProBMoT

- Criteria: RMSE and BIC (Bayesian Information Crit.)

$$RMSEObjective(m) = \sum_{i=1}^{2} \sqrt{\frac{1}{N} \sum_{j=1}^{N} (x_i[j] - y_i[j])^2} \qquad BIC(m) = N \ln(MSE(m)) + k \ln(N)$$

- The structures (dCZ left, ProbMoT right)





Systems vs. Synthetic Biology

Systems Biology: Re-constructing biological networks

- From **observed** behavior
- Reverse engineering

Synthetic biology: Constructing biological circuits (nets)

- That would produce **desired** behavior
- Design / engineering of biological circuits

What is common to both?

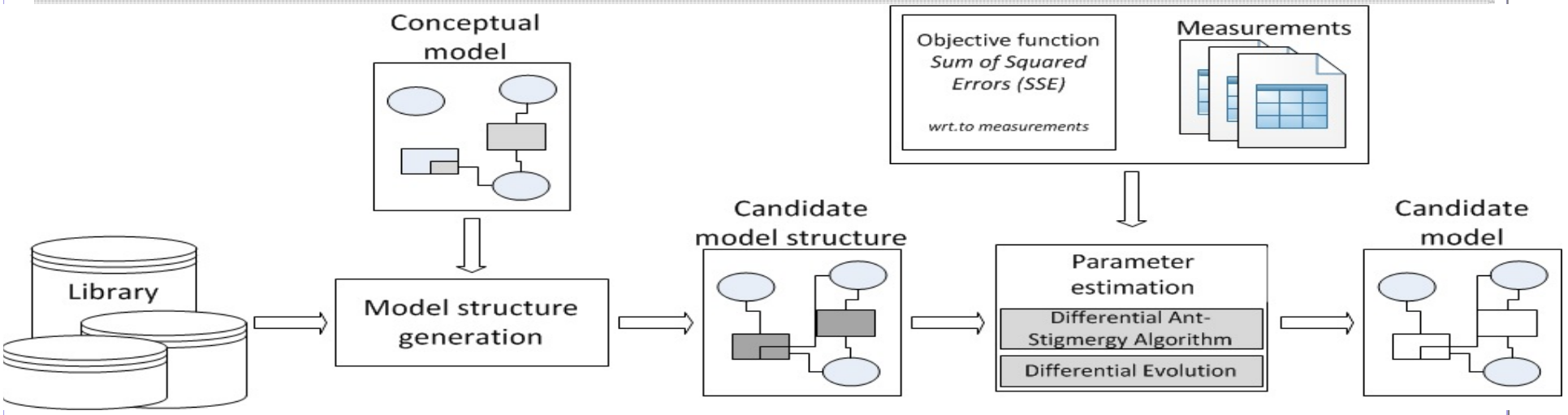
- The use of models of the dynamics of the circuits
- To investigate (in-silico) the behavior of the circuits

IPM for Synthetic Biology

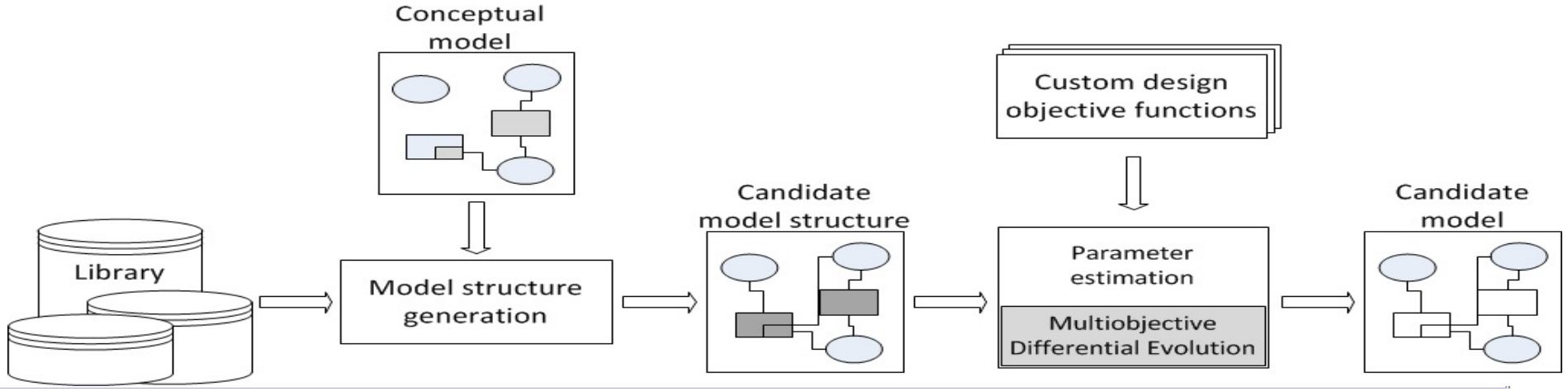
- No observed data. Instead, formalized expected behavior in the form of **custom objective functions**
- **Multi-objective** optimization needed
- Model parameters are fitted so that the candidate model exhibits desired behavior (objective functions)

- Input:
  - Library of domain knowledge, conceptual model
  - List of behavior objectives (objective functions)
- Output:
  - Suitable models and corresponding sets of parameters

ProBMoT for Systems Design vs. Identification



Instead of data, formalized desired behavior in the form of **custom design objective functions.** Multi-obj. opt. needed.



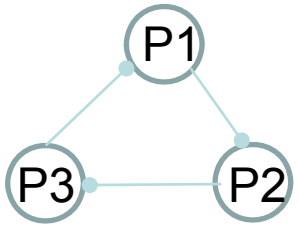
Design of biological circuits with complex behaviours

- Case studies:
  - Repressilator (Elowitz and Leibler)
  - Coupled repressilators (Gao et al)
- Task:
  - Propose design/model of the desired circuit and its parameters to optimize the custom objective function
- Objective function:
  - Largest Lyapunov exponent (λ_1)

    as an indicator of dynamical behavior
    - If $\lambda_1 = 0$ the system is oscillatory
    - If $\lambda_1 > 0$ the system is chaotic
    - If $\lambda_1 < 0$ the system is stable

Case study: Repressilator

- Repressilator
  - Synthetic genetic regulatory network
  - 3 repressor proteins & corresponding mRNA
  - Connected in a repression loop

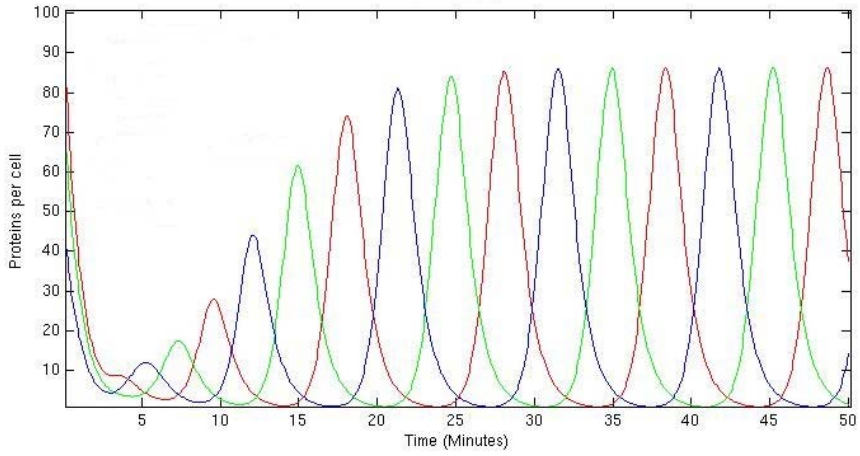


- Objective function – minimization of the absolute value of the largest Lyapunov exponent (targeting oscillatory beh.)

$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{1 + p_j^n} + \alpha_0$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_1)$$

- (i,j) varies trough (1,3), (2,1), (3,2)



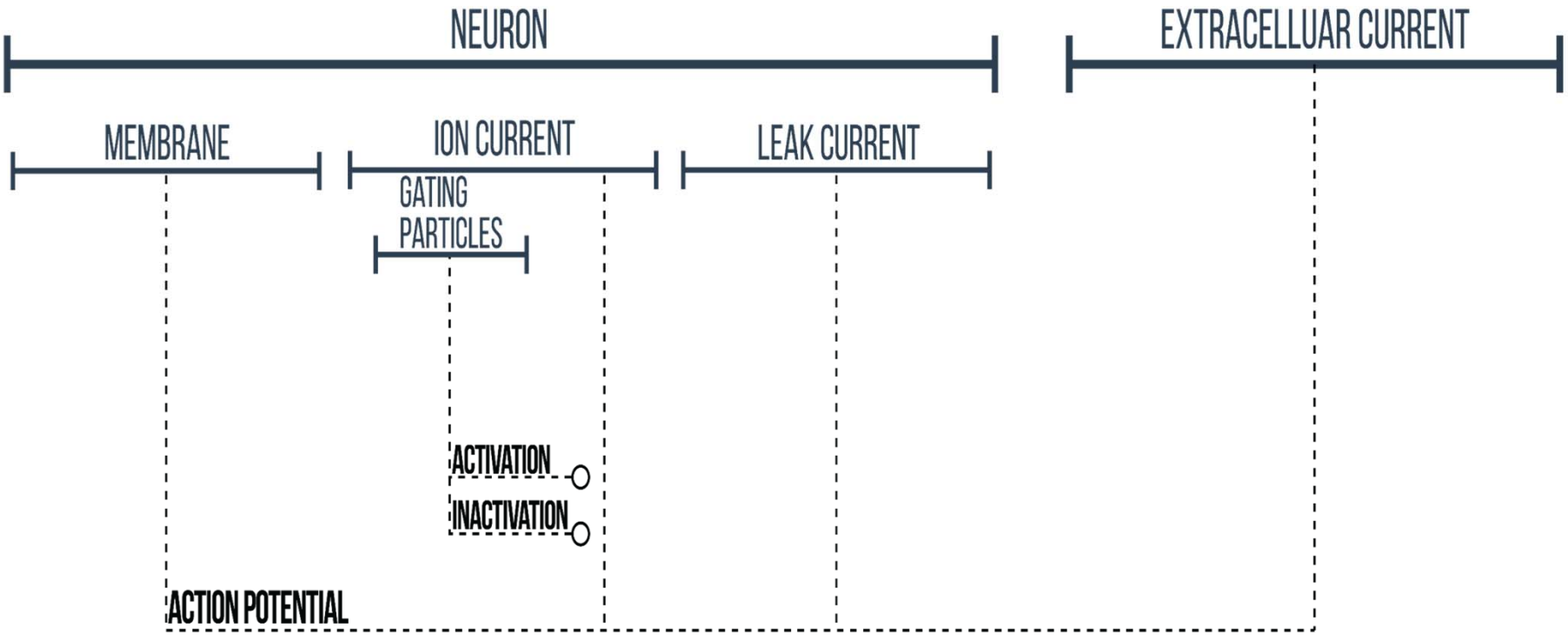
Case study: Coupled Repressilators

- Coupled repressilators
  - Two repressilators (x and y).
  - Coupling represented by modifying one equation in each repressilator (γ – coupling strength).
- Objective function – maximization of the largest Lyapunov exponent (targeting chaotic behavior)

$$\frac{dx_{m_3}}{dt} = -x_{m_3} + \frac{\alpha}{1 + \left(x_{p_2} - \gamma y_{p_2}\right)^n} + \alpha_0,$$

$$\frac{dx_{m_3}}{dt} = -y_{m_3} + \frac{\alpha}{1 + \left(y_{p_2} - \gamma x_{p_2}\right)^n} + \alpha_0$$

Library of domain knowledge for modeling neurons

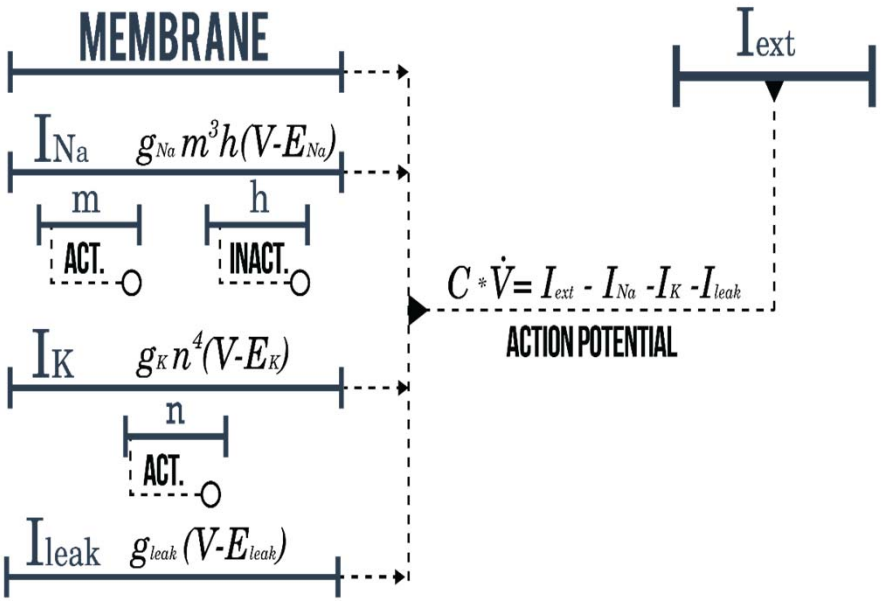


Library of domain knowledge for modeling neurons

```
template entity membrane{
     consts:
          C { range: <0,1>; unit:"uF/cm^-2"};
     vars:
          V {aggregation:sum; unit:"mV"; range:<-100,100>};}
template entity IonCurrent {
     consts:
          g { range: <0,200>; unit:"mS/cm^-2"},
          E { range: <-100, 100>; unit:"mV"};
     vars:
          Ic { aggregation:sum; range:<-100,100>}; }

template process Current ( m:membrane, iC:IonCurrent){}
template process ionCurrentProcess ( gP:gatingParticle) : Current{
     equations:
          iC.Ic = iC.g*pow(gP.gp,gp.n)*(m.V - iC.E); }

template process leakCurrent: Current{
     equations:
          iC.Ic = iC.g *(m.V - iC.E); }

template process membranePotential (m:membrane, iCs:IonCurrent<1,10>,
                                    eC: ExCurrent){
     equations:
          td(m.V) = (eC.I_ex - <iC:iCs>.Ic)/m.C; }
```

Hodgkin-Huxley Model

Process-based Model



Ordinary Differential Equations

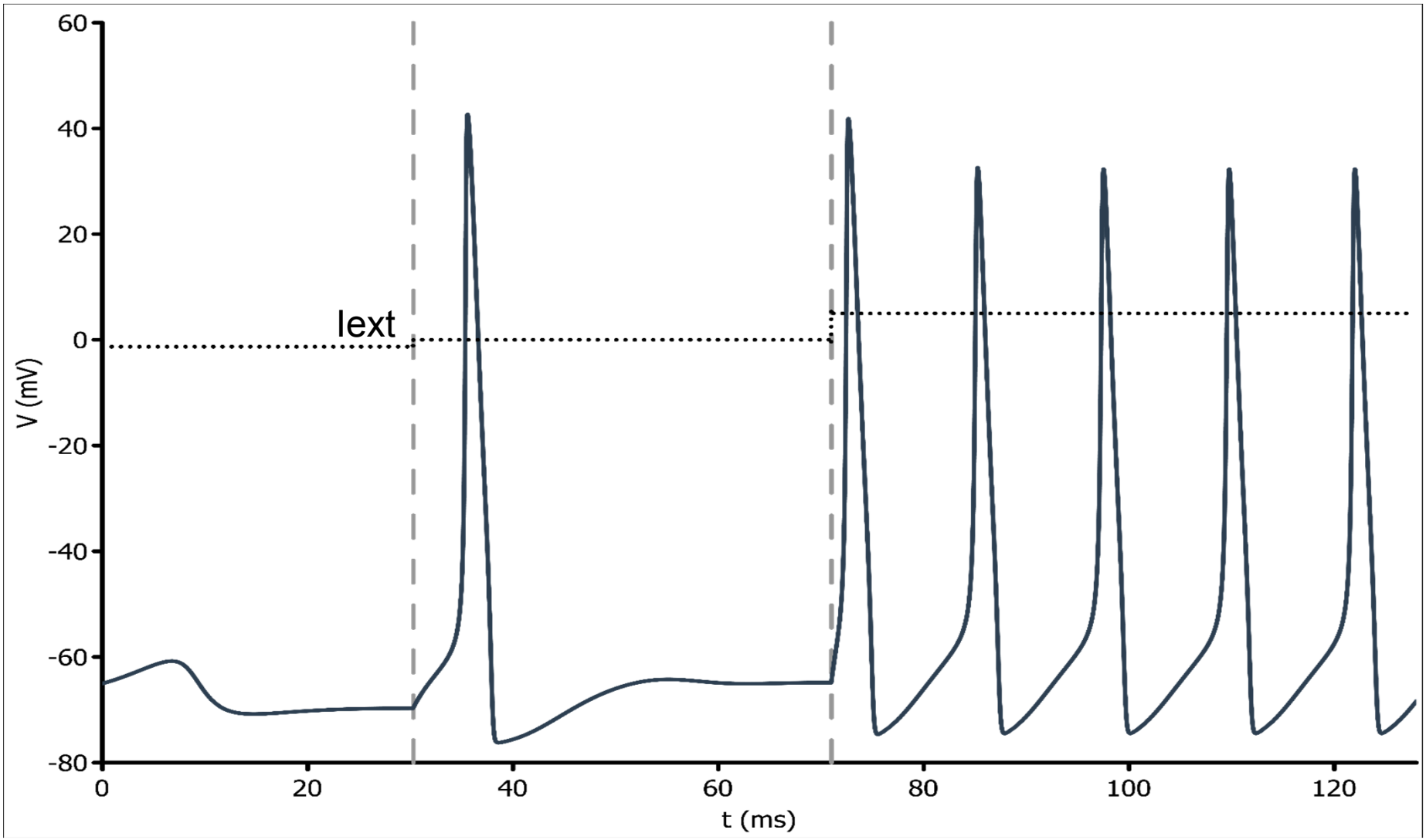
$$C * \dot{V} = I_{ext} - g_{Na} m^3 h(V-E_{Na}) - g_K n^4(V-E_K) - g_{leak}(V-E_{leak})$$

$$\dot{m} = [m - m_\infty(V)] / \tau_m(V)$$

$$\dot{h} = [h - h_\infty(V)] / \tau_h(V)$$

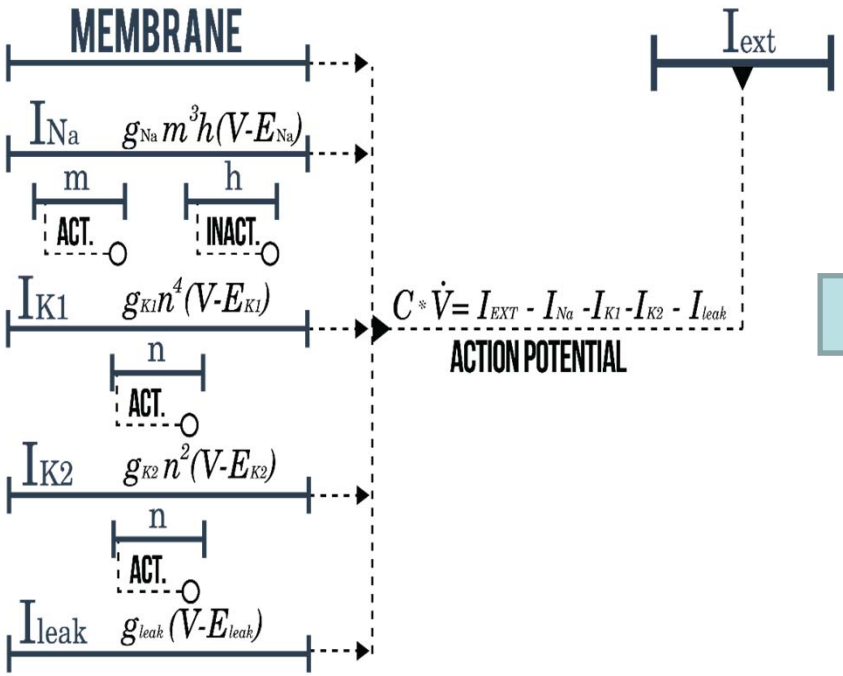
$$\dot{n} = [n - n_\infty(V)] / \tau_n(V)$$

Hodgkin-Huxley Model



Fast-spiking Cortical Interneuron

Process-based model



Ordinary Differential Equations

$$C * \dot{V} = I_{ext} - g_{Na} m^3 h(V-E_{Na}) - g_{K1} n_1^4 (V-E_{K1}) - g_{K2} n_2^2 (V-E_{K2}) - g_{leak} (V-E_{leak})$$

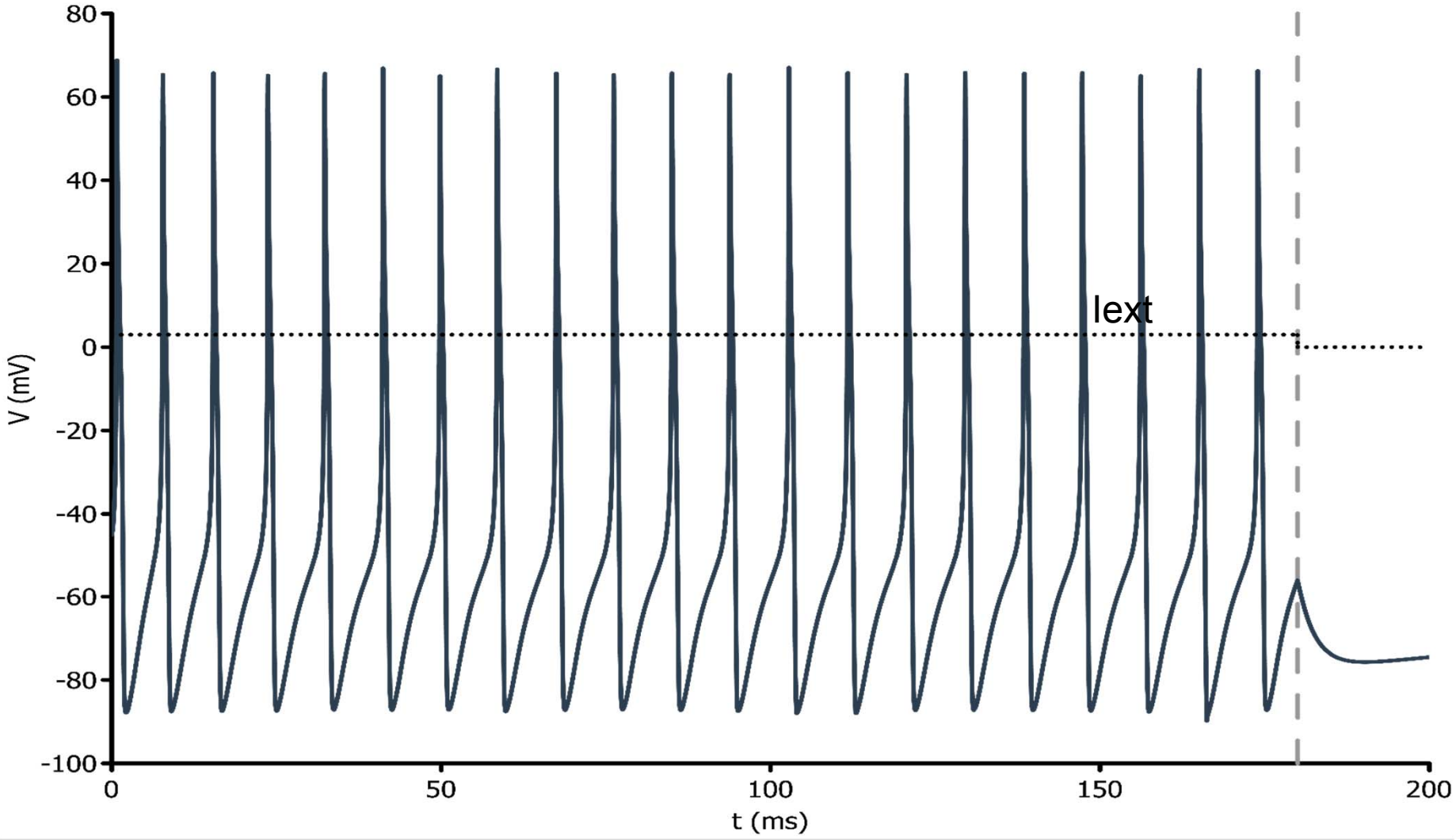
$$\dot{m} = [m - m_\infty(V)] / \tau_m(V)$$

$$\dot{h} = [h - h_\infty(V)] / \tau_h(V)$$

$$\dot{n}_1 = [n_1 - n_{1\infty}(V)] / \tau_{n1}(V)$$

$$\dot{n}_2 = [n_2 - n_{2\infty}(V)] / \tau_{n2}(V)$$

Fast-spiking Cortical Interneuron



Summary & Outlook

- Proposed process-based representation of models and domain knowledge
- Natural, understandable, ontologically grounded
- Includes both quantitative and qualitative aspects
- Proposed methods for learning process-based models

- Applications in systems biosciences: Systems ecology, Systems Biology, Synthetic Biology

- Summary: Automated modeling/identification, design

- Outlook: **Automating Systems Sciences**
  Using machine learning also for analysis & control