

COPASI Workshop

Session 5 : Modeling & Simulation Programs

EMBRIО Retreat

07/19/22

9-12:00

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Tepole & Umulis Lab

COPASI Workshop: Objectives

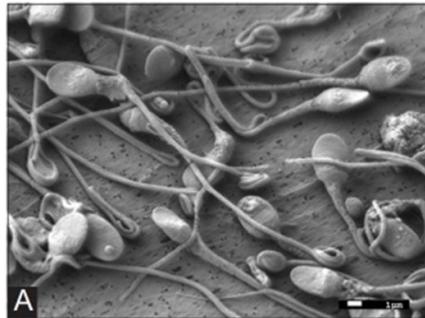
Participants will be introduced to:

1. The basics for modeling biochemical networks using COPASI
2. The 'COmputational Modeling in Biology' NEtwork (COMBINE) standards related to COPASI usage, such as:
 - a. SBGN (Systems Biology Graphical Notation)
 - b. SBML (Systems Biology Markup Language)
3. Sharing resulting models in online repositories (BioModels database)

Outline

1. Biological Networks: Involve coordinated interactions of thousands of molecules
2. COPASI: Software for modeling biological networks through mathematical modeling
3. Chemical Kinetics: How fast chemical reactions take place
4. Model Set-Up in COPASI: How set up model's reactions to get an ODE model
5. Time-Course Simulations: How to set up the time course simulations
6. Steady-State Simulations: How to set up the steady course simulations
7. Parameter Estimation: How to estimate unknown parameters in your model
8. COMBINE Standards: Coordinates the standards to model biological systems for transparency and exchangeability
 - a. SBML (Systems Biology Markup Language): An XML-based format for modeling
 - b. SBGN (Systems Biology Graphical Notation): An XML-based graphical representation for biological diagrams
 - c. Common annotation system based on RDF (Resource Description Framework)
9. BioModels Database: A repository for storing, exchange and retrieving models

Is it possible to understand how the interaction of molecular components inside cells induce the properties of life at a system level?



Nussdorfer, 2017



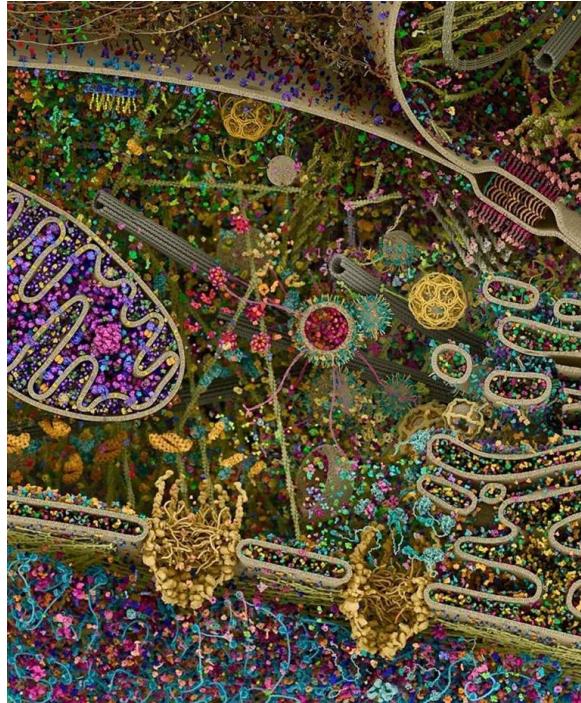
Suda, 2020



Kalra, 2018

1. Biological Networks

- Network Types
 - Gene Regulatory
 - Protein
 - Metabolic



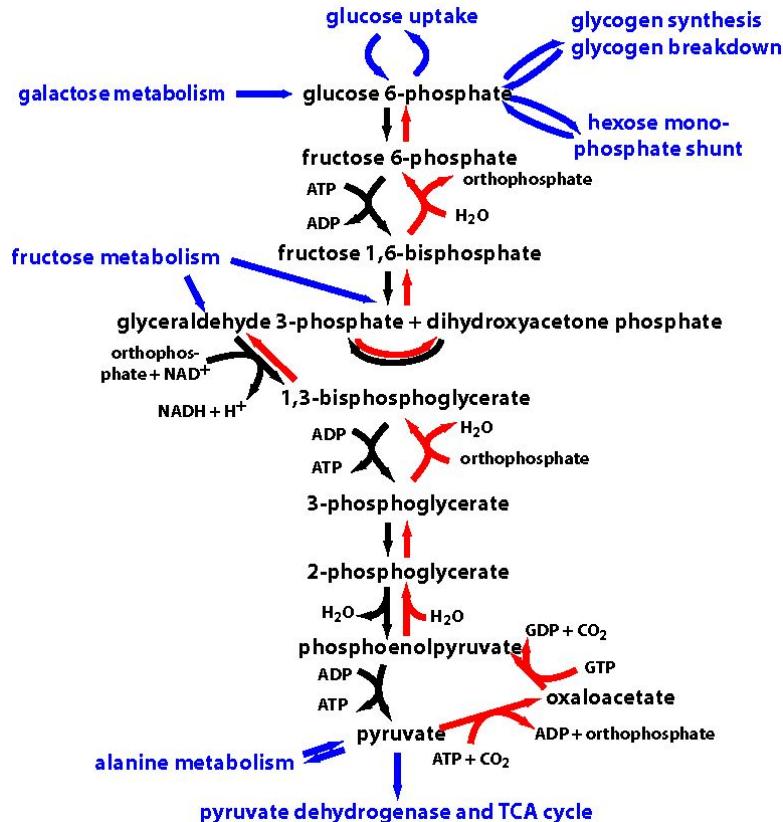
Evan Ingersoll & Gael McGill, 2018

1.1 Biological Networks: Data Sources for Metabolic Pathways and Interactions

- Books
- Literature via PubMed
- Databases
 - Reactome: reactome.org
 - KEGG: genome.jp/kegg
 - EcoCyc: ecocyc.org
 - RegulonDB: regulondb.ccg.unam.mx
 - STRING: string-db.org

Take a couple of minutes to review
Glucose Metabolism in Reactome

1.2 Why Model a Biological System?



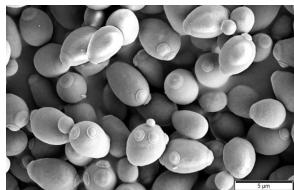
Adapted from lectures by Ursula Kummer

reactome.org/PathwayBrowser/#/R-HSA-70326



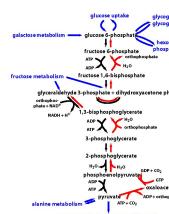
1.3 Typical Steps in Mathematical Modeling

Biological System

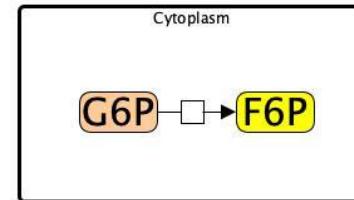


S. cerevisiae

Mental Diagram

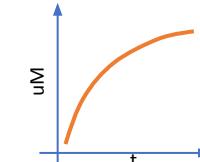


Glycolysis

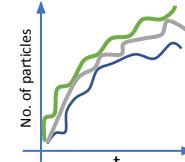


SBGN

Assumptions



Deterministic:
Thousands of
particles



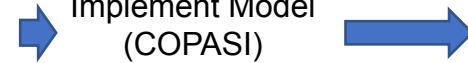
Stochastic: Few particles

Implement Model (COPASI)

Dynamical Model

Quantitative Results

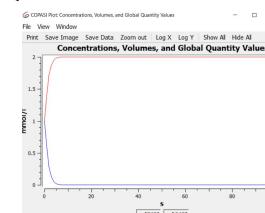
Model Analysis



$$\frac{d([F6P] \cdot V_{\text{compartment}})}{dt} = +V_{\text{compartment}} \cdot \frac{1 \cdot [G6P]}{1 + [G6P]}$$

$$\frac{d([G6P] \cdot V_{\text{compartment}})}{dt} = -V_{\text{compartment}} \cdot \frac{1 \cdot [G6P]}{1 + [G6P]}$$

CONC Plot Concentrations, Volumes, and Global Quantity Values File View Window



Steady State Result

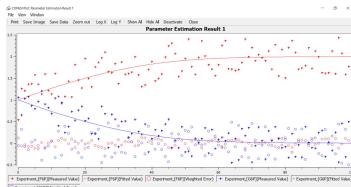
An equilibrium steady state (zero fluxes) was found

Species	Compartments	Model Quantities	Reactions
KINETIC STABILITY ANALYSIS			
The linear stability analysis based on the eigenvalues of the Jacobian matrix is only valid for steady states.			

Steady-State Simulation

→ Model Validation →

Serialize Mode



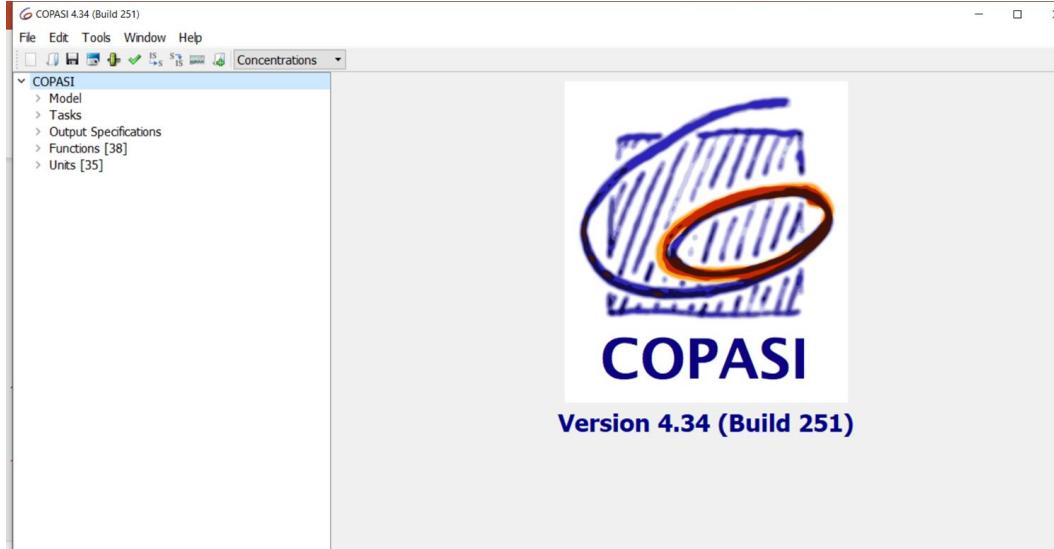
Test predictions

SBMI

Adapted from PLoS Comp Biol. 2021 DOI: [10.1371/journal.pcbi.1008921](https://doi.org/10.1371/journal.pcbi.1008921)

2. COPASI: Software for Modeling and Analysis

Available at copasi.org for all platforms & open source



Install COPASI, open it, &
explore the menus

COPASI models are
based on reactions

2.1 COPASI's Use in Research

 **COPASI**

Home Download Research Support ▾ Projects ▾ Events About ▾

COPASI's Use In Research

COPASI is widely used in many research projects for:

- modeling biological, biochemical, and chemical systems,
- in the development of theory and computational methods,
- in the development of "wet" laboratory methods,
- and as a part of other software tools.

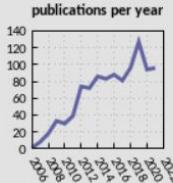
Here is a list of all publications that used COPASI to obtain results, organized by year. There are [links](#) to the full papers and tags by field of research.

2022

Abraha BW, Marchisio MA (2022) NOT Gates Based on Protein Degradation as a Case Study for a New Modular Modeling via SBML Level 3—Comp Package. *Frontiers in Bioengineering and Biotechnology* 10:845240 [Synthetic Biology](#) [Link](#)

Berzins K, Muiznieks R, Baumanis MR, Strazdina I, Shvirksts K, Prikule S, Galvanauskas V, Pleissner D, Pentjuss A, Grube M, Kalnenieks U, Stalidzans E (2022) Kinetic and Stoichiometric Modeling-Based Analysis of Docosahexaenoic Acid (DHA) Production Potential by *Cryptothecodium cohnii* from Glycerol, Glucose and Ethanol. *Marine Drugs* 20:115 [Metabolism](#) [Microbiology](#) [Biotechnology](#) [Environmental Sciences](#) [Link](#)

Borg Y, Alsford S, Pavlika V, Zaikin A, Nesbeth DN (2022) Synthetic biology tools for engineering Goodwin oscillation in *Trypanosoma brucei brucei*. *Heliyon* 8:e08891 [Synthetic Biology](#) [Link](#)


publications per year

Year	Publications
2000	~20
2001	~30
2002	~40
2003	~50
2004	~60
2005	~70
2006	~80
2007	~90
2008	~100
2009	~110
2010	~120
2011	~130
2012	~140
2013	~150
2014	~160
2015	~170
2016	~180
2017	~190
2018	~200
2019	~210
2020	~220
2021	~230
2022	~240


Where is COPASI used? Click for interactive map

2.2 Citation

BIOINFORMATICS

ORIGINAL PAPER

Vol. 22 no. 24 2006, pages 3067–3074
doi:10.1093/bioinformatics/btl485

Systems biology

COPASI—a COmplex PAthway Simulator

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ABSTRACT

Motivation: Simulation and modeling is becoming a standard approach to understand complex biochemical processes. Therefore, there is a big need for software tools that allow access to diverse simulation and modeling methods as well as support for the usage of these methods.

Results: Here, we present COPASI, a platform-independent and user-friendly biochemical simulator that offers several unique features. We discuss numerical issues with these features; in particular, the criteria to switch between stochastic and deterministic simulation methods, hybrid deterministic–stochastic methods, and the importance of random number generator numerical resolution in stochastic simulation.

Availability: The complete software is available in binary (executable) for MS Windows, OS X, Linux (Intel) and Sun Solaris (SPARC), as well as the full source code under an open source license from <http://www.copasi.org>.

Contact: mendes@vbi.vt.edu

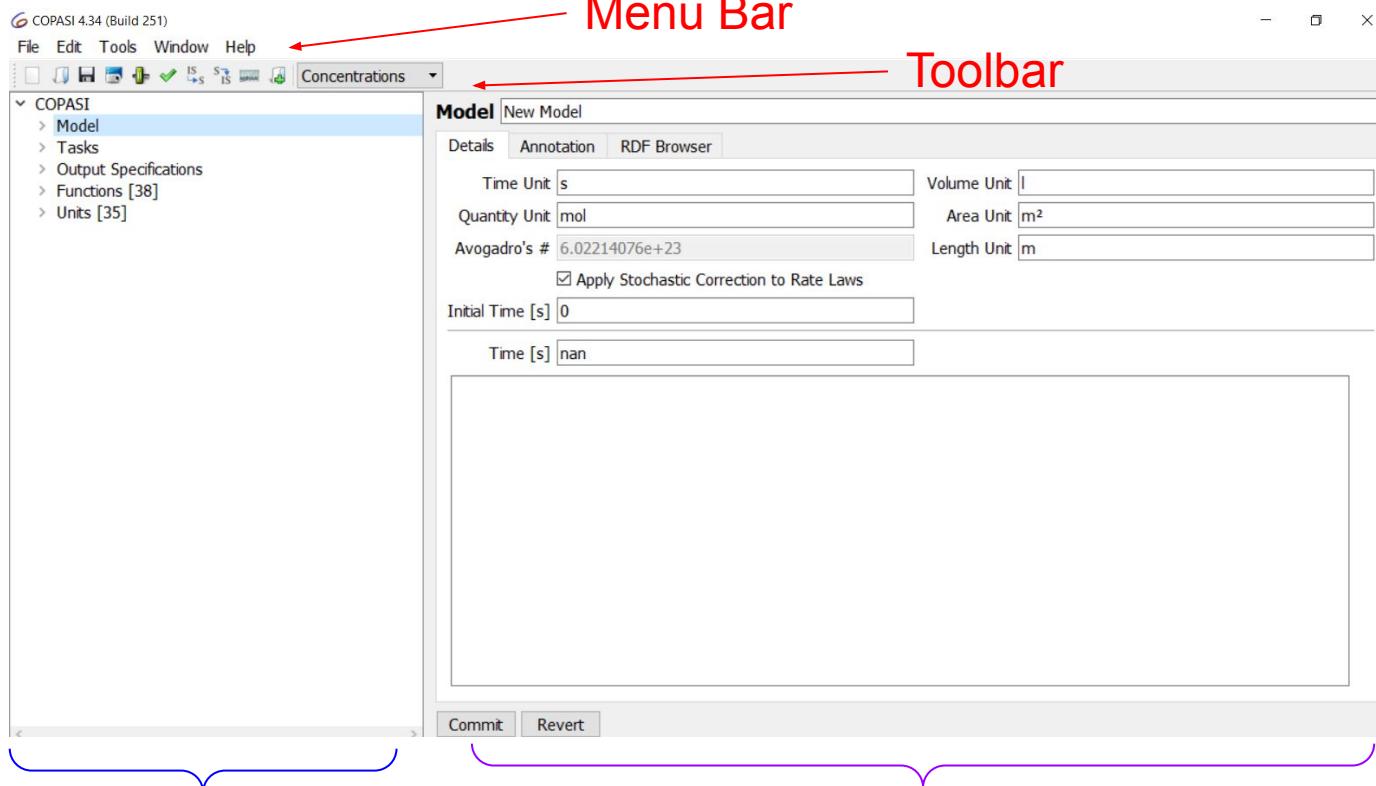
and flux analysis (Klamt *et al.*, 2003). However, some tools contain whole suites of functionalities, e.g. simulation, flux and control analysis (Tomita *et al.*, 1999; Sauro *et al.*, 2003; Meng *et al.*, 2004).

In order to improve the compatibility of these tools, markup languages such as SBML (Hucka *et al.*, 2003) and CellML (Lloyd *et al.*, 2004) were created to allow model exchange. Many tools are now able to read and write models in these file formats.

Here we present a new program—COPASI (COmplex PAthway Simulator)—which combines all of the above standards and some unique methods for the simulation and analysis of biochemical reaction networks. COPASI is the successor to Gepasi (Mendes, 1993, 1997) and is available for all major operating systems (Linux, Mac OS X, Windows, Solaris). As described below, COPASI supports non-expert users by, for example, automatically converting reaction equations to the appropriate mathematical formalism (ODEs or reaction propensities). The general features of COPASI

Downloaded from <https://academic.oup.com/bioinformatics/>

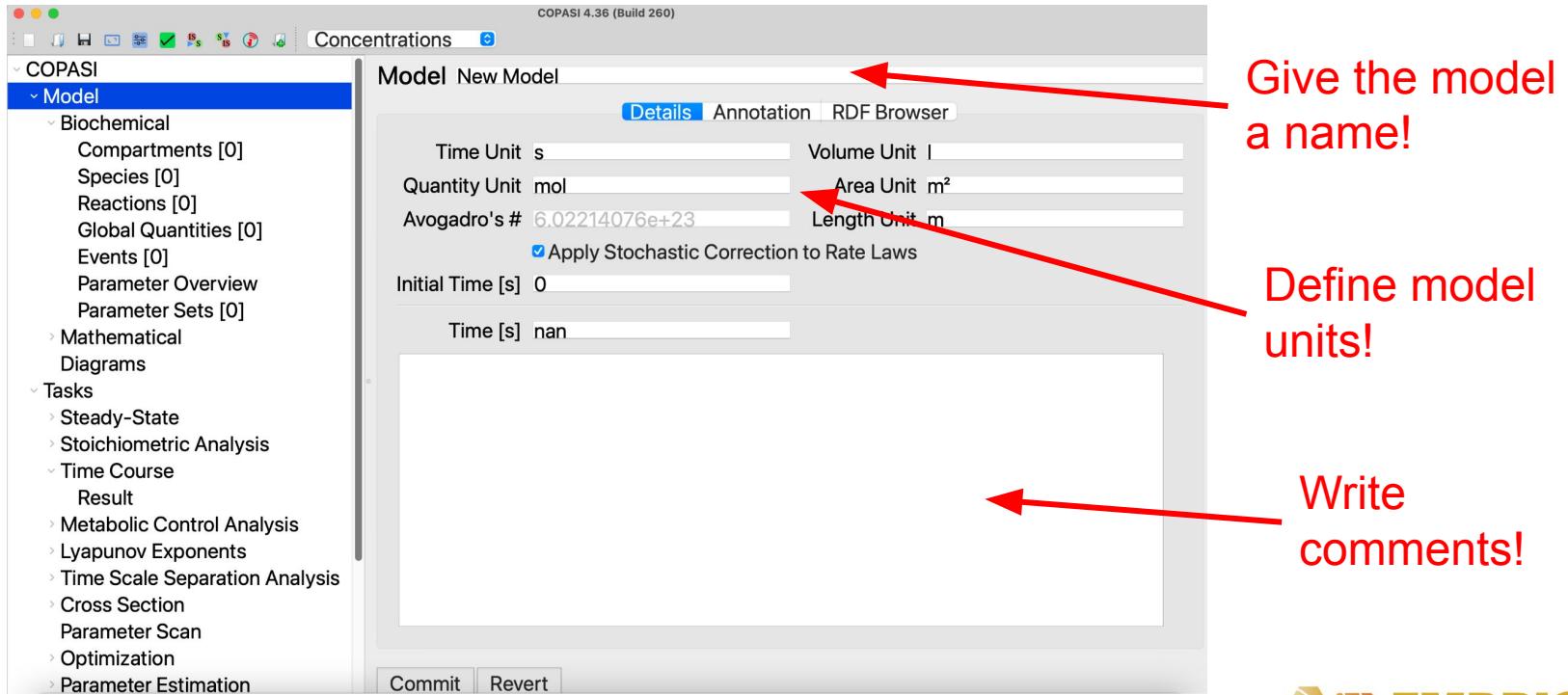
2.3 COPASI Graphical User Interface



Object Tree: Model, Tasks, Output Specifications, Functions, & Units

Controls related to the selected element in the object tree

2.4 General Definitions



2.5 General Definitions

The screenshot shows the COPASI 4.36 software interface with the title bar "BIOMD0000000329_url - COPASI 4.36 (Build 260) /Users/.../Downloads/BIOMD0000000329_url.cps". The left sidebar shows a tree view of the model components:

- COPASI
- Model (selected)
- Biochemical
 - Compartments [1] compartment
- Species [3]
 - activePLC
 - Calcium
 - G-alpha
- Reactions [8]
 - R1
 - R2
 - R3
 - R4
 - R5
 - R6
 - R7
 - R8
- Global Quantities [0]
- Events [0]
- Parameter Overview
- Parameter Sets [0]
- Mathematical Diagrams

The main panel displays the "Model Kummer2000 - Oscillations in Calcium Signalling" configuration. It includes the following settings:

- Time Unit: s
- Volume Unit: l
- Quantity Unit: nmol
- Area Unit: m²
- Avogadro's #: 6.02214076e+23
- Length Unit: m
- Apply Stochastic Correction to Rate Laws
- Initial Time [s]: 0
- Time [s]: nan

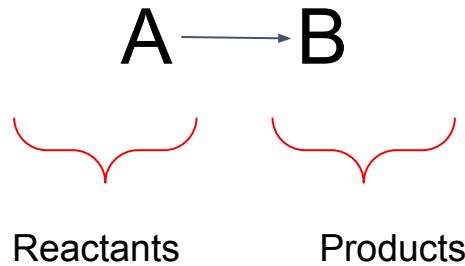
A detailed description of the model is provided in a text box:

Kummer2000 - Oscillations in Calcium Signalling
Simplified (3-variable) calcium oscillation model Kummer et al. (2000) Biophys. J. 79, 1188-1195 This model is defined in a small compartment with low concentrations. You can run it first with the LSODA ODE solver and then with the Gillespie Monte Carlo method (in Time Course widget). This illustrates that at low particle numbers, as here, the stochastic simulation and the ODE approach produce different results (the stochastic approach is more correct in these circumstances). This file also demonstrates the use of several different plots to visualize results, including a histogram.

This model is described in the article:

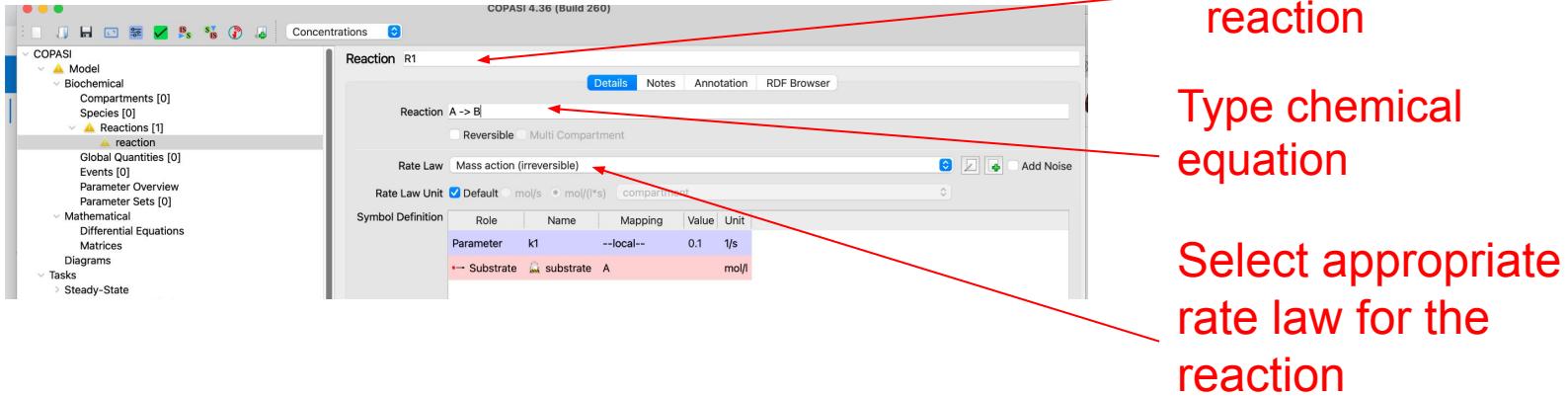
Commit Revert

2.6 Chemical Equation



A **chemical reaction** is usually depicted in the form of a **chemical equation** which describes the transformation of one or more reactants into one or more products. The reactants appear on the left of the equation and the products on the right. Both sides are separated by an arrow indicating the positive direction of the transformation. Such reaction can be studied by observing the change in concentration of A and/or B in time.

2.7 The most practical way to enter a model is to start by adding its component reactions



Type chemical equation

A → B (dash and right angle bracket)

A + B = C + D (equals sign means that substrates separate from products and the reaction is considered kinetically reversible)

3. Chemical Kinetics: Reaction Kinetics

- How fast chemical reactions take place?
- What factor influence the rate of reaction?
- What mechanisms are responsible?

3.1 Biochemical Networks

Chemical equation

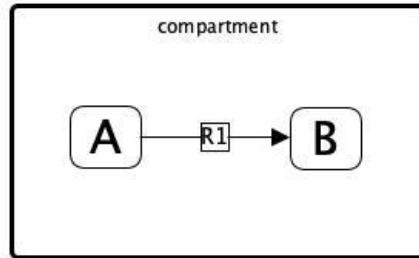


During a **reaction event** one molecule A reacts to form one molecule of B

$$1\text{mol} = 6.0221415 \times 10^{23} \text{ (Avogadro's constant)}$$

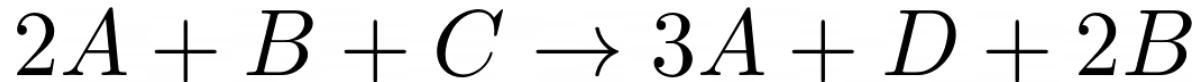
$$M = \text{Molar Concentration} = \frac{\text{mol}}{\text{l}} = \frac{\text{mol}}{\text{dm}^3}$$

Biochemical networks are a set of chemical species that can be converted into each other through chemical reactions



3.2 Stoichiometric Amount

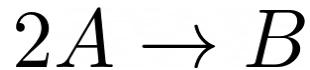
It is defined as the **number of molecules** of a particular reactant or product taking part in a reaction. They will be positive.



This notation means that during a **reaction event**, 2 molecules of A, one molecule of B and one molecule of C react to form 3 molecules of A, one molecule of D, and 2 molecules of B.

3.3 Stoichiometric Coefficients

$c_i = \text{Molar Amount of Product} - \text{Molar Amount of Reactant}$



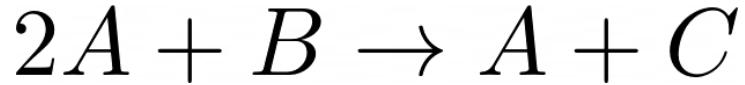
$$c_A = 0 - 2 = -2$$

$$c_B = 1 - 0 = 1$$

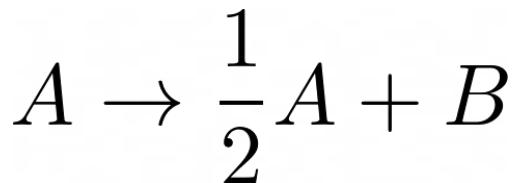
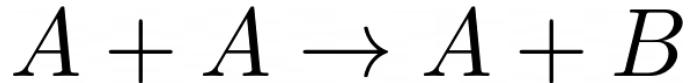
Note: Stoichiometric coefficients can be fractional amounts

3.4 Test Your Knowledge

List the **stoichiometric amounts** for the following reactions:



Write down the **stoichiometric coefficients** for the following reactions:

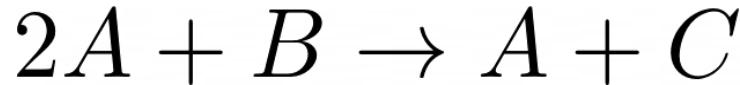


3.5 Solution

List the **stoichiometric amounts** for the following reactions:



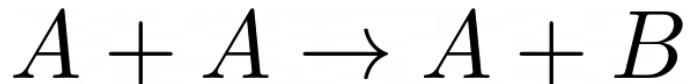
ADP has a stoichiometric amount of two, ATP a stoichiometric amount of one, and AMP also with a stoichiometric amount of one.



On the reactant side the stoichiometric amount for A is two and for B is one. On the product side, the stoichiometric amount for A is one and for C one.

3.6 Solution

Write down the **stoichiometric coefficients** for the following reactions:



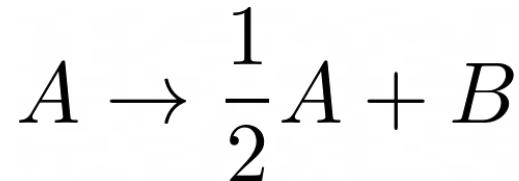
The stoichiometric amount of A on the reactant side is 2 and on the product side 1. Therefore the stoichiometric coefficient for A is $1 - 2 = -1$
The stoichiometric amount of B on the product side is 1 and on the reactant side, 0, therefore the stoichiometric coefficient for B is $1 - 0 = 1$

$$c_A = 1 - 2 = -1$$

$$c_B = 1 - 0 = 1$$

3.7 Solution

Write down the **stoichiometric coefficients** for the following reactions:

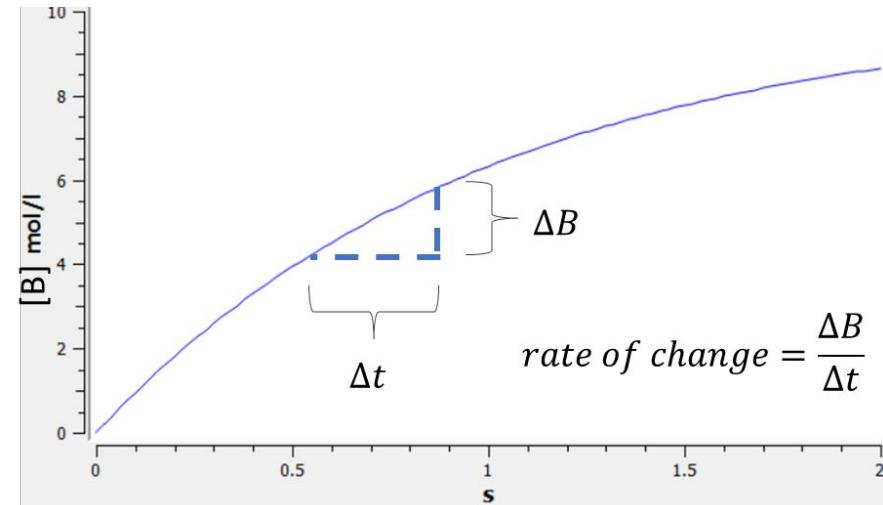
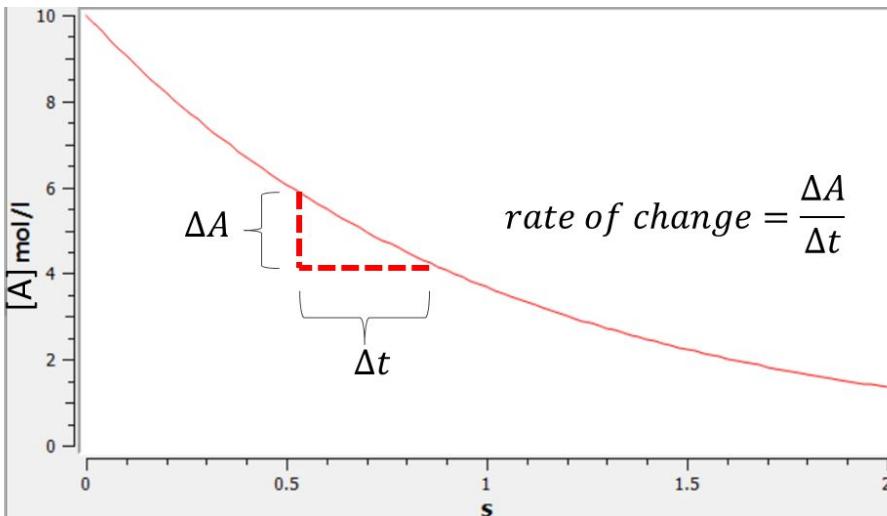


The stoichiometric amount of A on the reactant side is 1 and on the product side $\frac{1}{2}$. Therefore the stoichiometric coefficient for A is $\frac{1}{2} - 1 = -\frac{1}{2}$. The stoichiometric amount of B on the product side is 1 and on the reactant side, 0, therefore the stoichiometric coefficient for B is $1 - 0 = 1$.

$$c_A = \frac{1}{2} - 1 = -\frac{1}{2}$$

$$c_B = 1 - 0 = 1$$

3.8 Rate of change A->B

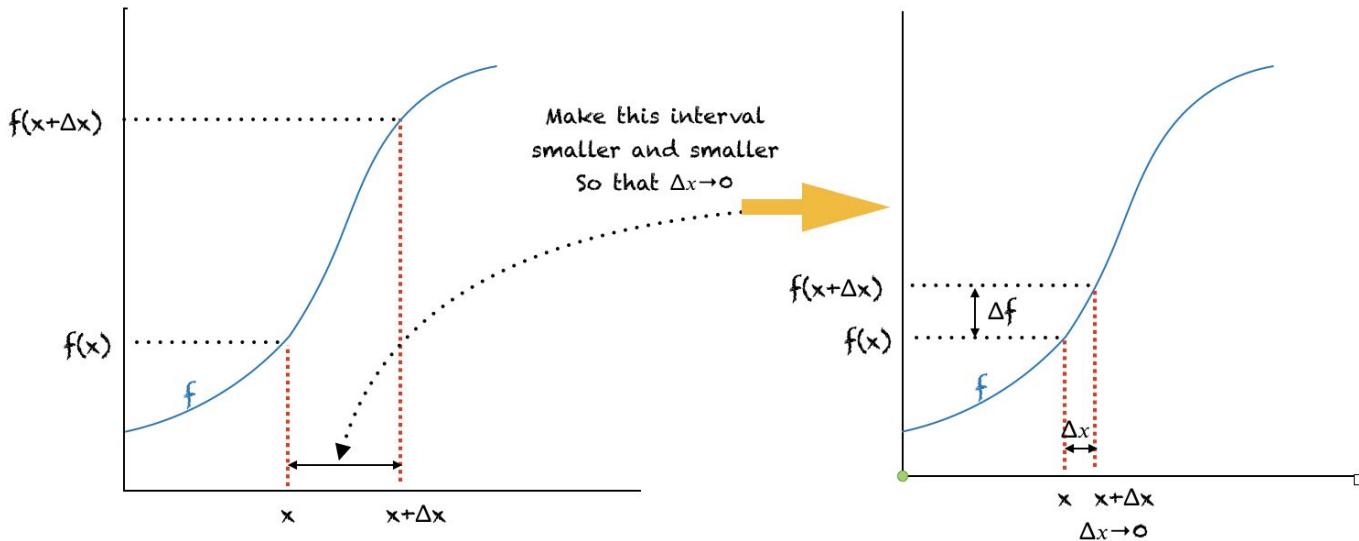


The rate of change can be defined as the rate of change in concentration or amount (depending on units) of a designated species.

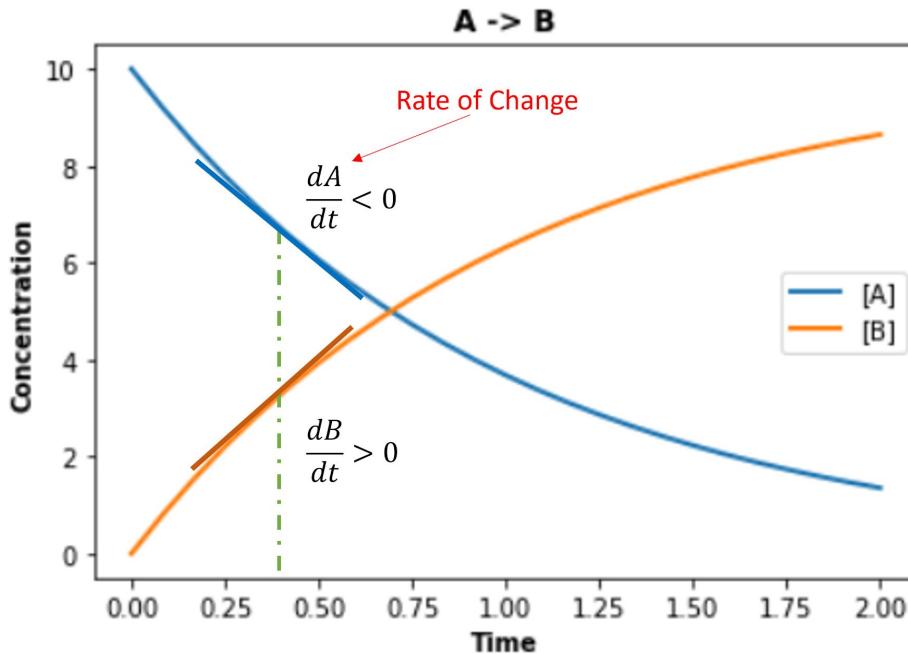
3.9 Derivative (Definition)

Derivative of f is the rate of change of f

$$f'(x) = \frac{df}{dx} = \lim_{\Delta x \rightarrow 0} \frac{f(x + \Delta x) - f(x)}{\Delta x} = \lim_{\Delta x \rightarrow 0} \frac{\Delta f}{\Delta x}$$



3.10 Instantaneous Rate of Change (Derivative)



Rate of Change

$$\frac{dX}{dt} \text{ [mol l}^{-1} \text{s}]$$

$$\left| \frac{dA}{dt} \right| = \left| \frac{dB}{dt} \right|$$

Total mass conservation

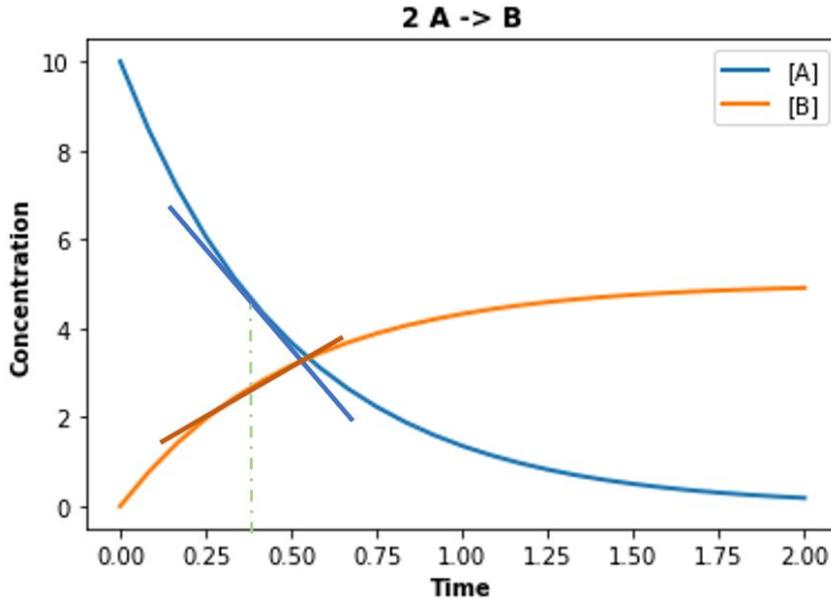
$$\frac{dA}{dt} + \frac{dB}{dt} = 0$$

Rates change as reactants are consumed and products made, the rate of change is better defined as the **instantaneous change in concentration**, or derivative

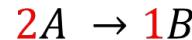
Adapted from lectures by Herbert Sauro

3.11 Reaction Rate v

The number of reaction events per time.



$$\left| \frac{dA}{dt} \right| \neq \left| \frac{dB}{dt} \right|$$



$$c_A = 0 - 2 = -2$$

$$c_B = 1 - 0 = +1$$

$$\frac{dA}{dt} \frac{1}{-2} = \frac{dB}{dt} \frac{1}{+1} = v$$

3.12 Reaction Kinetics

Rate of reaction: v

Rate of change: $\frac{dx}{dt}$

Stoichiometric coefficients: c_x

c_x {
+ for products
- for reactants

$$v = \frac{dx}{dt} \cdot \frac{1}{c_x} \text{ (mol} \cdot \text{l}^{-1} \cdot \text{s}^{-1}\text{)}$$

$$\frac{dx}{dt} = c_x v$$

Mathematical
expression
for my computer model



3.13 ODE-Based Models

Each chemical species in the network is represented by an **ordinary differential equation (ODE)** that **describes** the **rate of change** of that species along time

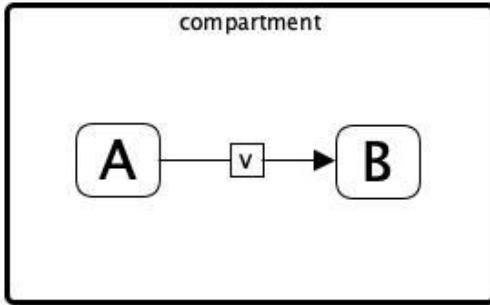
$$\frac{dx}{dt} = \sum_i c_i \cdot v_i \quad (mol \cdot l^{-1} \cdot s^{-1})$$

Rate Law

c_i : stoichiometric coefficient is the number of molecules of X consumed or produced in one cycle of reaction.

v_i : velocity of reaction i is described by a rate law

3.14 What Determines v ?



- Temperature
- Concentration
- Pressure
- pH
- etc

How does concentration affect v ?

[A], a or A	v
5 mM	$3 \text{ mol} \cdot l^{-1} \cdot s^{-1}$
10 mM	$6 \text{ mol} \cdot l^{-1} \cdot s^{-1}$

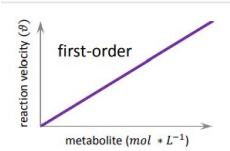
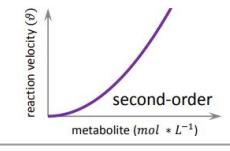
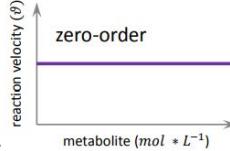
$$v \propto A$$
$$v = kA$$

Law of mass-action or
Mass-action Kinetics

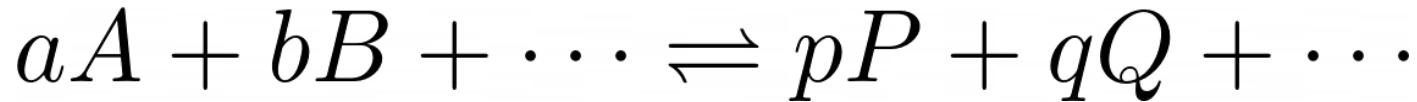
Rate constant

3.15 Mass-Action Kinetics

Elementary reactions are chemical reactions that involve intermediates that do not participate in a reaction

Reaction	Rate law	name	graph
$A \rightarrow B$	$v = kA$ $k(\text{unit : } t^{-1})$	reaction of order 1 e.g., radioactive decay	
$A + A \rightarrow B$	$v = kA^2$ $k[\text{units : } 1/(M \cdot t)]$	reaction of order 2 e.g., two reactants react with each other	
$\rightarrow B$	$v = kA^0 = k$ $k[\text{units : } M/t]$	reaction of order 0 e.g., constant supply	

3.16 Mass-Action Kinetics (General)



$$v_{net} = v_f - v_r$$

v_{net} : net reaction rate

$$v_f = k_1 A^a B^b \dots$$

v_f : forward reaction rate

$$v_r = k_2 P^p Q^q \dots$$

v_r : reverse reaction rate

k_1, k_2 are rate constants

3.17 Enzyme Kinetics

Michaelis - Menten/Briggs-Haldane Kinetics



$$\frac{dS}{dt} = -k_1 \cdot S \cdot E + k_{-1} \cdot ES$$

$$\frac{dE}{dt} = -k_1 \cdot S \cdot E + k_{-1} \cdot ES + k_2 \cdot ES$$

$$\frac{ES}{dt} = +k_1 \cdot S \cdot E - k_{-1} \cdot ES - k_2 \cdot ES$$

$$\frac{dP}{dt} = +k_2 \cdot ES$$

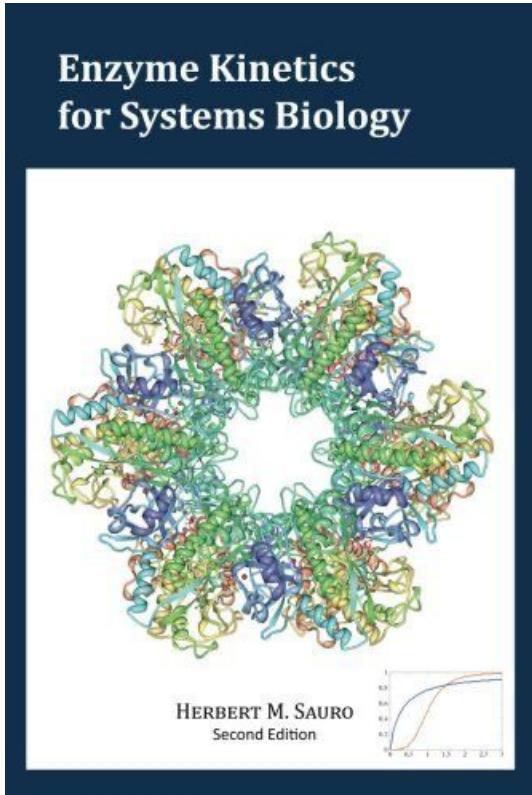
$$v = \frac{k_2 \cdot S \cdot E_0}{K_M + S} = \boxed{\frac{v_{max} \cdot S}{K_M + S}}$$

$$K_M = \frac{k_{-1}}{k_1} \quad v_{max} = E_0 \cdot k_2$$

Conserved entities: in many cases the total enzyme concentration can be considered constant: $E + ES = E_0 = \text{constant}$

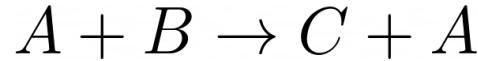
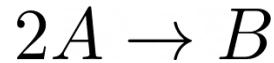
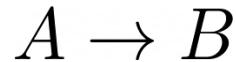
Assumptions: fast equilibrium of ES formation and S in excess compared to E

**3.18 For a comprehensive derivation of rate laws
please refer to**



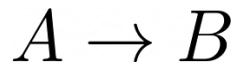
3.19 Test Your Knowledge

Write down the **mass-action rate laws** for the following reversible reactions. Assume that the forward and reverse rate constants are k_1 and k_2 , respectively.

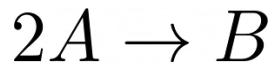


3.19 Solution

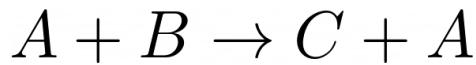
Write down the **mass-action rate laws** for the following reversible reactions. Assume that the forward and reverse rate constants are k_1 and k_2 respectively.



$$v = k_1 A - k_2 B$$



$$v = k_1 A^2 - k_2 B$$



$$v = k_1 AB - k_2 CA = A(k_1 B - k_2 C)$$

4. Model Set-Up: Terminology

Variables: values **do** change → components, e.g., species concentrations.

Parameters: values **can** change → reactions, e.g., values of enzyme activities, e.g., V_{max} , K_m , etc but not during the analyzed time.

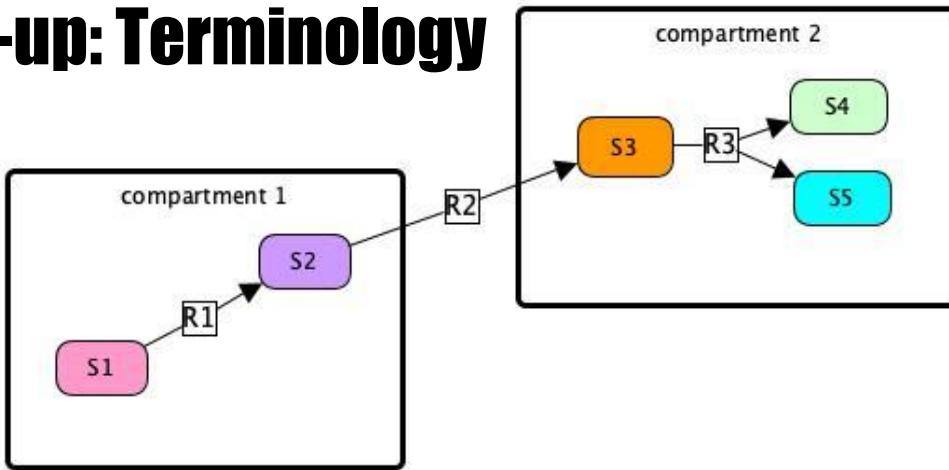
Constants: values **never** change → fixed values, e.g., Avogadro number.

4.1 Model Set-Up: Data Sources for Regulatory Information and constants

- Books
- Publications
- Databases about activators and inhibitors as well as kinetic constants
 - Sabio-RK: sabio.h-its.org
 - BRENDA: brenda-enzymes.org

Take a couple of minutes to review these websites

4.2 Model Set-up: Terminology



- Compartments: Have a volume and contain species
- Species: Have a concentration
- Reactions: Consume and produce species and have a reaction rate (arbitrary kinetic functions)

4.3 Entering Reactions

The screenshot shows the COPASI 4.36 software interface. The left sidebar contains a tree view of project components: Compartments [1], Species [2] (with entries A and B), Reactions [1] (with entry R1 selected), Global Quantities [0], Events [0], Parameter Overview, Parameter Sets [0], Mathematical Diagrams, Tasks (with sub-options Steady-State, Stoichiometric Analysis, Time Course Result, Metabolic Control Analysis, Lyapunov Exponents, Time Scale Separation Analysis, Cross Section, Parameter Scan, Optimization), and a Help section.

The main workspace is titled "Reaction R1" under the "Concentrations" tab. It displays the following details:

- Reaction A → B**
- Reversible Multi Compartment
- Rate Law:** Mass action (irreversible)
- Rate Law Unit:** Default mol/s mol/(l*s) compartment
- Symbol Definition:** A table with columns Role, Name, Mapping, Value, and Unit.

Role	Name	Mapping	Value	Unit
Parameter	k1	--local--	0.1	1/s
Substrate	substrate A			mol/l
- Flux [mol/s]:** nan
- Buttons:** Commit, Revert, New, Copy, Delete

4.4 Species

The screenshot shows the COPASI 4.36 software interface. The left sidebar menu is open, showing various model components: Model, Biochemical, Species [2], Reactions [1], Global Quantities [0], Events [0], Parameter Overview, Parameter Sets [0], Mathematical Diagrams, Tasks, Output Specifications, Functions [38], and Units [35]. The 'Species [2]' section is expanded, and 'Species A' is selected, which is highlighted with a gray background.

The main panel displays the 'Species A' configuration. At the top, there are tabs for Details, Notes, Annotation, and RDF Browser. The 'Details' tab is active. Below the tabs, the following parameters are shown:

- Compartment: compartment
- Simulation Type: reactions
- Initial Concentration [mol/l]: 1
- Concentration [mol/l]: nan
- Rate [mol/(l*s)]: 0
- Transition Time [s]: 0

Below these fields, two sections show associations:

- Involved in 1 Compartments: Compartments[compartment]
- Involved in 1 Reactions: R1: A -> B

At the bottom of the panel are buttons for Commit, Revert, New, Copy, and Delete.

You can change initial concentrations, set compartment, & change simulation type: reactions, fixed, assignment, or ODE

4.5 Species: Initial Concentrations

The screenshot shows the COPASI 4.36 software interface. The left sidebar displays a tree view of the model structure:

- COPASI
- Model
 - Biochemical
 - Compartments [1]
 - compartment
 - Species [2]
 - A
 - B
 - Reactions [1]
 - R1
 - Global Quantities [0]
 - Events [0]
 - Parameter Overview
 - Parameter Sets [0]
 - Mathematical
 - Diagrams
- Tasks
- Output Specifications
- Functions [38]
- Units [35]

The main window title is "Concentrations". The central area contains a table titled "Search:" with the following data:

#	Name	Compartment	Type	Unit	Initial Concentration [Unit]
1	A	compartment	reactions	mol/l	1
2	B	compartment	reactions	mol/l	0
	New Species	compartment	reactions	mol/l	1

At the bottom of the main window are buttons: New, Delete, and Delete All.

4.6 Compartments

The screenshot shows the COPASI 4.36 (Build 260) software interface. The left sidebar menu is expanded to show the 'Model' section, specifically the 'Compartments [1]' subsection, which is highlighted. The main workspace displays the configuration for a single compartment named 'compartment'. The 'Details' tab is selected, showing the following parameters:

- Dimensionality: 3D - Volume
- Simulation Type: fixed
- Initial Volume [l]: 1
- Volume [l]: nan
- Rate [l/s]: 0
- Contained Species: A
- Species: B

At the bottom of the workspace are 'Commit' and 'Revert' buttons, and a row of buttons for 'New', 'Copy', and 'Delete' operations.

You can define any number of compartments of any positive size

There is a default compartment called 'compartment' of unit (1) volume

5. Time Course Simulations

The screenshot shows the COPASI 4.36 software interface for a model named "ex_ab". The left sidebar contains a tree view of the model structure:

- Compartments [1]
 - compartment
- Species [2]
 - A
 - B
- Reactions [1]
 - R1
- Global Quantities [0]
- Events [0]
- Parameter Overview
- Parameter Sets [0]
- Mathematical Diagrams
- Tasks
 - Steady-State
 - Stoichiometric Analysis
 - Time Course
 - Result
 - Metabolic Control Analysis
 - Lyapunov Exponents
 - Time Scale Separation Analysis
 - Cross Section
 - Parameter Scan
 - Optimization

The "Time Course" task is selected in the tasks list.

The main panel displays the "Time Course" configuration:

- Duration [s] 30 Intervals 100 Interval Size [s] 0.3 Automatic
- Start in Steady State
- Suppress Output Before [s] 0
- Output Events
- Save Result in Memory
- Integration Interval [s] 0 to 30
- Output Interval [s] 0 to 30
- Method: Deterministic (LSODA)
- Integrate Reduced Model
- Relative Tolerance: 1e-06
- Absolute Tolerance: 1e-12
- Max Internal Steps: 100000
- Max Internal Step Size: 0

At the bottom are buttons for Run, Revert, Report, and Output Assistant.

5.1 Time-Course Simulation Results

ex_ab - COPASI 4.36 (Build 260) /Users/.../copasi_embrio/ex_ab.cps

Concentrations

COPASI

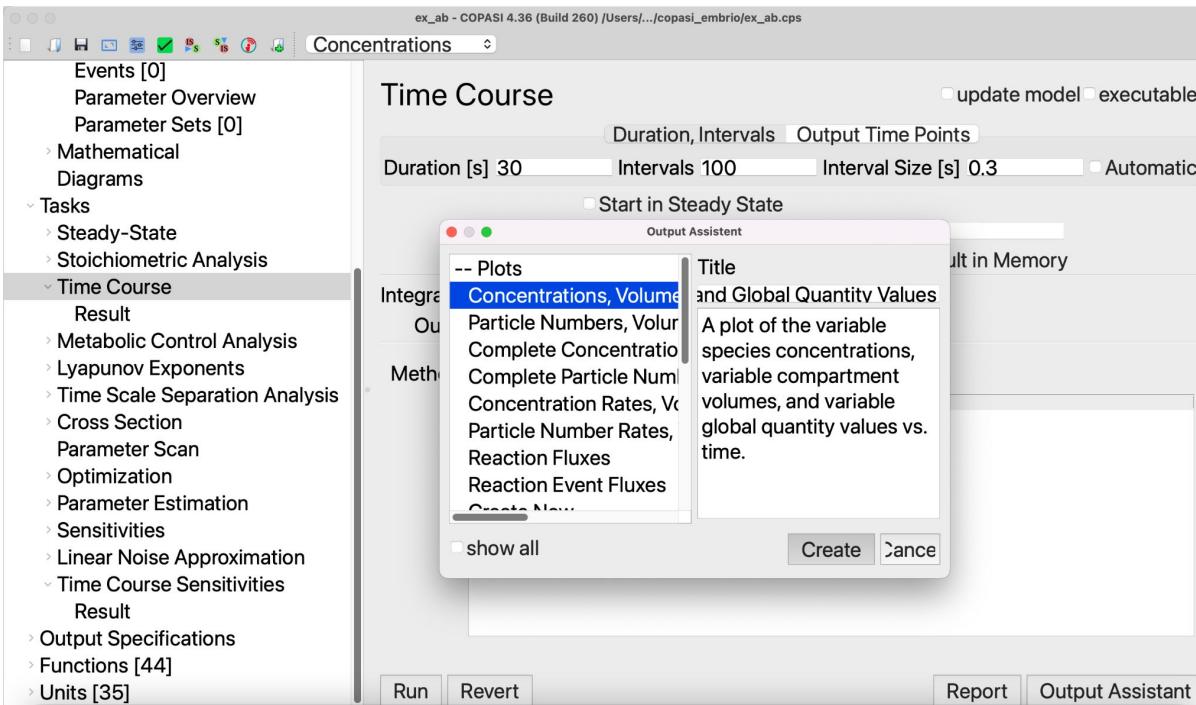
- Model
 - Biochemical
 - Compartments [1]
compartment
 - Species [2]
A
B
 - Reactions [1]
R1
 - Global Quantities [0]
 - Events [0]
 - Parameter Overview
 - Parameter Sets [0]
- Mathematical Diagrams
- Tasks
 - Steady-State
 - Stoichiometric Analysis
 - Time Course
 - Result
- Metabolic Control Analysis
- Lyapunov Exponents
- Time Scale Separation Analysis

Time Course Result

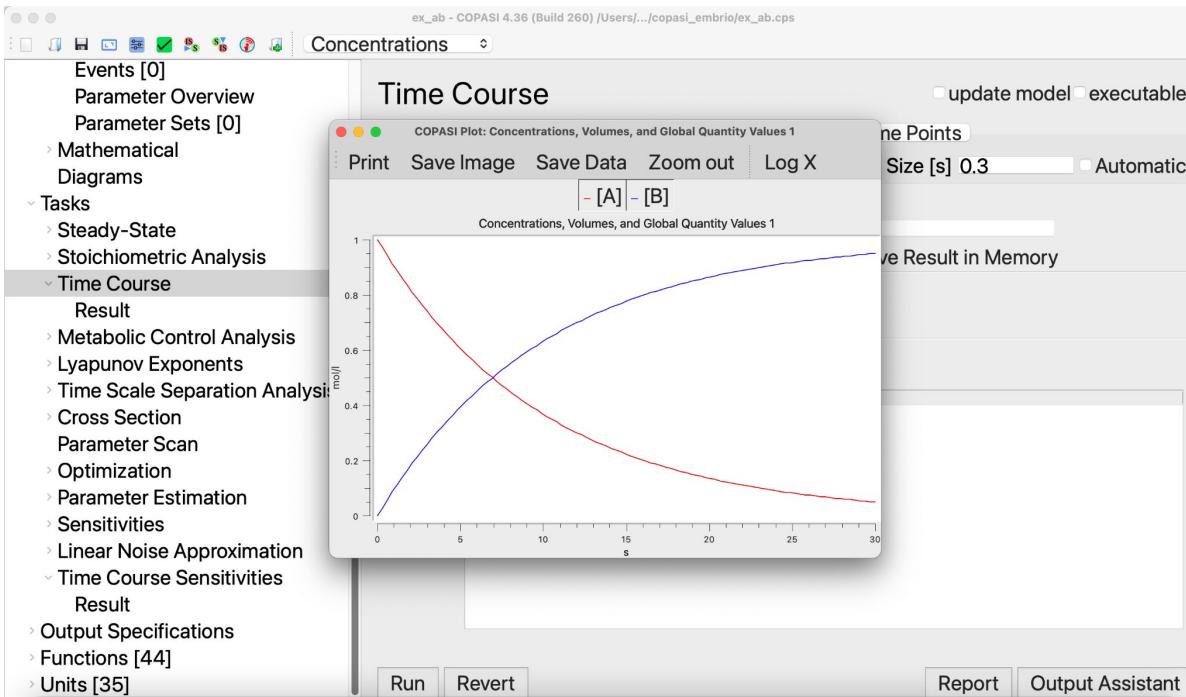
Save

	Time	A	B
1	0	1	0
2	0.3	0.970446	0.0295545
3	0.6	0.941765	0.0582355
4	0.9	0.913931	0.0860688
5	1.2	0.88692	0.11308
6	1.5	0.860708	0.139292
7	1.8	0.83527	0.16473
8	2.1	0.810584	0.189416
9	2.4	0.786628	0.213372
10	2.7	0.763379	0.236621
11	3	0.740818	0.259182
12	3.3	0.718924	0.281076
13	3.6	0.697676	0.302324
14	3.9	0.677057	0.322943
15	4.2	0.657047	0.342953
16	4.5	0.637628	0.362372
17	4.8	0.618783	0.381217

5.2 Create a Graph

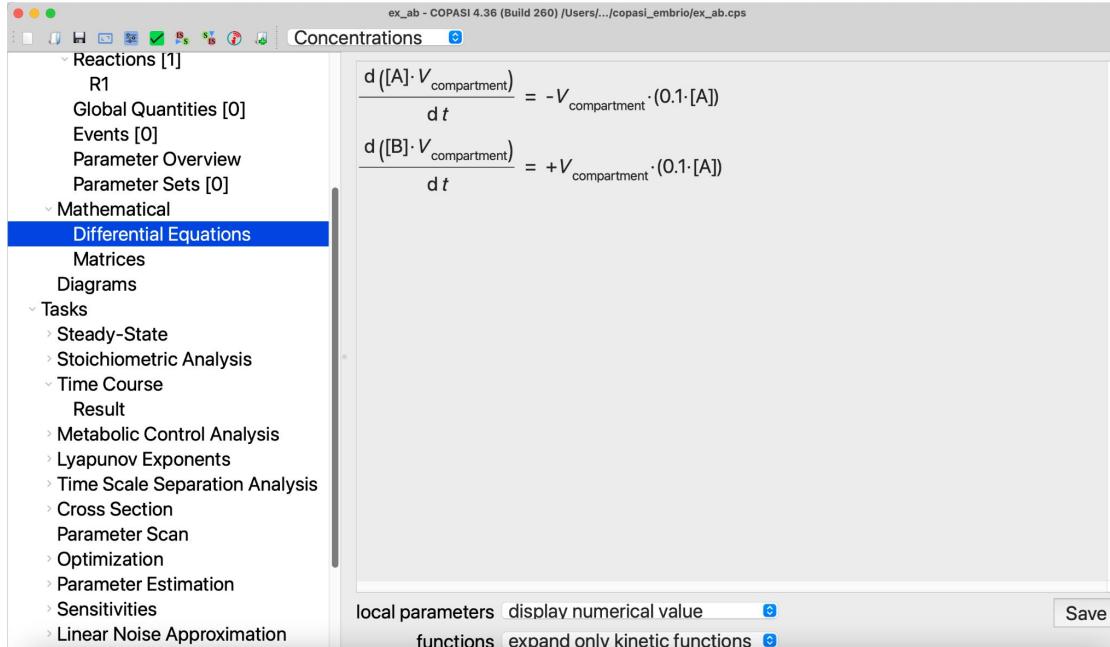


5.3 Basic Plotting



5.4 Looking at the ODEs

Have a look at the ODE version of your model in COPASI



The screenshot shows the COPASI 4.36 software interface with the title bar "ex_ab - COPASI 4.36 (Build 260) /Users/.../copasi_embrio/ex_ab.cps". The left sidebar has a tree view of the model structure:

- Reactions [1]
 - R1
- Global Quantities [0]
- Events [0]
- Parameter Overview
- Parameter Sets [0]
- Mathematical
 - Differential Equations
 - Matrices
 - Diagrams
- Tasks
 - Steady-State
 - Stoichiometric Analysis
 - Time Course
 - Result
 - Metabolic Control Analysis
 - Lyapunov Exponents
 - Time Scale Separation Analysis
 - Cross Section
 - Parameter Scan
 - Optimization
 - Parameter Estimation
 - Sensitivities
 - Linear Noise Approximation

5.5 Run a Simulation

Implement a model of only one reaction: G6P \rightarrow F6P. Take into account that GPI (Glucose-6-phosphate isomerase) interconverts G6P and F6P.

Run a simulation and plot the result using the output assistant.

Manually vary a parameter and see the impact: you can e. g. change initial concentrations of the species G6P and F6P

5.6 Solution

COPASI 4.36 (Build 260) /Users/.../basic/PGI_1.cps

Concentrations

Reaction PGI

Reaction G6P -> F6P

Reversible Multi Compartment

Rate Law Henri-Michaelis-Menten (irreversible)

Rate Law Unit Default mmol/s mmol/(l*s) compartment

Symbol Definition	Role	Name	Mapping	Value	Unit
Substrate	substrate	G6P		mmol/l	
Parameter	Km	--local--	1	mmol/l	
Parameter	V	--local--	1	mmol/(l*s)	

Flux [mmol/s] -5.137118107e-18

Commit Revert New Copy Delete

PGI

Global Quantities [0]

Events [0]

Parameter Overview

Parameter Sets [0]

Biochemical

Compartments [1]

Species [2]

F6P

G6P

Reactions [1]

PGI

Mathematical

Differential Equations

Matrices

Diagrams

Tasks

Steady-State

Stoichiometric Analysis

Time Course

Result

Metabolic Control Analysis

Lyapunov Exponents

Time Scale Separation Analysis

Cross Section

Parameter Scan

Optimization

Parameter Estimation

Sensitivities

Linear Noise Approximation

Time Course Sensitivities

6. Steady-State

- Species concentrations do not change with time
- Consumption rates are in balance with production rates

Newton Method

- Fast
- Not guaranteed to converge

Integration

- Slower
- Will converge for steady states

Backwards Integration

- Only needed in rare cases

6.1 Steady - State Simulations

The screenshot shows the COPASI 4.36 software interface. The title bar reads "PGI_1 - COPASI 4.36 (Build 260) /Users/.../basic/PGI_1.cps". The left sidebar menu is expanded to show the "COPASI" section, with "Steady-State" selected. The main panel is titled "Steady State" and contains a table of parameters:

Name	Value
Resolution	1e-09
Derivation Factor	0.001
Use Newton	<input checked="" type="checkbox"/>
Use Integration	<input checked="" type="checkbox"/>
Use Back Integration	<input type="checkbox"/>
Accept Negative Concentrations	<input type="checkbox"/>
Iteration Limit	50
Maximum duration for forward integration	1000000000
Maximum duration for backward integration	1000000
Target Criterion	Distance and Rate

At the bottom of the main panel are buttons for "Run", "Revert", "Report", and "Output Assistant". There are also checkboxes for "update model", "executable", "calculate Jacobian", and "perform Stability Analysis".

6.2 Steady-State Simulations

The screenshot shows the COPASI 4.36 software interface. The left sidebar displays the model structure under the 'COPASI' heading, including 'Model' (Biochemical, Compartments [1], Species [2] F6P, G6P, Reactions [1] PGI), 'Global Quantities [0]', 'Events [0]', 'Parameter Overview', 'Parameter Sets [0]', 'Mathematical' (Differential Equations, Matrices, Diagrams), and 'Tasks' (Steady-State, Stoichiometric Analysis, Time Course, Metabolic Control Analysis, Lyapunov Exponents, Time Scale Separation Analysis, Cross Section, Parameter Scan, Optimization, Parameter Estimation, Sensitivities, Linear Noise Approximation). The 'Steady-State' task is currently selected.

The main panel title is 'Steady State Result'. A message states: 'An equilibrium steady state (zero fluxes) was found.' Below this is a table titled 'Species' with columns: Name, Type, Concentration [mmol/l], Rate [mmol/(l*s)], and Transition Time [s]. The data shows:

Name	Type	Concentration [mmol/l]	Rate [mmol/(l*s)]	Transition Time [s]
1 F6P	reactions	2	0	inf
2 G6P	reactions	0	0	nan

Buttons at the top right include 'Update Model' and 'Save to File'.

6.3 Steady State Results

The screenshot shows the COPASI interface with the title bar "PGI_1 - COPASI 4.36 (Build 260) /Users/.../basic/PGI_1.cps". The left sidebar menu is expanded, showing categories like COPASI, Model, Biochemical, Species, Reactions, Global Quantities, Events, Parameter Overview, Parameter Sets, Mathematical, Differential Equations, Matrices, Diagrams, Tasks, and Steady-State. Under Tasks, "Steady-State" is selected, and "Result" is highlighted. The main window title is "Steady State Result". A message states: "An equilibrium steady state (zero fluxes) was found." Below this are tabs: Species, Compartments, Model Quantities, Reactions, Stability (which is selected), Jacobian (Complete), Jacobian (Reduced), and Protocol. The "Stability" tab contains the following text:

KINETIC STABILITY ANALYSIS
The linear stability analysis based on the eigenvalues of the Jacobian matrix is only valid for steady states.

Summary:
This state is asymptotically stable.

Eigenvalue statistics:
Largest real part: -1
Largest absolute imaginary part: 0
1 are purely real
0 are purely imaginary
0 are complex
0 are equal to zero
0 have positive real part
1 have negative real part
stiffness = 1.00000
time hierarchy = nan

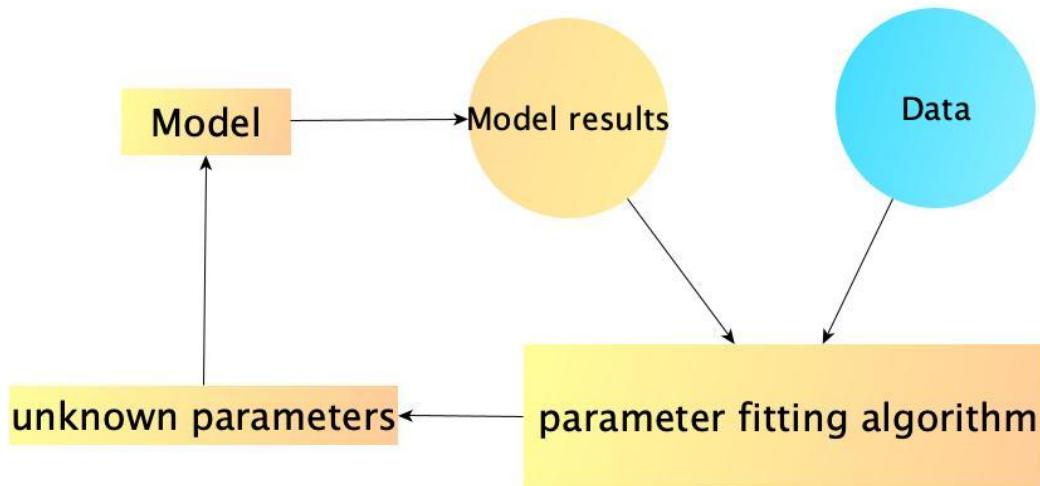
Fold bifurcation test functions (standard, bifurcation discovery tool): 1.00000, 1.57283
Hopf bifurcation test functions (standard, bifurcation discovery tool): 1.00000, -100.000

Oscillation indicator: 0.00000

7. Parameter Estimation

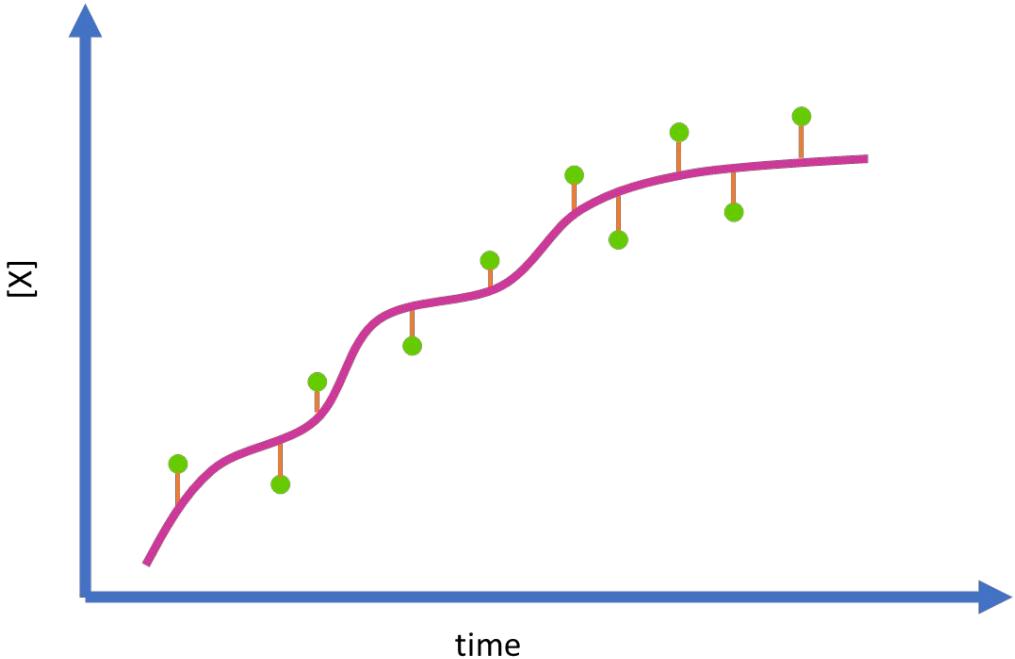
- When starting a model usually many parameters are not known.
- How to find these parameter values?
 - Experimental Approach: Design experiments for measuring the specific values
 - Systems Biology Approach: Adapt a complete model to **experimental data**

7.1 Basic Idea of Parameter Fitting



Change the model parameters to fit experimental data

7.2 Least Squares Distance Measure



$$D(p) = \sum_{i=1}^N (x_i - y_i(p))^2$$

x_i : measured values for time t_i

$y_i(p)$: simulated values for time t_i ,
parameter p

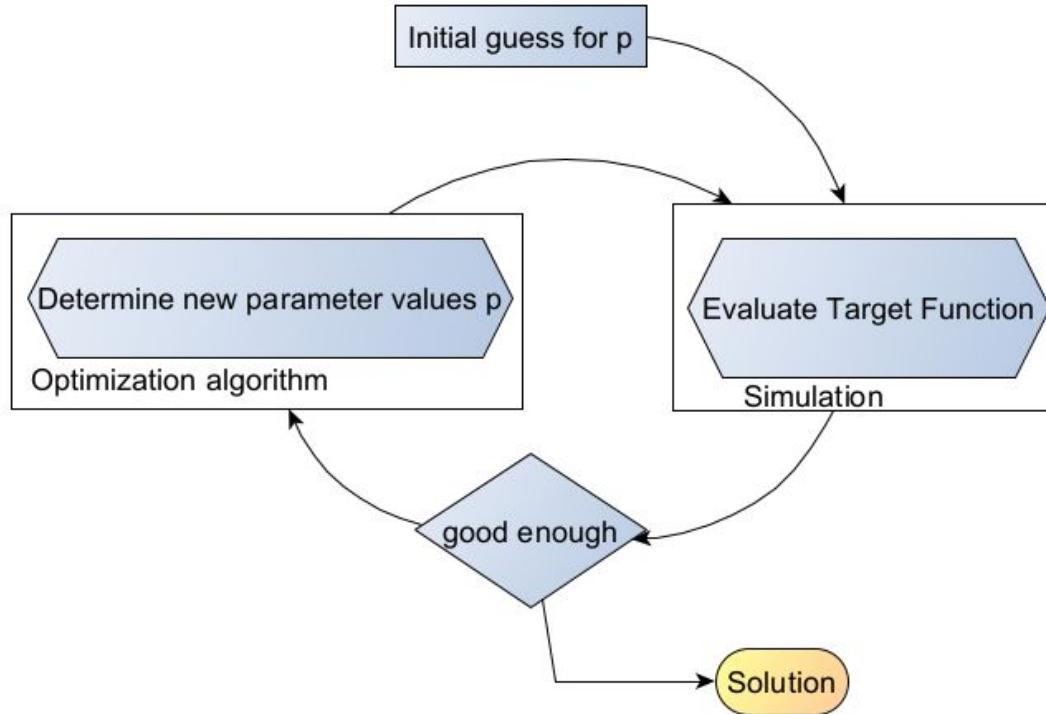
7.3 Parameter Space

- For a complete specification of the parameter fitting problem, we still need to specify the unknown parameters
- List the parameters with allowed range of values
- These parameters span an N-dimensional space, the parameter space
- One specific set of parameters correspond to a point in parameter space

7.4 Optimization Problem

- We now need a way to find the set of parameters (a point in parameter space) for which the distance D is minimal.
- A systematic scan of the parameter space is not possible when the dimensionality is large (many unknown parameters).
- Example: 10 parameters with 10 values each means 10^{10} evaluations. Even if we can do 100 simulations per second, this would take 3 years.

7.5 Numerical Optimization Cycle



7.6 Optimization Algorithms

- Based on derivatives
- Using geometry
- Stochastic algorithms
- Based on genetics

7.7 Parameter Estimation

PGI - COPASI 4.36 (Build 260) /Users/.../solution/PGI.cps

The screenshot shows the COPASI software interface with the title bar "PGI - COPASI 4.36 (Build 260) /Users/.../solution/PGI.cps". The left sidebar contains a tree view of the model components: Compartment, Species [2] (F6P, G6P), Reactions [1] (PGI), Global Quantities [0], Events [0], Parameter Overview, Parameter Sets [0], Mathematical (Differential Equations, Matrices, Diagrams), Tasks (Steady-State, Result, Stoichiometric Analysis, Time Course, Result, Metabolic Control Analysis, Lyapunov Exponents, Time Scale Separation Analysis, Cross Section, Parameter Scan, Optimization), and a selected category, Parameter Estimation. The main panel is titled "Parameter Estimation" and includes tabs for Experimental Data and Validation Data. It features sections for Randomize Start Values, Create Parameter Sets, Calculate Statistics (which is checked), Use Time Sens, Parameters (2), and Constraints (0). Two parameters are listed:
1 $1e-3 \leq (\text{PGI}).\text{Km} \leq 1000$; Start Value = 0.493
2 $1e-3 \leq (\text{PGI}).\text{V} \leq 1000$; Start Value = 0.042

Object: $(\text{PGI}).\text{Km}$
Lower Bound: $- \infty$ (checkbox checked)
Upper Bound: $+ \infty$ (checkbox checked)
Start Value: 0.493
Affected Experiments: all (checkbox checked)
Affected Validations: all (checkbox checked)

Duplicate for each Experiment

Method: Current Solution Statistics
Name | Value

Run | Revert | Report | Output Assistant

7.8 Parameter Estimation

PGI - COPASI 4.36 (Build 260) /Users/.../solution/PGI.cps

Concentrations

Parameter Estimation

Experimental Data

File: data.tsv

Experiment

Header 1

First Row 1 Last Row 102

Separator <tab>

Copy Settings: from previous to next to all following

Experiment Type: Steady State Time Course

Weight Method: Mean Square Normalize Weights per Experiment

Column Name	Type	Model Object	Weight
1 Time	Time		
2 f6p	dependent	[F6P]	(0.06974111816)
3 g6p	dependent	[G6P]	(1)

OK Revert Cancel

Run Revert Report Output Assistant

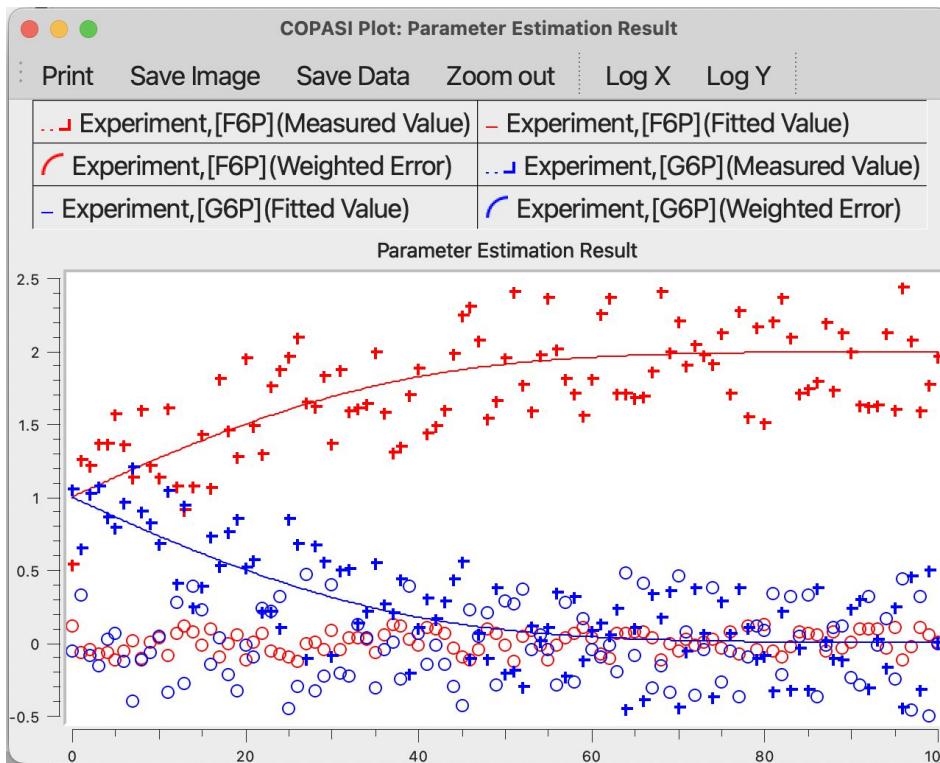
Compartments

- Species [2]
 - F6P
 - G6P
- Reactions [1]
 - PGI
- Global Quantities [0]
- Events [0]
- Parameter Overview
- Parameter Sets [0]
- Mathematical
 - Differential Equations
 - Matrices
 - Diagrams
- Tasks
 - Steady-State Result
 - Stoichiometric Analysis
 - Time Course Result
 - Metabolic Control Analysis
 - Lyapunov Exponents
 - Time Scale Separation Analysis
 - Cross Section
 - Parameter Scan
 - Optimization
 - Parameter Estimation
 - Sensitivities
 - Linear Noise Approximation
 - Time Course Sensitivities Result
 - Output Specifications
 - Functions [44]
 - Units [35]

data.txt

Time	f6p	g6p	
0	0.542665	1.05985	
1	1.26191	0.648619	
2	1.21388	1.02597	
3	1.36402	1.0719	
4	1.36938	0.86603	
5	1.57511	0.792192	
6	1.3688	0.965716	
7	1.13482	1.20437	
8	1.59985	0.901008	
9	1.21718	0.819852	
10	1.13717	0.684395	
11	1.60987	1.04289	
12	1.07598	0.4041	
13	0.918335	0.941001	
14	1.07895	0.243066	
15	1.43156	0.385129	
16	1.06641	0.731728	
17	1.81217	0.530307	
18	1.45907	0.765928	
19	1.27645	0.851192	
20	1.9564	0.517892	
21	1.49294	0.57381	
22	1.30211	0.221771	
23	1.76124	0.218049	
24	1.87111	0.101363	
25	1.9669	0.851707	

7.9 Parameter Estimation



Experimental data facilitated by Ursula Kummer

7.10 Test Your Knowledge

Open the file PG1.cps and analyze the implemented model.

7.11 COPASI Outputs

- Mathematical model of the biochemical system as ODEs
- Time course result
- Steady state result
- Parameter values
- Auto-generated diagram (low detail diagram; not SBGN)
- SBML file with necessary elements to reproduce the model
- SBGN and SBML will be discussed later

8. Reproducibility: A Central Problem in Computational Studies

- Problems reproducing studies arise because of
 - Difficulties resulting from models not being deposited in public databases
 - Differences between deposited models and models used for published simulations
 - Difficulties in utilizing and modifying models because models are not human-readable

8.1 COMBINE: Computational Modeling in Biology NEtwork

 the computational modeling in biology network

HARMONY 2022 Standards Events Documents Forums About Search

COMBINE

- Home
- Help
- Sign-in

Coordinating standards for modeling in biology

The "COperational Modeling in Biology NEtwork" (COMBINE) is an initiative to coordinate the development of the various community [standards and formats](#) for computational models. By doing so, it is expected that the federated projects will develop a set of interoperable and non-overlapping standards covering all aspects of modeling in biology. The global COMBINE effort is led by the [COMBINE Coordination Board](#).

Building on the experience of mature projects, which already have stable specifications, software support, user-base and community governance, COMBINE will help foster or support fledgling efforts aimed at filling gaps or new needs. As those efforts mature, they may become part of the [core set of COMBINE standards](#).

One of the initial activities of COMBINE is to coordinate the organization of scientific and technical [events](#) common to several standards. Those events, as others related to our field of research are [gathered in a calendar](#).

To receive announcements from COMBINE, subscribe to the Twitter feed [COMBINE news](#).

To discuss the goals, organization and operation of COMBINE, subscribe to [COMBINE discuss](#) mailing list.

To report issues about the co.mrbine.org website, send a mail to [combine-support @ googlegroups.com](mailto:combine-support@googlegroups.com)

Recent tweets by @combine_coord

 COMBINE
@combine_coord 

Join us October 6-8, 2022 for #COMBINE2022! Co-located with #ICSB2022. In Berlin (Germany).

COMBINE Community meet-up Oct 6-7, 9a.m.-6p.m
** COMBINE Forum Oct 8, 8a.m.-1:30p.m.

Details and Call for papers to come. Be on the look out!


COMBINE Meeting OCT 6-7, 2022
COMBINE Forum OCT 8, 2022
Berlin, Germany

May 28, 2022

co.mrbine.org/about



8.2 BioModels: A Mathematical Model Database

The screenshot shows the BioModels database homepage. At the top is a dark header with the BioModels logo, EMBL-EBI links, and a search bar. Below the header is a banner with network diagrams and a search bar. The main content area has a dark background with white text. It features a summary of the database's mission and usage, followed by six cards with icons and statistics:

Category	Description	Count
Submission / Update	Manually Curated	1,053 models
Non-curated	Auto generated	1,373 models
GO Chart	GO Chart	833 models
BioModels Parameters	1,132 classes	1,036,608 records

At the bottom are three buttons: "Model of The Month" (December, 2021), "Browse by Modelling Approach", and "Find us on Twitter".

ebi.ac.uk/biomodels



8.3 Model Exchange with SBML (Systems Biology Markup Language)

- Each modeling tool has its pros, but often output formats vary
- SBML was designed to exchange biochemical models between tools
- SBML is based on the XML file format
 - Contains necessary elements to describe a model mathematically
- Only the model, not the simulation/analysis strategies, is exchanged
 - Handled separately by COMBINE SED-ML (Simulation Experiment Description Markup Language; not covered here)

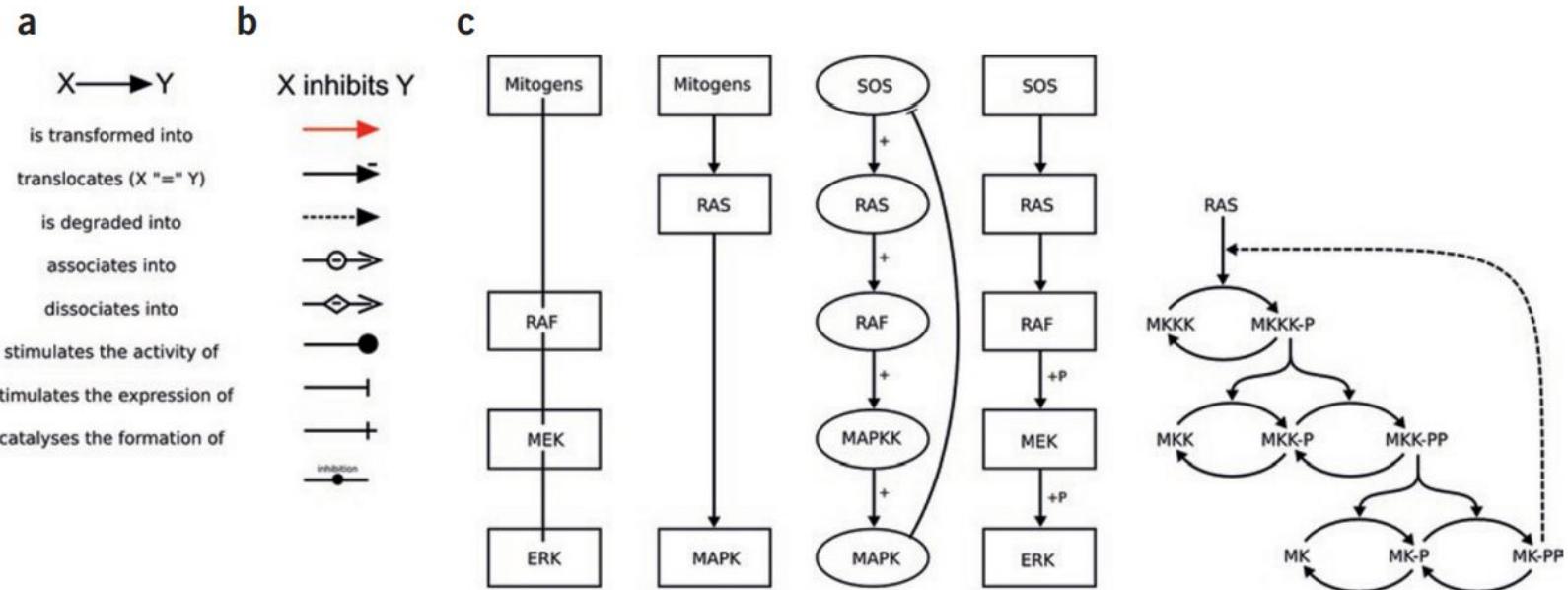
8.4 General Structure of a SBML File

- Model elements are linked:
 - Via identifiers used in mathematical constructs and elements describing reactions, species, etc.
 - Via annotations (e.g., CHEBI)

```
<unitDefinition id="mmole">
  <listOfUnits>
    <unit kind="mole" exponent="1" scale="-3" multiplier="1" />
  </listOfUnits>
</unitDefinition>
...
<compartment id="c" name="cell compartment" size="1e-05" units="litre" constant="true" ... />
...
<species metaid="meta_glc" id="glc" name="glucose" initialConcentration="5" sboTerm="SBO:0000247"
  compartment="c" substanceUnits="mmole" hasOnlySubstanceUnits="false" boundaryCondition="false"
  constant="false" fbc:charge="0" fbc:chemicalFormula="C6H12O6">
  <annotation>
    ...
    <bqbiol:is>
      <rdf:li rdf:resource="http://identifiers.org/chebi/CHEBI:4167"/>
    ...
  </annotation>
  ...
<parameter id="Vmax_GK" value="1e-06" sboTerm="SBO:0000186" constant="true" units="mmole_per_s" ...>
<parameter id="Km_glc" value="0.5" sboTerm="SBO:0000027" constant="true" units="mM" ...>
...
<reaction id="GK" name="Glucokinase" reversible="false" compartment="c" sboTerm="SBO:0000176" ...>
...
  <speciesReference species="glc" stoichiometry="1" constant="true"/>
...
<kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> Vmax_GK </ci>
      <apply>
        <divide/>
        <ci> glc </ci>
        <apply>
          <plus/>
          <ci> Km_glc </ci>
          <ci> glc </ci>
        </apply>
      </apply>
    </math>
  </kineticLaw>

```

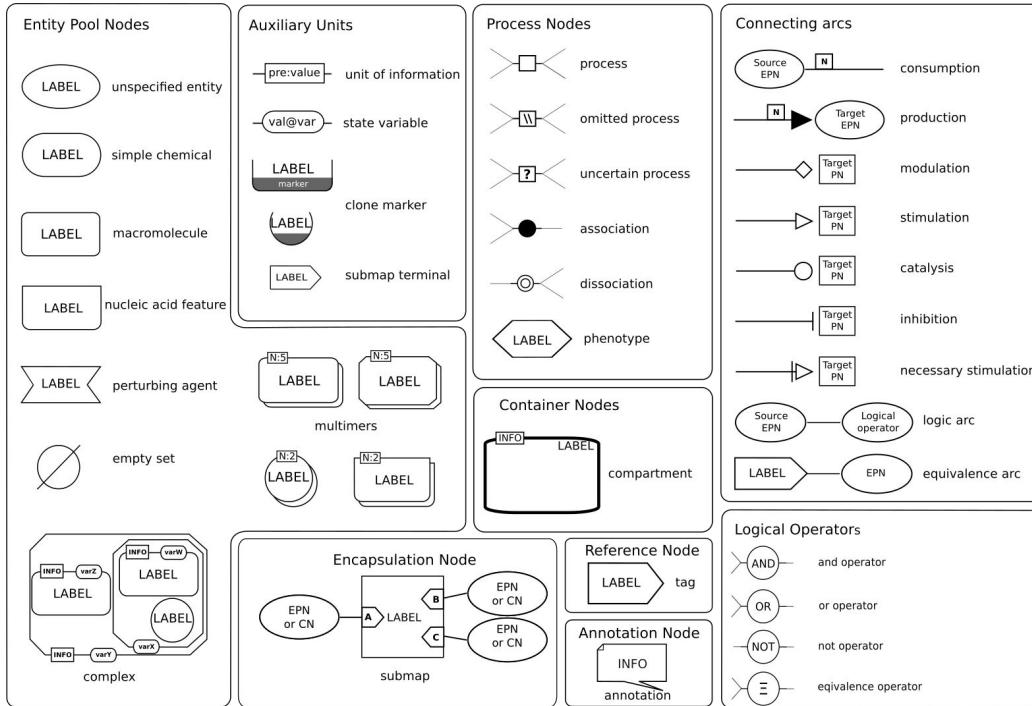
8.5 Inconsistency and Ambiguity of Current Non Standardized Notation



8.6 SBGN (Systems Biology Graphical Notation)

SBGN Process Description Map: Temporal Courses of Biochemical Interactions

SBGN standardizes
the graphical notation
of biological processes



sbgn.github.io/referencecards
sbgn.github.io

8.7 Newt - Online Tool to Generate SBGN Diagrams

The screenshot shows the homepage of the Newt Pathway Viewer & Editor. At the top, there is a dark header with the text "newt Pathways Simplified" and a subtext "View, design, and analyze pathways in SBGN and more...". Below the header is a navigation bar with links: HOME (orange), SOFTWARE, GALLERY, TUTORIALS, FAQ, and CONTACT US. The main content area has a light blue background. It features a "Welcome to Newt Pathway Viewer & Editor" section with a brief description of the tool and a "Launch newt" button. To the right, there is a sidebar with a search bar and a "Latest News" section. The sidebar also includes a small diagram of a biological pathway.

Welcome to Newt Pathway Viewer & Editor

Newt is a free, web based, open source viewer and editor for pathways in [Systems Biological Graphical Notation \(SBGN\)](#) and [Simple Interaction Format \(SIF\)](#). It was written with a series of libraries and extensions based on [Cytoscape.js](#) with utmost customization in mind.

[Launch newt](#)

What distinguishes Newt from other viewers and editors for biological maps can be summarized as:

- Rich and refined, yet easy-to-use web based UI
- Convenient construction and annotation of pathways from scratch as well as viewing and editing existing maps
- Full support for compound structures (including automatic layout) to properly represent compartments, molecular complexes, and sub-maps
- Semantic validation and guided fix for SBGN PD maps
- State-of-the-art complexity management capabilities through hide-show or highlight parts of a map and collapse-expand compound structures

Search

ENHANCED BY

Latest News

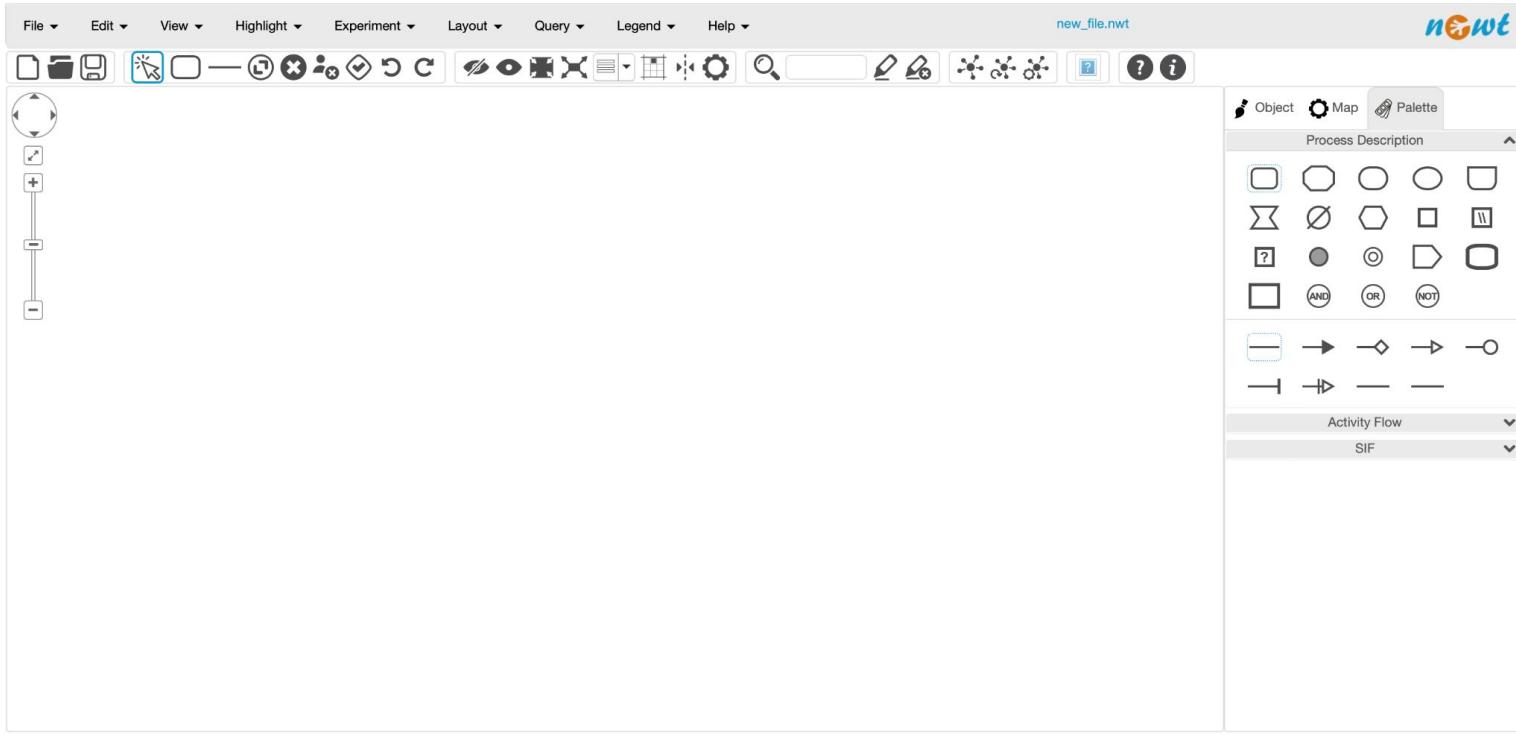
Newt release
April 1, 2020

Newt 3.0 was released to include some [new features](#) such as experiment data overlay, bug fixes, and more.

Newt release
October 5, 2019

Newt 2.0 was released to include some [significant improvements](#) such as SIF support, conversion to and from SBML models, interactive validation and fix of PD maps.

8.8 Newt Website



share.getcloudapp.com/NQulp426

8.9 Test your Knowledge

- Find the model of glycolysis by Teusink et. al. in BioModels database
- Open the file in COPASI
- Run a simulation
- Try to change the parameter you think will impact the model behaviour a lot.
- Find the model of calcium oscillations by Kummer on BioModels database.
- Analyse the model in COPASI

Summary

1. Biological Networks: Involve coordinated interactions of thousands of molecules
2. COPASI: Software for modeling biological networks through mathematical modeling
3. Chemical Kinetics: How fast chemical reactions take place
4. Model Set-Up in COPASI: How set up model's reactions to get an ODE model
5. Time-Course Simulations: How to set up the time course simulations
6. Steady-State Simulations: How to set up the steady course simulations
7. Parameter Estimation: How to estimate unknown parameters in your model
8. COMBINE Standards: Coordinates the standards to model biological systems for transparency and exchangeability
 - a. SBML (Systems Biology Markup Language): An XML-based format for modeling
 - b. SBGN (Systems Biology Graphical Notation): A standard graphical representation through diagrams based on XML
 - c. Common annotation system based on RDF (Resource Description Framework)
9. BioModels Database: A repository for storing, exchange and retrieving models

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- David Umulis
- Adrian Tepole

COMBINE Community

- Ursula Kummer
- Frank Bergmann
- Sven Sahle
- Stephan Hoops
- Pedro Mendes
- Augustin Luna

Important Links

copasi.org

co.mbine.org

sbml.org

sbgn.github.io

newteditor.org

ebi.ac.uk/biomodels

ebi.ac.uk/biomodels/BIOMD0000000253