V11 – DGL-Modelle / Copasi / SBML

Aufstellen von Bilanzgleichungen

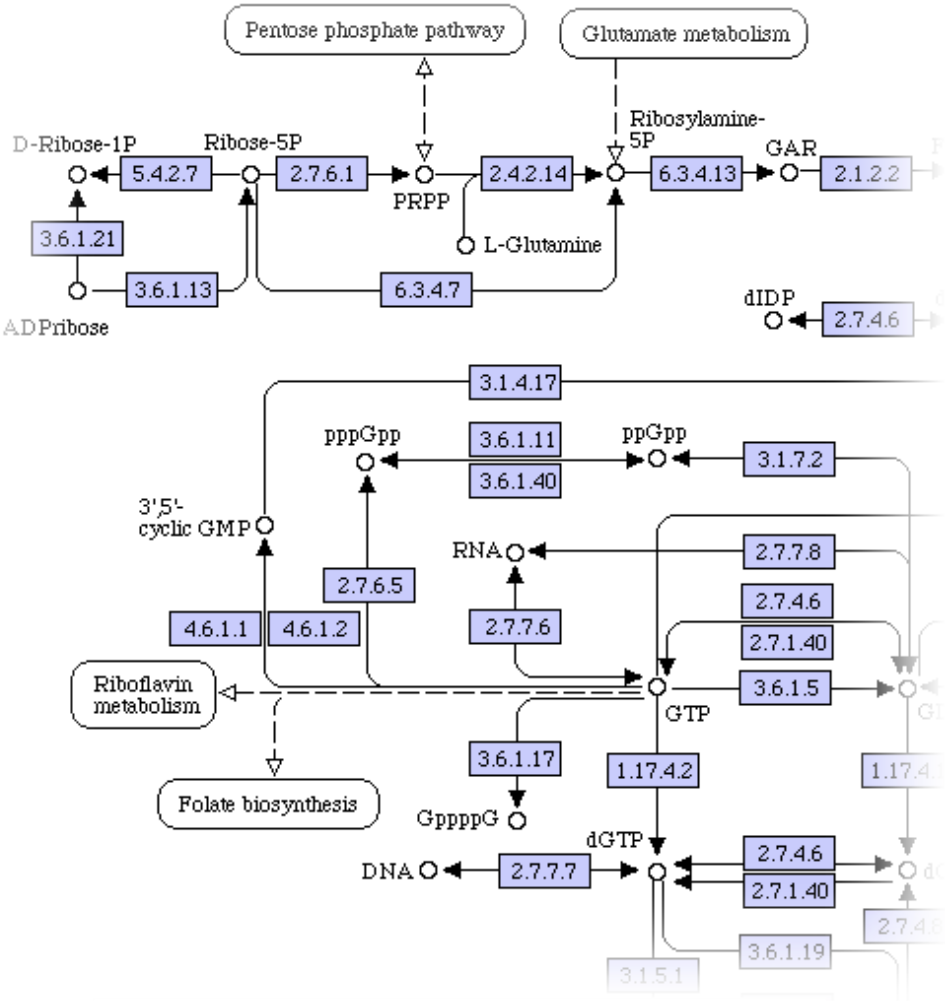
Dynamische Simulationen: Was ist das? Wozu?

Simulations-Tool: Copasi

Vereinfachte Kinetiken: MM, Inhibierung, Hill

kinetische Daten: KEGG, SABIO-RK

Wdh: über die Formel zur Formel



Ausschnitt aus http://www.genome.jp/dbget-bin/show_pathway?ec00230+3.6.1.9

i) biologisches Netzwerk

ii) Metabolite identifizieren (incl. Konzentrationen)

iii) Einzelreaktionen aufstellen, Reaktionsraten?

iv) Reaktionen in DGLs übersetzen

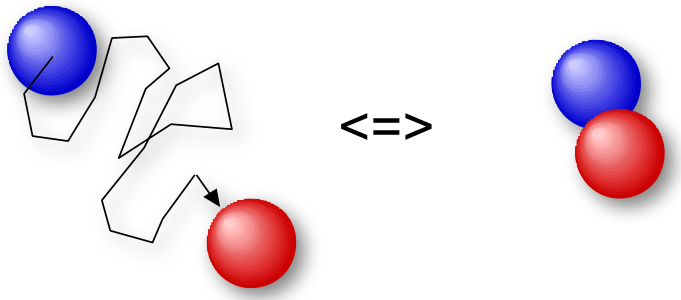
v) Anfangswerte einsetzen und simulieren

vi) Ergebnisse analysieren

Massenwirkungsgesetz

Einfachste chemische Reaktion

A + B <=> AB



Zeitliche Änderung von [A]:

Gewinn: Dissoziation

AB => A + B

$$\frac{d}{dt}[A] = G_A - L_A$$

Verlust: Assoziation

A + B => AB

AB zerfällt

=> G_A proportional zu [AB]

$$G_A = k_r [AB]$$

phänomenologischer Faktor

A und B müssen sich finden

=> L_A abhängig von [A] *und* [B]

$$L_A = k_f [A] [B]$$

$$\frac{d}{dt}[A] = k_r [AB] - k_f [A] [B]$$

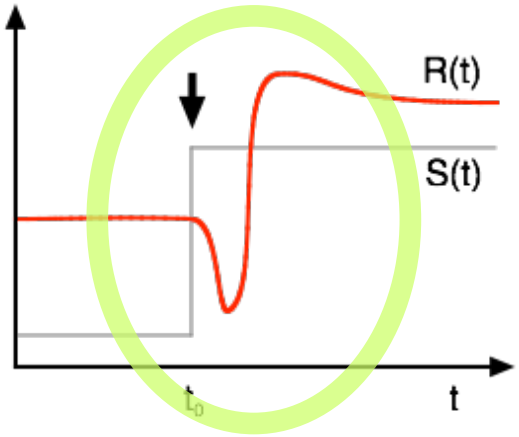
Dynamische Simulationen

Zwei Anwendungsgebiete

zeitabhängiges Verhalten

Reaktionen des Systems auf Änderungen der äußeren Bedingungen (Randbedingungen)

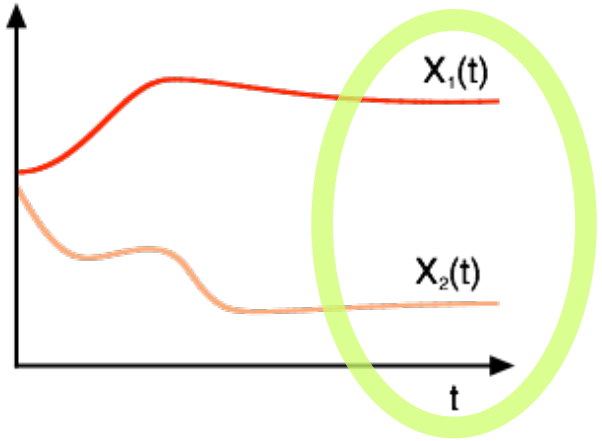
$$\frac{d\vec{X}(t)}{dt}$$



stationäre Zustände (steady state)

Suche nach Konzentrationen und Flüssen bei konstanten Randbedingungen

$$\frac{d\vec{X}(t)}{dt} = 0$$

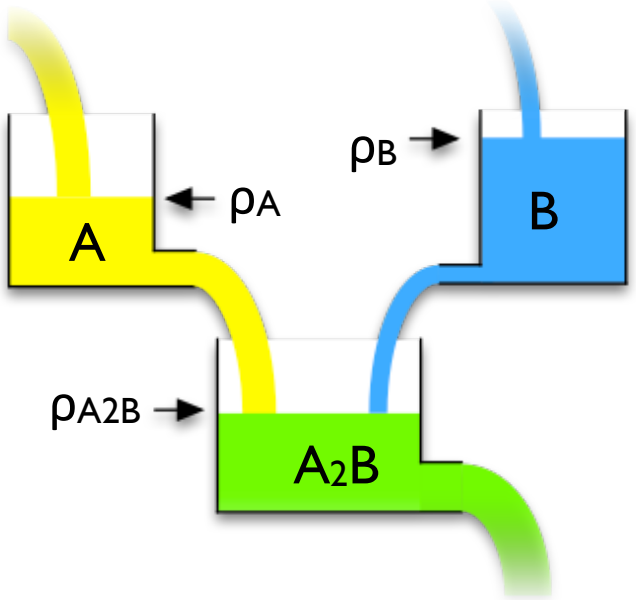


Was lernt man aus dem Steady-State?

Konzentrationen = konst.

=> Zufluss = Abfluss

$$\frac{dA_2B(t)}{dt} = G_{A_2B} - L_{A_2B} = 0$$



Beispiel: 2A + B <=> A_2B

$$\frac{dA_2B(t)}{dt} = k_a A^2 B - k_d A_2 B = 0$$

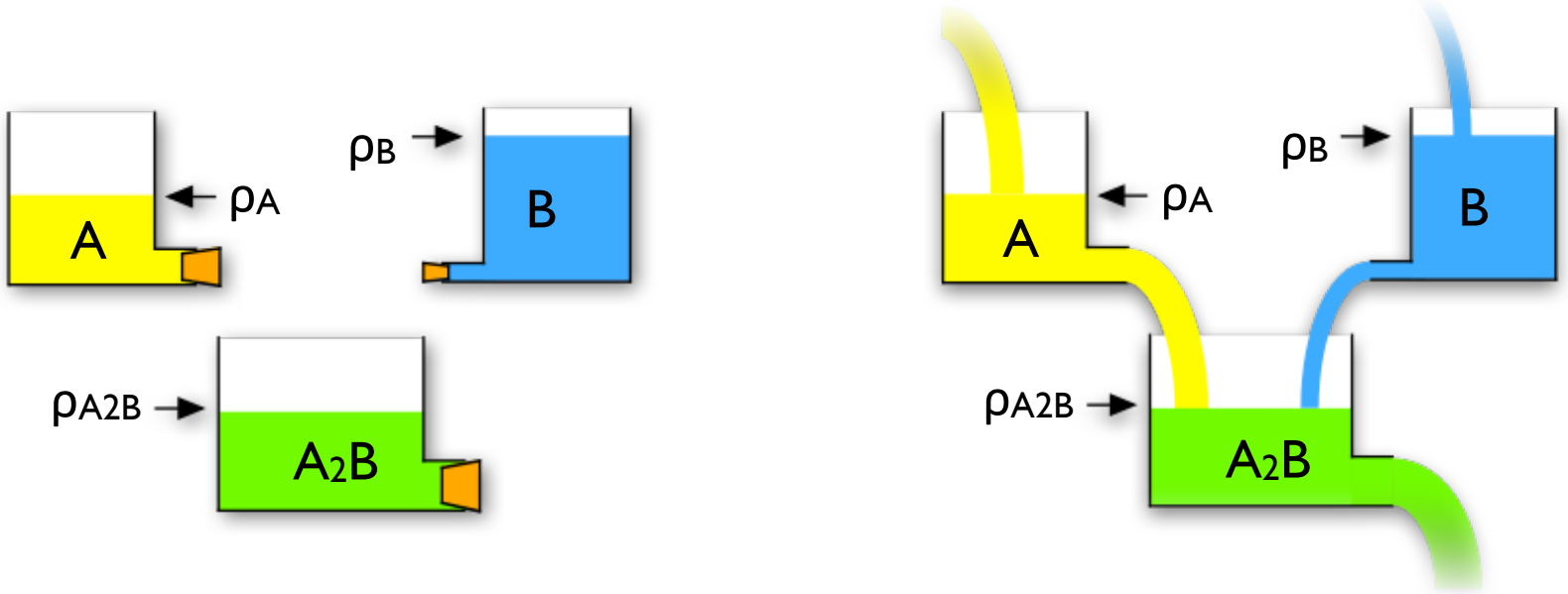
=> Gleichgewichts-Konzentrationen: $A_2B = \frac{k_a}{k_d} A^2 B$

Steady state: + Bedingungen zwischen Konzentrationen und Raten
=> stationäre Betriebsmodi

– wie schnell wird der steady state erreicht?

– absolute Mengen / effektive Volumina

Statisches vs. dynamisches Gleichgewicht



jeweils: $\frac{d\vec{X}(t)}{dt} = 0$

Infos aus zeitabhängigen Simulationen

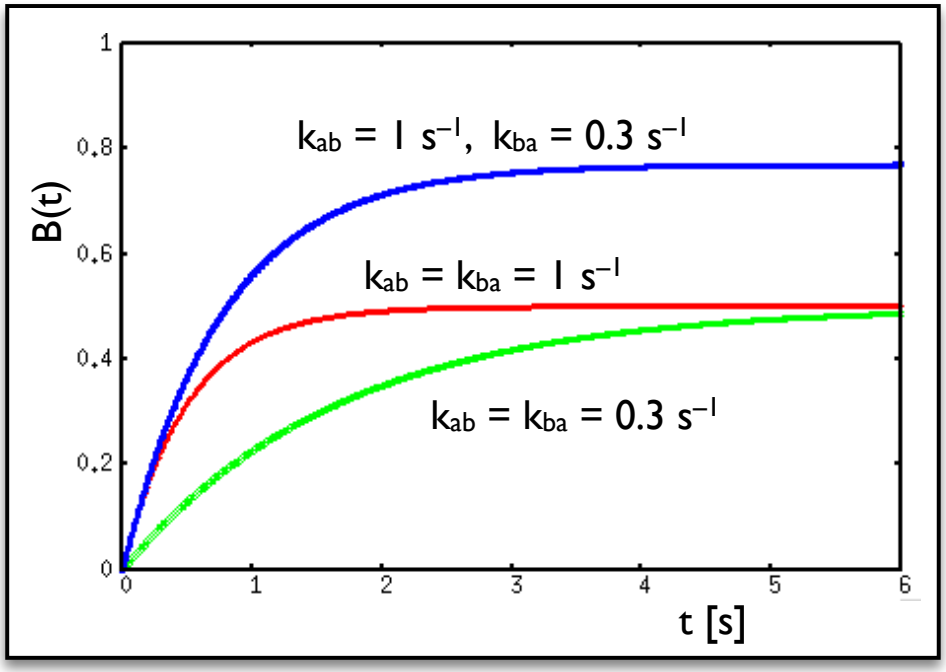
Ganz einfach: A <=> B

$$\frac{dA(t)}{dt} = k_{ba}B - k_{ab}A$$

$$A + B = \text{const.}$$

Gleichgewicht:

$$B = \frac{k_{ab}}{k_{ba}} A$$



mit Anfangsbedingungen:

$A(t=0) = A_0$

$B(t=0) = 0$

$$B(t \to \infty) = \frac{k_{ab}}{k_{ab} + k_{ba}} A_0$$

=> Gleichgewichtsverteilungen

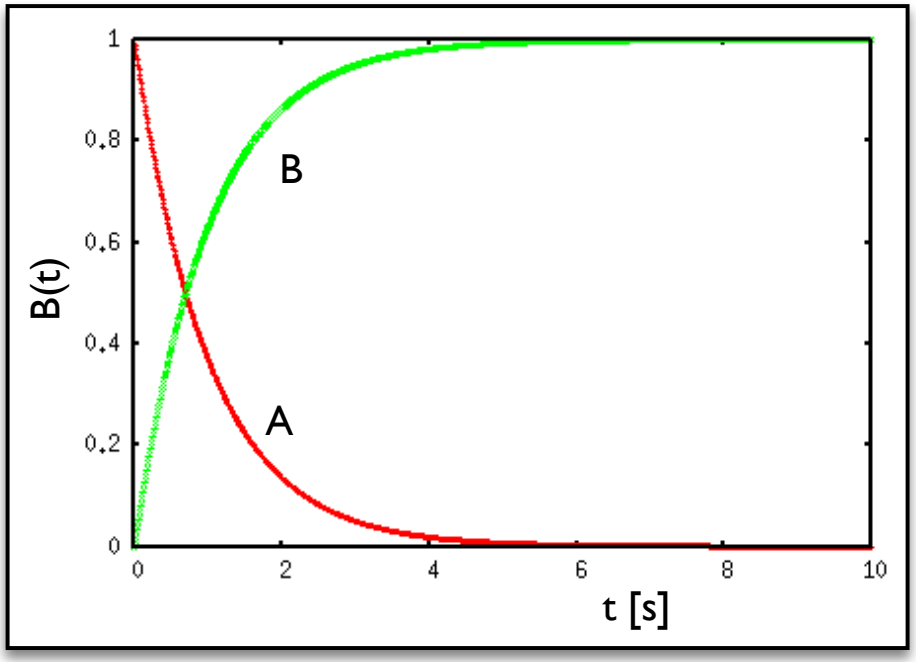
=> wie schnell wird ein "Signal" weitergegeben?

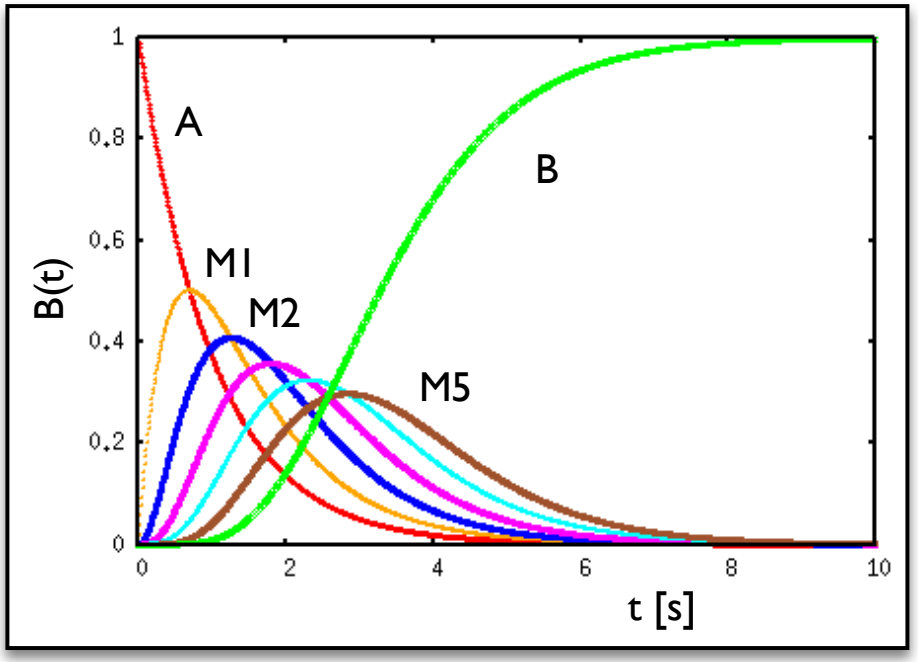
Länge von Reaktionspfaden

Vergleiche:

A => B

A => M1 => M2 => M3 => M4 => M5 => B





$A_0 = 1, \quad k = 1\ s^{-1}$

=> Zwischenprodukte verzögern die Antwort

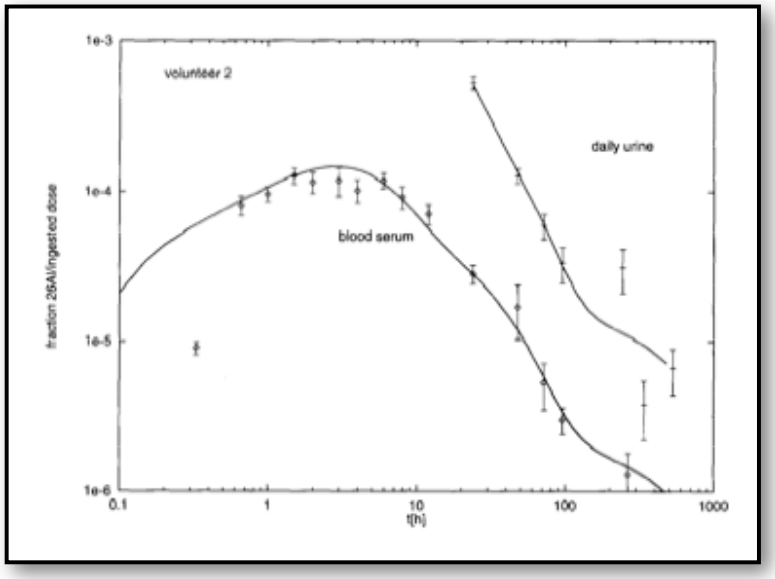
=> Vorsicht beim Weglassen von Zwischenschritten

Puffer: Al-Metabolismus

Al ist das dritthäufigste Element (8%) und das häufigste Metall in der Erdkruste. Normalerweise ist Al harmlos, kann aber auch zu Osteopathie, Anämie oder Enzephalopathie führen.

Experimente zur Al-Aufnahme und -Ausscheidung:

- orale Gabe von 100 ng ^{26}Al ($T_{1/2}$ = 0.7 Myr)
- Blutproben nach 20 min, 40 min, …, 46 d
- Tagesurin
- Messung der ^{26}Al-Menge



Messwerte: Blut- und Urinproben, Gewebeproben bei Ratten

=> zeitabhängige Verteilung und Speicherung in verschiedenen Geweben

=> Modellierung als Multi-Kompartment-Modell

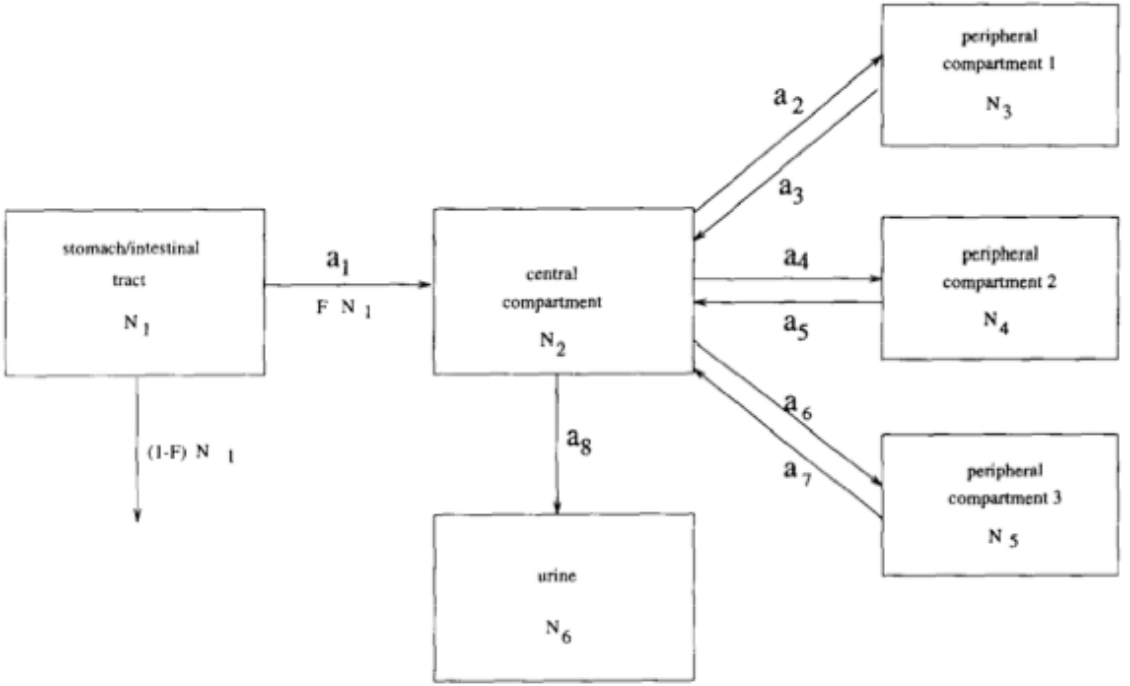
Modellierung des AL-Metabolismus

i) Al wird aufgenommen (oral oder intravenös), kommt ins Blut

ii) Al verteilt sich vom Blut in das umliegende Gewebe/Organe

iii) dynamisches Gleichgewicht zwischen Blut und periphären Gewebe-Speichern

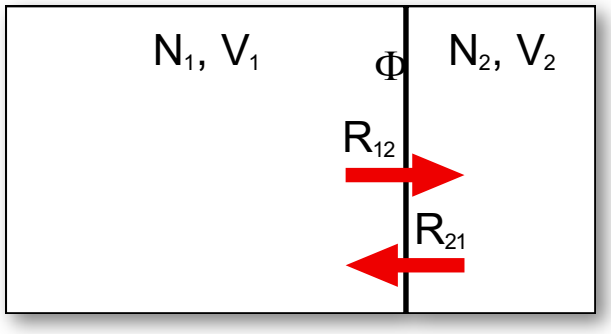
iv) Blut wird über Leber/Niere ausgeschieden



Hohl, …, Nolte, Ittel, *Nucl. Inst. Meth.* B **92** (1994) 478

Erhalte Übergangsraten zwischen (Lebensdauern) und Volumina der Kompartimente aus der Simulation durch Parameterfit
=> Hilfe für die physiologische Zuordnung

Unterschiedlich große Kompartimente



Teilchenaustausch durch Interface der Fläche Φ:

$$\frac{dN_{12}}{dt} = k_{12}\Phi\frac{N_1}{V_1} \qquad \frac{dN_{21}}{dt} = k_{21}\Phi\frac{N_2}{V_2}$$

Änderungen der Anzahlen (Gesamtanzahl bleibt erhalten):

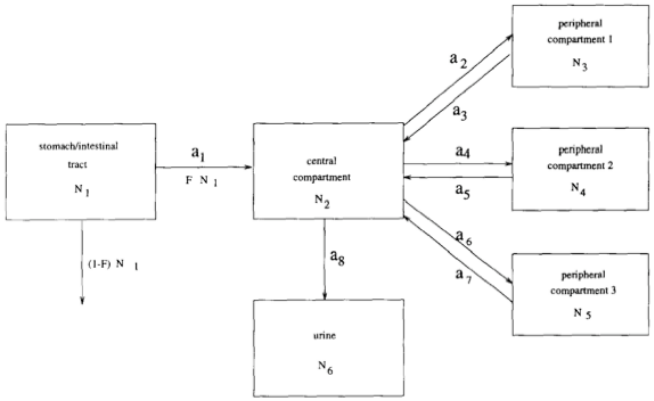
$$\frac{dN_1}{dt} = -\frac{dN_{12}}{dt} + \frac{dN_{21}}{dt} \qquad \frac{dN_2}{dt} = -\frac{dN_1}{dt}$$

Änderungen der entsprechenden Dichten:

$$\frac{d}{dt}\frac{N_1}{V_1} = \frac{1}{V_1}\frac{dN_1}{dt} = \frac{\tilde{k}_{21}}{V_1}\frac{N_2}{V_2} - \frac{\tilde{k}_{12}}{V_1}\frac{N_1}{V_1} \qquad \frac{d}{dt}\frac{N_2}{V_2} = \frac{V_1}{V_2}\frac{d}{dt}\frac{N_1}{V_1}$$

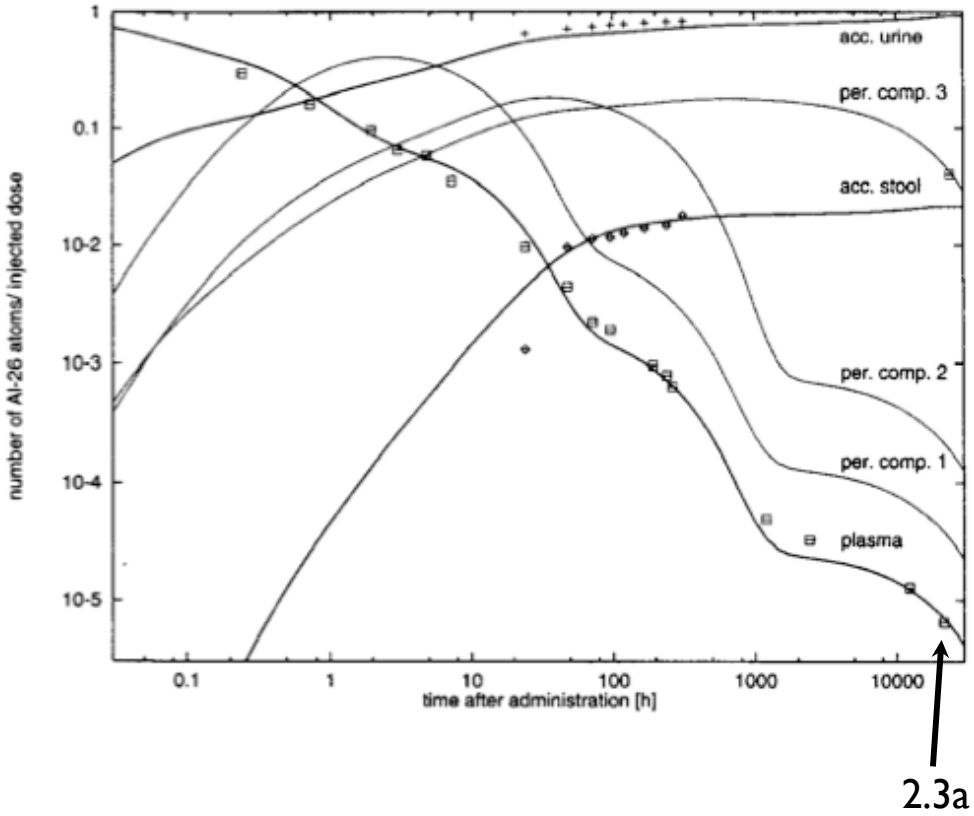
=> Simulationen mit Teilchenzahlen, Dichten "on the fly"

Ergebnisse



Drei Gewebetypen (Kompartimente) reichen, um die Messwerte zu beschreiben
=> schnelles, mittleres und langsames Kompartiment

Zeitabh. Verhalten bestimmt von Volumen *und* Austauschraten.



^{26}Al konnte nach mehr als zwei Jahren immer noch im Blut nachgewiesen werden
=> Speicherung in den Knochen

Complex Pathway Simulator

Entwickelt in den Gruppen von
Pedro Mendes (Virginia Bioinf. Inst.) und Ursula Kummer (EML HD)

"COPASI is a software application for simulation
and analysis of biochemical networks."

http://www.copasi.org/

Copasi-Features

Current Features:

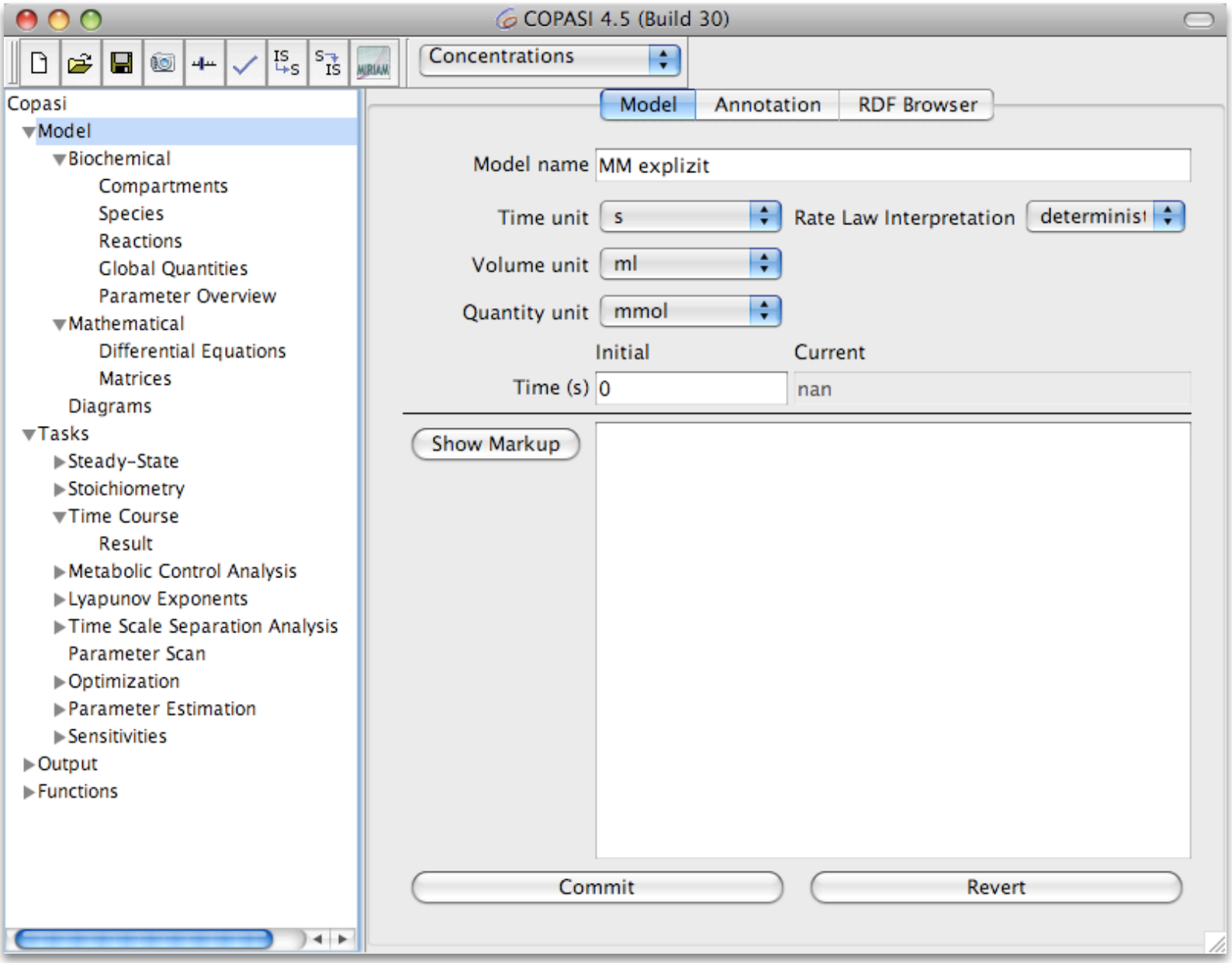
- Model:
  - Chemical reaction network.
  - Arbitrary kinetic functions.
  - ODEs for compartments, species, and global quantities.
  - Assignments for compartments, species, and global quantities.
  - Initial assignments for compartments, species, and global quantities.
- Analysis:
  - Stochastic and deterministic time course simulation
  - Steady state analysis (including stability).
  - Metabolic control analysis/sensitivity analysis.
  - Elementary mode analysis .
  - Mass conservation analysis.
  - Time scale separation analysis
  - Calculation of Lyapunov exponents.
  - Parameter scans.
  - Optimization of arbitrary objective functions.
  - Parameter estimation using data from time course and/or steady state experiments simultaneously.
- Graphical User Interface (CopasiUI)
  - Sliders for interactive parameter changes.
  - Plots and Histograms.
- Command Line (CopasiSE) for batch processing.
- SBML import (L1V1+2, L2V1-3) and export (L1V2, L2V1-3).
- Loading of Gepasi files.
- Export to Berkeley Madonna, XPPAUT, and C source code of the ODE system generated from the model.
- Versions for MS Windows, Linux, Mac OS X, and Solaris SPARC.

We keep a list of currently known problems in COPASI.

VIRGINIA BIOINFORMATICS INSTITUTE AT VIRGINIA TECH VBI

By the Mendes group at VBI and Kummer group at EML Research.

EML Research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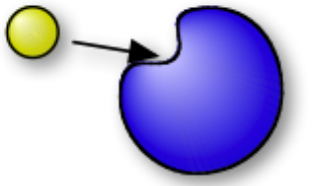
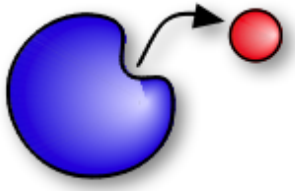
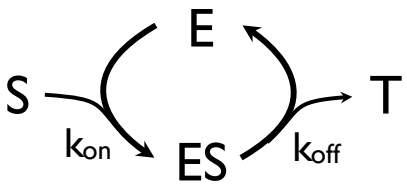
Commit
Revert

Enzyme: Michaelis-Menten-Kinetik







Reaktionsrate:

$$V = k_{off} ES$$

Steady state:

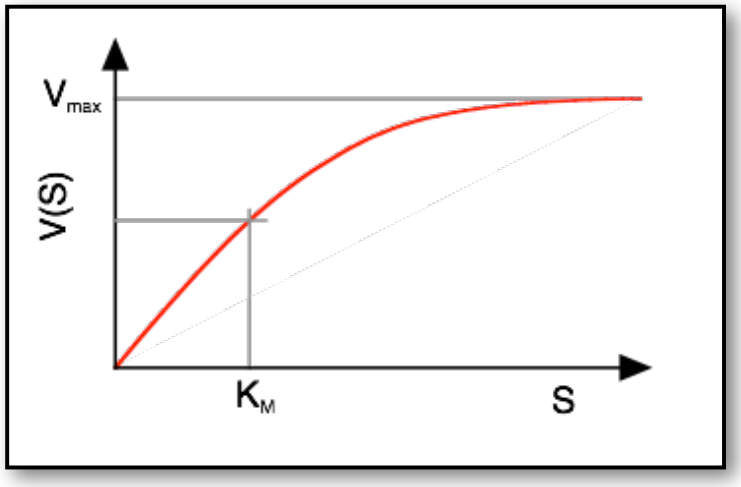
$$k_{on} E \cdot S = k_{off} ES$$

$$ES = \frac{k_{on}\, E \cdot S}{k_{off}} = \frac{E \cdot S}{K_M}$$

Die Gleichung

Effektiver Umsatz nach MM: $$V = V_{max} \frac{S}{S + K_M}$$

$$V_{max} = k_{off} E_T$$



$$K_M = \frac{k_{off}}{k_{on}}$$

Vorteile:
- analytische Formel für den Umsatz
- Interpretation der Kennlinie: V_{max}, K_M
- Enzym kann ignoriert werden

Aber: weniger kinetische Informationen

k_{on}, k_{off}, E_T => V_{max}, K_M

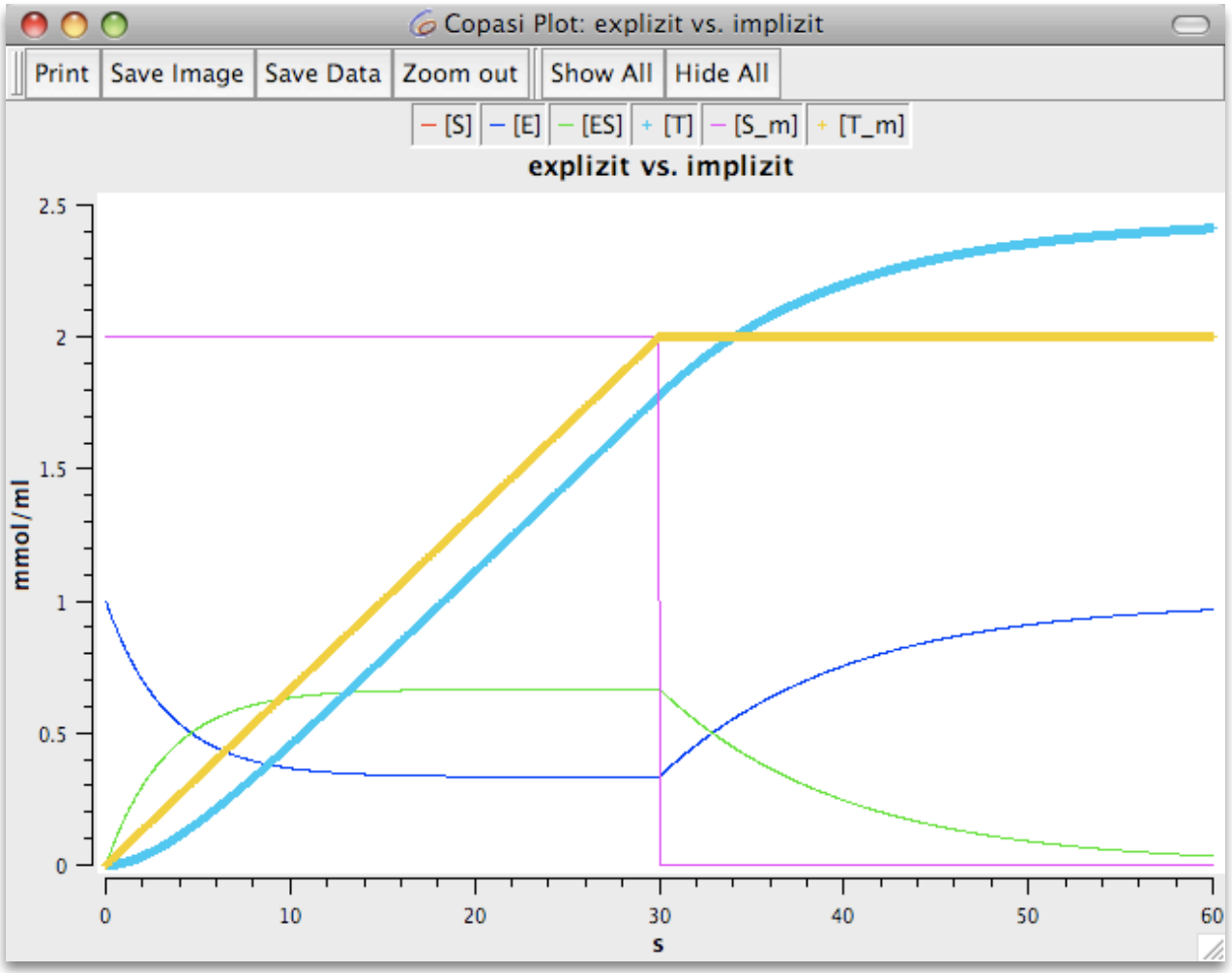
MM vs. explizite Modellierung

Wenn E verschiedene Substrate katalysiert
=> MM geht nicht

Zeitverhalten:
MM-Kinetik vs.
explizite Modellierung

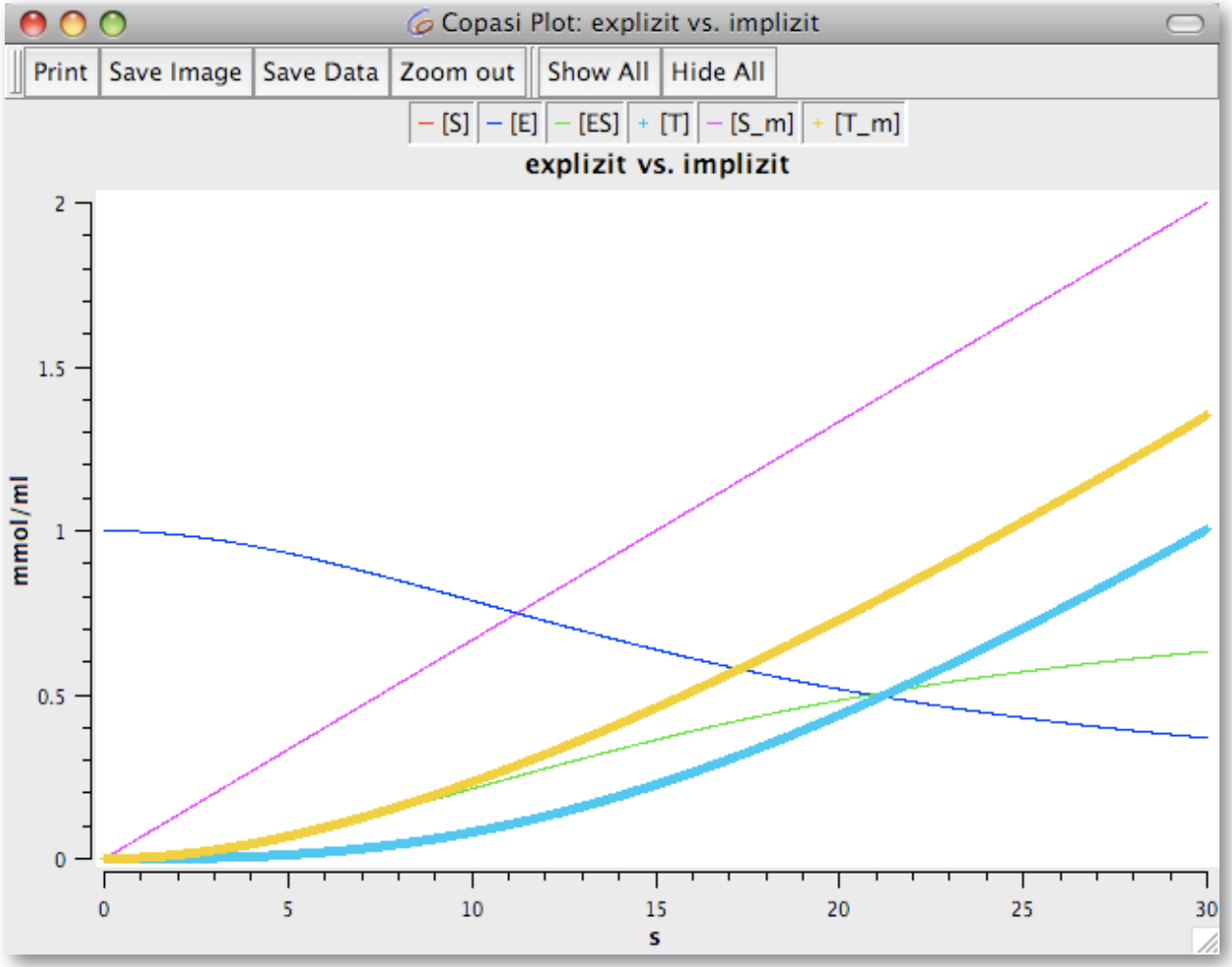
=> Einschwingen

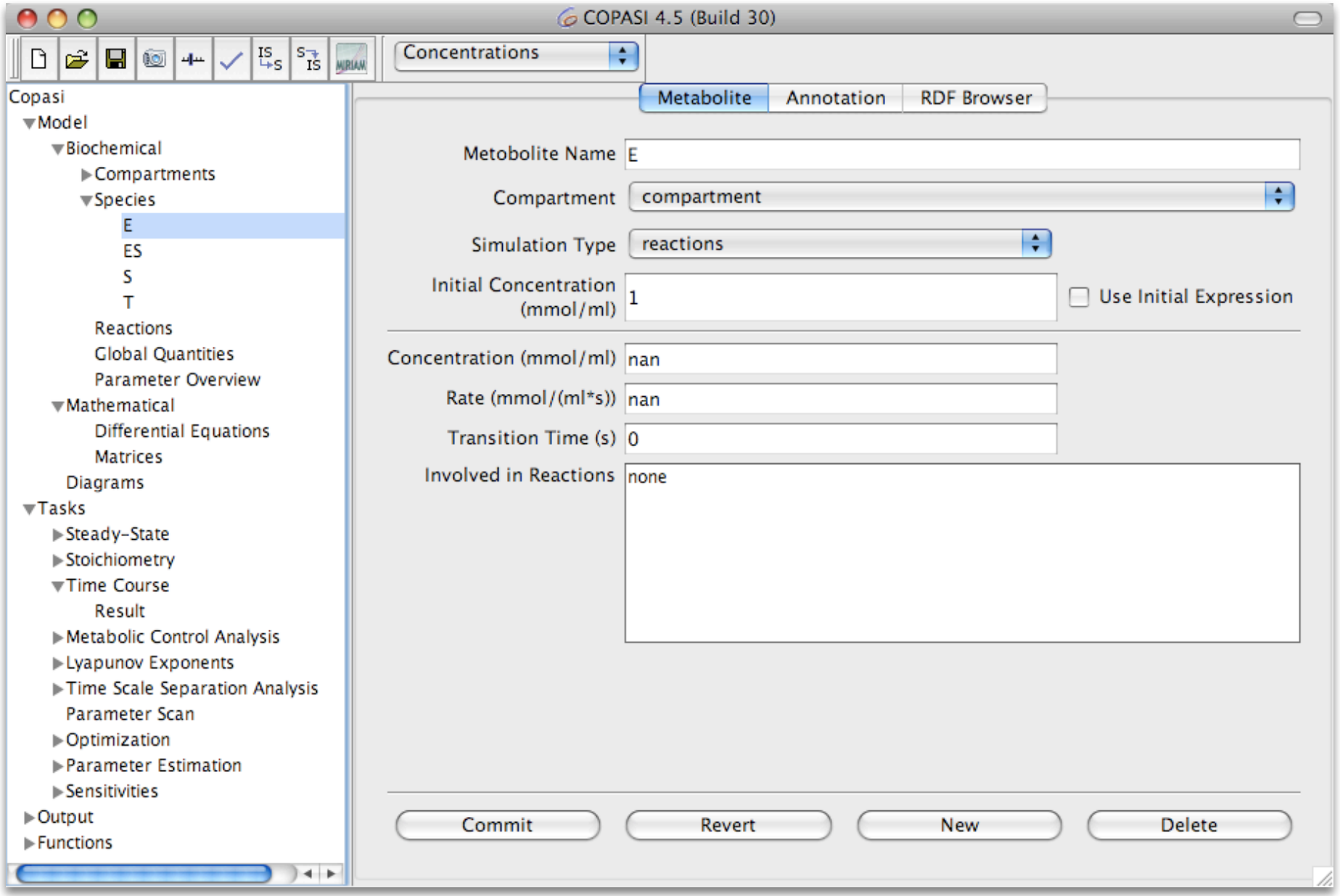
=> anderer
Gesamtumsatz



Nochmal: explizit vs. MM

linearer Anstieg von S

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Metobolite Name
E
Compartment
compartment
Simulation Type
reactions
Initial Concentration (mmol/ml)
1
Use Initial Expression
Concentration (mmol/ml)
nan
Rate (mmol/(ml*s))
nan
Transition Time (s)
0
Involved in Reactions
none
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Revert
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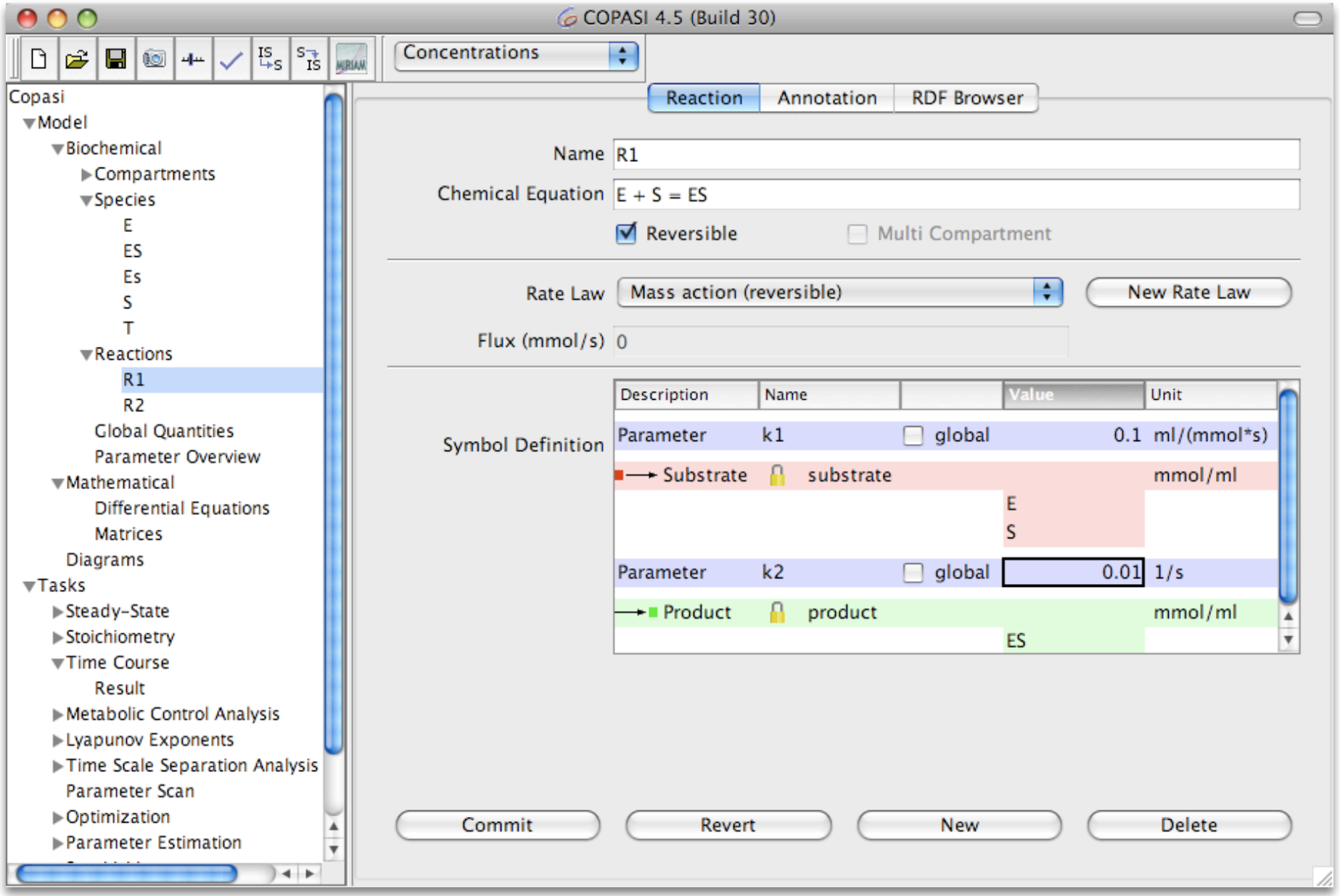
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Rate Law
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New Rate Law
Flux (mmol/s)
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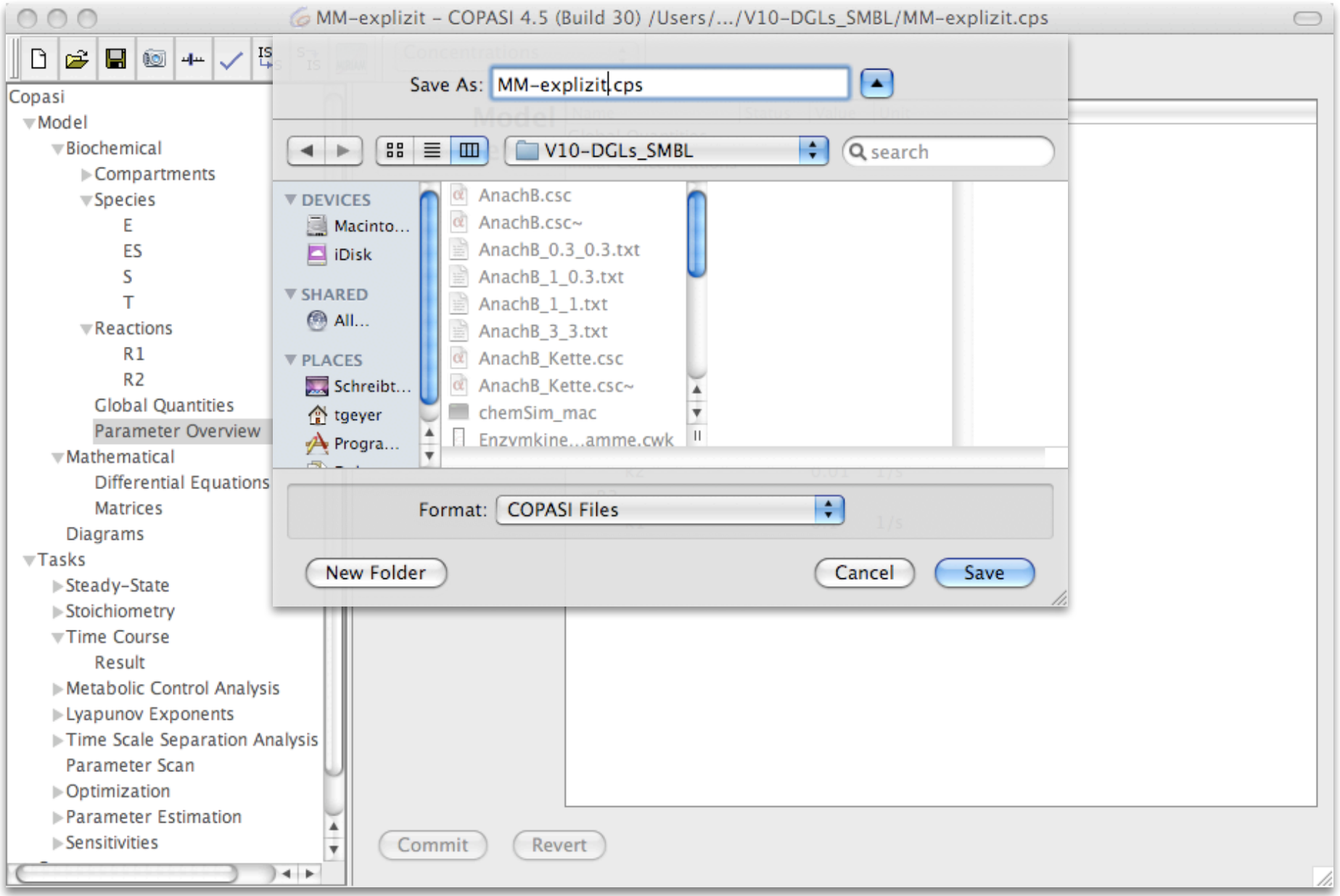
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AnachB_1_1.txt
AnachB_3_3.txt
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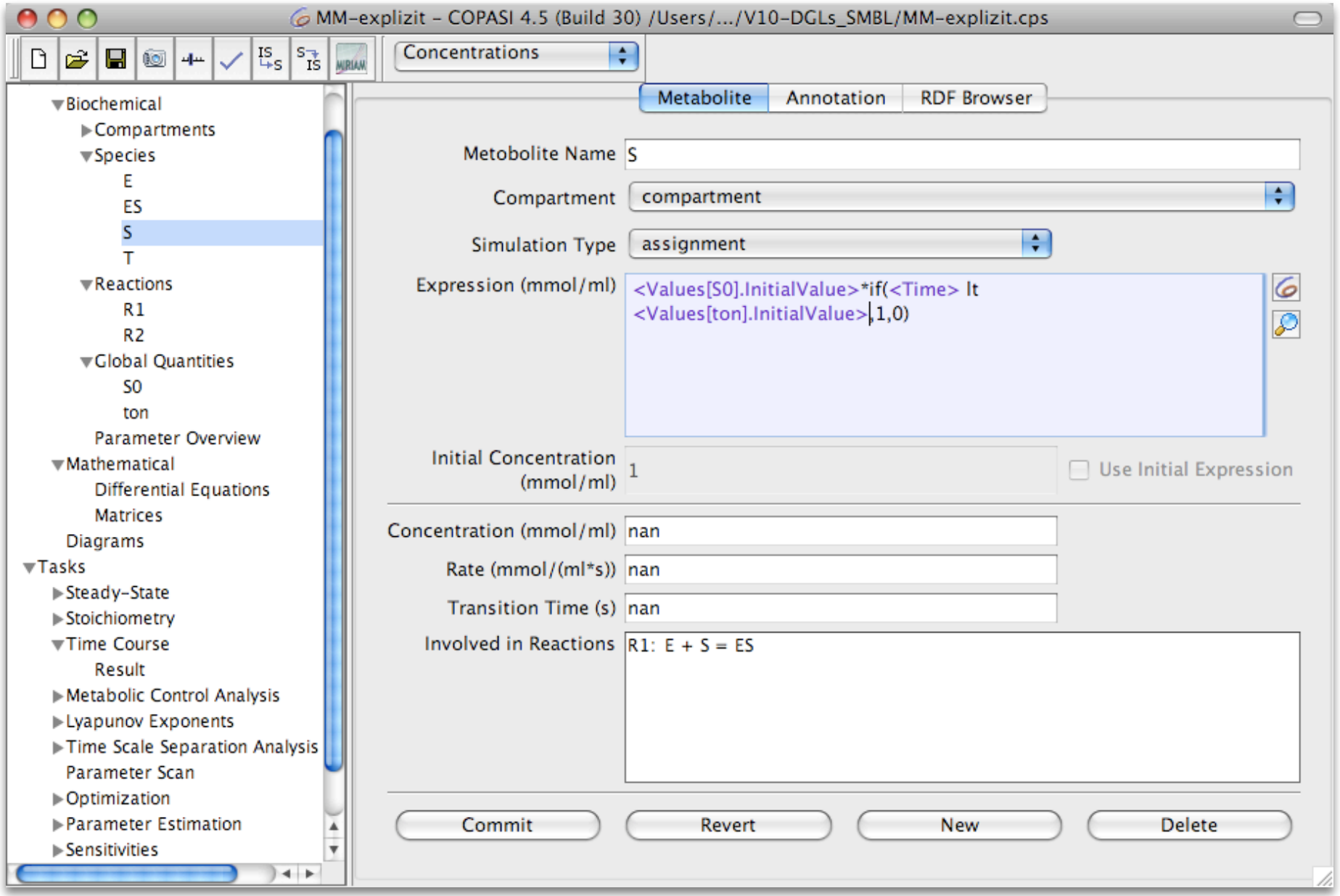
New Folder
Cancel
Save
Commit
Revert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Compartment
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Simulation Type
assignment
Expression (mmol/ml)
<Values[S0].InitialValue>*if(<Time> lt
<Values[ton].InitialValue>,1,0)
Initial Concentration (mmol/ml)
1
Use Initial Expression
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Transition Time (s)
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Involved in Reactions
R1: E + S = ES
Commit
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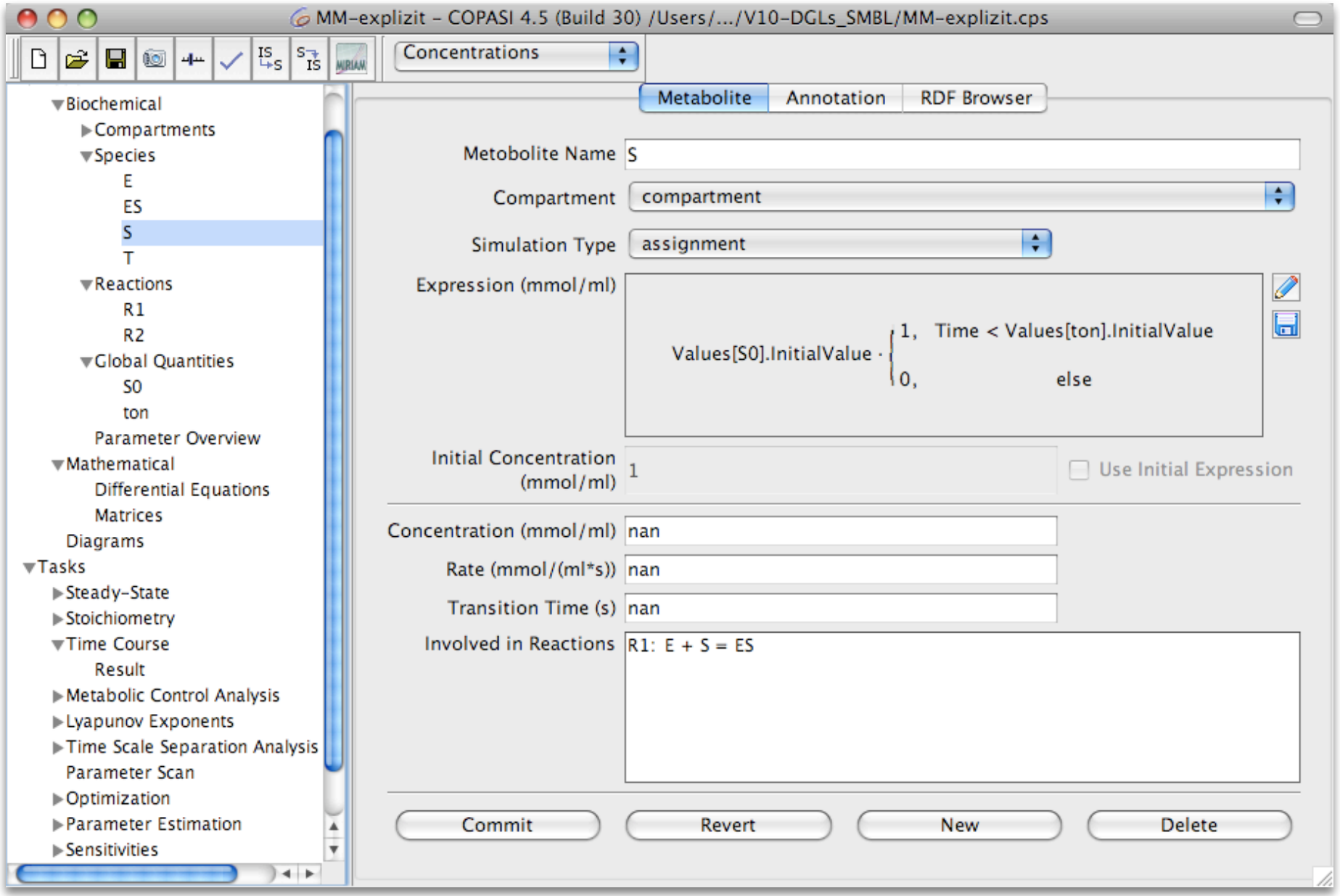
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Simulation Type
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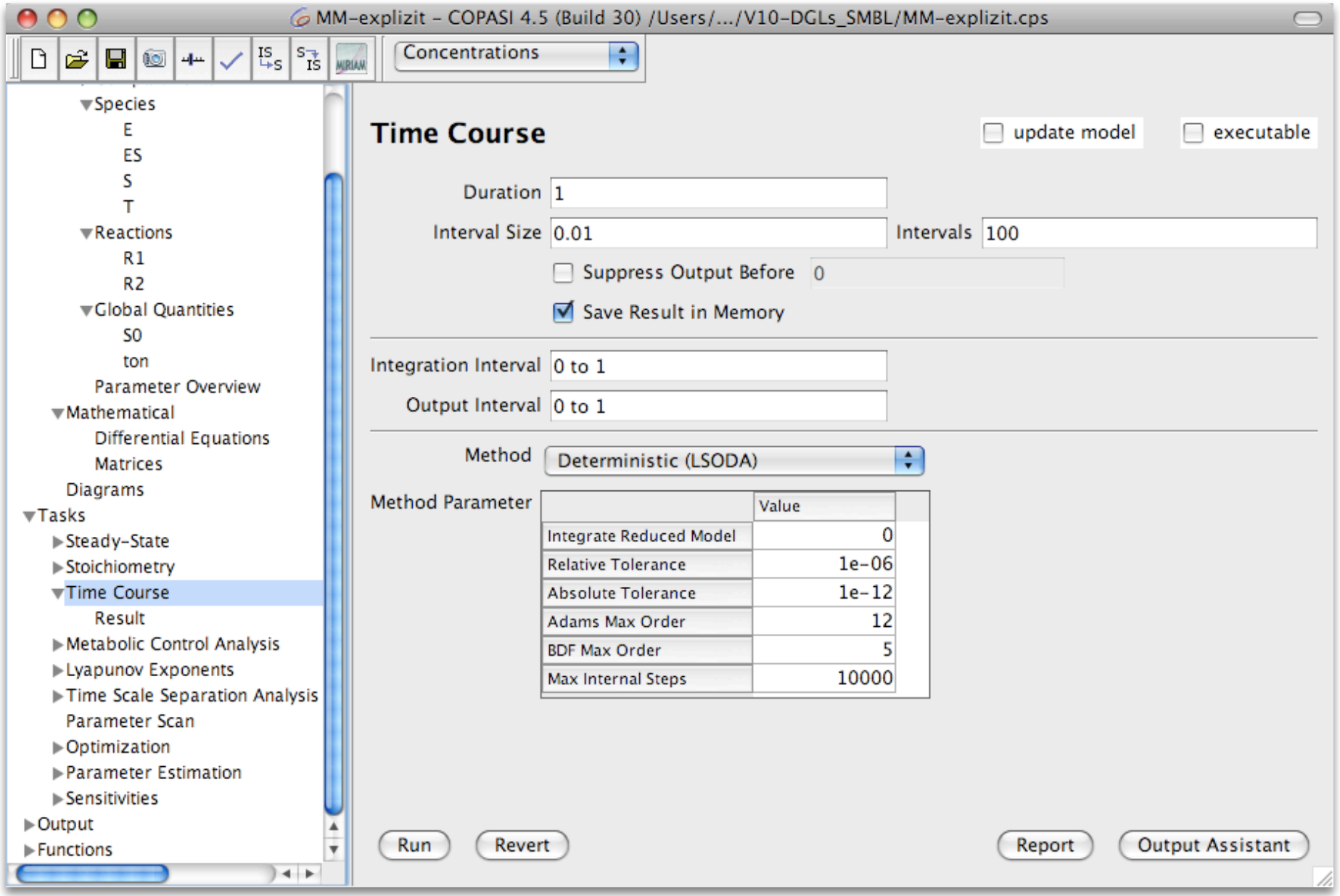
Expression (mmol/ml)
Values[S0].InitialValue · { 1, Time < Values[ton].InitialValue ; 0, else
Initial Concentration (mmol/ml)
1
Use Initial Expression
Concentration (mmol/ml)
nan
Rate (mmol/(ml*s))
nan
Transition Time (s)
nan
Involved in Reactions
R1: E + S = ES
Commit
Revert
New
Delete


MM-explizit - COPASI 4.5 (Build 30) /Users/.../V10-DGLs_SMBL/MM-explizit.cps
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Reactions
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R2
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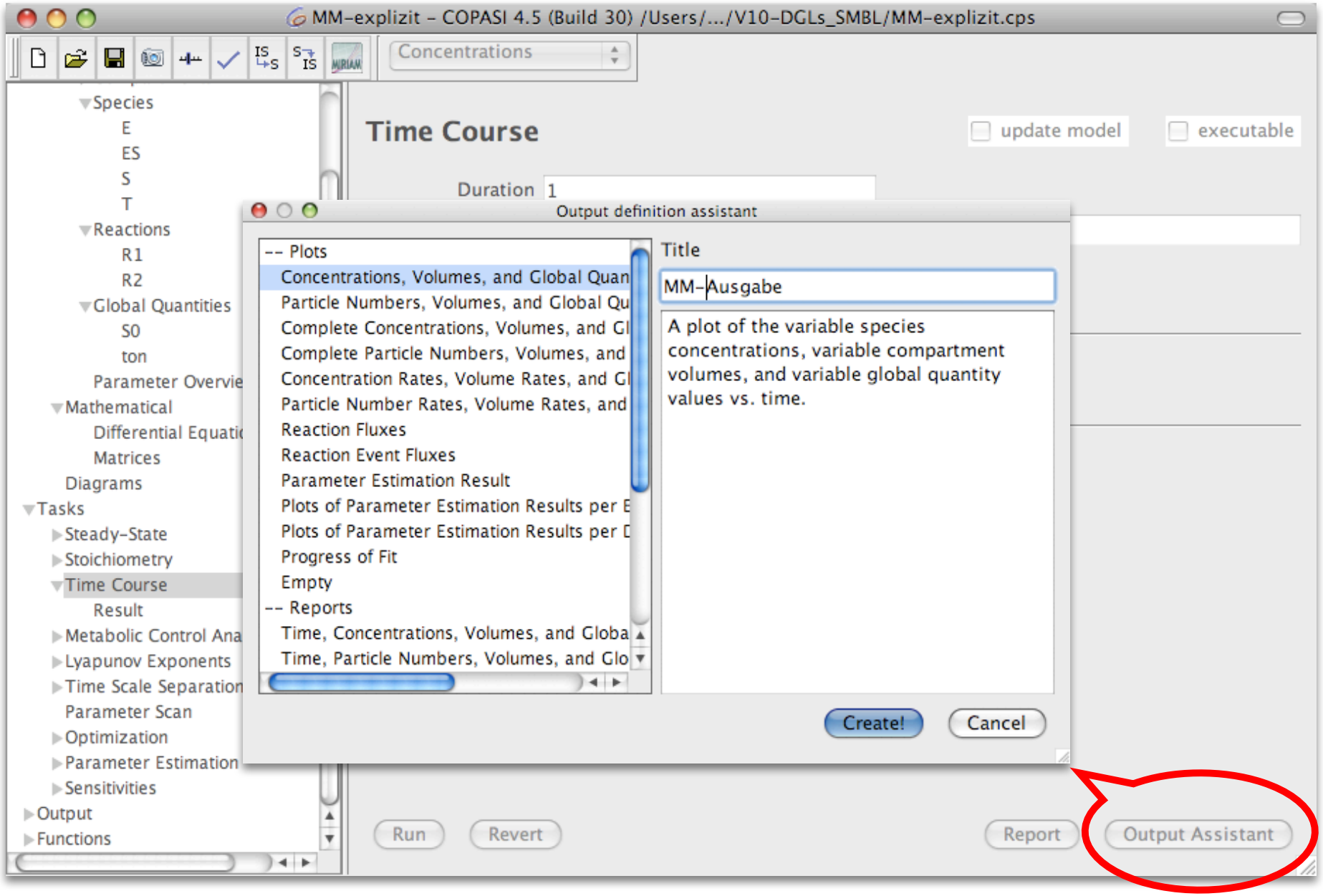
Parameter Overview
Mathematical
Differential Equations
Matrices
Diagrams
Tasks
Steady-State
Stoichiometry
Time Course
Result
Metabolic Control Analysis
Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
Output
Functions
Time Course
update model
executable
Duration 1
Interval Size 0.01
Intervals 100
Suppress Output Before 0
Save Result in Memory
Integration Interval 0 to 1
Output Interval 0 to 1
Method Deterministic (LSODA)
Method Parameter
Value
Integrate Reduced Model 0
Relative Tolerance 1e-06
Absolute Tolerance 1e-12
Adams Max Order 12
BDF Max Order 5
Max Internal Steps 10000
Run
Revert
Report
Output Assistant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-- Plots
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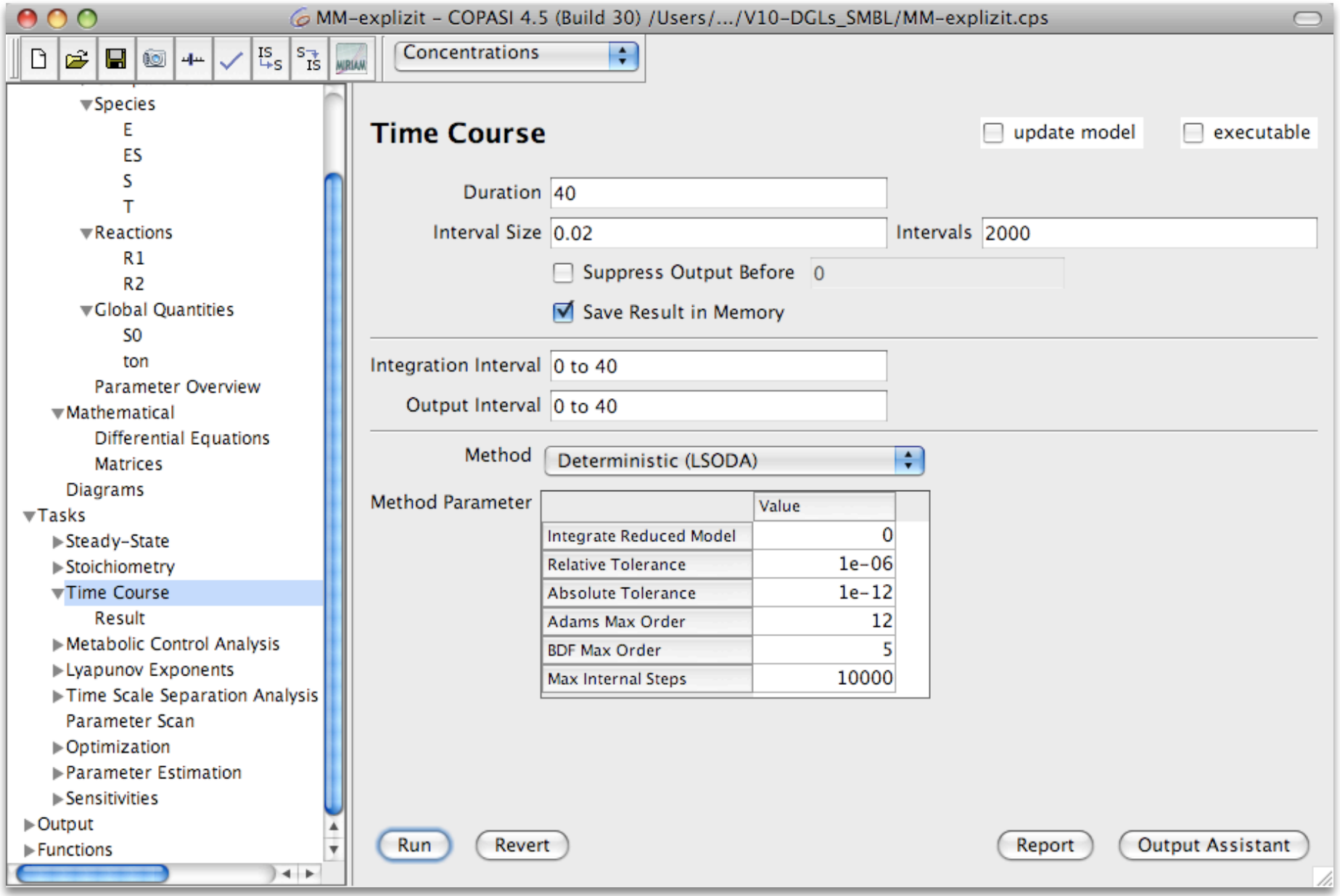
Complete Concentrations, Volumes, and Gl
Complete Particle Numbers, Volumes, and
Concentration Rates, Volume Rates, and Gl
Particle Number Rates, Volume Rates, and
Reaction Fluxes
Reaction Event Fluxes
Parameter Estimation Result
Plots of Parameter Estimation Results per E
Plots of Parameter Estimation Results per D
Progress of Fit
Empty
-- Reports
Time, Concentrations, Volumes, and Globa
Time, Particle Numbers, Volumes, and Glo
Title
MM-Ausgabe
A plot of the variable species concentrations, variable compartment volumes, and variable global quantity values vs. time.
Create!
Cancel
Run
Revert
Report
Output Assistant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Stoichiometry
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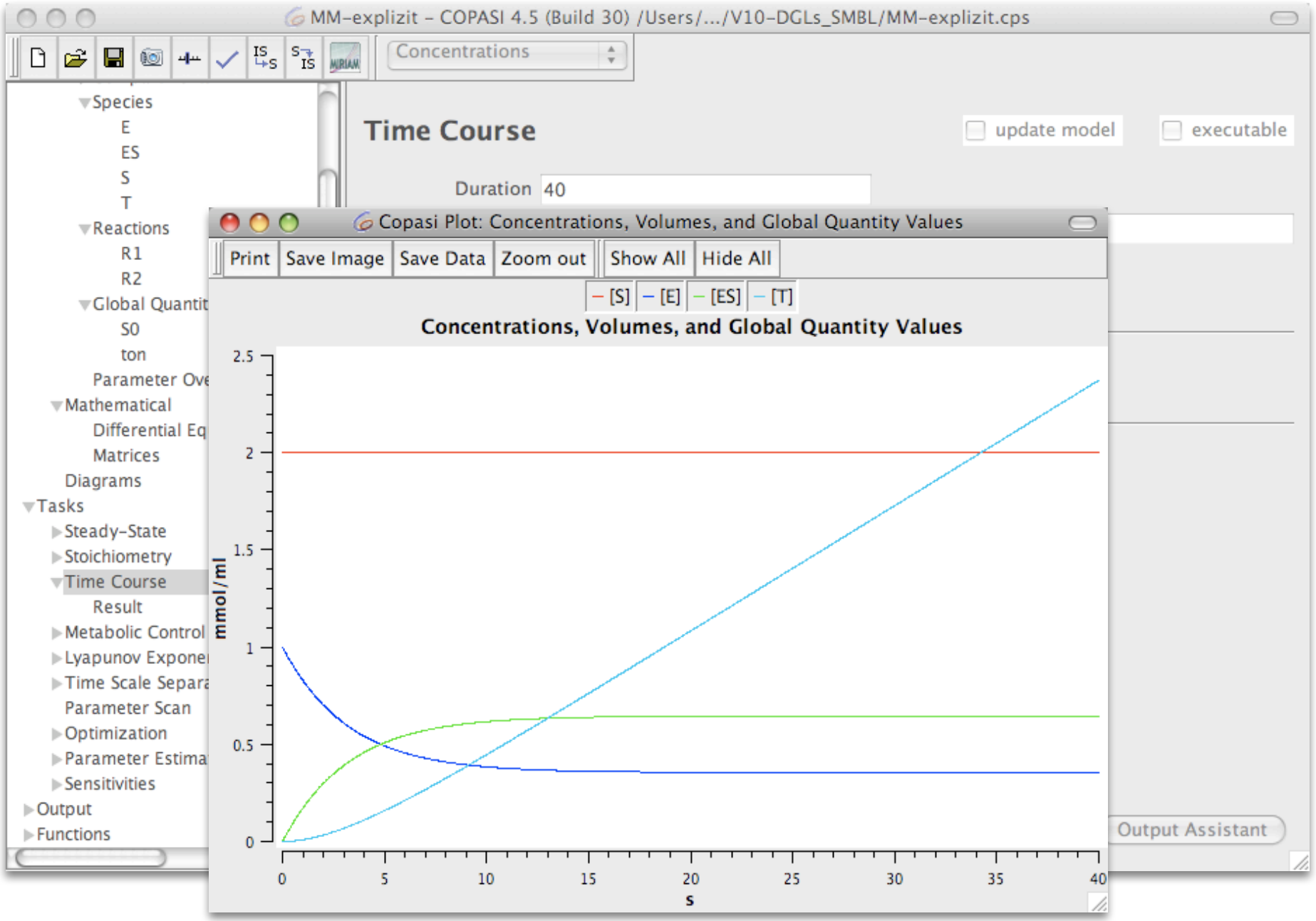
Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
Output
Functions
Time Course
update model
executable
Duration 40
Interval Size 0.02
Intervals 2000
Suppress Output Before 0
Save Result in Memory
Integration Interval 0 to 40
Output Interval 0 to 40
Method Deterministic (LSODA)
Method Parameter
Value
Integrate Reduced Model 0
Relative Tolerance 1e-06
Absolute Tolerance 1e-12
Adams Max Order 12
BDF Max Order 5
Max Internal Steps 10000
Run
Revert
Report
Output Assistant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Duration 40
Output Assistant
Copasi Plot: Concentrations, Volumes, and Global Quantity Values
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Save Image
Save Data
Zoom out
Show All
Hide All
[S]
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Concentrations, Volumes, and Global Quantity Values
mmol/ml
2.5
2
1.5
1
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0
0
5
10
15
20
25
30
35
40
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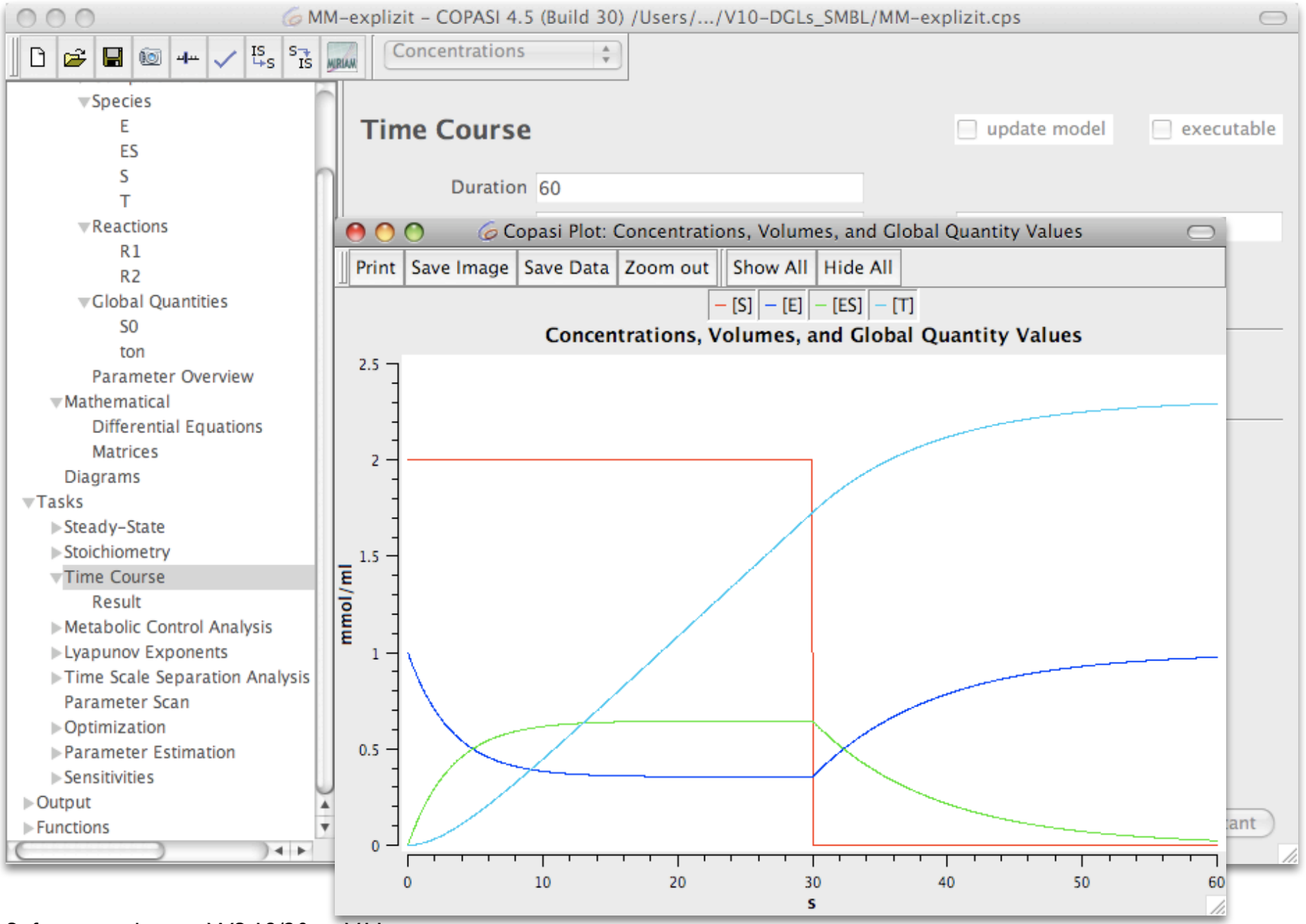
MM-explizit - COPASI 4.5 (Build 30) /Users/.../V10-DGLs_SMBL/MM-explizit.cps
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Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
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Parameter Estimation
Sensitivities
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executable
Duration 60
Copasi Plot: Concentrations, Volumes, and Global Quantity Values
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Concentrations, Volumes, and Global Quantity Values
mmol/ml
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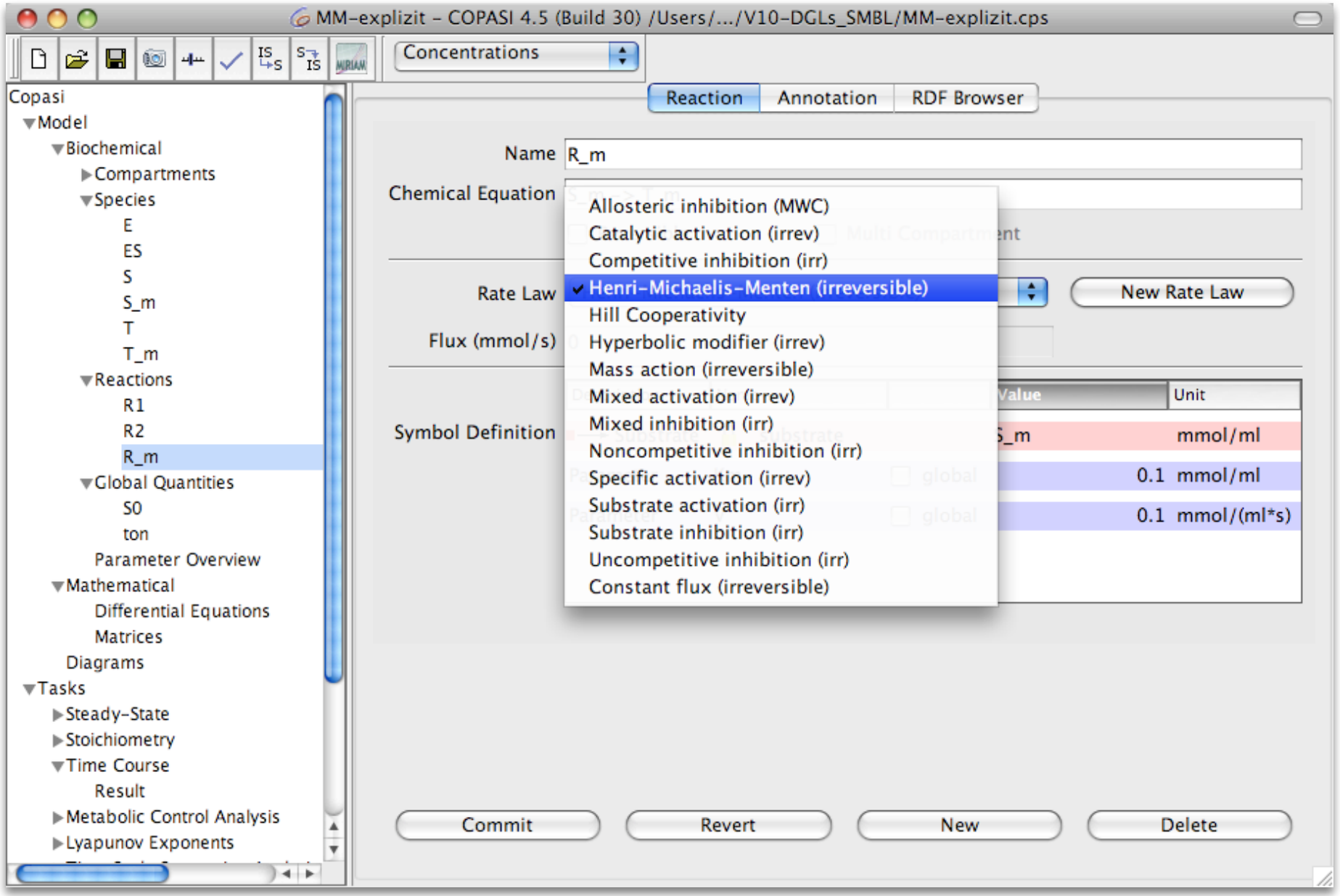
40
50
60
s


MM-explizit - COPASI 4.5 (Build 30) /Users/.../V10-DGLs_SMBL/MM-explizit.cps
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Steady-State
Stoichiometry
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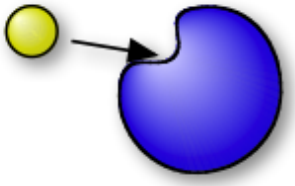
Result
Metabolic Control Analysis
Lyapunov Exponents
Reaction
Annotation
RDF Browser
Name
R_m
Chemical Equation
Rate Law
New Rate Law
Flux (mmol/s)
Symbol Definition
Value
Unit
S_m
mmol/ml
0.1
mmol/ml
0.1
mmol/(ml*s)
Allosteric inhibition (MWC)
Catalytic activation (irrev)
Competitive inhibition (irr)
Henri-Michaelis-Menten (irreversible)
Hill Cooperativity
Hyperbolic modifier (irrev)
Mass action (irreversible)
Mixed activation (irrev)
Mixed inhibition (irr)
Noncompetitive inhibition (irr)
Specific activation (irrev)
Substrate activation (irr)
Substrate inhibition (irr)
Uncompetitive inhibition (irr)
Constant flux (irreversible)
Commit
Revert
New
Delete

Vereinfachte Kinetiken

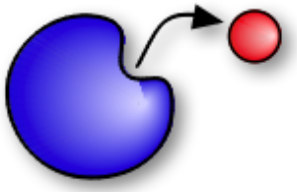
Enzymreaktion:

Michaelis-Menten



$E + S \xrightarrow{k_{on}} ES$

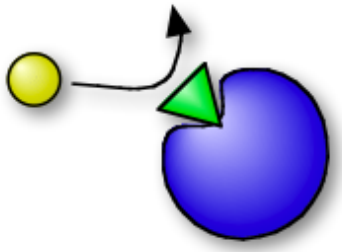
ES => ES'



$ES' \xrightarrow{k_{off}} E + T$

kompetitive Inhibition:

Inhibitor vs. Substrat

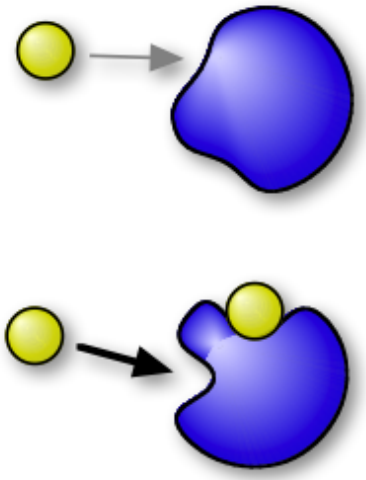


$E + S \xrightarrow{k_{on}} ES$

$E + I \xrightarrow{k_I} EI$

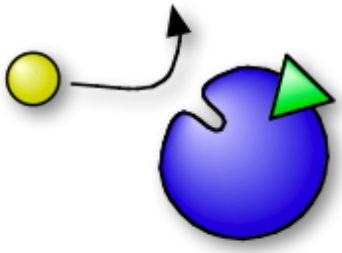
Kooperative Bindung:

Hill-Kinetik



nicht-kompetitive Inhibition:

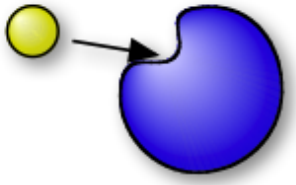
Inhibitor verändert Enzym

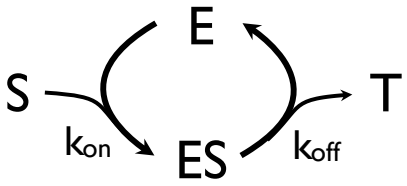


$E + S \xrightarrow{k_{on}} ES$

$EI + S \xrightarrow{k_{on}'} EIS$

Enzyme: Michaelis-Menten-Kinetik

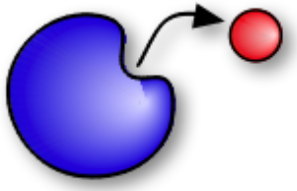




Reaktionsrate:

$$V = k_{off} ES$$

Steady state: $k_{on} E \cdot S = k_{off} ES$



$$ES = \frac{k_{on}\, E \cdot S}{k_{off}} = \frac{E \cdot S}{K_M}$$

Gesamtmenge an Enzym ist konstant:

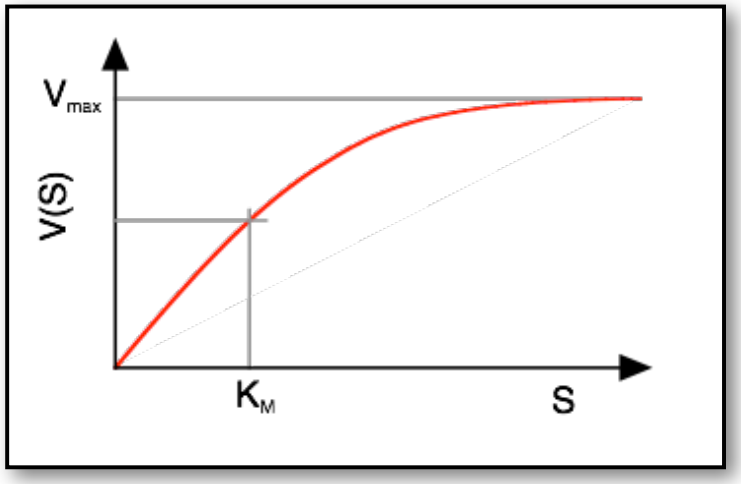
$$E_T = E + ES \quad \Rightarrow \quad ES = E_T \frac{S}{S + K_M}$$

Umsatz: $V = V_{max} \frac{S}{S + K_M}$

Die Gleichung

Effektiver Umsatz nach MM: $$V = V_{max} \frac{S}{S + K_M}$$

$$V_{max} = k_{off} E_T$$



$$K_M = \frac{k_{off}}{k_{on}}$$

Vorteile:
- analytische Formel für den Umsatz
- Interpretation der Kennlinie: V_{max}, K_M
- Enzym kann ignoriert werden

Aber: weniger kinetische Informationen

k_{on}, k_{off}, E_T => V_{max}, K_M

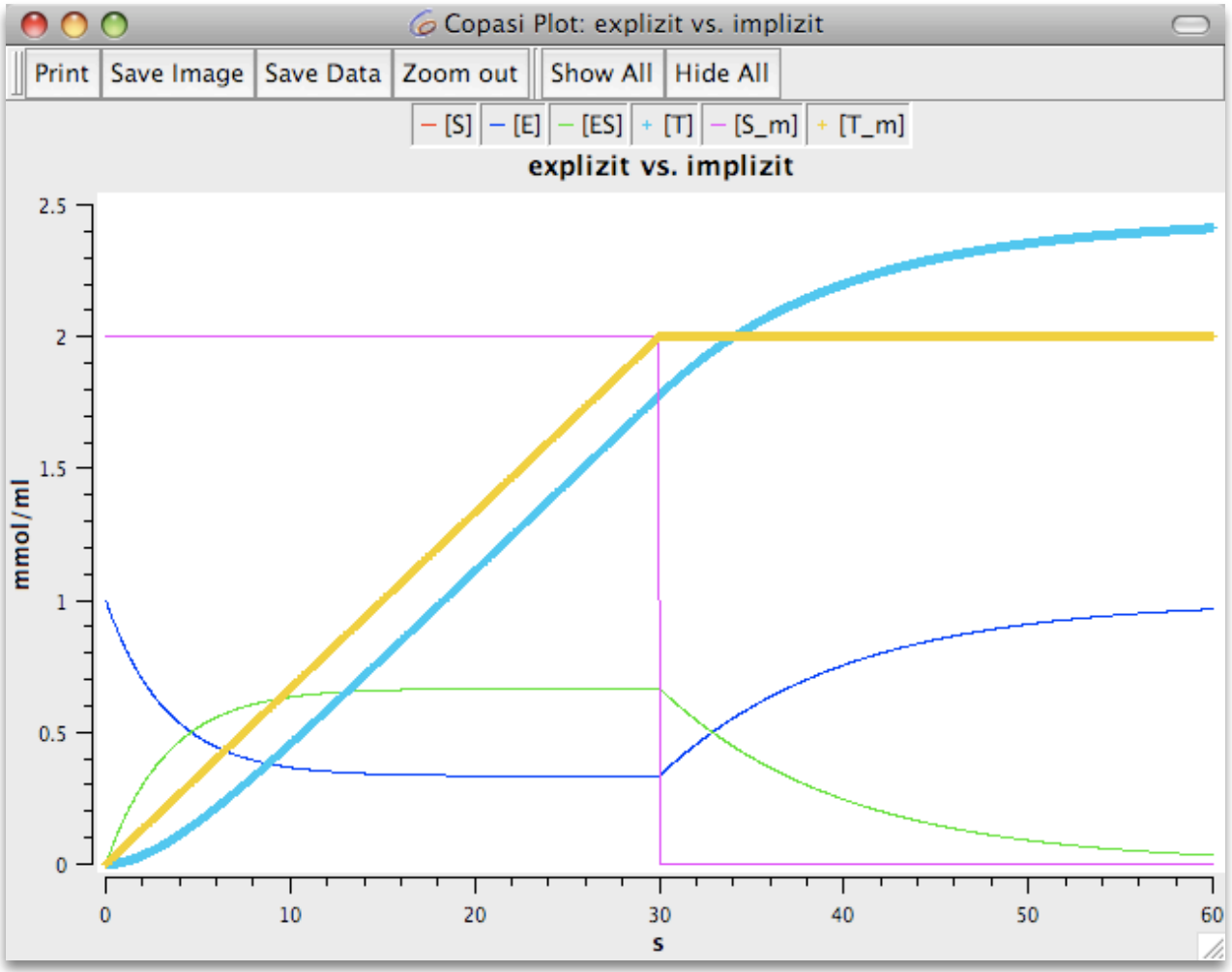
MM vs. explizite Modellierung

Wenn E verschiedene Substrate katalysiert
=> MM geht nicht

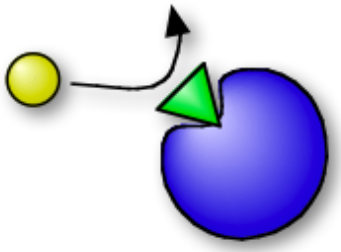
Zeitverhalten:
MM-Kinetik vs.
explizite Modellierung

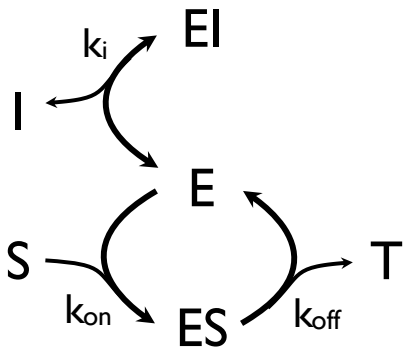
=> Einschwingen

=> anderer
Gesamtumsatz



Kompetitive Hemmung





Zwei Pfade:

$E + S \xrightarrow{k_{on}} ES$ $\quad E + I \xrightarrow{k_I} EI$

=> I verdrängt S

S << I: weniger freies E verfügbar

=> weniger ES

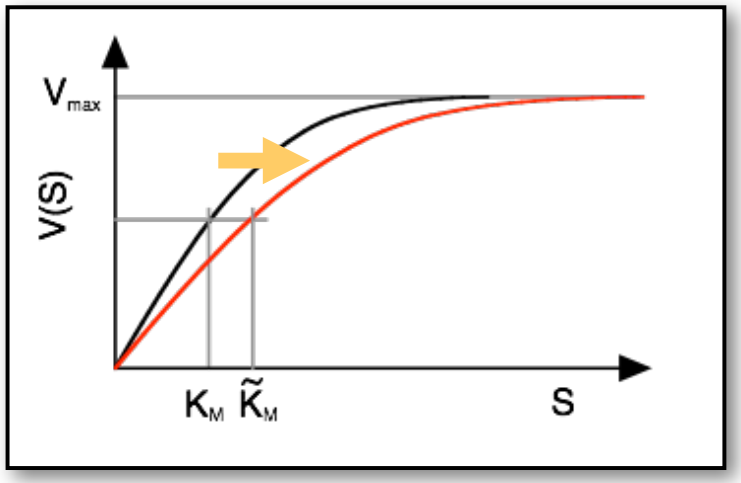
=> V reduziert

$$\tilde{K}_M = K_M (1 + I/K_I)$$

S >> I: S verdrängt I

=> Inhibition unterdrückt

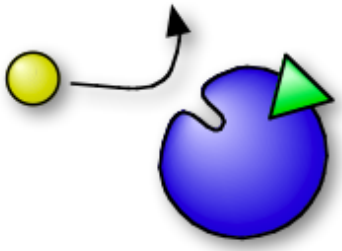
=> V_{max} unverändert

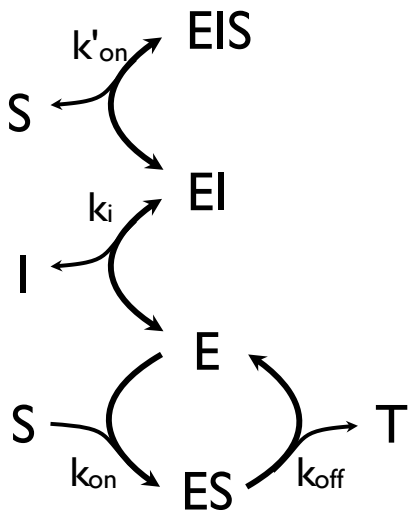


$$V = V_{max} \frac{S}{S + K_M (1 + I/K_I)}$$

Nichtkompetitive Inhibition

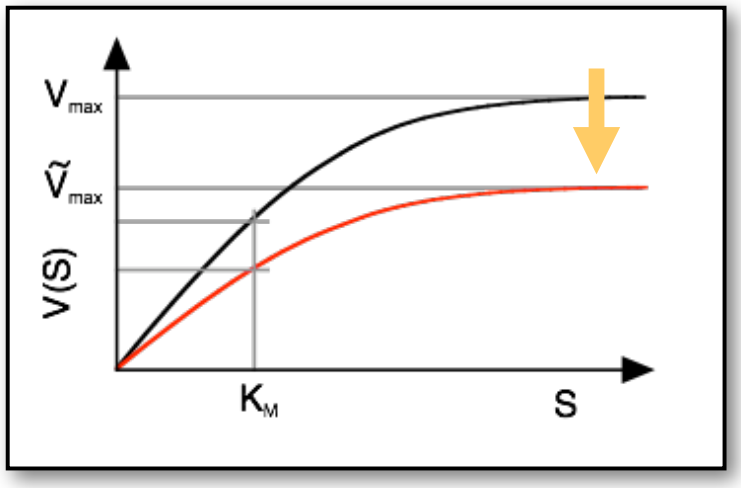
Inhibitor blockiert Enzym





=> I reduziert effektives E_T

$$\Rightarrow \tilde{V}_{max} = \frac{V_{max}}{1 + I/K_I}$$



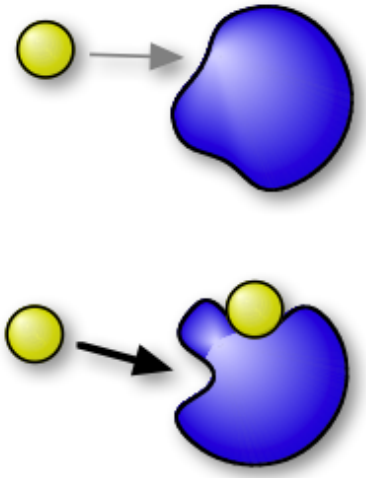
Analytische Formeln

=> Wirkungsweise von I aus steady state

Anzahl Parameter:

- explizit: k_{on}, k_{off}, E_T, $k_{i,on}$, $k_{i,off}$, k'_{on}, k'_{off}
- effektiv: V_{max}, K_M, K_i

Kooperativität: Hill-Kinetik



Archibald Hill (1913): "Bindung des ersten Metaboliten vereinfacht Bindung des/der nächsten."
Wurde formuliert um die kooperative Bindung von Sauerstoff an Hämoglobin zu erklären (n = 2.8 ... 3.0)

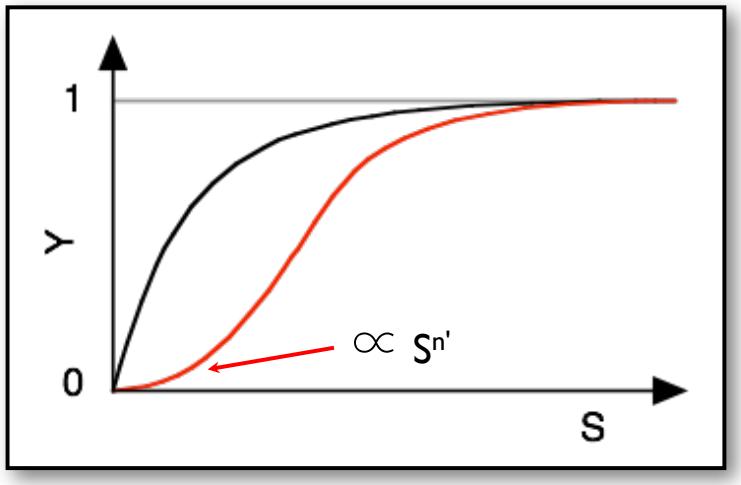
Zum Vergleich: E + S <=> ES $K = \frac{E \cdot S}{ES}$

$$Y = \frac{ES}{E + ES} = \frac{S}{S + K}$$ Anteil an besetzten Bindungstaschen

Mehrere Substrat-Moleküle gleichzeitig:

E + n S <=> ES_n

$$Y = \frac{S^{n'}}{S^{n'} + K^{n'}}$$



Hill-Koeffizient: $1 \leq n' \leq n$

Wann effektive Kinetiken?

Pro:

- weniger Aufwand (Modell, Simulation, Parameter)
- analytische Lösungen für einfache Systeme
- korrekter Steady state

Contra:

- weniger Parameter => weniger kinetische Informationen
- falsches dynamisches Verhalten

"Effektive Kinetiken brauchbar für langsame Signale"

"langsam" = Relaxationszeiten aller Zwischenschritte deutlich kürzer als Änderungen des Signals

Woher bekommt man die Daten?

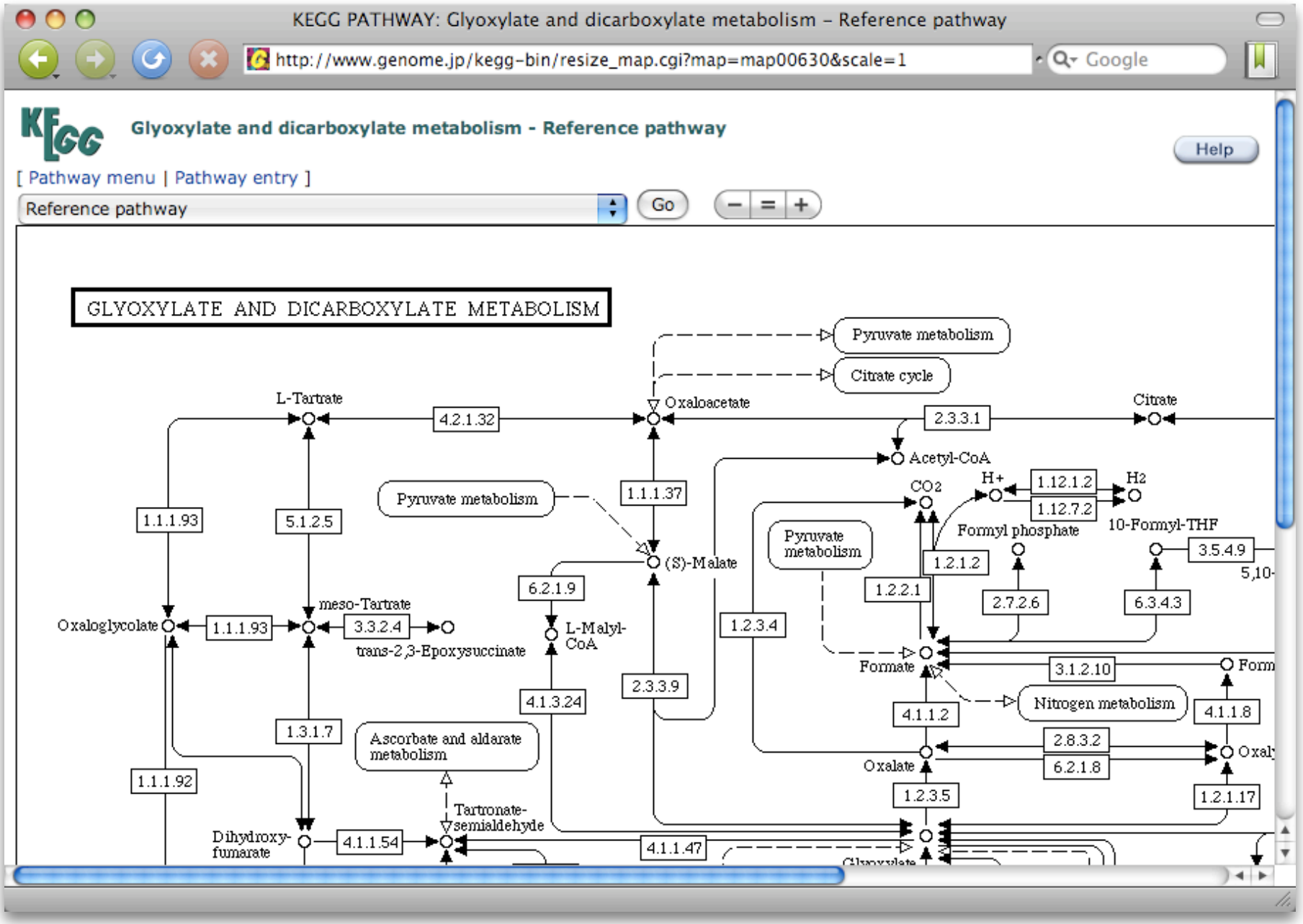
- Experten fragen
- Originalartikel lesen
- lesen lassen:
  - => Student, HiWi
  - => Datenbanken

Pfade: KEGG

http://www.genome.jp/kegg/

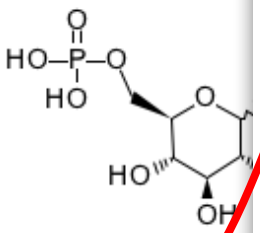
kinetische Daten: SABIO-RK

http://sabio.villa-bosch.de/welcome_new.jsp?

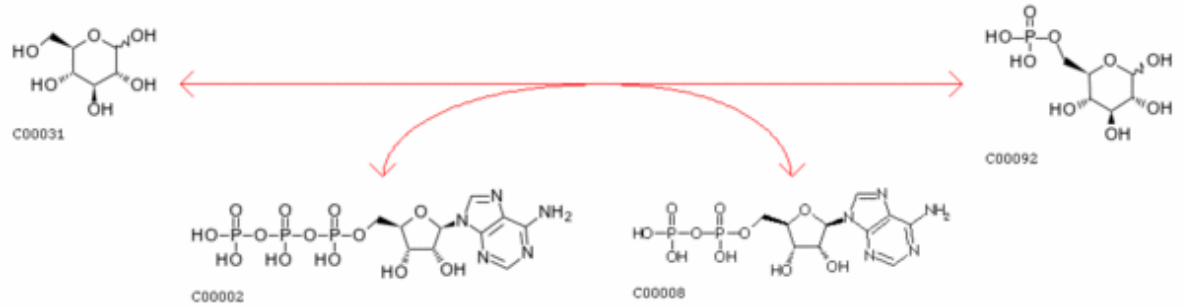

KEGG PATHWAY: Glyoxylate and dicarboxylate metabolism – Reference pathway
http://www.genome.jp/kegg-bin/resize_map.cgi?map=map00630&scale=1
Google
KEGG
Glyoxylate and dicarboxylate metabolism - Reference pathway
Help
[Pathway menu | Pathway entry]
Reference pathway
Go
GLYOXYLATE AND DICARBOXYLATE METABOLISM
Pyruvate metabolism
Citrate cycle
L-Tartrate
4.2.1.32
Oxaloacetate
2.3.3.1
Citrate
Acetyl-CoA
1.1.1.37
Pyruvate metabolism
CO2
H+
1.12.1.2
1.12.7.2
H2
Formyl phosphate
10-Formyl-THF
1.1.1.93
5.1.2.5
(S)-Malate
Pyruvate metabolism
1.2.1.2
1.2.2.1
2.7.2.6
3.5.4.9
6.3.4.3
5,10-
6.2.1.9
meso-Tartrate
Oxaloglycolate
1.1.1.93
3.3.2.4
trans-2,3-Epoxysuccinate
L-Malyl-CoA
1.2.3.4
Formate
3.1.2.10
Form
2.3.3.9
4.1.3.24
Nitrogen metabolism
4.1.1.2
4.1.1.8
1.3.1.7
Ascorbate and aldarate metabolism
2.8.3.2
6.2.1.8
Oxalate
Oxaly
1.1.1.92
1.2.3.5
1.2.1.17
Tartronate-semialdehyde
Dihydroxy-fumarate
4.1.1.54
4.1.1.47

Inside KEGG

KEGG **COMPOUND: C00092** Help

Entry	C00092
Name	D-Glucose 6-phospl Glucose 6-phospha Robison ester
Formula	C6H13O9P
Mass	260.0297
Structure	 C00092 Mol file KCF file
Reaction	R00299 R00303 R007 R00838 R00839 R008 R05804 R06043 R060 R08125 R08404 R086
Pathway	PATH: ko00500 Sta PATH: ko00521 Str PATH: ko00562 Inos PATH: map01062 Bi PATH: ko02020 Two- PATH: ko02060 Phosphotransferase system (PTS)
Enzyme	1.1.1.49 1.1.1.200 2.4.1.1 (E) 2.4.1.15 2.4.1.36 2.4.1.216 2.7.1.1 2.7.1.2 2.7.1.61 2.7.1.63 2.7.1.142 2.7.1.147 3.1.3.9 3.1.3.58 3.2.1.86 3.2.1.93 3.2.1.122 3.5.-.- 5.3.1.9 5.4.2.2 5.4.2.5 5.5.1.4
Other DBs	CAS: 56-73-5

KEGG **REACTION: R00299** Help

Entry	R00299 Reaction
Name	ATP:D-glucose 6-phosphotransferase
Definition	ATP + D-Glucose <=> ADP + D-Glucose 6-phosphate
Equation	C00002 + C00031 <=> C00008 + C00092
	 C00031 C00092 C00002 C00008
RPair	RP: RP00003 C00002_C00008 main RP: RP00060 C00031_C00092 main RP: RP08556 C00002_C00092 trans
Pathway	PATH: rn00521 Streptomycin biosynthesis
Enzyme	2.7.1.1 2.7.1.2
LinkDB	All DBs

Reaktionsraten?

Raten: SABIO-RK

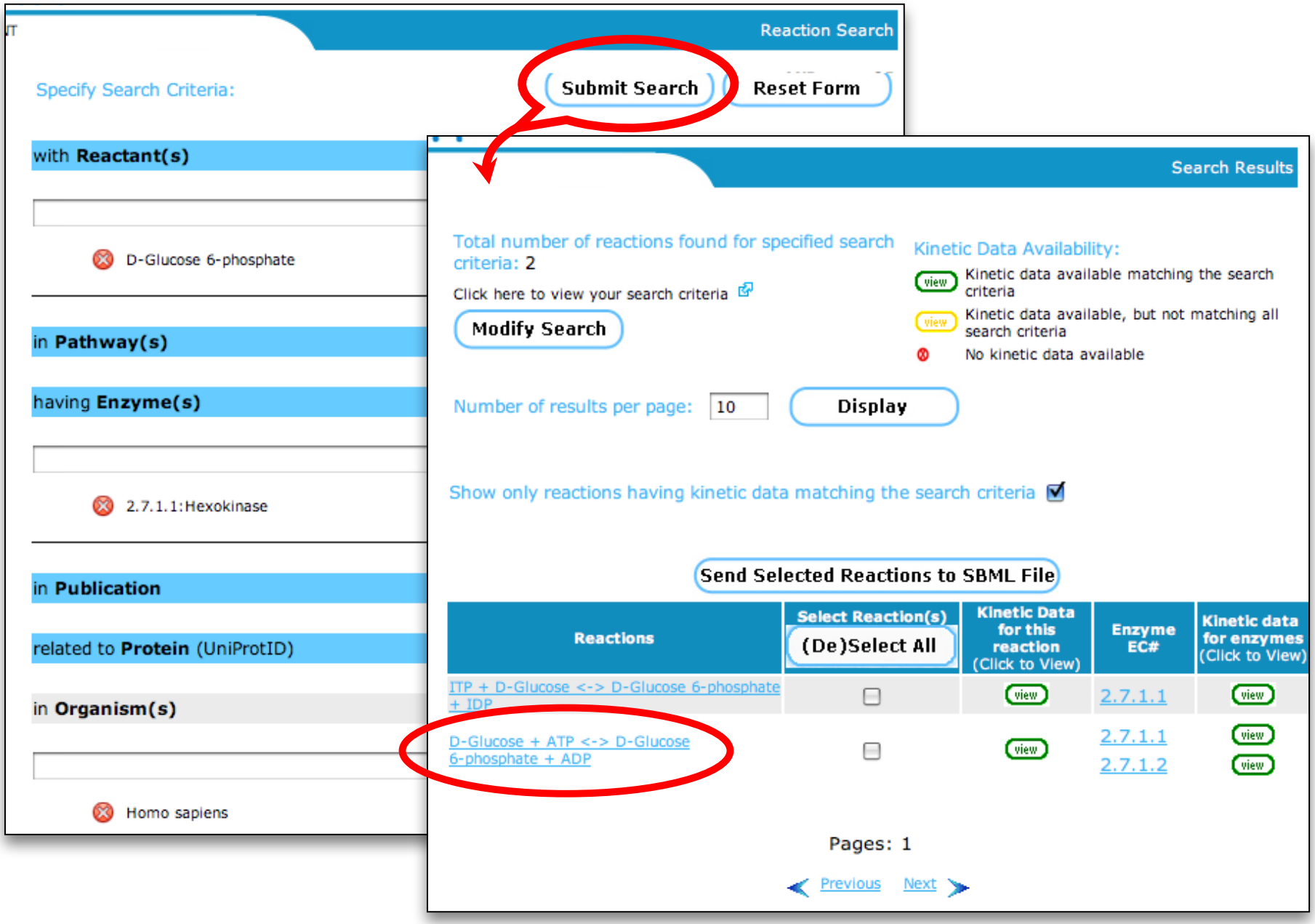
What is SABIO-RK? TOP

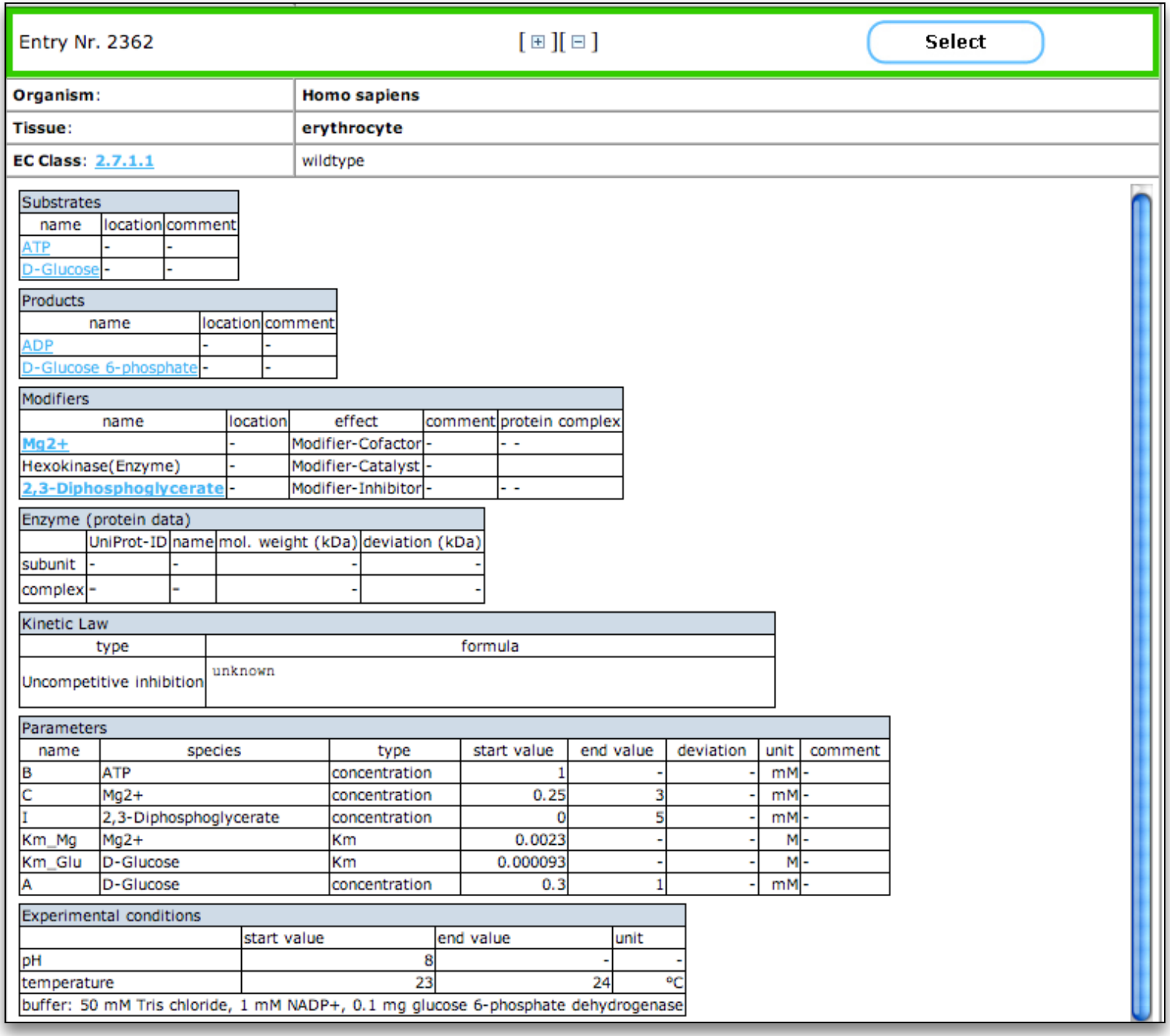
The SABIO-RK (System for the Analysis of Biochemical Pathways - Reaction Kinetics) is a web-based application based on the SABIO relational database that contains information about biochemical reactions, their kinetic equations with their parameters, and the experimental conditions under which these parameters were measured. It aims to support modellers in the setting-up of models of biochemical networks, but it is also useful for experimentalists or researchers with interest in biochemical reactions and their kinetics. Information about reactions and their kinetics can be exported in SBML (Systems Biology Mark-Up Language) format.
This project is sponsored by the Klaus Tschira Foundation and partially by the German BMBF (Bundesministerium fï¿½r Bildung und Forschung).

Data Provenance TOP

There are two main sources for the data contained in SABIO. Most of the reactions, their association with pathways and their enzymatic classification, is extracted from the KEGG (KEGG: Kyoto Encyclopedia of Genes and Genomes) database. The other main source of data are publications. The reaction kinetics data are obtained by manual extraction from literature sources and curated.

Suche in SABIO-RK





Entry Nr. 2362 [⊞][⊟] Select

Organism:	**Homo sapiens**
Tissue:	**erythrocyte**
EC Class: 2.7.1.1	wildtype

Substrates

name	location	comment
ATP	-	-
D-Glucose	-	-

Products

name	location	comment
ADP	-	-
D-Glucose 6-phosphate	-	-

Modifiers

name	location	effect	comment	protein complex
Mg2+	-	Modifier-Cofactor	-	- -
Hexokinase(Enzyme)	-	Modifier-Catalyst	-	
2,3-Diphosphoglycerate	-	Modifier-Inhibitor	-	- -

Enzyme (protein data)

	UniProt-ID	name	mol. weight (kDa)	deviation (kDa)
subunit	-	-	-	-
complex	-	-	-	-

Kinetic Law

type	formula
Uncompetitive inhibition	unknown

Parameters

name	species	type	start value	end value	deviation	unit	comment
B	ATP	concentration	1	-	-	mM	-
C	Mg2+	concentration	0.25	3	-	mM	-
I	2,3-Diphosphoglycerate	concentration	0	5	-	mM	-
Km_Mg	Mg2+	Km	0.0023	-	-	M	-
Km_Glu	D-Glucose	Km	0.000093	-	-	M	-
A	D-Glucose	concentration	0.3	1	-	mM	-

Experimental conditions

	start value	end value	unit
pH	8	-	-
temperature	23	24	°C
buffer: 50 mM Tris chloride, 1 mM NADP+, 0.1 mg glucose 6-phosphate dehydrogenase			

Zusammenfassung

Dynamische Simulationen:

- zeitliches Verhalten
- steady state = stationäre Lösung des DGL-Systems
- Puffergrößen und Reaktionsraten

Copasi:

- Simulation und Analyse chemischer Reaktionen

Vereinfachte Kinetiken:

- hilft im steady state, problematisch bei zeitabh. Prozessen
- Bsp: kinetische Isolierung von Signalpfaden

Simulationsparameter?

- KEGG – Pfade
- SABIO-RK: hand-kurierte Reaktionsparameter

Systems Biology Markup Language

XML-Dialekt für Speicherung und Austausch biochemischer Modelle

=> Archivierung

=> Transfer von Modellen in andere Softwaretools

Acknowledgements

We are deeply indebted to the many funding agencies and organizations that have supported SBML over the years.

Since 2003, primary support for the continued development of SBML, as well as supporting software and activities, has come from the **National Institute of General Medical Sciences (NIH/NIGMS)** under grants R01 GM070923 and R01 GM077671. Additional support is provided by the **California Institute of Technology** (USA) and **Keio University** (Japan).

The development of SBML from its inception through 2003 was principally funded by the **Japan Science and Technology Agency** under the **ERATO Kitano Symbiotic Systems Project**.

Additional support has in the past been provided by the following organizations and agencies: the **Systems Biology Institute** (Japan), the **University of Hertfordshire** (UK), the **Molecular Sciences Institute** (USA), the **National Human Genome Research Institute** (USA), the **International Joint Research Program of NEDO** (Japan), the **ERATO-SORST** Program of the Japan Science and Technology Agency (Japan), the **Ministry of Agriculture** (Japan), the **Ministry of Education, Culture, Sports, Science and Technology** (Japan), the **BBSRC e-Science Initiative** (UK), the **DARPA IPTO Bio-Computation Program** (USA), the Army Research Office's **Institute for Collaborative Biotechnologies** (USA), and the **Air Force Office of Scientific Research** (USA).

von http://sbml.org/Acknowledgments

SBML <= XML

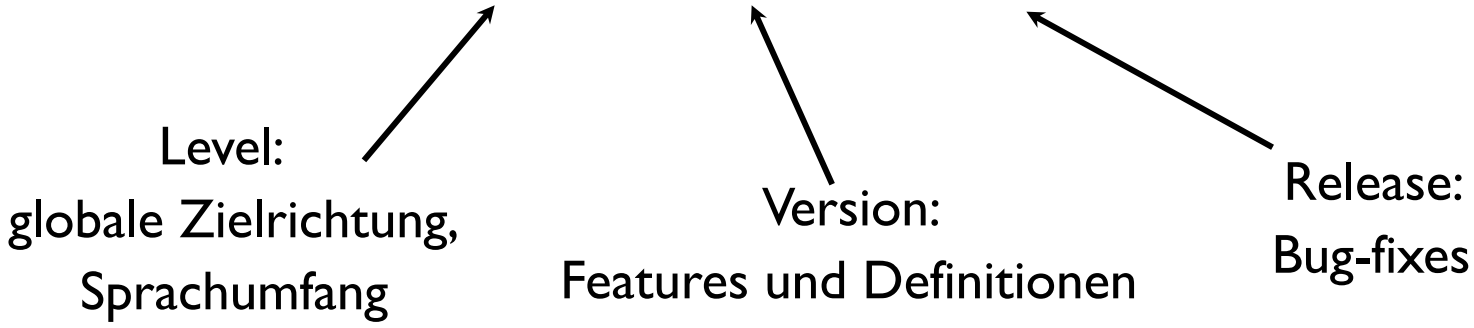
XML = eXtensible Markup Language

- hierarchische Baumstruktur:
  => Schachtelung von <Object> … </Object> oder <Objekt [Parameter…]/>
- genau ein Wurzelobjekt: <sbml…>

Aktuelle Dialekte: siehe http://sbml.org/Documents/Specifications

SBML Level 1, Version 2
http://www.sbml.org/specifications/sbml-level-1/version-2/sbml-level-1-v2.pdf

SBML Level 2, Version 4, Release 1
http://precedings.nature.com/documents/2715/version/1



Was ist enthalten?

beginning of model definition
- list of function definitions (optional)
- list of unit definitions (optional)
- list of compartment types (optional)
- list of species types (optional)
- list of compartments (optional)
- list of species (optional)
- list of parameters (optional)
- list of initial assignments (optional)
- list of rules (optional)
- list of constraints (optional)
- list of reactions (optional)
- list of events (optional)

end of model definition

http://sbml.org/More_Detailed_Summary_of_SBML

Ein Beispiel

$$E + S \underset{k_{off}}{\overset{k_{on}}{<=>}} ES \overset{k_{cat}}{=>} E + P$$

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="3" xmlns="http://www.sbml.org/sbml/level2/version3">
  <model name="EnzymaticReaction">
    <listOfUnitDefinitions>
      <unitDefinition id="per_second">
        <listOfUnits>
          <unit kind="second" exponent="-1"/>
        </listOfUnits>
      </unitDefinition>
      <unitDefinition id="litre_per_mole_per_second">
        <listOfUnits>
          <unit kind="mole"   exponent="-1"/>
          <unit kind="litre"  exponent="1"/>
          <unit kind="second" exponent="-1"/>
        </listOfUnits>
      </unitDefinition>
    </listOfUnitDefinitions>
    <listOfCompartments>
      <compartment id="cytosol" size="1e-14"/>
    </listOfCompartments>
    <listOfSpecies>
      <species compartment="cytosol" id="ES" initialAmount="0"     name="ES"/>
      <species compartment="cytosol" id="P"  initialAmount="0"     name="P"/>
      <species compartment="cytosol" id="S"  initialAmount="1e-20" name="S"/>
      <species compartment="cytosol" id="E"  initialAmount="5e-21" name="E"/>
    </listOfSpecies>
    <listOfReactions>
      <reaction id="veq">
        <listOfReactants>
          <speciesReference species="E"/>
          <speciesReference species="S"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="ES"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci>cytosol</ci>
              <apply>
                <minus/>
                <apply>
                  <times/>
                  <ci>kon</ci>
                  <ci>E</ci>
                  <ci>S</ci>
                </apply>
                <apply>
                  <times/>
                  <ci>koff</ci>
                  <ci>ES</ci>
                </apply>
              </apply>
            </apply>
          </math>
          <listOfParameters>
            <parameter id="kon"  value="1000000" units="litre_per_mole_per_second"/>
            <parameter id="koff" value="0.2"     units="per_second"/>
          </listOfParameters>
        </kineticLaw>
      </reaction>
      <reaction id="vcat" reversible="false">
        <listOfReactants>
          <speciesReference species="ES"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="E"/>
          <speciesReference species="P"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci>cytosol</ci>
              <ci>kcat</ci>
              <ci>ES</ci>
            </apply>
          </math>
          <listOfParameters>
            <parameter id="kcat" value="0.1" units="per_second"/>
          </listOfParameters>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

Nochmal:

$$E + S \underset{k_{off}}{\overset{k_{on}}{<=>}} ES \overset{k_{cat}}{=>} E + P$$

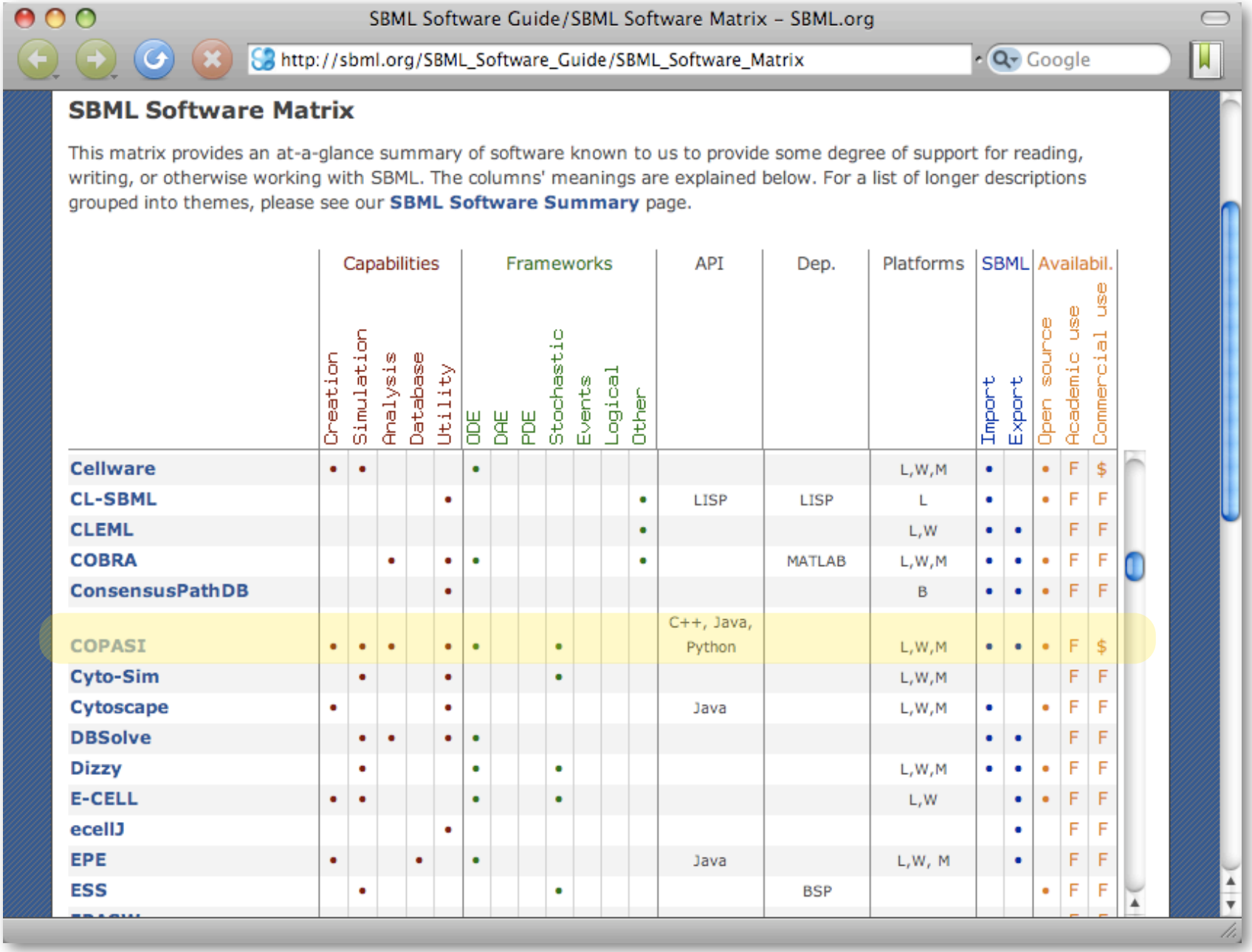
```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="3" xmlns="http://www.sbml.org/sbml/level2/version3">
  <model name="EnzymaticReaction">
    <listOfUnitDefinitions>
      :
    </listOfUnitDefinitions>
    <listOfCompartments>
      <compartment id="cytosol" size="1e-14"/>
    </listOfCompartments>
    <listOfSpecies>
      <species compartment="cytosol" id="ES" initialAmount="0"     name="ES"/>
      <species compartment="cytosol" id="P"  initialAmount="0"     name="P"/>
      <species compartment="cytosol" id="S"  initialAmount="1e-20" name="S"/>
      <species compartment="cytosol" id="E"  initialAmount="5e-21" name="E"/>
    </listOfSpecies>
    <listOfReactions>
      :
    </listOfReactions>
  </model>
</sbml>
```

Details: Einheiten

```
<listOfUnitDefinitions>
        <unitDefinition id="per_second">
                <listOfUnits>
          <unit kind="second" exponent="-1"/>
      </listOfUnits>
   </unitDefinition>
   <unitDefinition id="litre_per_mole_per_second">
      <listOfUnits>
         <unit kind="mole"   exponent="-1"/>
         <unit kind="litre"  exponent="1"/>
         <unit kind="second" exponent="-1"/>
      </listOfUnits>
   </unitDefinition>
</listOfUnitDefinitions>
```

per_seconds := s^{-1}

$$\frac{\text{litre}}{\text{mol s}}$$

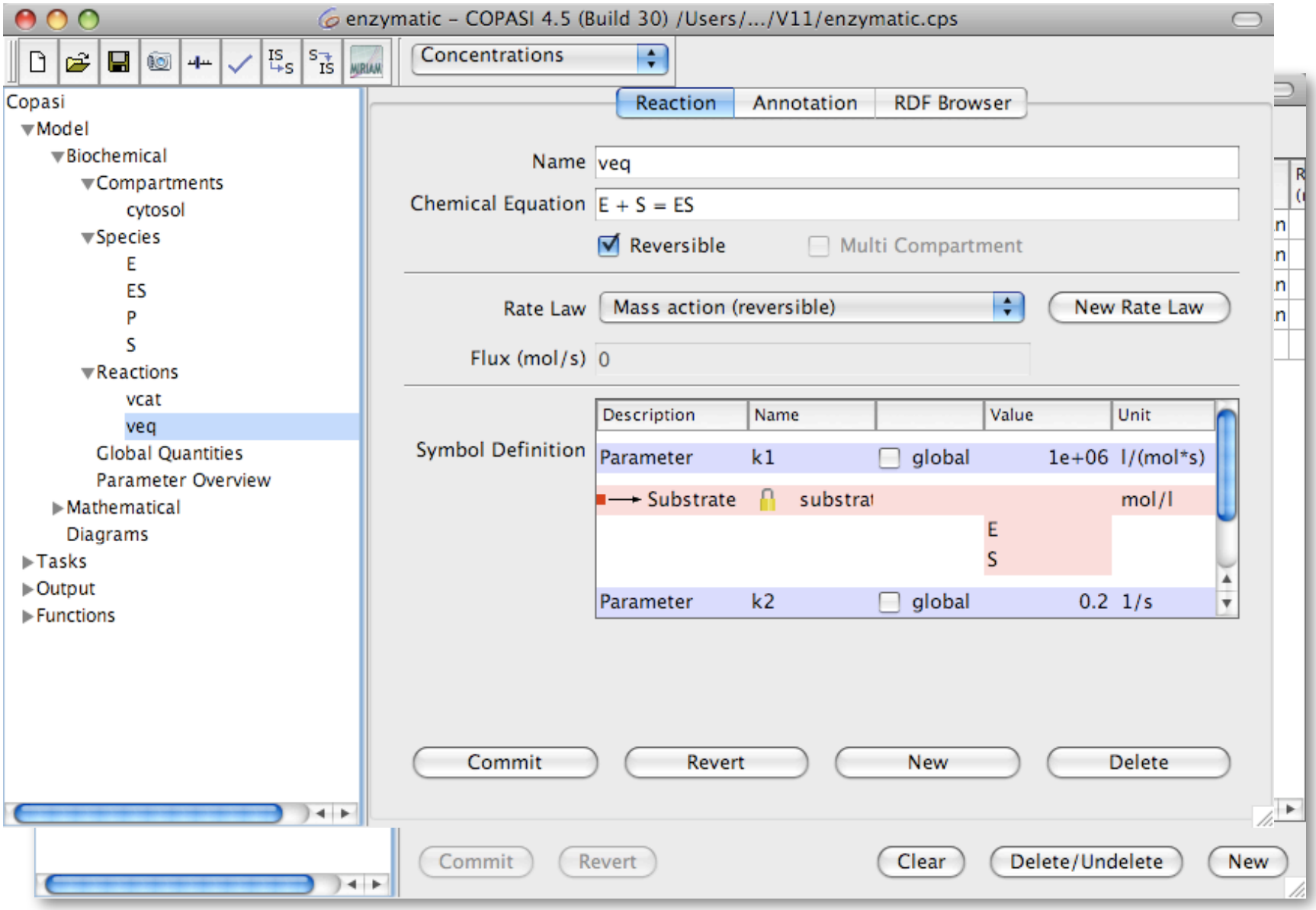


SBML Software Matrix

This matrix provides an at-a-glance summary of software known to us to provide some degree of support for reading, writing, or otherwise working with SBML. The columns' meanings are explained below. For a list of longer descriptions grouped into themes, please see our **SBML Software Summary** page.

	Capabilities					Frameworks							API	Dep.	Platforms	SBML		Availabil.		
	Creation	Simulation	Analysis	Database	Utility	ODE	DAE	PDE	Stochastic	Events	Logical	Other				Import	Export	Open source	Academic use	Commercial use
Cellware	•	•				•						•			L,W,M	•		•	F	$
CL-SBML					•							•	LISP	LISP	L	•		•	F	F
CLEML												•			L,W	•	•		F	F
COBRA			•		•	•						•		MATLAB	L,W,M	•	•	•	F	F
ConsensusPathDB					•										B	•	•	•	F	F
COPASI	•	•	•		•	•			•				C++, Java, Python		L,W,M	•	•	•	F	$
Cyto-Sim		•			•				•						L,W,M				F	F
Cytoscape	•				•								Java		L,W,M	•		•	F	F
DBSolve		•	•		•	•										•	•		F	F
Dizzy		•				•			•						L,W,M	•	•	•	F	F
E-CELL	•	•				•			•						L,W		•	•	F	F
ecellJ					•												•		F	F
EPE	•			•		•							Java		L,W, M		•		F	F
ESS		•							•					BSP				•	F	F

Import nach Copasi



Details: eine Reaktion

```
<listOfReactions>     :
      <reaction id="vcat" reversible="false">
         <listOfReactants>
             <speciesReference species="ES"/>
         </listOfReactants>
         <listOfProducts>
             <speciesReference species="E"/>
             <speciesReference species="P"/>
         </listOfProducts>
         <kineticLaw>
             <math
xmlns="http://www.w3.org/1998/Math/MathML">
                 <apply>
                     <times/>
                     <ci>cytosol</ci>
                     <ci>kcat</ci>
                     <ci>ES</ci>
                 </apply>
             </math>
             <listOfParameters>
                 <parameter id="kcat" value="0.1"
units="per_second"/>
             </listOfParameters>
          </kineticLaw>
      </reaction>
 </listOfReactions>
```

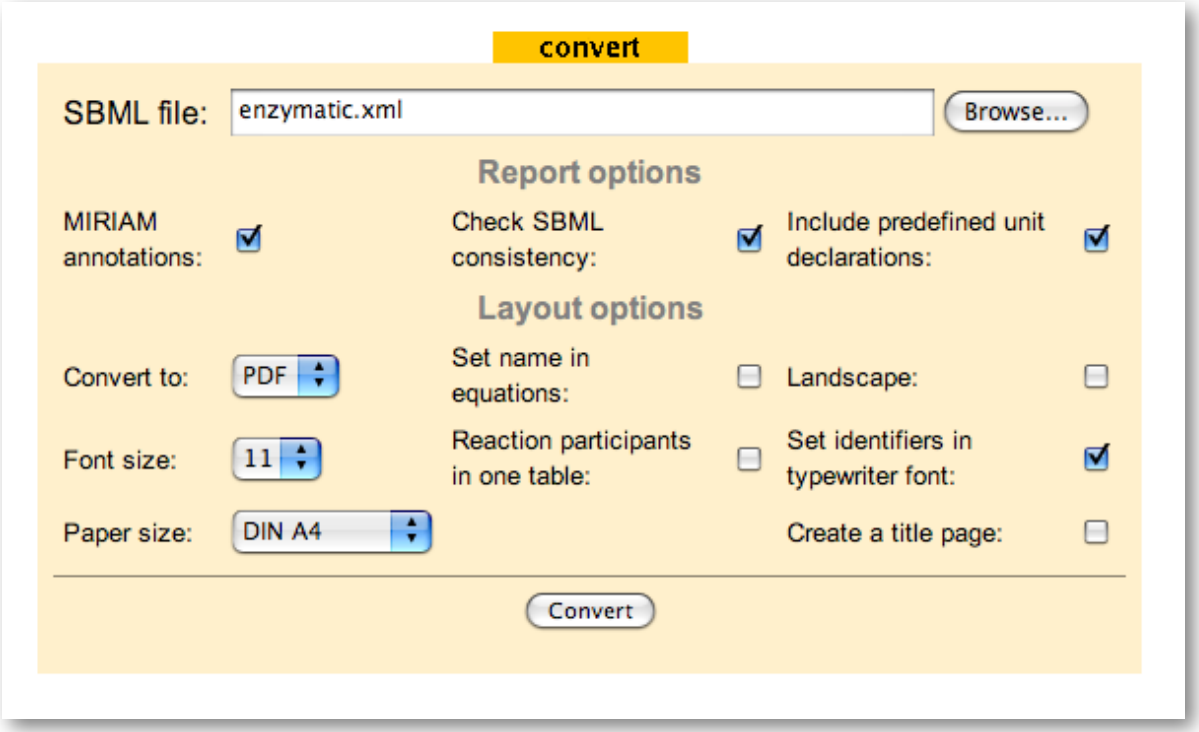
$$E + S \underset{k_{off}}{\overset{k_{on}}{<=>}} ES \overset{k_{cat}}{=>} E + P$$

$$\Rightarrow \frac{dN}{dt} = V_{cytosol}\, k_{cat}\, [ES]$$

lokaler Parameter!

SBML lesbar machen

SBML2LaTeX
Conversion of SBML files into human-readable reports



http://webservices.cs.uni-tuebingen.de/

Dräger A, Planatscher H, Wouamba DM, Schröder A, Hucka M, Endler L, Golebiewski M, Müller W, and Zell A: "SBML2LaTeX: Conversion of SBML files into human-readable reports", Bioinformatics 2009

Drei Minuten später:

SBML Model Report

Model name: "EnzymaticReaction"

SBML2LaTeX

June 30, 2009

1 General Overview

This is a document in SBML Level 2 Version 3 format. Table 1 gives an overview of the quantities of all components of this model.

Table 1: The SBML components in this model.
All components are described in more detail in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	1
species types	0	species	4
events	0	constraints	0
reactions	2	function definitions	0
global parameters	0	unit definitions	2
rules	0	initial assignments	0

2 Unit Definitions

This is an overview of seven unit definitions. The units `substance`, `volume`, `area`, `length`, and `time` are predefined by SBML and not mentioned in the model.

2.1 Unit `per_second`

Definition s^{-1}

2.2 Unit `litre_per_mole_per_second`

Definition $mol^{-1} \cdot l \cdot s^{-1}$

2.3 Unit `substance`

Notes Mole is the predefined SBML unit for `substance`.

Definition mol

2.4 Unit `volume`

Notes Litre is the predefined SBML unit for `volume`.

Definition l

2.5 Unit `area`

Notes Square metre is the predefined SBML unit for `area` since SBML Level 2 Version 1.

Definition m^2

2.6 Unit `length`

Notes Metre is the predefined SBML unit for `length` since SBML Level 2 Version 1.

Definition m

2.7 Unit `time`

Notes Second is the predefined SBML unit for `time`.

Definition s

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
cytosol			3	10^{-14}	l	☑	

3.1 Compartment cytosol

This is a three-dimensional compartment with a constant size of 10^{-14} litre.

4 Species

This model contains four species. Section 6 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
ES	ES	cytosol	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
P	P	cytosol	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
S	S	cytosol	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
E	E	cytosol	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Reactions

This model contains two reactions. All reactions are listed in the following table and are subsequently described in detail. If a reaction is affected by one or more modifiers, the identifiers of the modifier species are written above the reaction arrow.

Table 4: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	veq		$\mathrm{E} + \mathrm{S} \rightleftharpoons \mathrm{ES}$	
2	vcat		$\mathrm{ES} \longrightarrow \mathrm{E} + \mathrm{P}$	

5.1 Reaction veq

This is a reversible reaction of two reactants forming one product.

Reaction equation

$$E + S \rightleftharpoons ES \tag{1}$$

Reactants

Table 5: Properties of each reactant.

Id	Name	SBO
E	E	
S	S	

Product

Table 6: Properties of each product.

Id	Name	SBO
ES	ES	

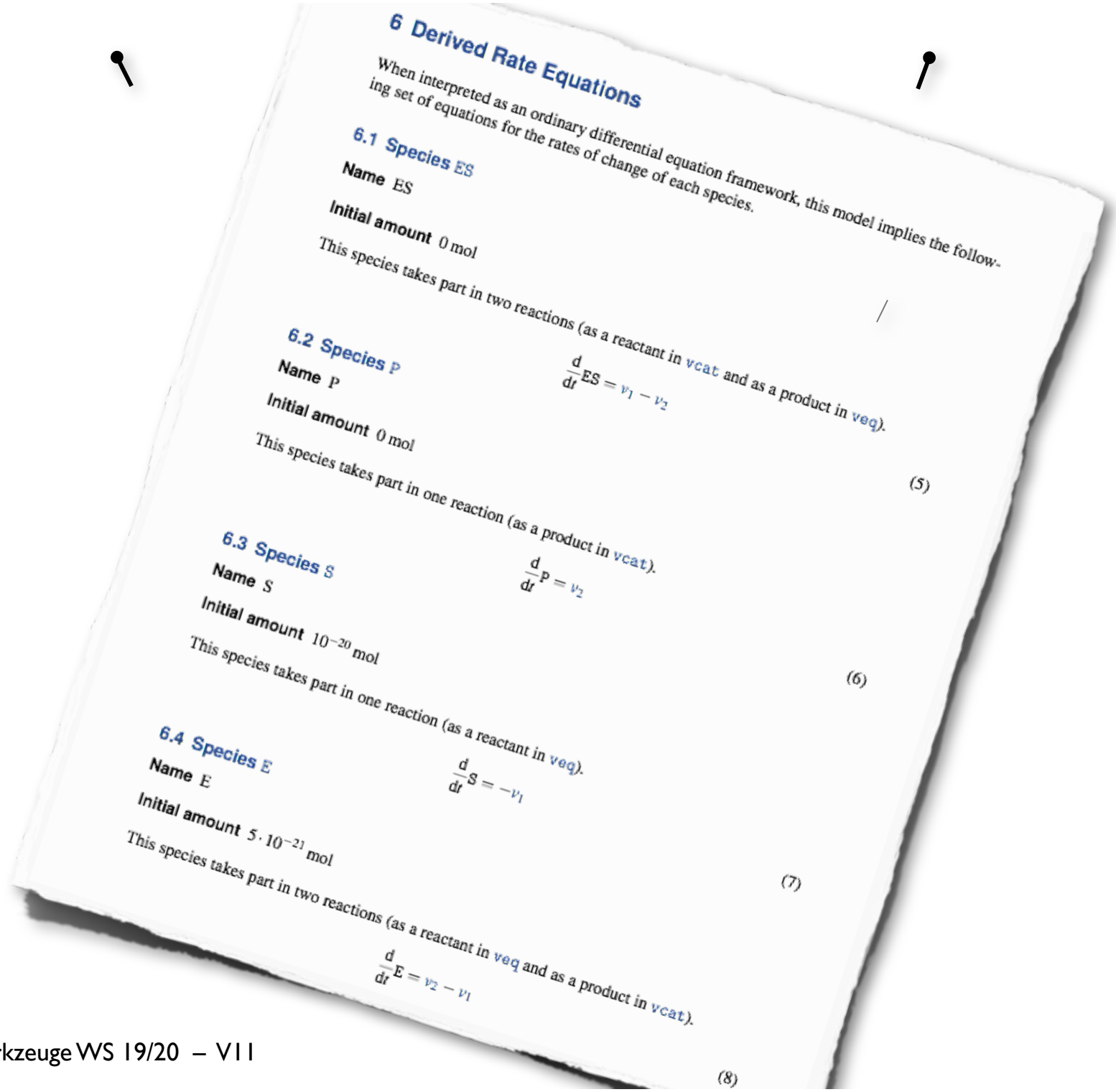
Kinetic Law

Derived unit $s^{-1} \cdot mol$

$$v_1 = \mathrm{vol}(\mathtt{cytosol}) \cdot (\mathtt{kon} \cdot [E] \cdot [S] - \mathtt{koff} \cdot [ES]) \tag{2}$$

Table 7: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kon			1000000.0	$mol^{-1} \cdot l \cdot s^{-1}$	☑
koff			0.2	s^{-1}	☑



6 Derived Rate Equations

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rates of change of each species.

6.1 Species ES

Name ES

Initial amount 0 mol

This species takes part in two reactions (as a reactant in vcat and as a product in veq).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ES} = v_1 - v_2 \tag{5}$$

6.2 Species P

Name P

Initial amount 0 mol

This species takes part in one reaction (as a product in vcat).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P} = v_2 \tag{6}$$

6.3 Species S

Name S

Initial amount 10^{-20} mol

This species takes part in one reaction (as a reactant in veq).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{S} = -v_1 \tag{7}$$

6.4 Species E

Name E

Initial amount $5 \cdot 10^{-21}$ mol

This species takes part in two reactions (as a reactant in veq and as a product in vcat).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E} = v_2 - v_1 \tag{8}$$

es gibt bereits sehr viele Modelle