V10
DGL-Modelle

20. Dezember 2012

nach einer Vorlesung von Dr. Tihamer Geyer

Übersicht

Aufstellen von Bilanzgleichungen

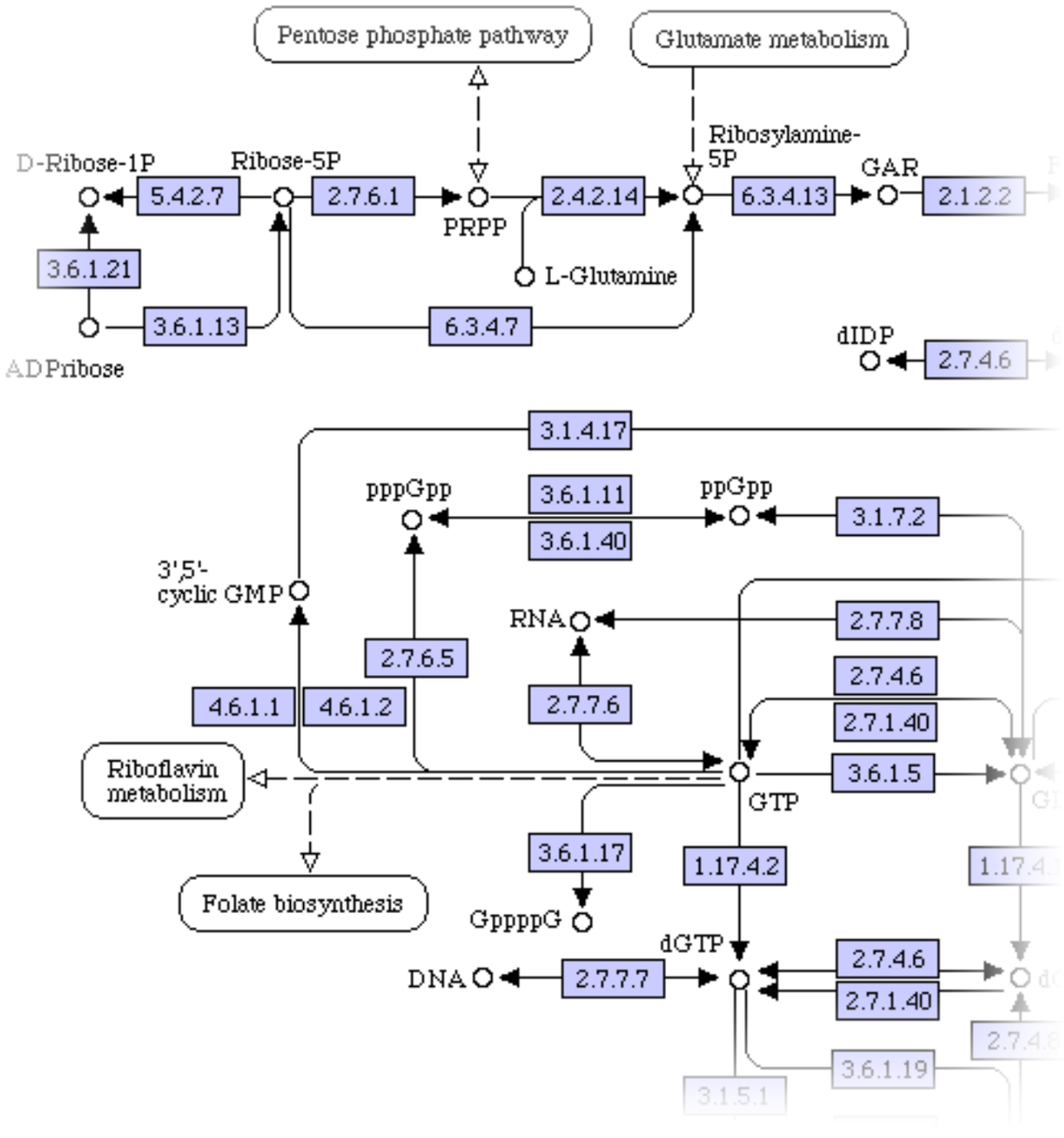
Dynamische Simulationen: Was ist das? Wozu?

Simulations-Tool: Copasi

Vereinfachte Kinetiken: MM, Inhibierung, Hill

kinetische Daten: KEGG, SABIO-RK

Wdh: über die Formel zur Formel



i) biologisches Netzwerk

ii) Metabolite identifizieren (incl. Konzentrationen)

iii) Einzelreaktionen aufstellen, Reaktionsraten?

iv) Reaktionen in DGLs übersetzen

v) Anfangswerte einsetzen und simulieren

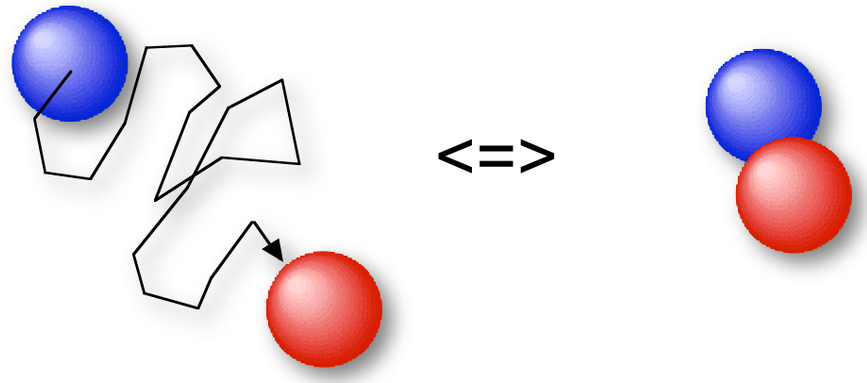
vi) Ergebnisse analysieren

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

Massenwirkungsgesetz

Einfachste chemische Reaktion

A + B <=> AB



Zeitliche Änderung von [A]:

Gewinn: Dissoziation

AB => A + B

AB zerfällt

=> G_A proportional zu [AB]

$$G_A = k_r [AB]$$

phänomenologischer Faktor

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

Verlust: Assoziation

A + B => AB

A und B müssen sich finden

=> L_A abhängig von [A] *und* [B]

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

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

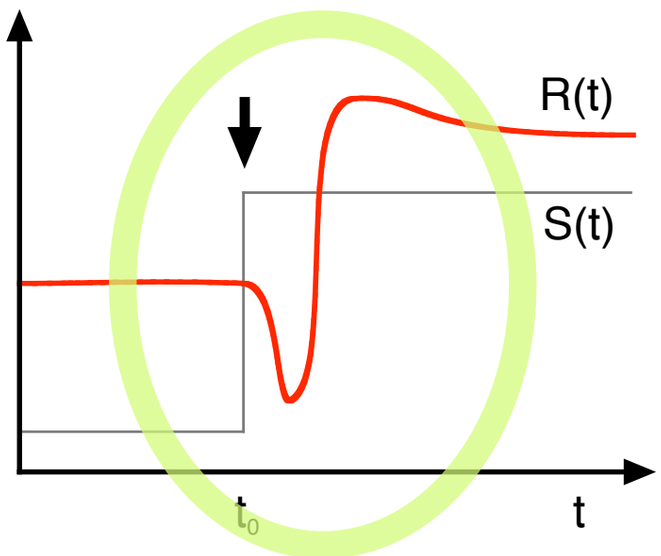
Dynamische Simulationen

Zwei Anwendungsgebiete

zeitabhängiges Verhalten

Reaktionen des Systems auf Änderungen der äußeren Bedingungen (Randbedingungen)

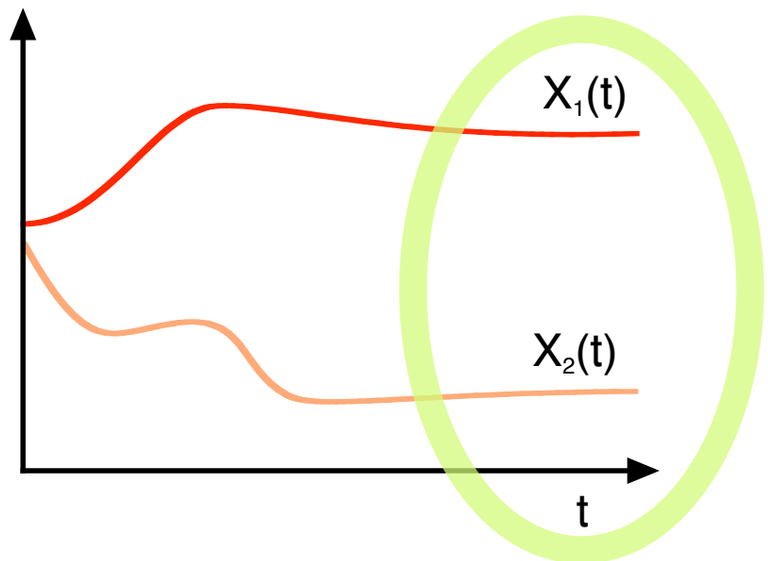
$$\frac{d\vec{X}(t)}{dt}$$



stationäre Zustände (steady state)

Suche nach Konzentrationen und Flüssen bei konstanten Randbedingungen

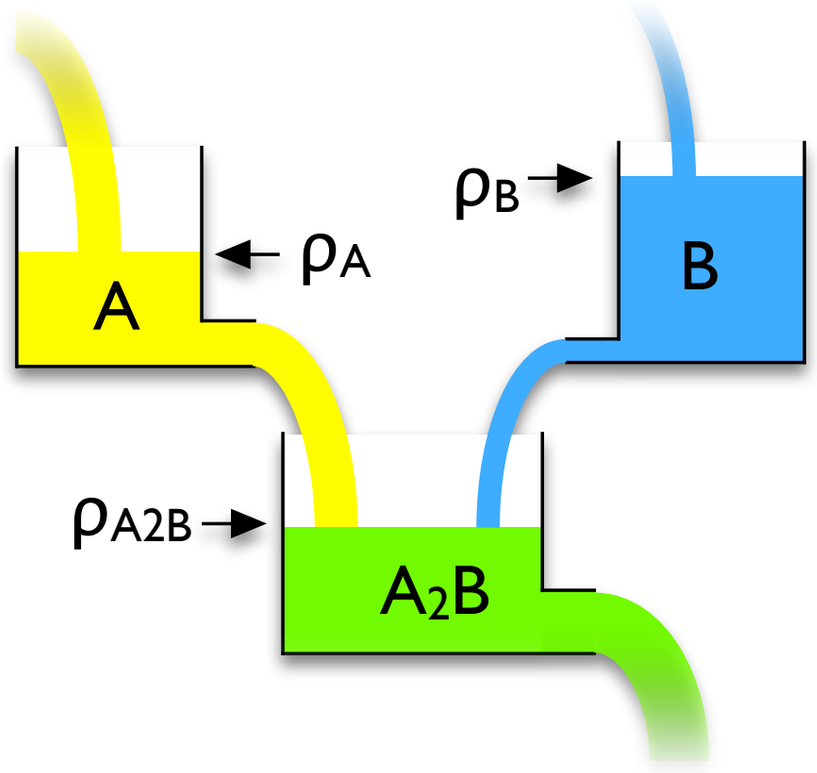
$$\frac{d\vec{X}(t)}{dt} = 0$$



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

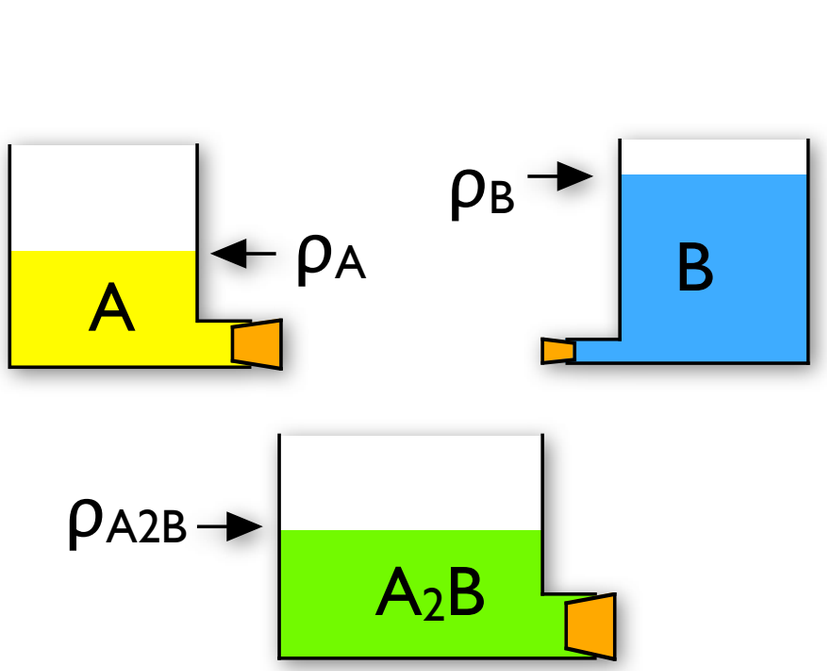
$$\frac{dA_2B(t)}{dt} = k_a A^2 B - k_d A_2 B = 0$$

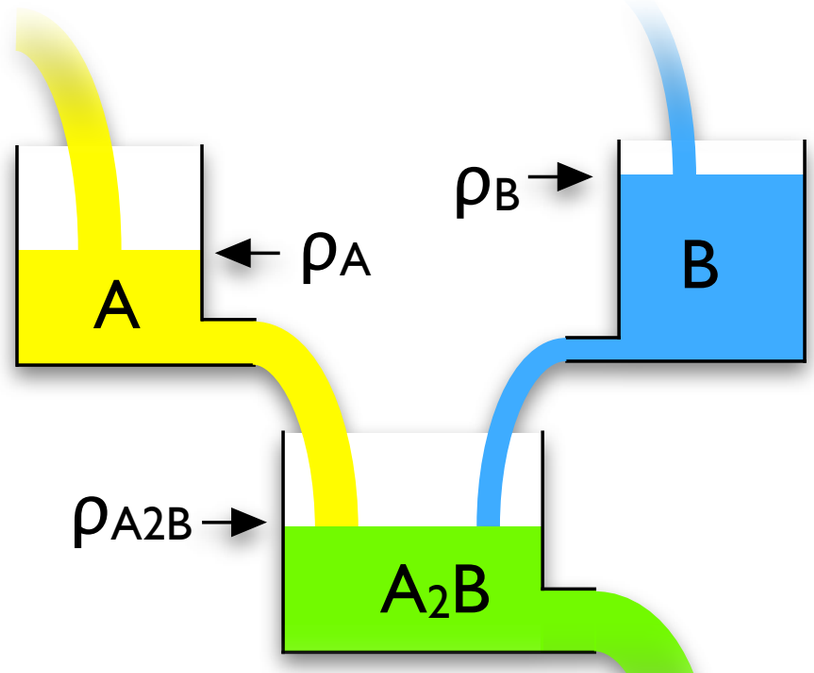
=> Gleichgewichts-Konzentrationen: $A_2B = \frac{k_a}{k_d} A^2 B$

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

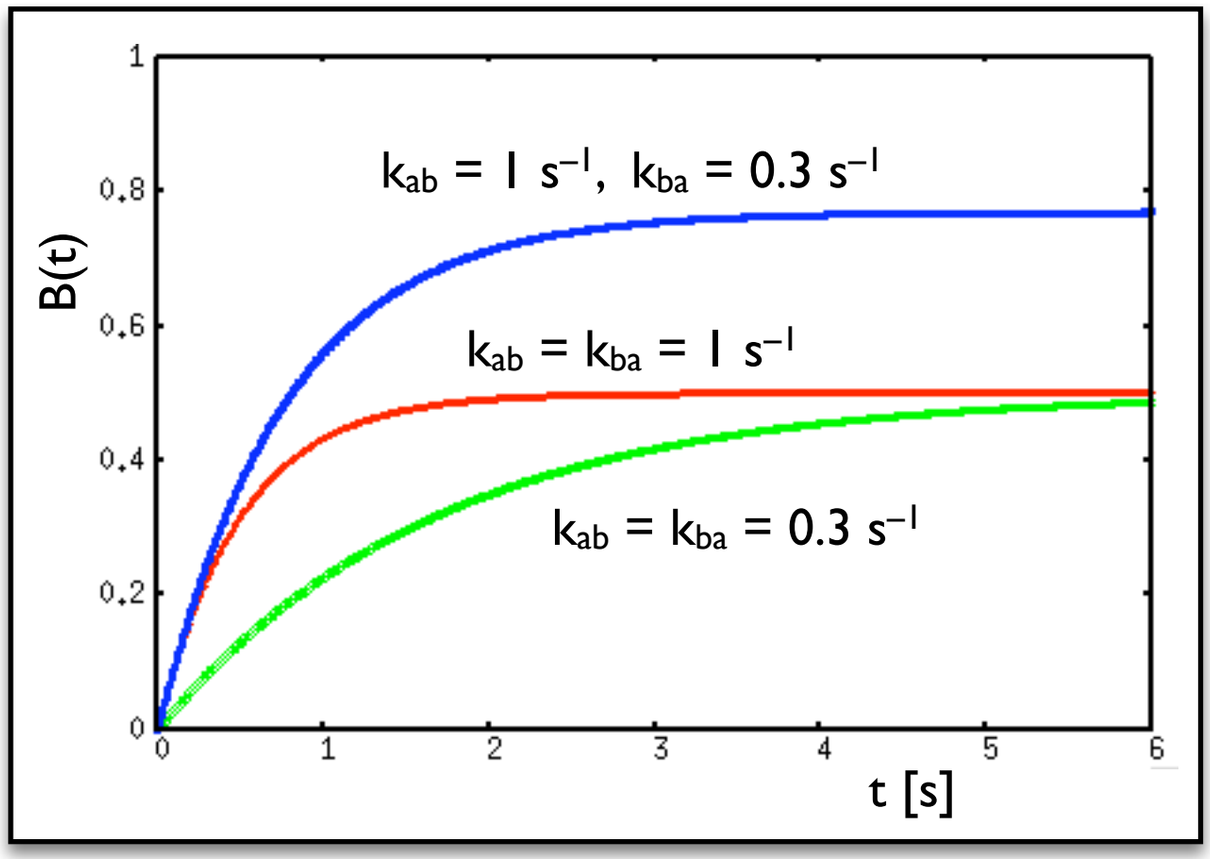
Ganz einfach: A <=> B

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

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

Gleichgewicht:

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



mit Anfangsbedingungen:

A(t=0) = A_0

B(t=0) = 0

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

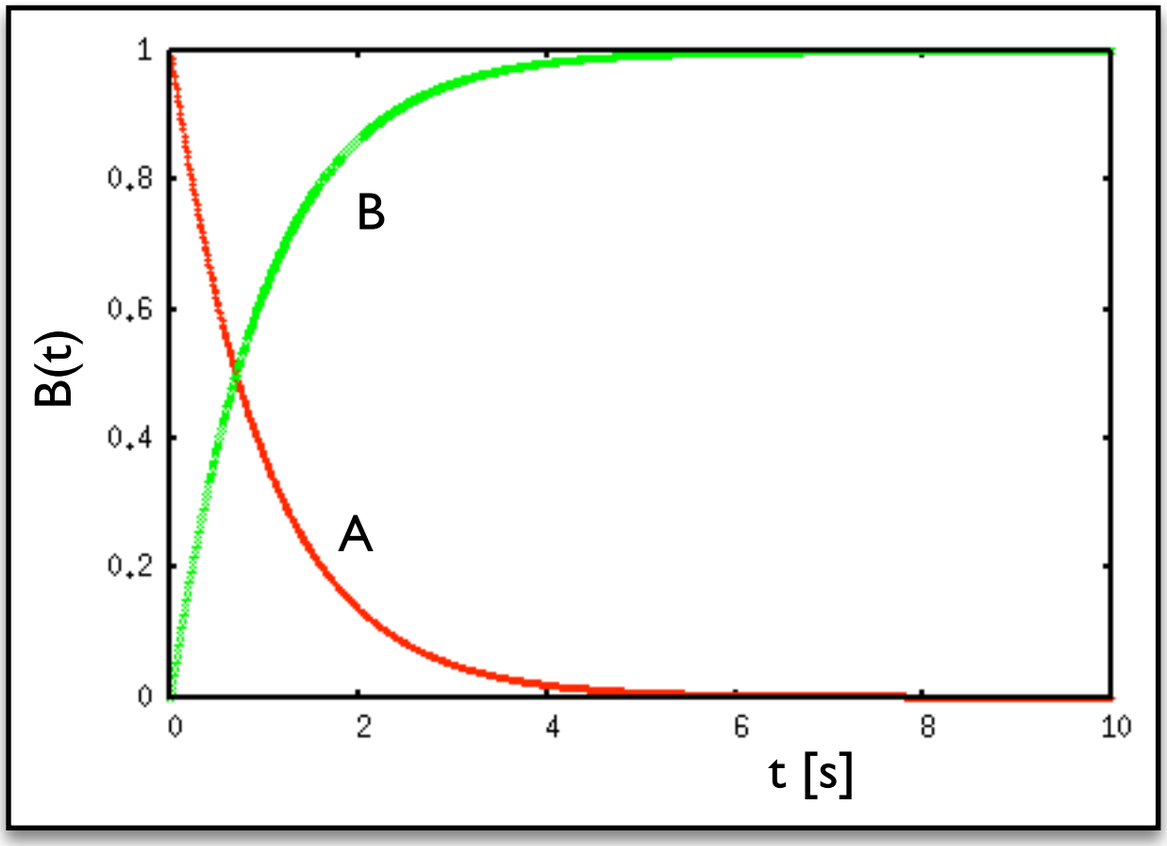
=> Gleichgewichtsverteilungen

=> wie schnell wird ein "Signal" weitergegeben?

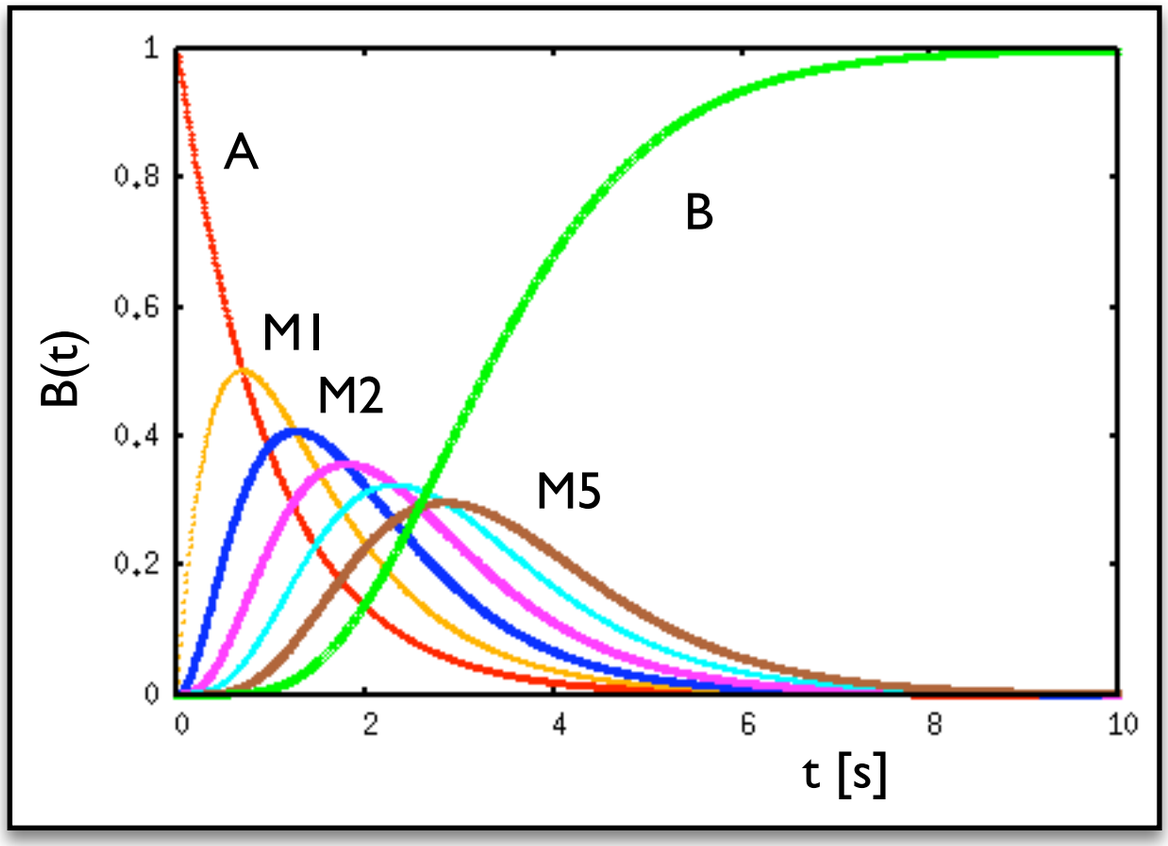
Länge von Reaktionspfaden

Vergleiche:

A => B



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



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

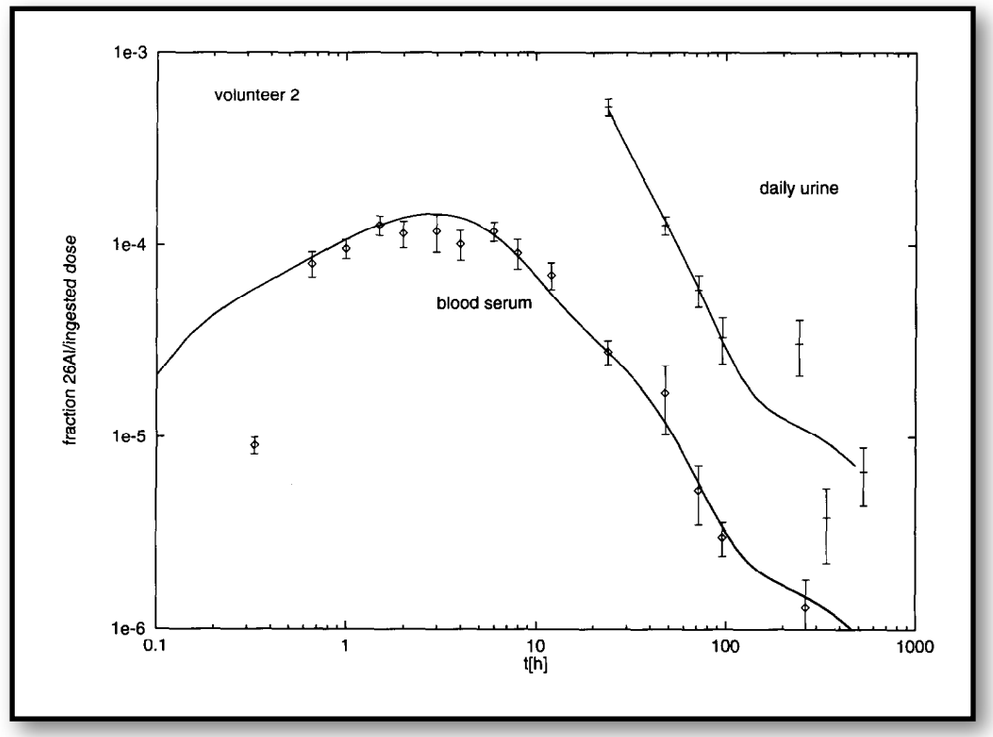
=> Zwischenprodukte verzögern die Antwort
=> Vorsicht beim Weglassen von Zwischenschritten

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

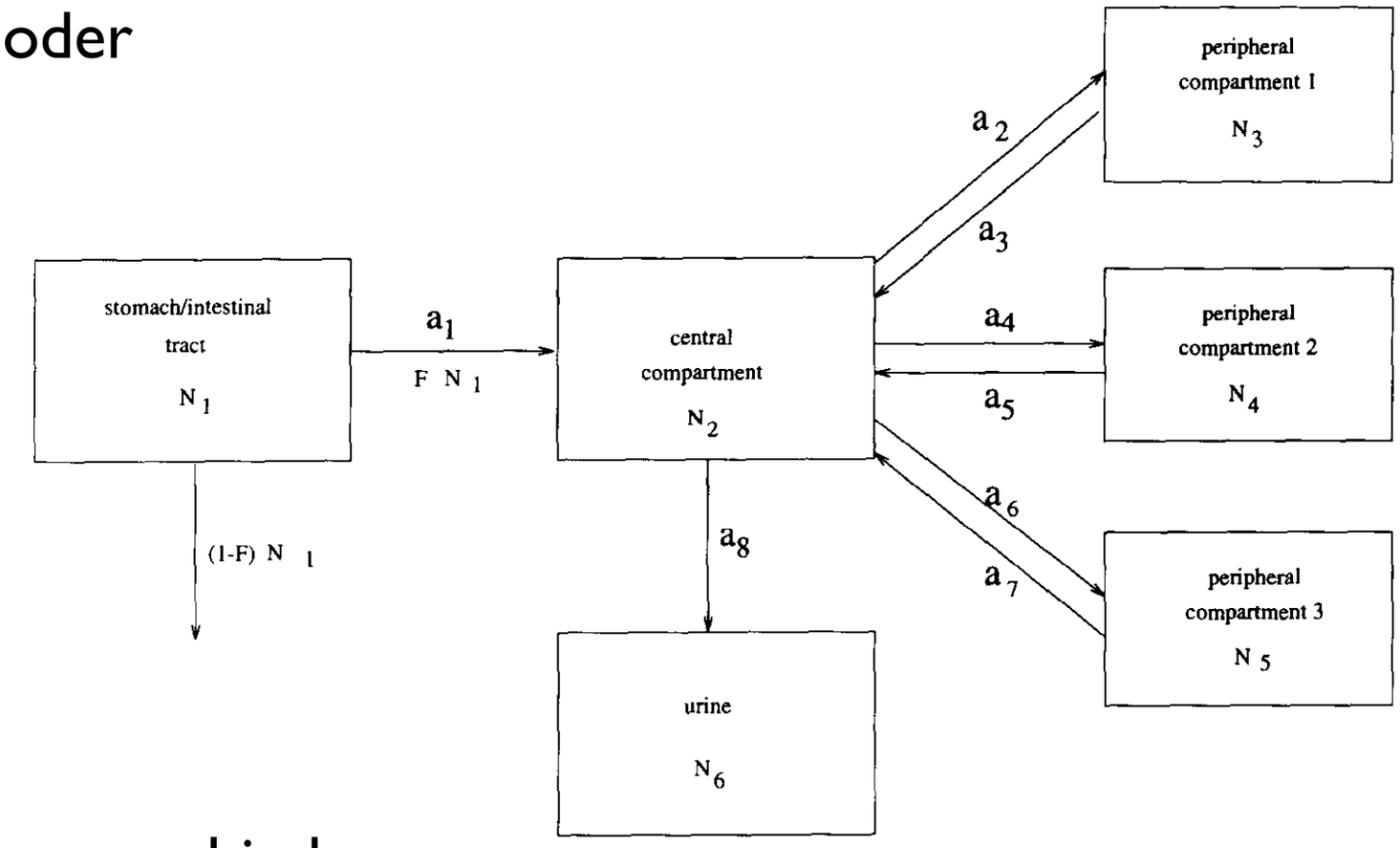
Modellierung des AL-Metabolismus

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

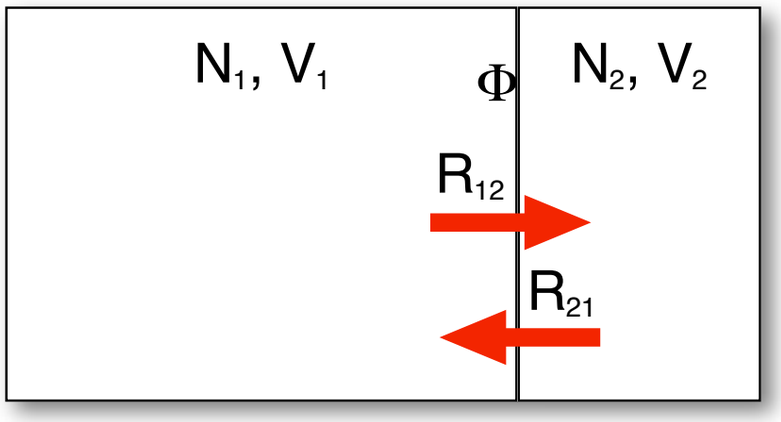
iv) Blut wird über Leber/Niere ausgeschieden



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):

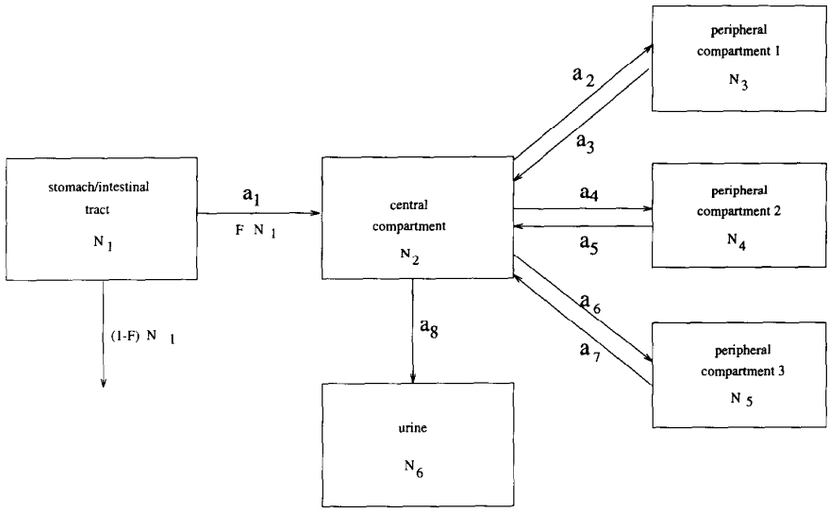
$$\frac{dN_1}{dt} = -\frac{dN_{12}}{dt} + \frac{dN_{21}}{dt} \qquad \frac{dN_2}{dt} = -\frac{dN_1}{dt}$$

Änderungen der entsprechenden Dichten:

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

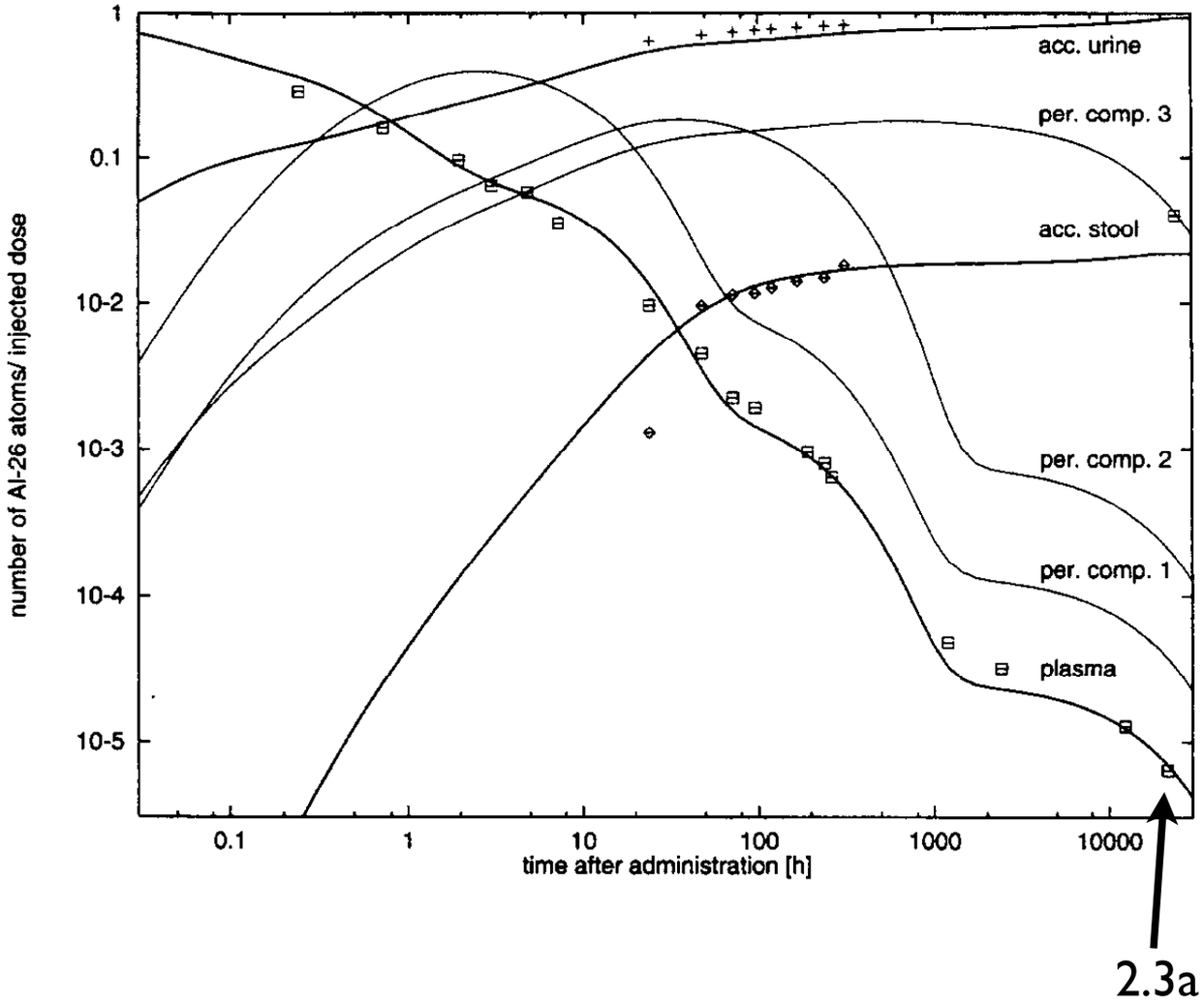
=> Simulationen mit Teilchenzahlen, Dichten "on the fly"

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 **Pa**thway **Si**mulator

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/

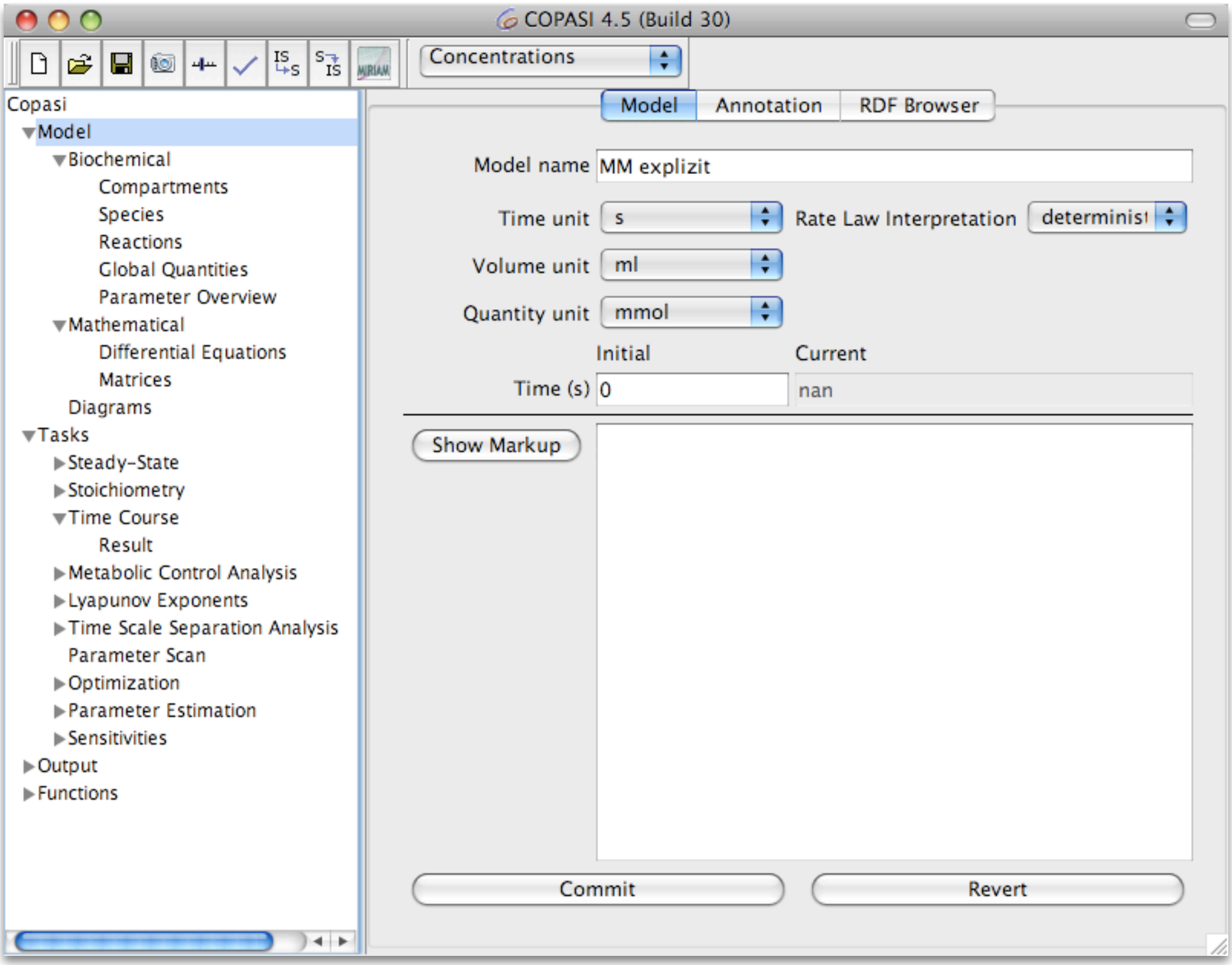
Copasi-Features

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.

By the Mendes group at VBI and Kummer group at EML Research.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RDF Browser
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Time unit
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Volume unit
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Quantity unit
mmol
Initial
Current
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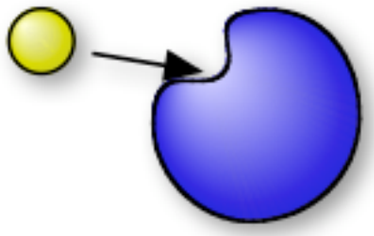
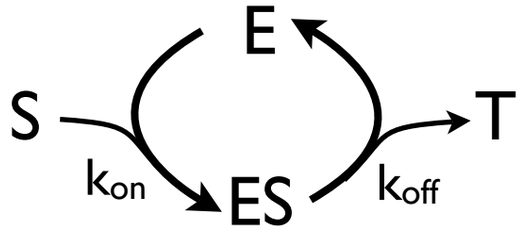
nan
Show Markup
Commit
Revert

Enzyme: Michaelis-Menten-Kinetik



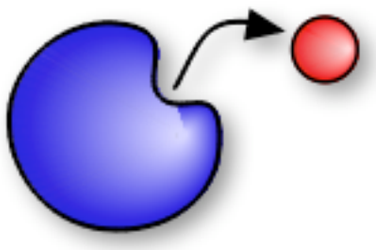


Reaktionsrate:

$$V = k_{off} ES$$

Steady state:

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

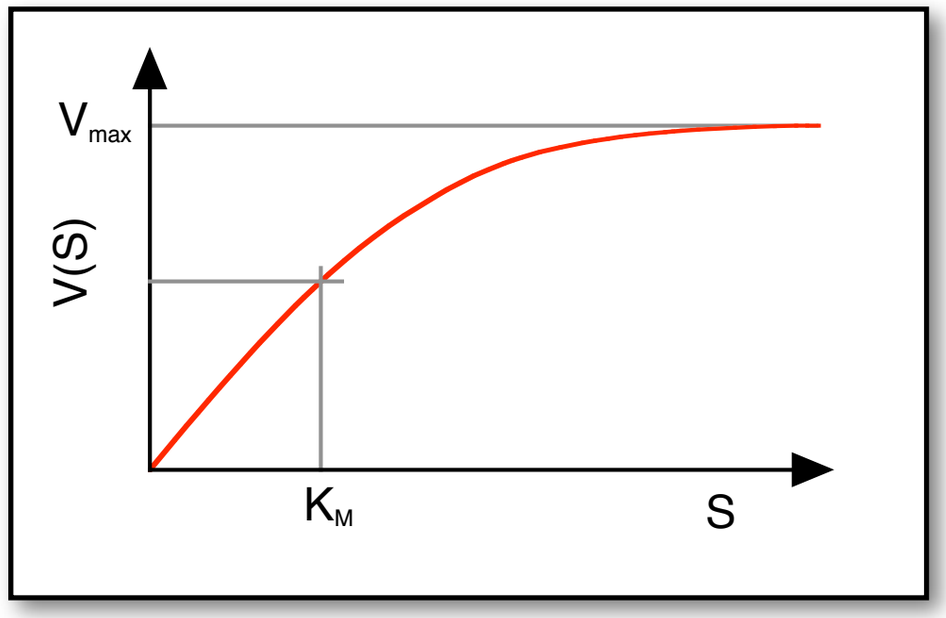


$$ES = \frac{k_{on}\, E \cdot S}{k_{off}} = \frac{E \cdot S}{K_M}$$

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

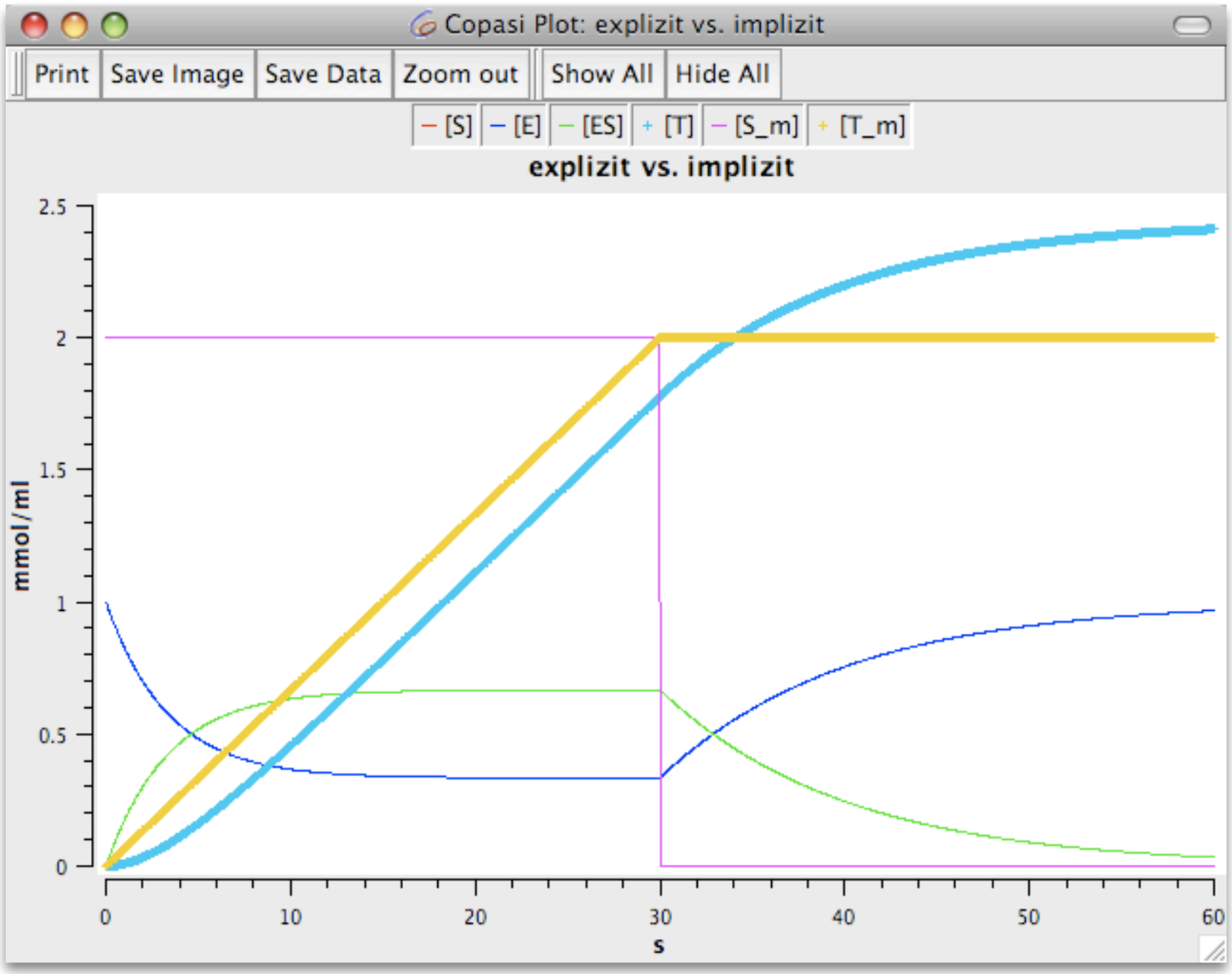
MM vs. explizite Modellierung

Wenn E verschiedene Substrate katalysiert
=> MM geht nicht

Zeitverhalten:
MM-Kinetik vs.
explizite Modellierung

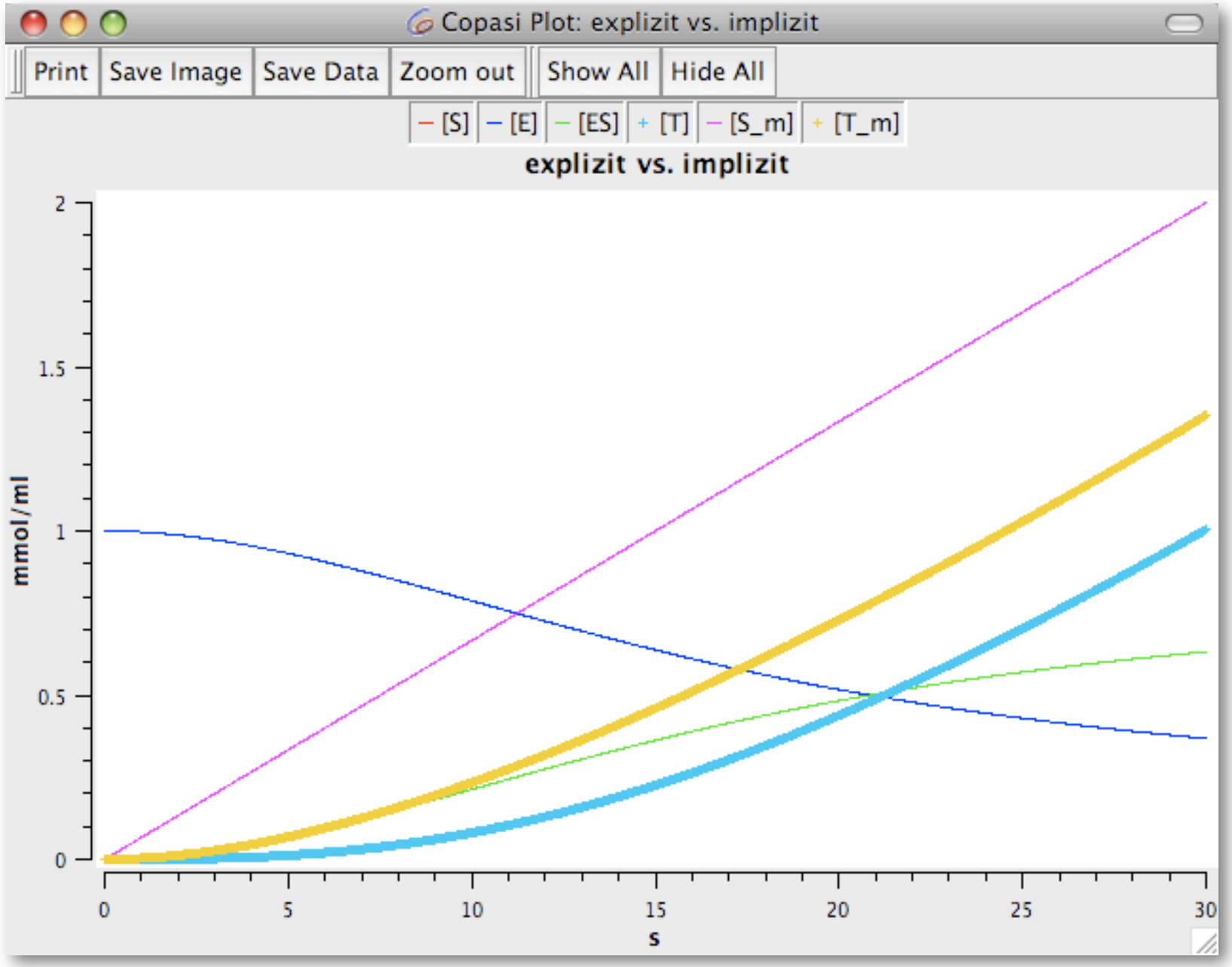
=> Einschwingen

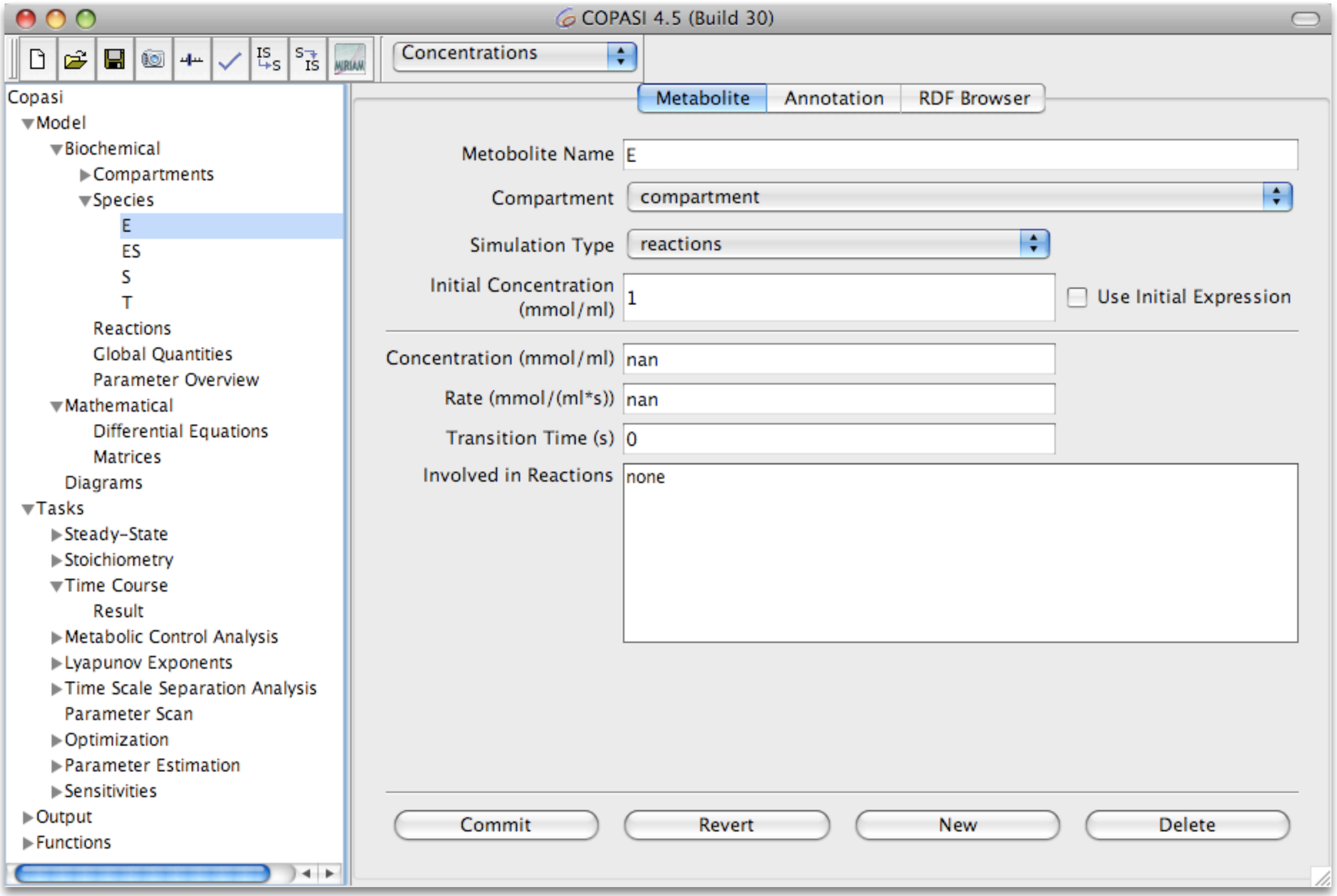
=> anderer
Gesamtumsatz



Nochmal: explizit vs. MM

linearer Anstieg von S

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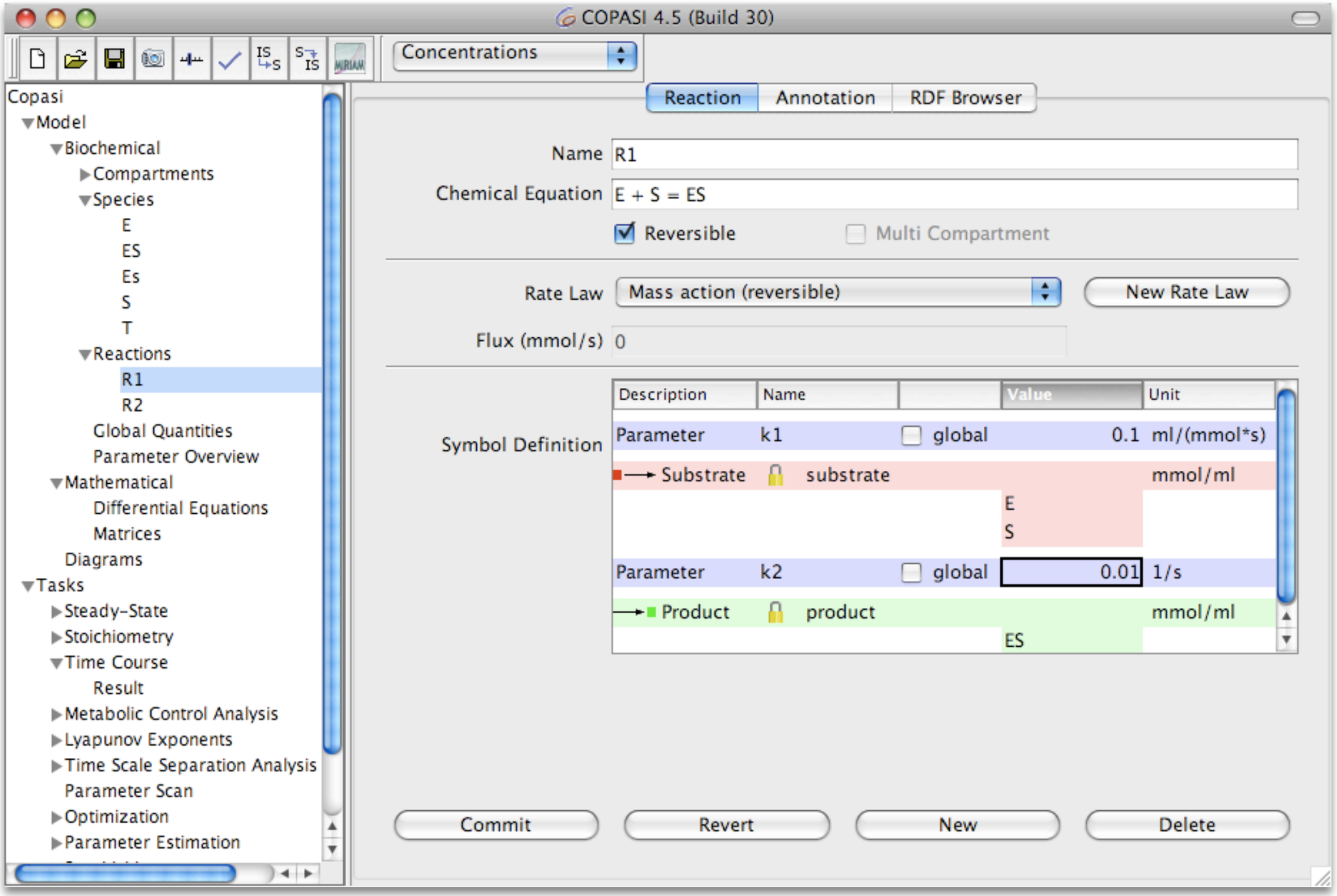
Metobolite Name
E
Compartment
compartment
Simulation Type
reactions
Initial Concentration (mmol/ml)
1
Use Initial Expression
Concentration (mmol/ml)
nan
Rate (mmol/(ml*s))
nan
Transition Time (s)
0
Involved in Reactions
none
Commit
Revert
New
Delete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E + S = ES
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New Rate Law
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k1
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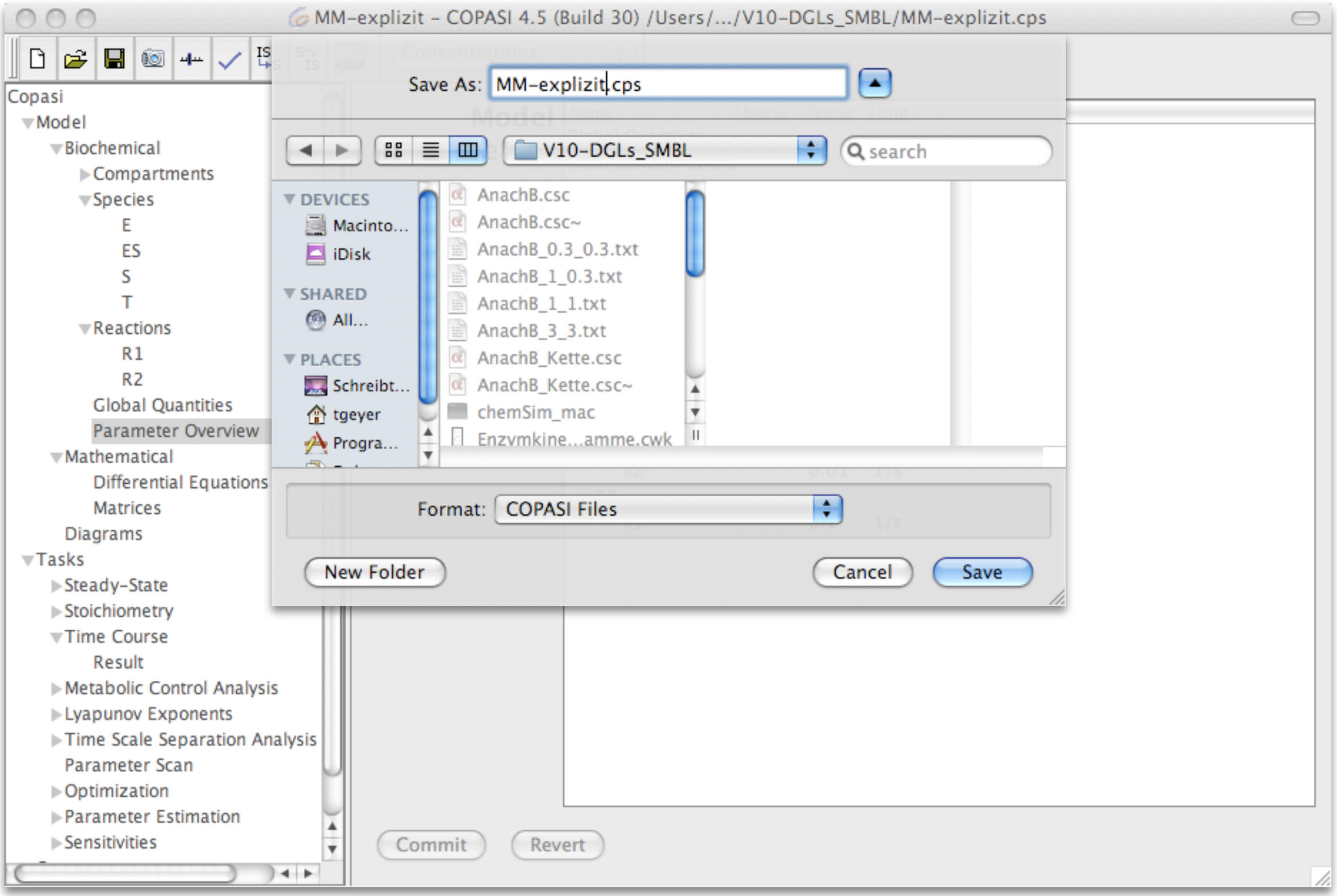
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AnachB_1_1.txt
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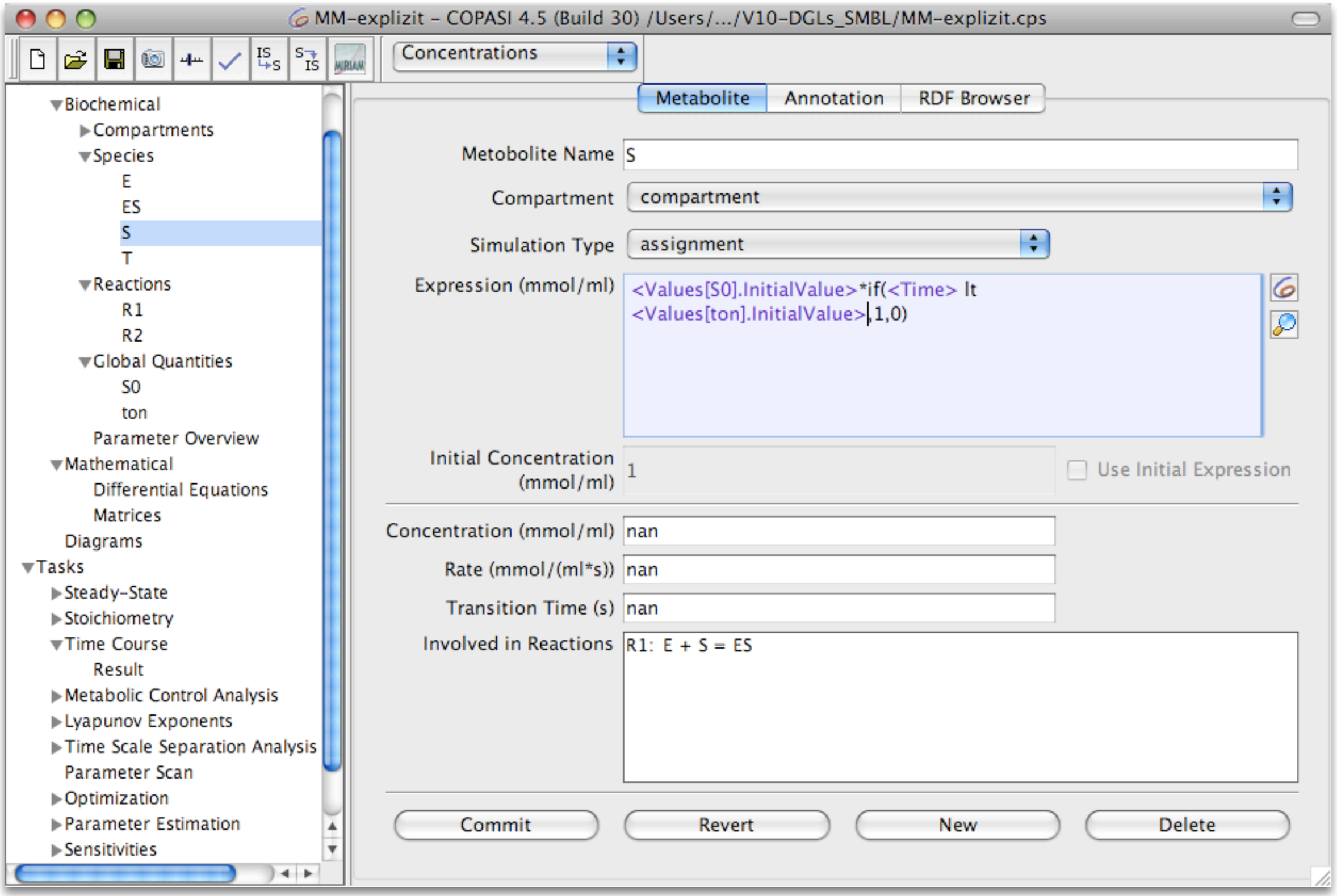
Save
Commit
Revert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compartment
Simulation Type
assignment
Expression (mmol/ml)
<Values[S0].InitialValue>*if(<Time> lt
<Values[ton].InitialValue>,1,0)
Initial Concentration (mmol/ml)
1
Use Initial Expression
Concentration (mmol/ml)
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Rate (mmol/(ml*s))
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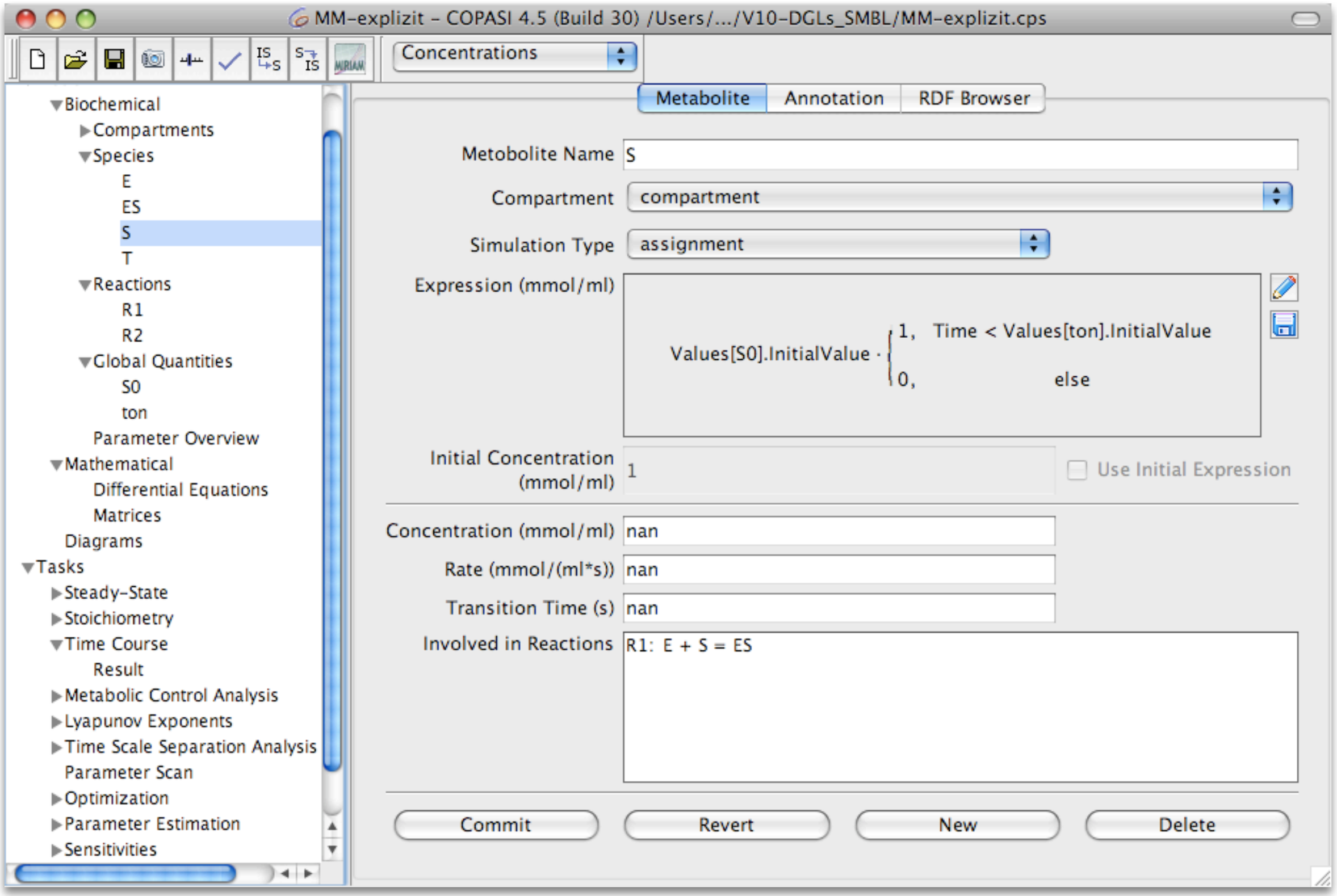
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Metobolite Name
S
Compartment
compartment
Simulation Type
assignment
Expression (mmol/ml)
Values[S0].InitialValue · { 1, Time < Values[ton].InitialValue ; 0, else
Initial Concentration (mmol/ml)
1
Use Initial Expression
Concentration (mmol/ml)
nan
Rate (mmol/(ml*s))
nan
Transition Time (s)
nan
Involved in Reactions
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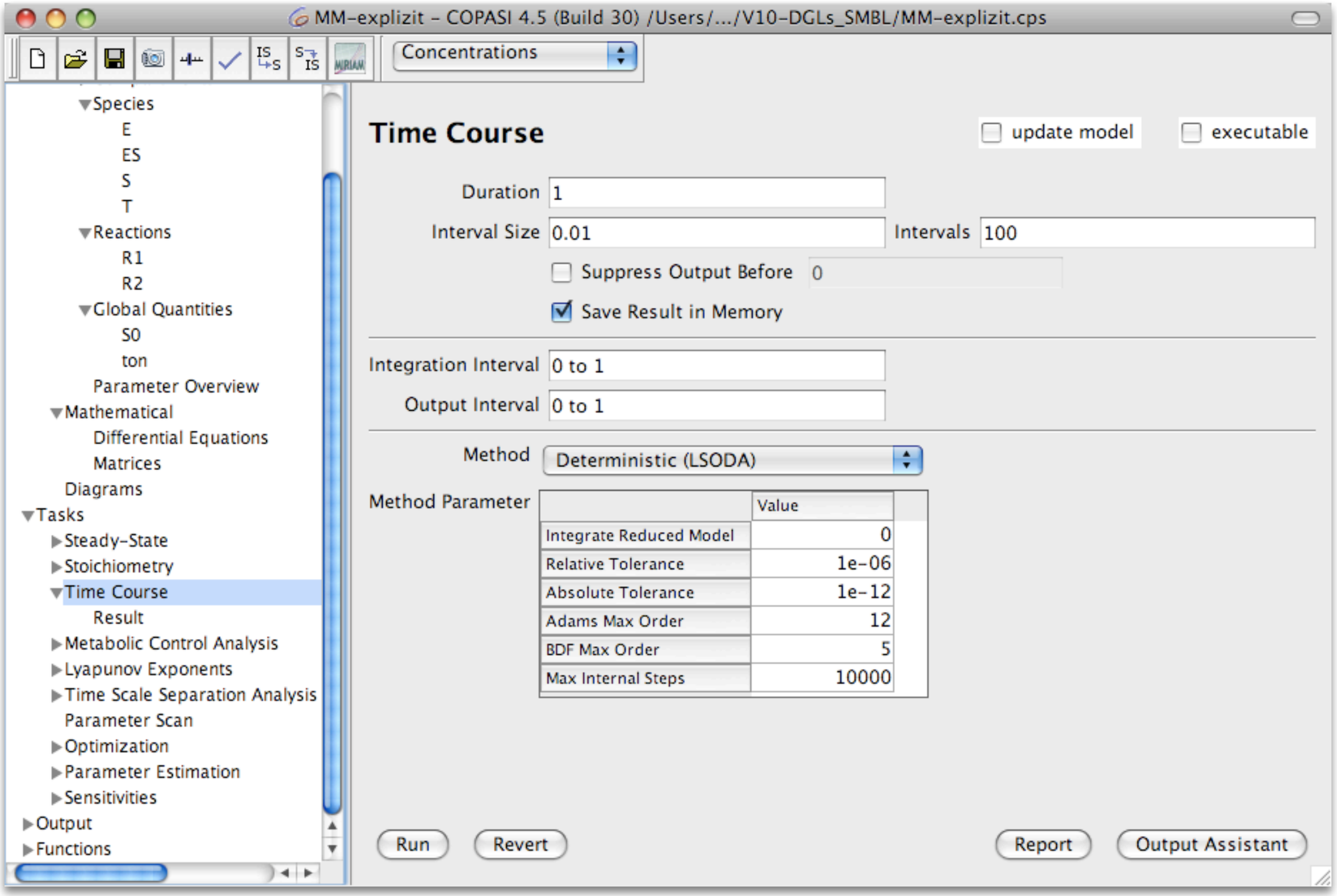
MM-explizit - COPASI 4.5 (Build 30) /Users/.../V10-DGLs_SMBL/MM-explizit.cps
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Differential Equations
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Time Course
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Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
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Time Course
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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
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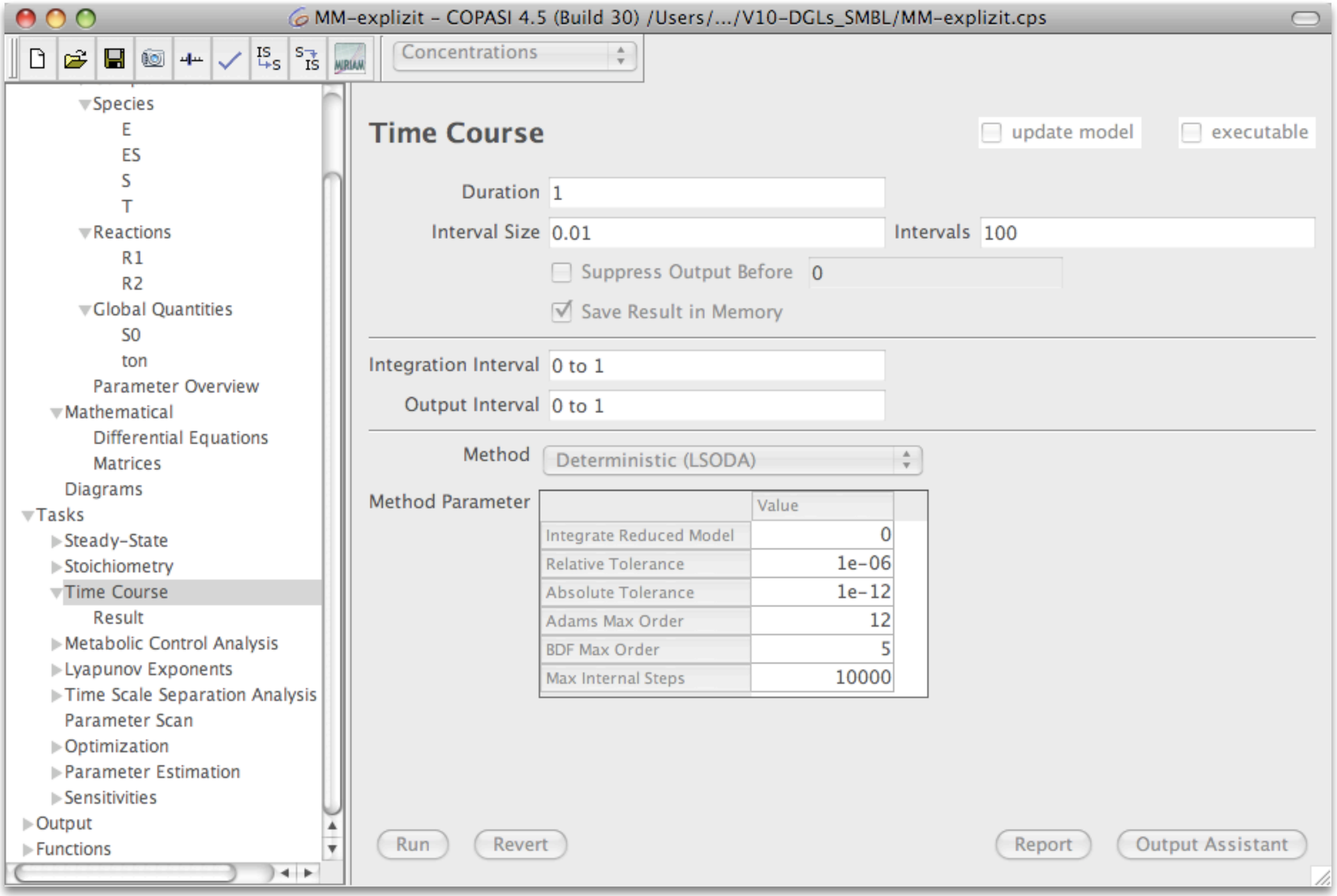
Absolute Tolerance 1e-12
Adams Max Order 12
BDF Max Order 5
Max Internal Steps 10000
Run
Revert
Report
Output Assistant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BDF Max Order 5
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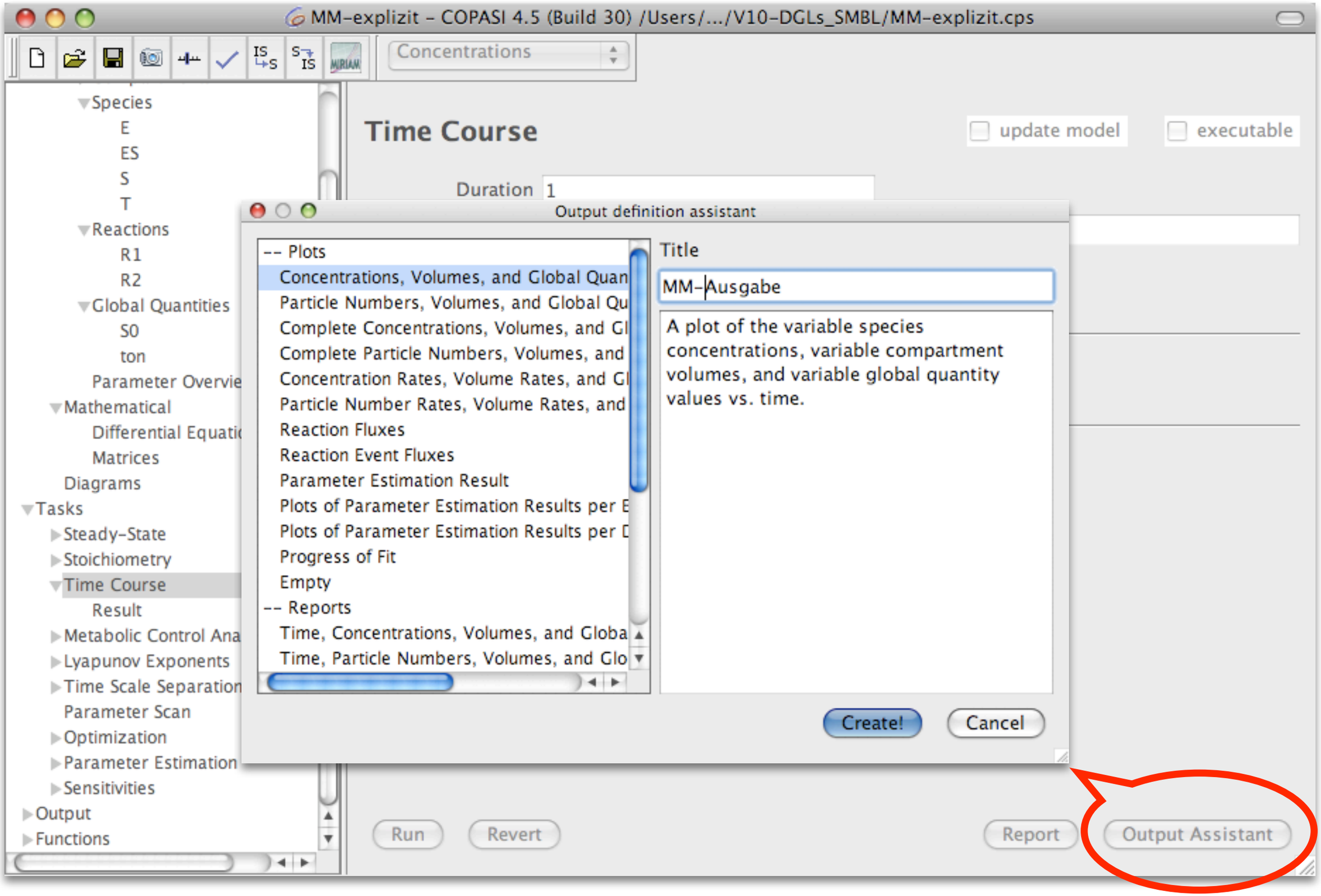
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Reaction Fluxes
Reaction Event Fluxes
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Plots of Parameter Estimation Results per E
Plots of Parameter Estimation Results per D
Progress of Fit
Empty
-- Reports
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Time, Particle Numbers, Volumes, and Glo
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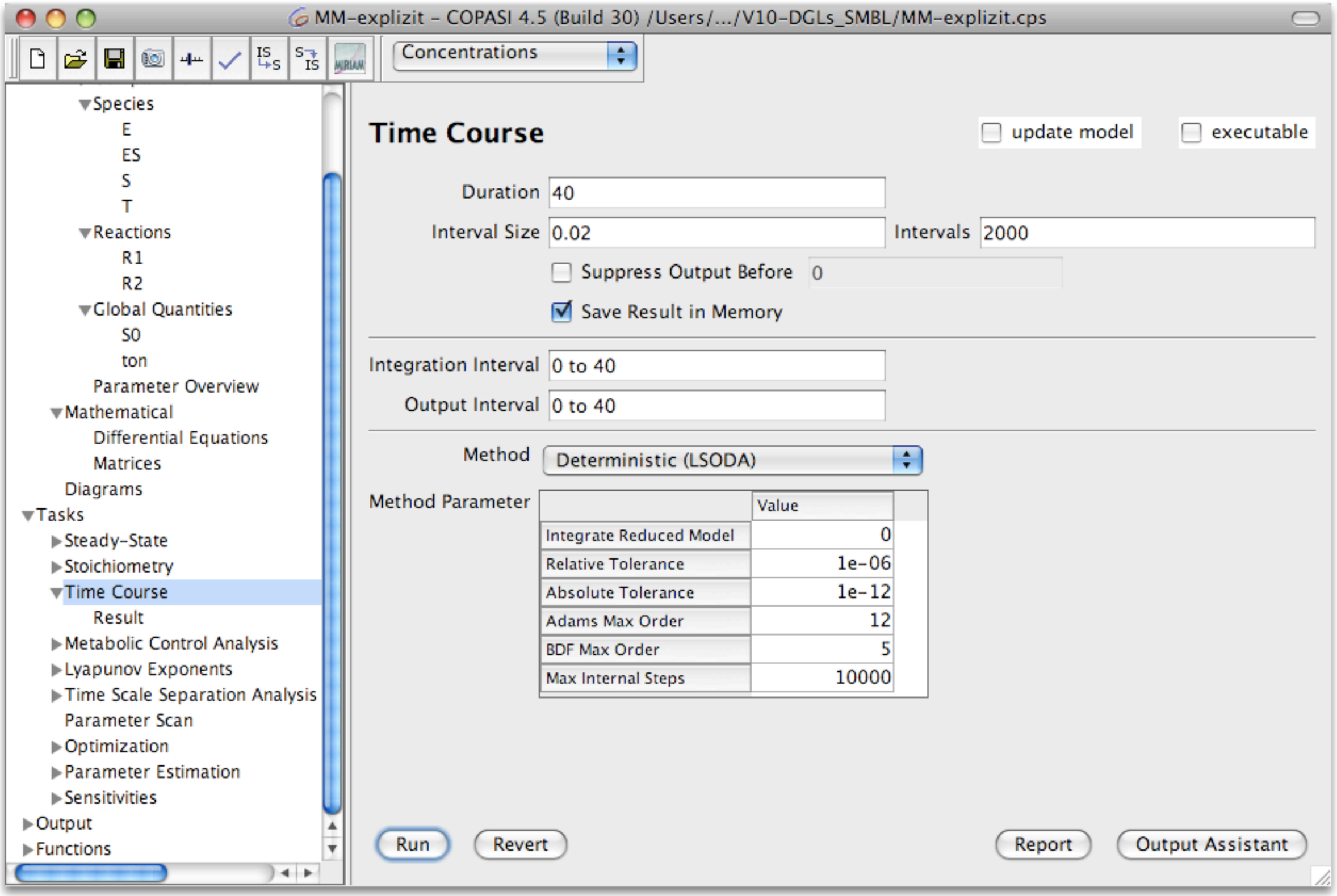
MM-Ausgabe
A plot of the variable species concentrations, variable compartment volumes, and variable global quantity values vs. time.
Create!
Cancel
Run
Revert
Report
Output Assistant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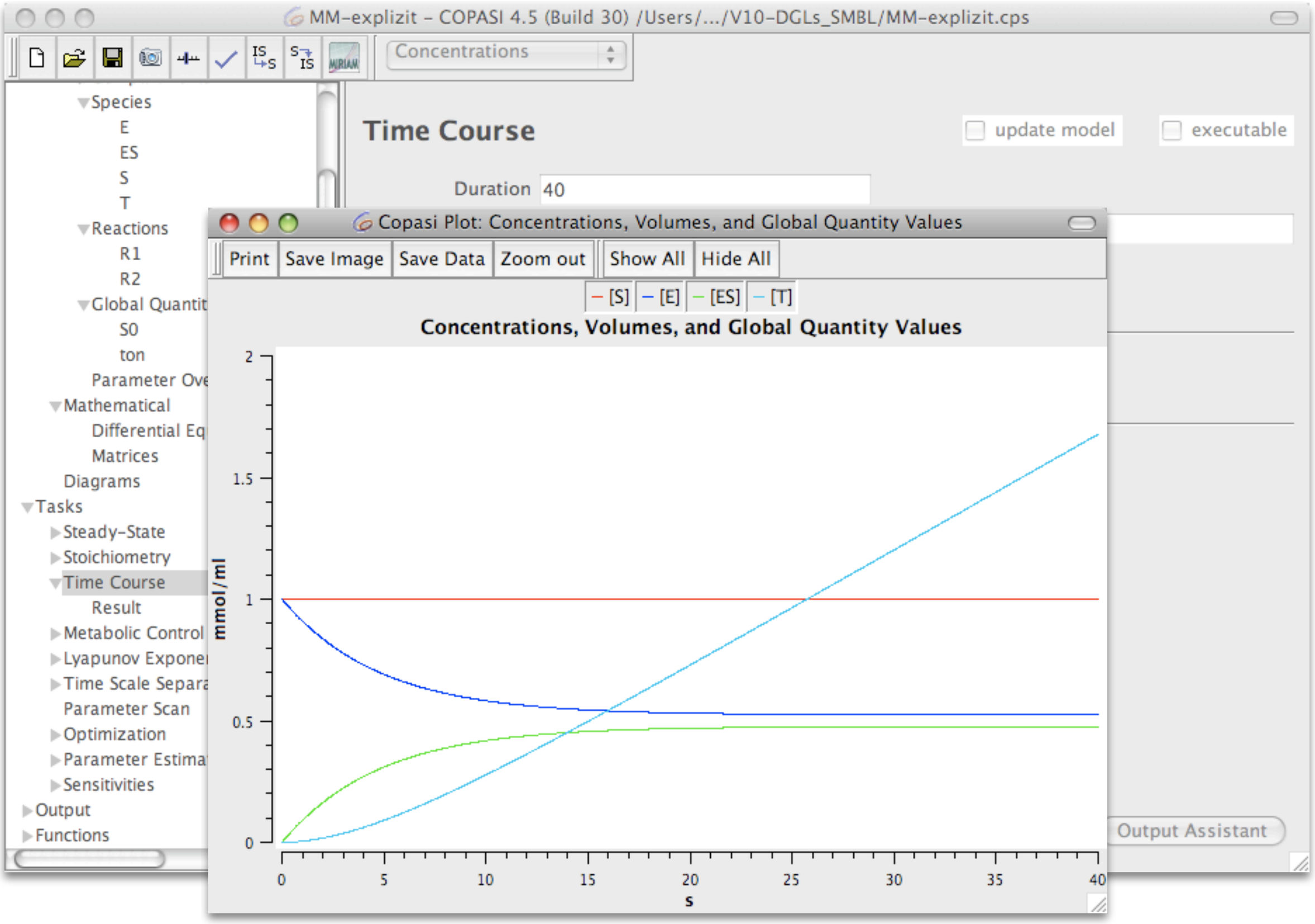
Duration 40
Interval Size 0.02
Intervals 2000
Suppress Output Before 0
Save Result in Memory
Integration Interval 0 to 40
Output Interval 0 to 40
Method Deterministic (LSODA)
Method Parameter
Value
Integrate Reduced Model 0
Relative Tolerance 1e-06
Absolute Tolerance 1e-12
Adams Max Order 12
BDF Max Order 5
Max Internal Steps 10000
Run
Revert
Report
Output Assistant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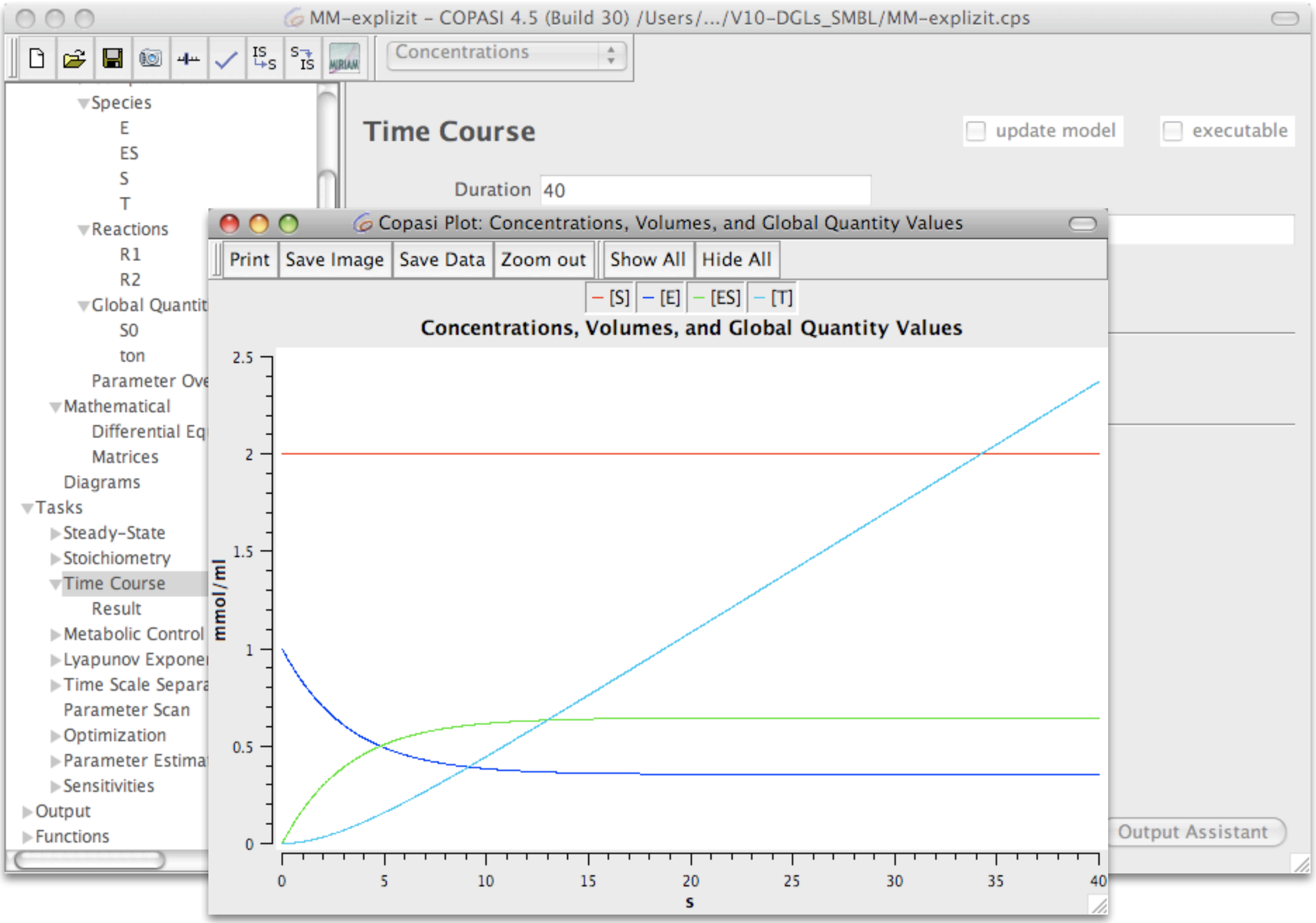
Output Assistant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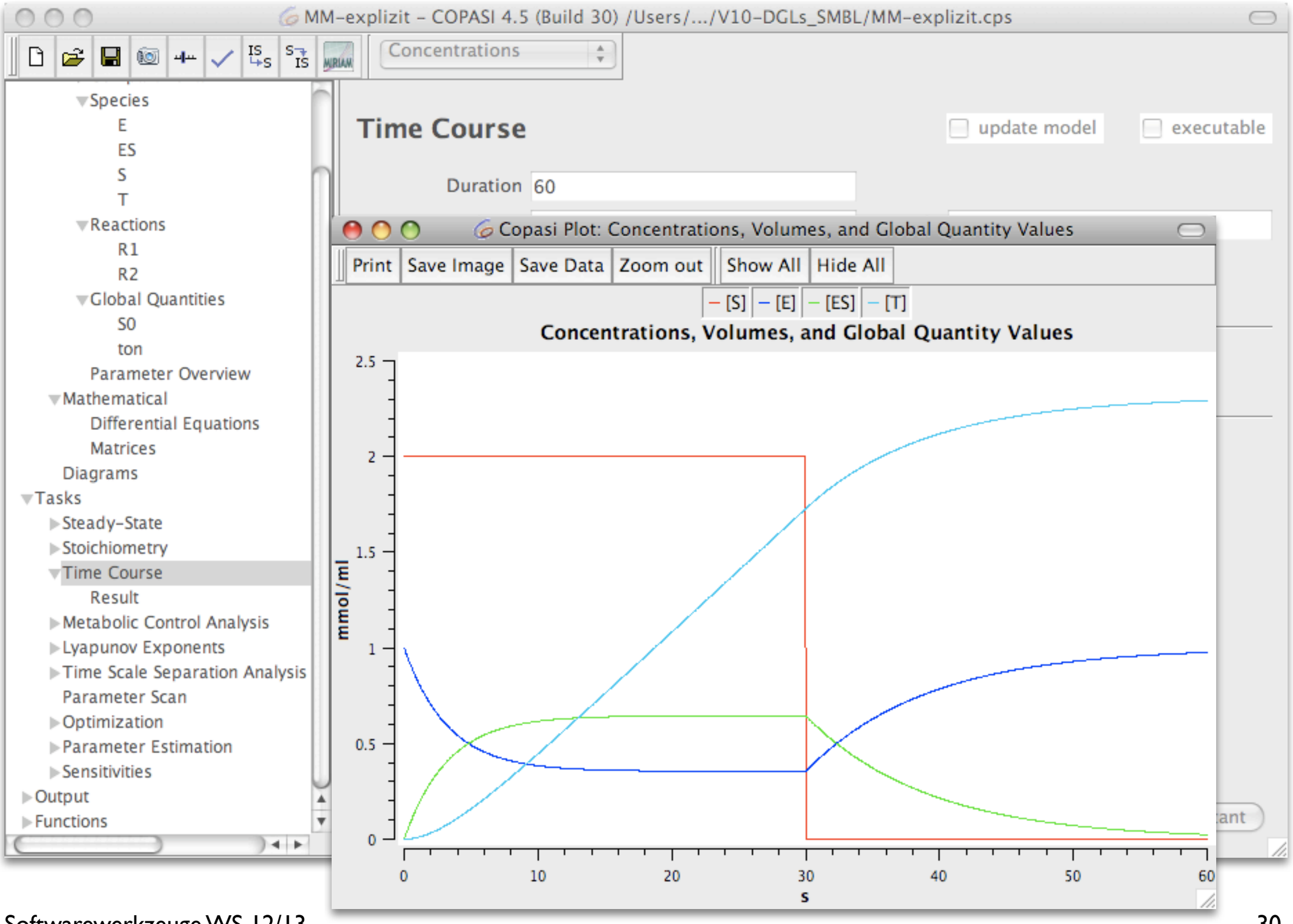
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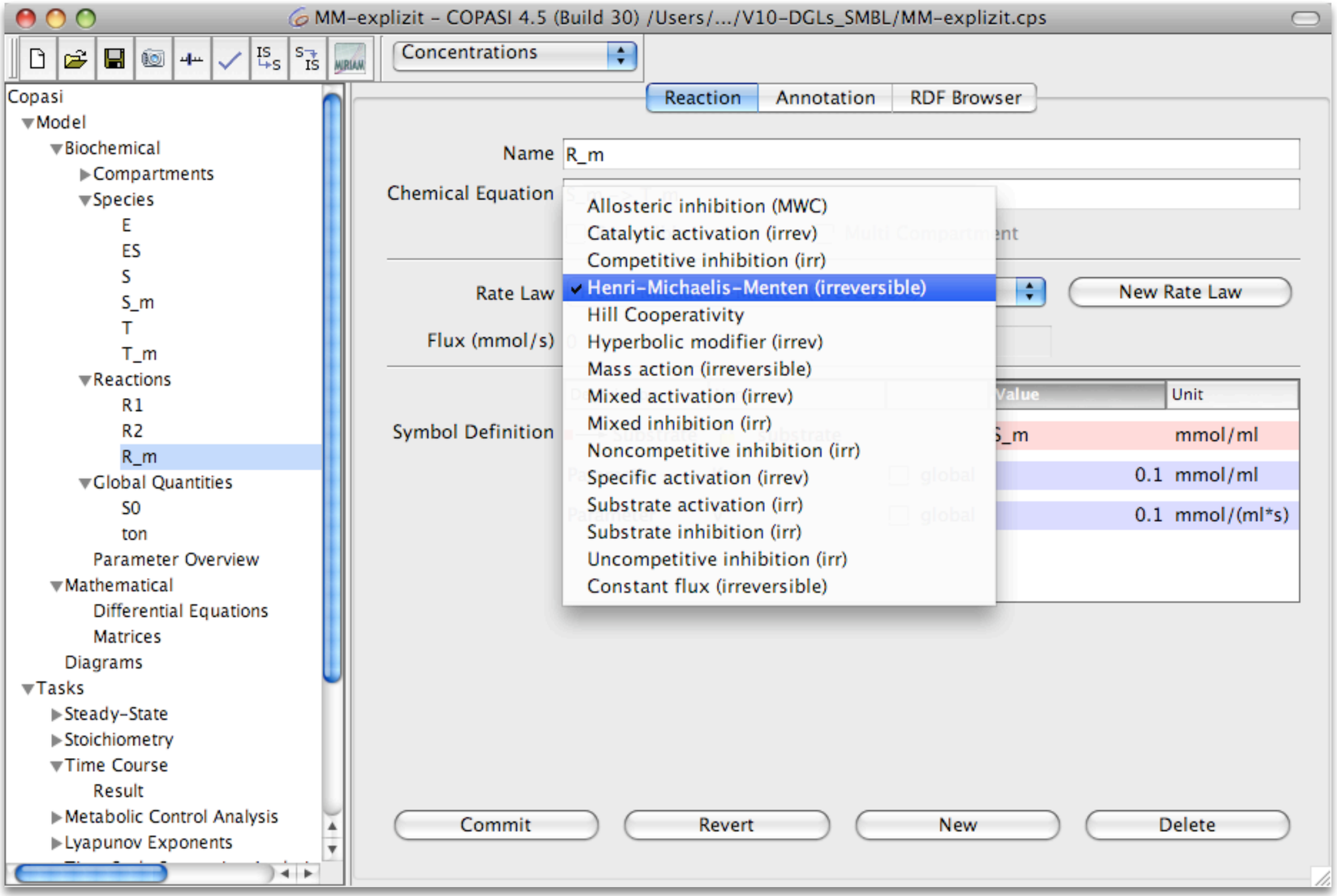
MM-explizit - COPASI 4.5 (Build 30) /Users/.../V10-DGLs_SMBL/MM-explizit.cps
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Lyapunov Exponents
Reaction
Annotation
RDF Browser
Name
R_m
Chemical Equation
Rate Law
Flux (mmol/s)
Symbol Definition
Allosteric inhibition (MWC)
Catalytic activation (irrev)
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)
New Rate Law
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S_m
mmol/ml
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mmol/ml
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Revert
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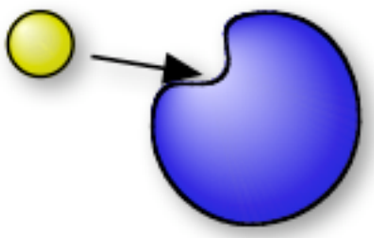
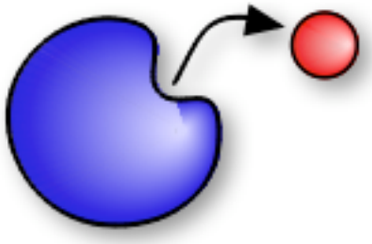
Vereinfachte Kinetiken

Enzymreaktion:
Michaelis-Menten



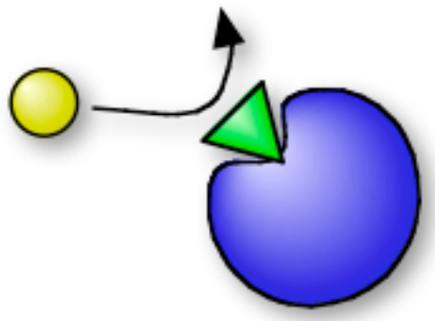
k_{on}
E + S => ES

ES => ES'



k_{off}
ES' => E + T

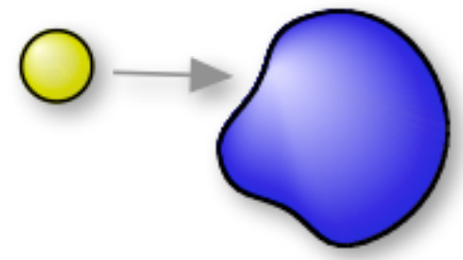
kompetitive Inhibition:
Inhibitor vs. Substrat

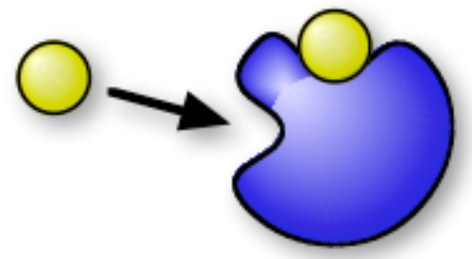


k_{on}
E + S => ES

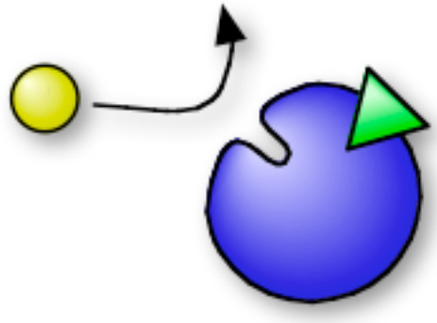
k_{I}
E + I <=> EI

Kooperative Bindung:
Hill-Kinetik





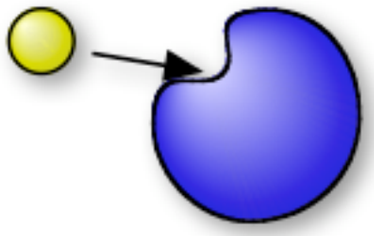
nicht-kompetitive Inhibition:
Inhibitor verändert Enzym

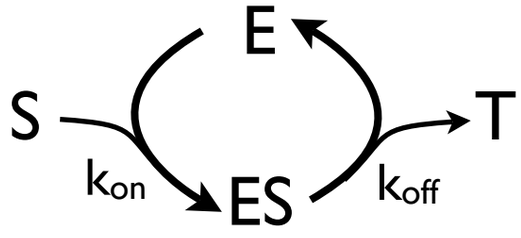


k_{on}
E + S => ES

k_{on}'
EI + S <=> EIS

Enzyme: Michaelis-Menten-Kinetik

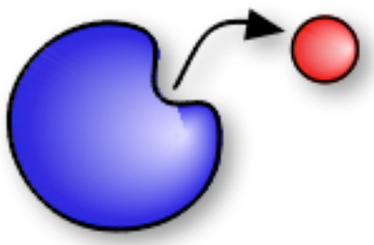




Reaktionsrate:

$$V = k_{off} ES$$

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:

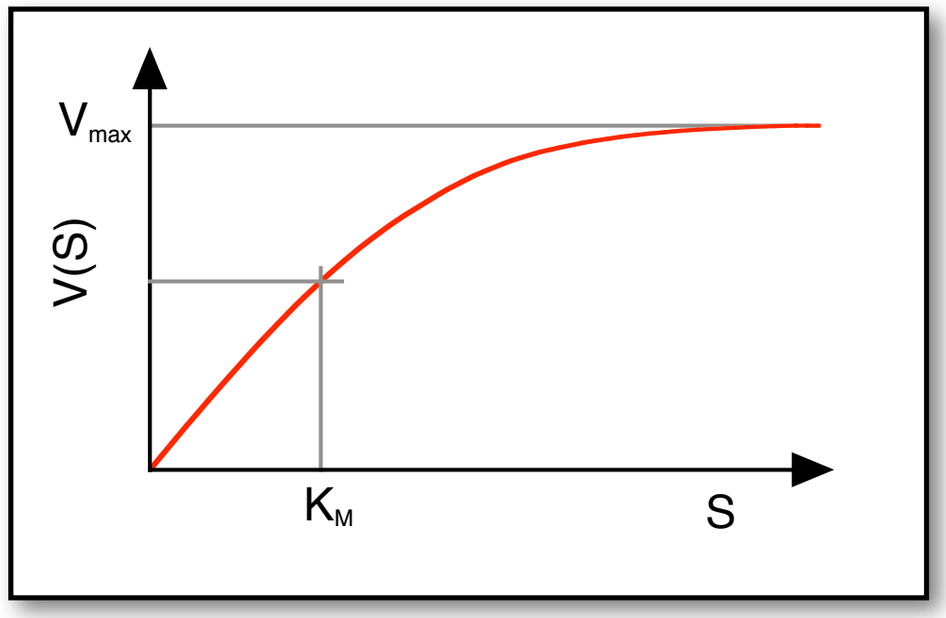
$$E_T = E + ES \quad \Rightarrow \quad ES = E_T \frac{S}{S + K_M}$$

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

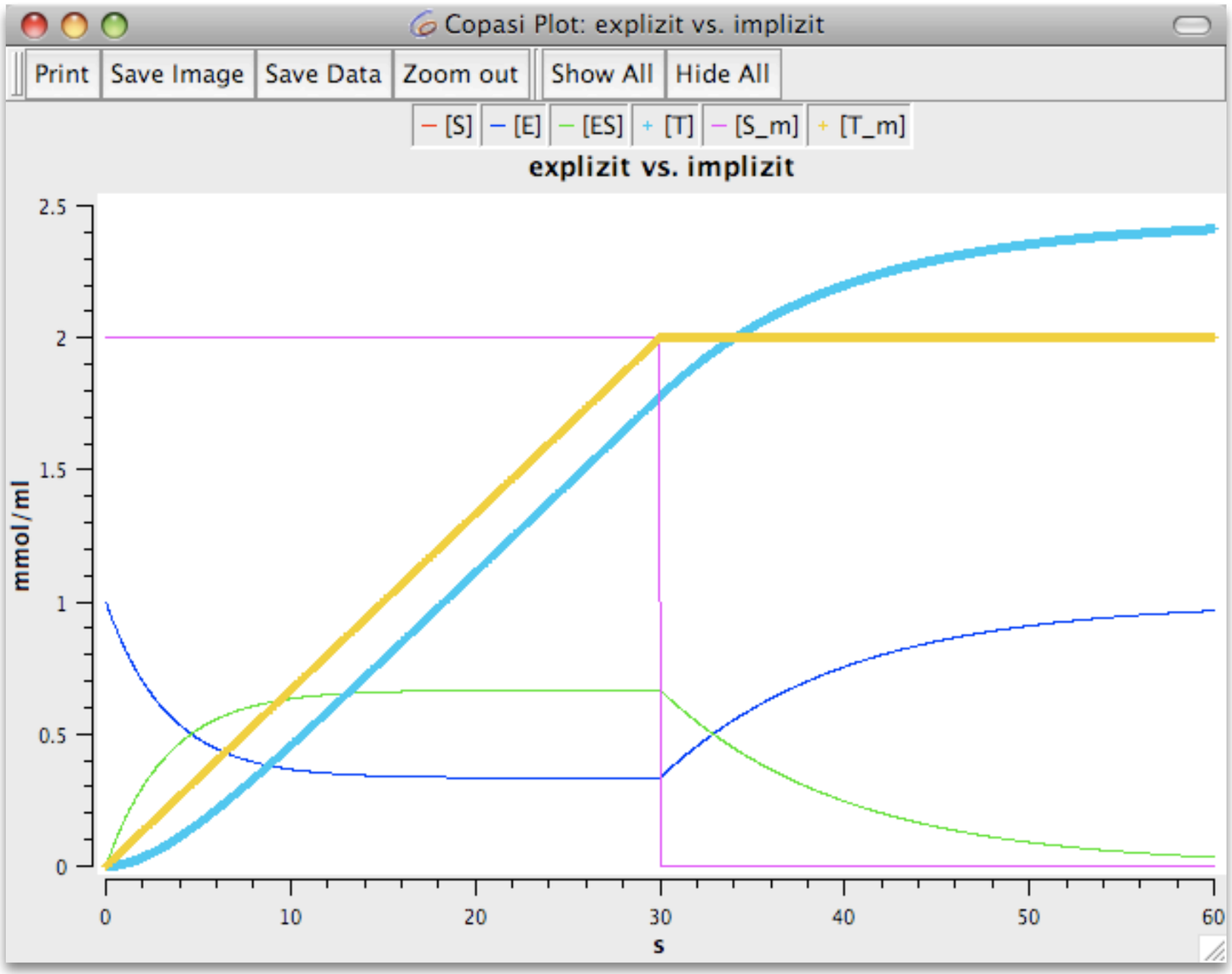
MM vs. explizite Modellierung

Wenn E verschiedene Substrate katalysiert
=> MM geht nicht

Zeitverhalten:
MM-Kinetik vs.
explizite Modellierung

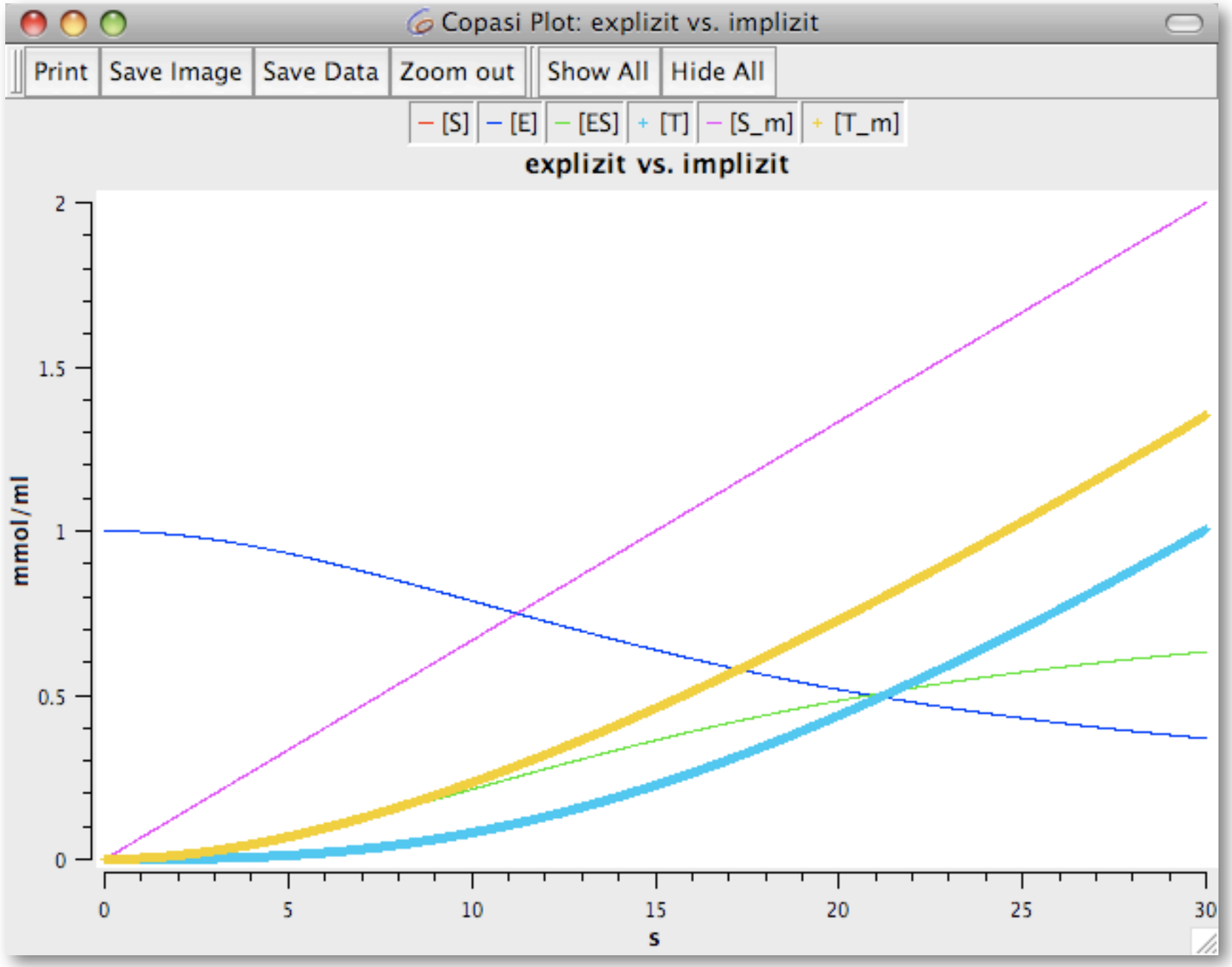
=> Einschwingen

=> anderer
Gesamtumsatz

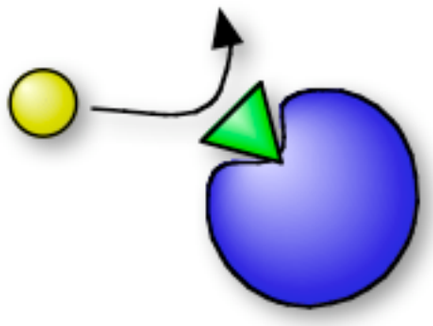


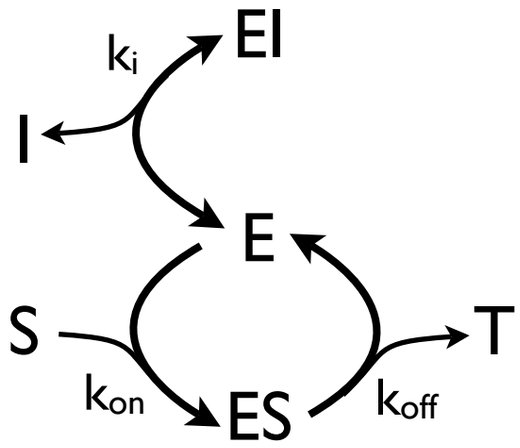
Nochmal: explizit vs. MM

linearer Anstieg von S



Kompetitive Hemmung





Zwei Pfade:

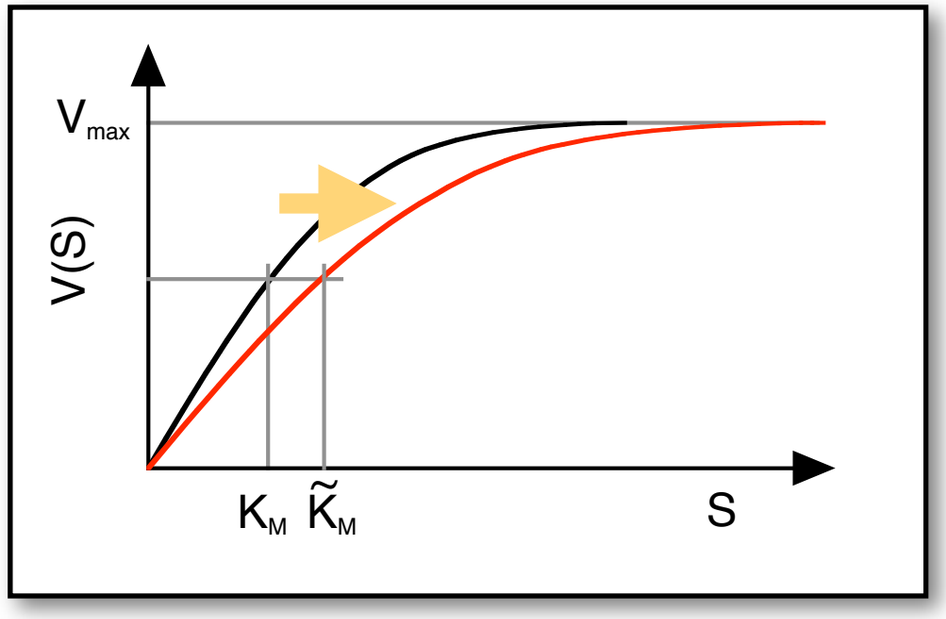
$$E + S \xrightarrow{k_{on}} ES \qquad E + I \xrightarrow{k_I} EI$$

=> I verdrängt S

S << I: weniger freies E verfügbar
=> weniger ES
=> V reduziert

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

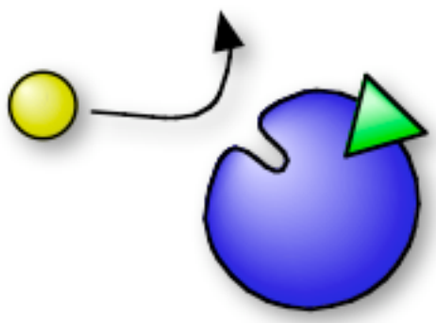
S >> I: S verdrängt I
=> Inhibition unterdrückt
=> V_{max} unverändert

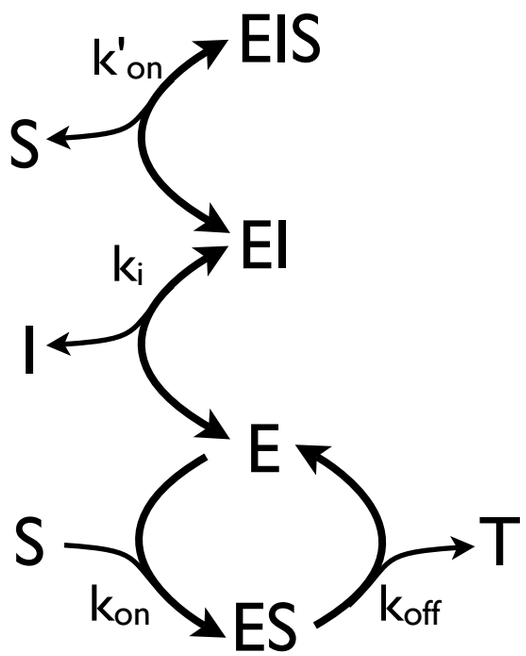


$$V = V_{max} \frac{S}{S + K_M (1 + I/K_I)}$$

Nichtkompetitive Inhibition

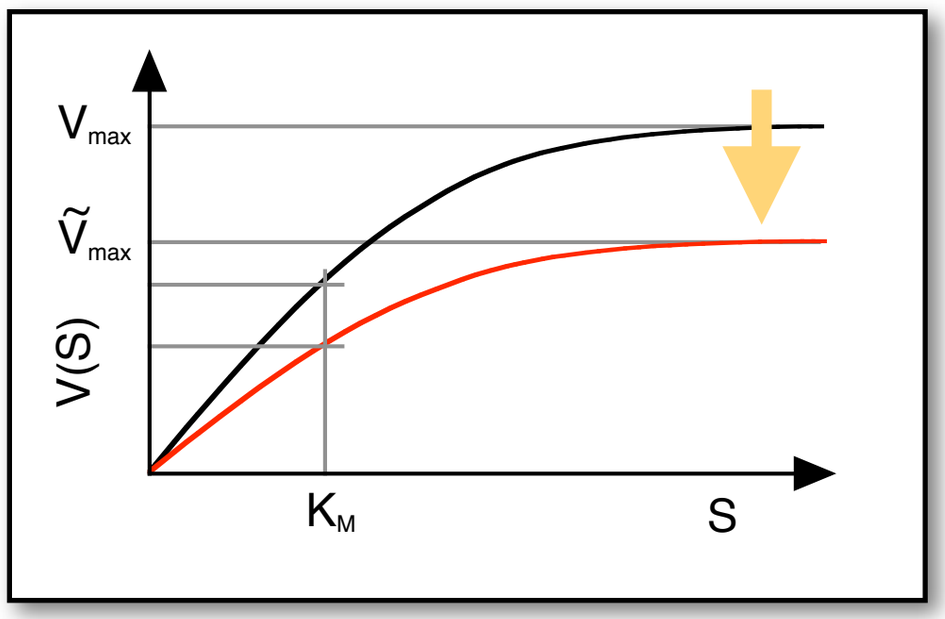
Inhibitor blockiert Enzym





=> I reduziert effektives E_T

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

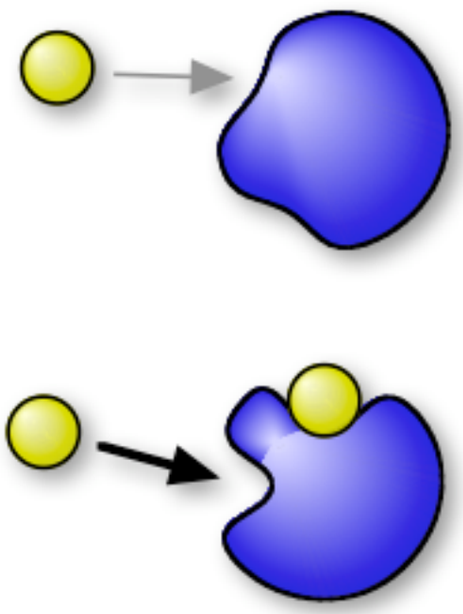


Analytische Formeln
=> Wirkungsweise von I aus steady state

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 $K = \frac{E \cdot S}{ES}$

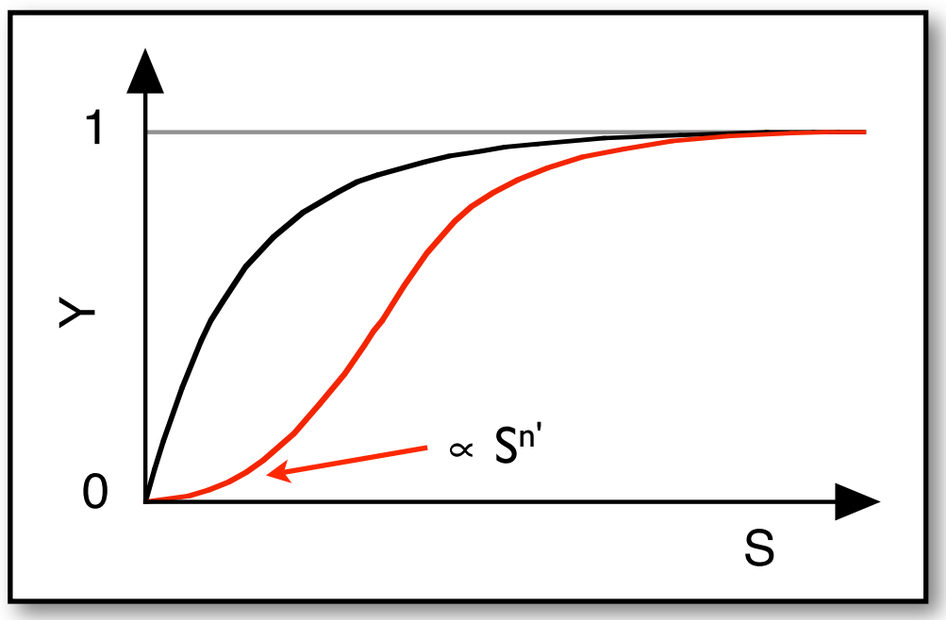
$$Y = \frac{ES}{E + ES} = \frac{S}{S + K}$$ Anteil an besetzten Bindungstaschen

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

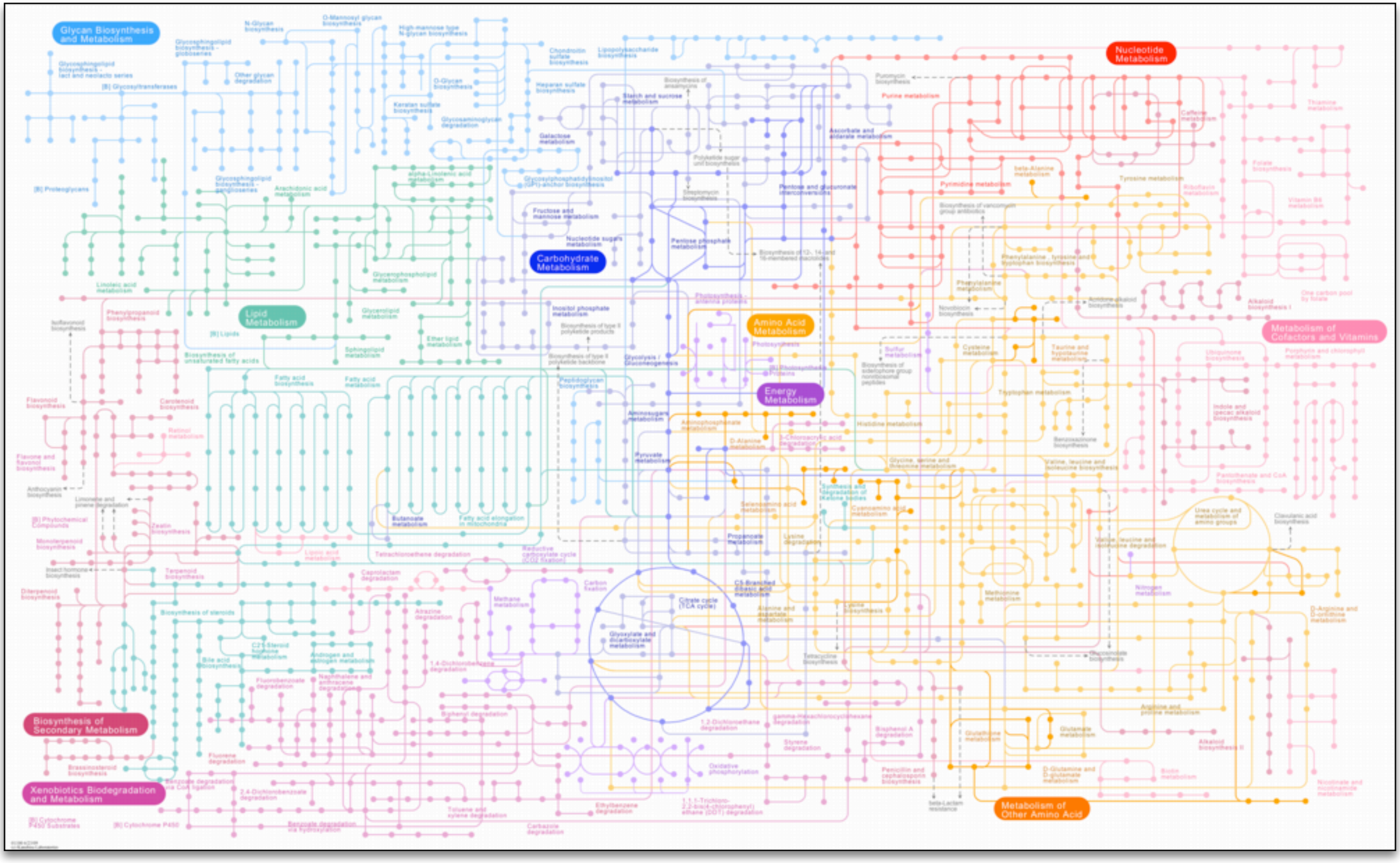
Pfade: KEGG

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

kinetische Daten: SABIO-RK

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

KEGG-Pfade


Glycan Biosynthesis and Metabolism
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Amino Acid Metabolism
Energy Metabolism
Metabolism of Cofactors and Vitamins
Biosynthesis of Secondary Metabolism
Xenobiotics Biodegradation and Metabolism
Metabolism of Other Amino Acid
Citrate cycle (TCA cycle)
Pentose phosphate metabolism
Glycolysis / Gluconeogenesis
Fatty acid biosynthesis
Fatty acid metabolism
Purine metabolism
Pyrimidine metabolism
Tyrosine metabolism
Phenylalanine metabolism
Tryptophan metabolism
Histidine metabolism
Cysteine metabolism
Glutamate metabolism
Arginine and proline metabolism
Glycine, serine and threonine metabolism
Valine, leucine and isoleucine biosynthesis
Lysine biosynthesis
Methionine metabolism
Alanine and aspartate metabolism
Oxidative phosphorylation
Photosynthesis
Nitrogen metabolism
Sulfur metabolism
Glutathione metabolism
Starch and sucrose metabolism
Galactose metabolism
Fructose and mannose metabolism
Nucleotide sugars metabolism
Glycerophospholipid metabolism
Glycerolipid metabolism
Sphingolipid metabolism
Ether lipid metabolism
Inositol phosphate metabolism
Peptidoglycan biosynthesis
Aminosugars metabolism
Pyruvate metabolism
Propanoate metabolism
Butanoate metabolism
Fatty acid elongation in mitochondria
Terpenoid backbone biosynthesis
Biosynthesis of steroids
Bile acid biosynthesis
Androgen and estrogen metabolism
Carbon fixation
Methane metabolism
Glyoxylate and dicarboxylate metabolism
Reductive carboxylate cycle (CO2 fixation)
Caprolactam degradation
Atrazine degradation
Fluorobenzoate degradation
Naphthalene and anthracene degradation
1,4-Dichlorobenzene degradation
Biphenyl degradation
Fluorene degradation
Benzoate degradation via CoA ligation
2,4-Dichlorobenzoate degradation
Toluene and xylene degradation
Benzoate degradation via hydroxylation
Carbazole degradation
Ethylbenzene degradation
1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane (DDT) degradation
1,2-Dichloroethane degradation
gamma-Hexachlorocyclohexane degradation
Styrene degradation
Bisphenol A degradation
Penicillin and cephalosporin biosynthesis
beta-Lactam resistance
Tetracycline biosynthesis
Novobiocin biosynthesis
Streptomycin biosynthesis
Polyketide sugar unit biosynthesis
Biosynthesis of ansamycins
Biosynthesis of vancomycin group antibiotics
Biosynthesis of type II polyketide backbone
Biosynthesis of type II polyketide products
Biosynthesis of 12-, 14- and 16-membered macrolides
Biosynthesis of siderophore group nonribosomal peptides
Acridone alkaloid biosynthesis
Indole and oxindole alkaloid biosynthesis
Benzoxazinone biosynthesis
Alkaloid biosynthesis I
Alkaloid biosynthesis II
Ubiquinone biosynthesis
Porphyrin and chlorophyll metabolism
Thiamine metabolism
Riboflavin metabolism
Vitamin B6 metabolism
Folate biosynthesis
Pantothenate and CoA biosynthesis
Biotin metabolism
Nicotinate and nicotinamide metabolism
One carbon pool by folate
Clavulanic acid biosynthesis
Caffeine metabolism
Ascorbate and aldarate metabolism
Pentose and glucuronate interconversions
beta-Alanine metabolism
Taurine and hypotaurine metabolism
Selenoamino acid metabolism
Cyanoamino acid metabolism
Synthesis and degradation of ketone bodies
Valine, leucine and isoleucine degradation
Lysine degradation
Urea cycle and metabolism of amino groups
D-Arginine and D-ornithine metabolism
D-Glutamine and D-glutamate metabolism
Puromycin biosynthesis
Glycosphingolipid biosynthesis - globosenes
Glycosphingolipid biosynthesis - lact and neolacto series
Glycosphingolipid biosynthesis - ganglio series
N-Glycan biosynthesis
O-Mannosyl glycan biosynthesis
High-mannose type N-glycan biosynthesis
O-Glycan biosynthesis
Other glycan degradation
Keratan sulfate biosynthesis
Chondroitin sulfate biosynthesis
Heparan sulfate biosynthesis
Glycosaminoglycan degradation
Lipopolysaccharide biosynthesis
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis
alpha-Linolenic acid metabolism
Arachidonic acid metabolism
Linoleic acid metabolism
Phenylpropanoid biosynthesis
Isoflavonoid biosynthesis
Flavonoid biosynthesis
Carotenoid biosynthesis
Retinol metabolism
Flavone and flavonol biosynthesis
Anthocyanin biosynthesis
Limonene and pinene degradation
Zeatin biosynthesis
Monoterpenoid biosynthesis
Insect hormone biosynthesis
Diterpenoid biosynthesis
Brassinosteroid biosynthesis
Biosynthesis of unsaturated fatty acids
Lipoic acid metabolism
Tetrachloroethene degradation
Cysteine and methionine metabolism
Phenylalanine, tyrosine and tryptophan biosynthesis
Biosynthesis of amino acids
Glycolysis / Gluconeogenesis
Photosynthesis - antenna proteins
Photosynthesis
Carbon metabolism
2-Oxocarboxylic acid metabolism
Aminophosphonate metabolism
3-Chloroacrylic acid degradation
Glycine, serine and threonine metabolism
Valine, leucine and isoleucine biosynthesis
Lysine biosynthesis
Tetracycline biosynthesis
Novobiocin biosynthesis
Streptomycin biosynthesis
Polyketide sugar unit biosynthesis
Biosynthesis of ansamycins
Biosynthesis of vancomycin group antibiotics
Biosynthesis of type II polyketide backbone
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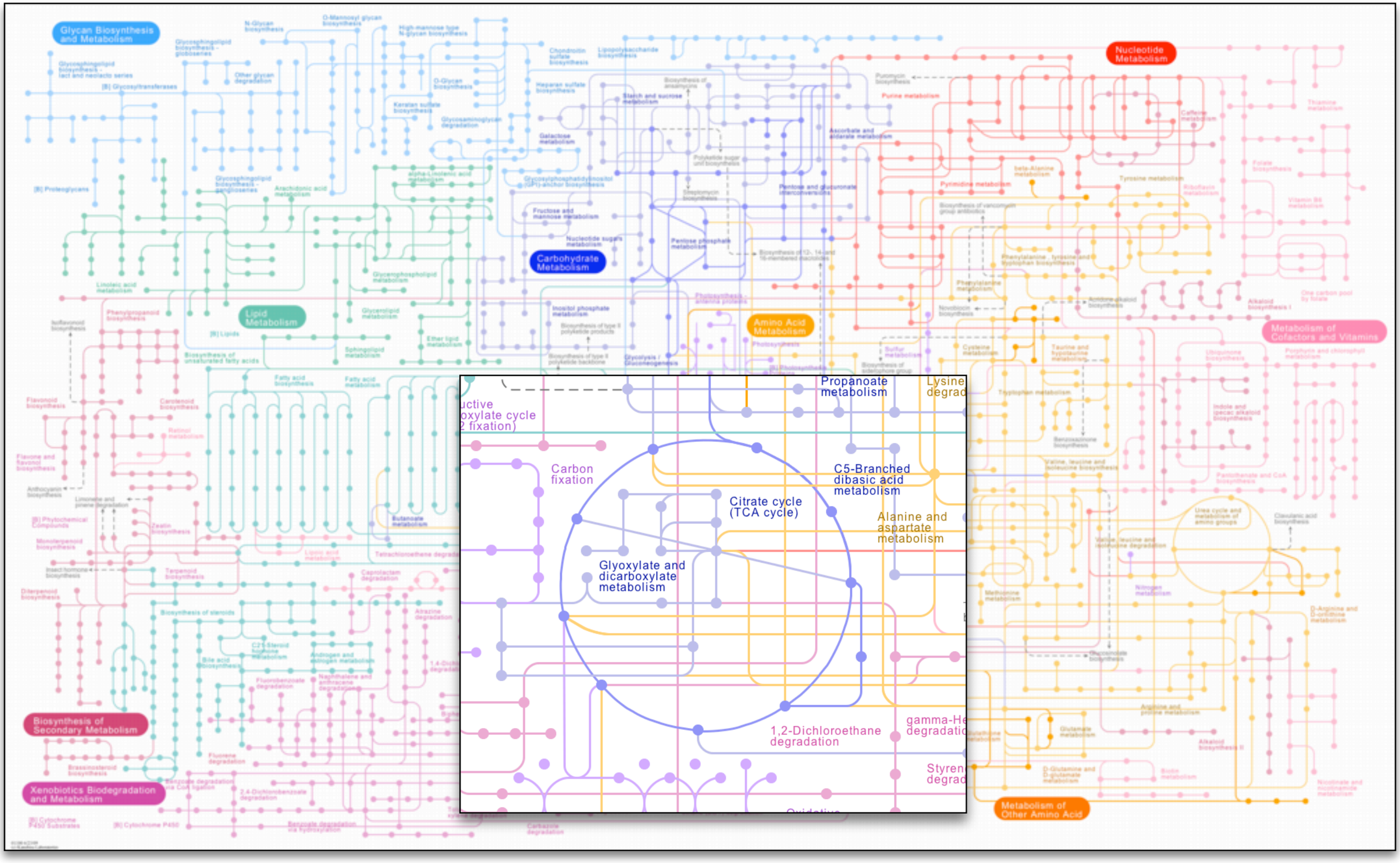
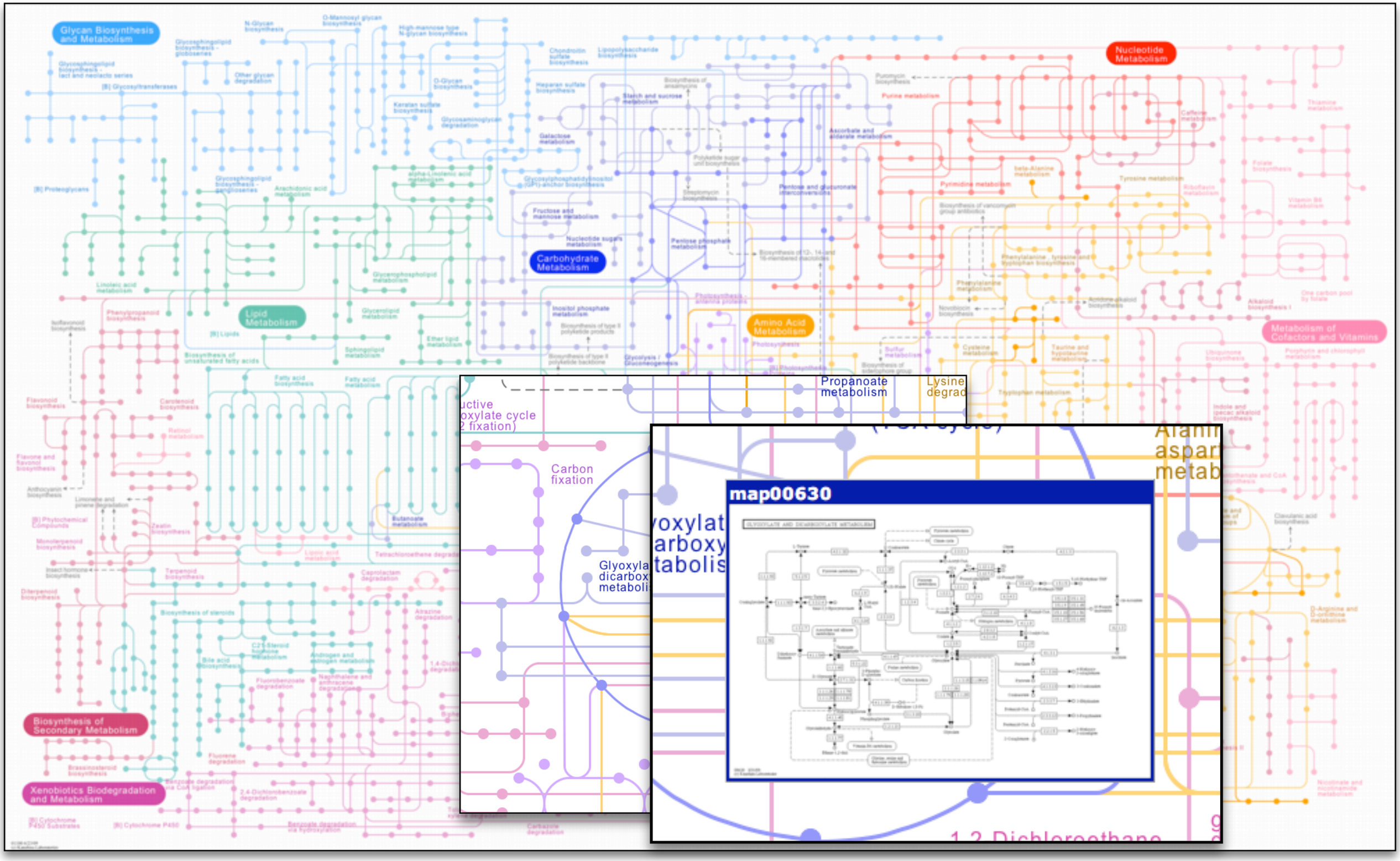
Urea cycle and metabolism of amino groups
D-Arginine and D-ornithine metabolism
D-Glutamine and D-glutamate metabolism
Puromycin biosynthesis
[BR] Glycosyltransferases
[BR] Proteoglycans
[BR] Lipids
[BR] Photosynthesis Proteins
[BR] Phytochemical Compounds
[BR] Cytochrome P450 Substrates
[BR] Cytochrome P450

KEGG-Pfade


Glycan Biosynthesis and Metabolism
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Amino Acid Metabolism
Metabolism of Cofactors and Vitamins
Biosynthesis of Secondary Metabolism
Xenobiotics Biodegradation and Metabolism
Metabolism of Other Amino Acid
Carbon fixation
Citrate cycle (TCA cycle)
Glyoxylate and dicarboxylate metabolism
C5-Branched dibasic acid metabolism
Alanine and aspartate metabolism
Propanoate metabolism
1,2-Dichloroethane degradation

KEGG-Pfade


Glycan Biosynthesis and Metabolism
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Amino Acid Metabolism
Metabolism of Cofactors and Vitamins
Biosynthesis of Secondary Metabolism
Xenobiotics Biodegradation and Metabolism
Propanoate metabolism
Carbon fixation
map00630

KEGG PATHWAY: Glyoxylate and dicarboxylate metabolism – Reference pathway

http://www.genome.jp/kegg-bin/resize_map.cgi?map=map00630&scale=1

Google

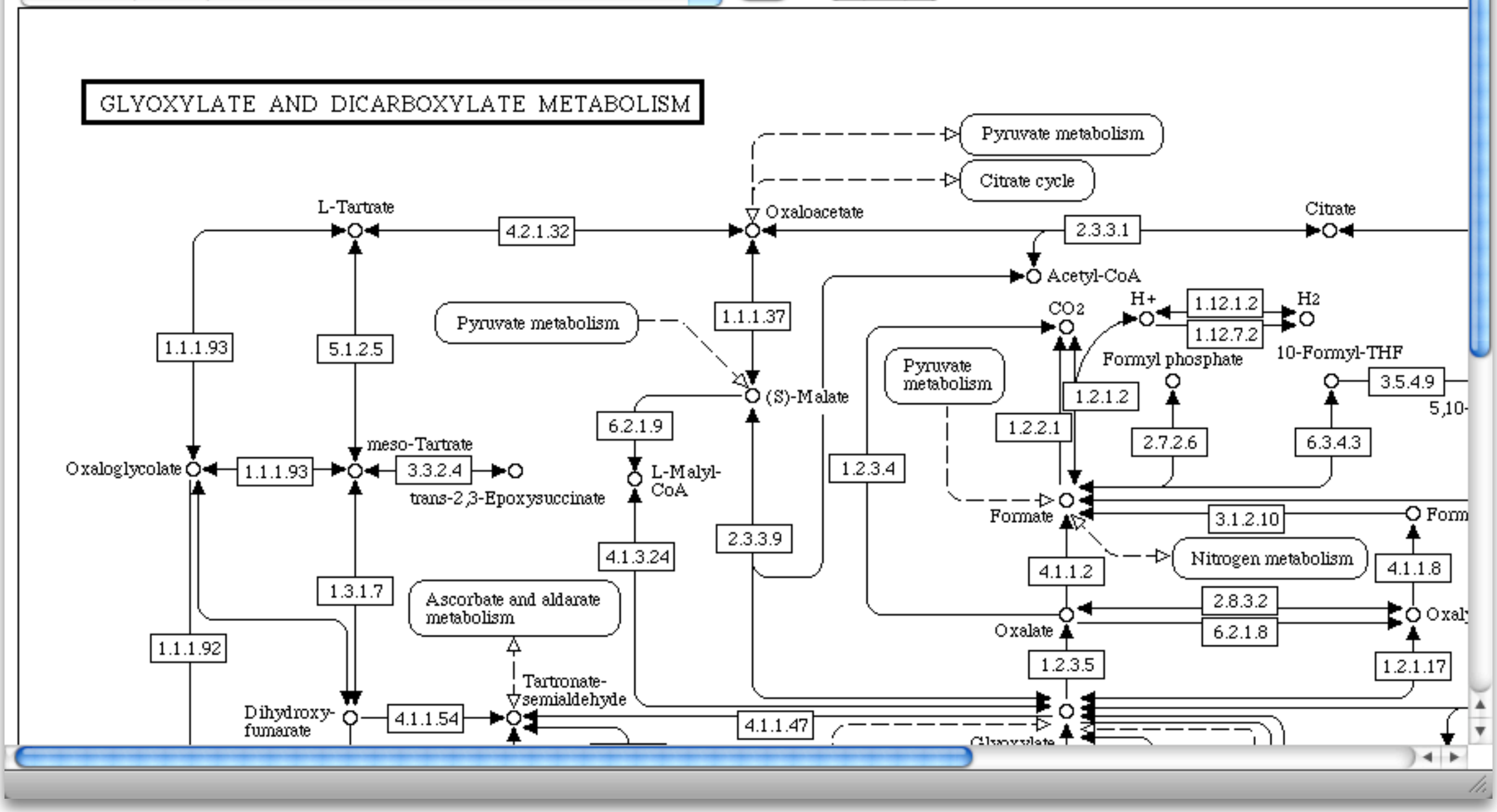
KEGG

Glyoxylate and dicarboxylate metabolism - Reference pathway

Help

[Pathway menu | Pathway entry]

Reference pathway Go

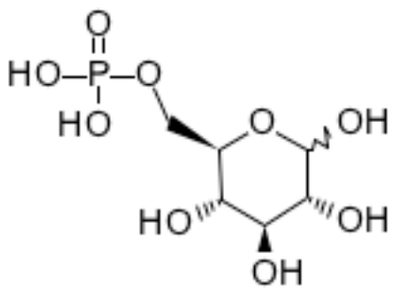


Inside KEGG

KEGG

COMPOUND: C00092

Help

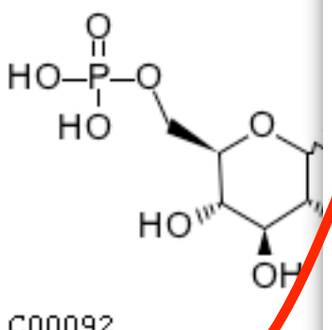
Entry	C00092 Compound
Name	D-Glucose 6-phosphate; Glucose 6-phosphate; Robison ester
Formula	C6H13O9P
Mass	260.0297
Structure	 C00092 Mol file KCF file DB search Jmol KegDraw
Reaction	R00299 R00303 R00725 R00771 R00834 R00835 R00836 R00837 R00838 R00839 R00840 R00850 R01139 R02168 R02185 R05767 R05804 R06043 R06044 R06112 R06113 R06115 R06125 R07324 R08125 R08404 R08617 R08639
Pathway	PATH: ko00500 Starch and sucrose metabolism PATH: ko00521 Streptomycin biosynthesis PATH: ko00562 Inositol phosphate metabolism PATH: map01062 Biosynthesis of terpenoids and steroids PATH: ko02020 Two-component system 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

Inside KEGG

KEGG

COMPOUND: C00092

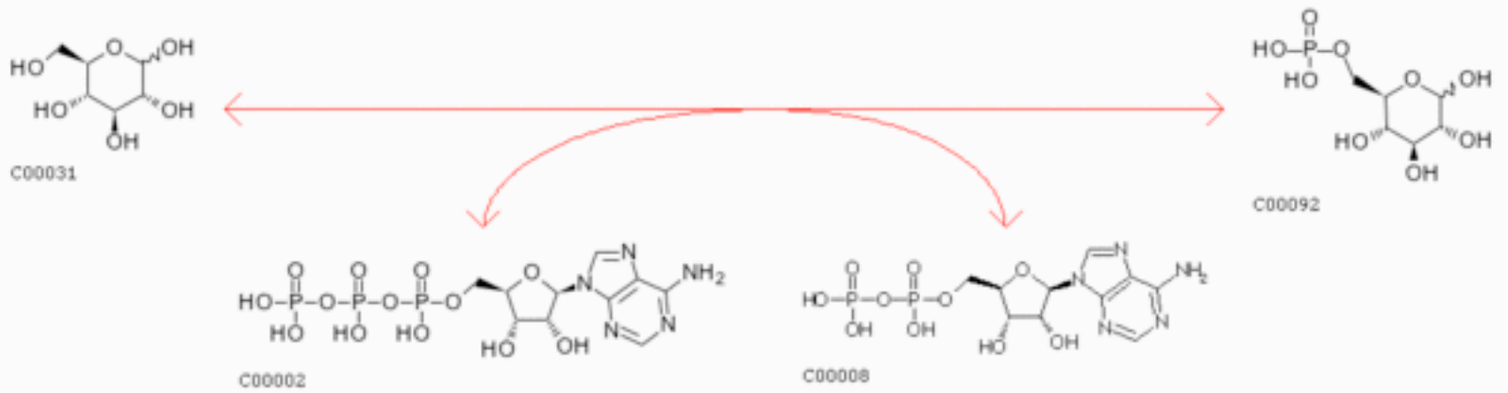
Help

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 Ino PATH: map01062 Bi PATH: ko02020 Two-component system 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

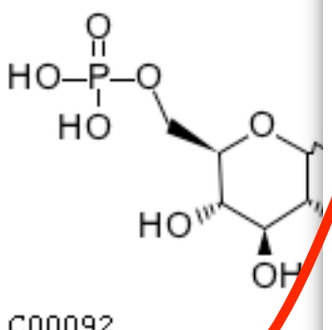
Help

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

Inside KEGG

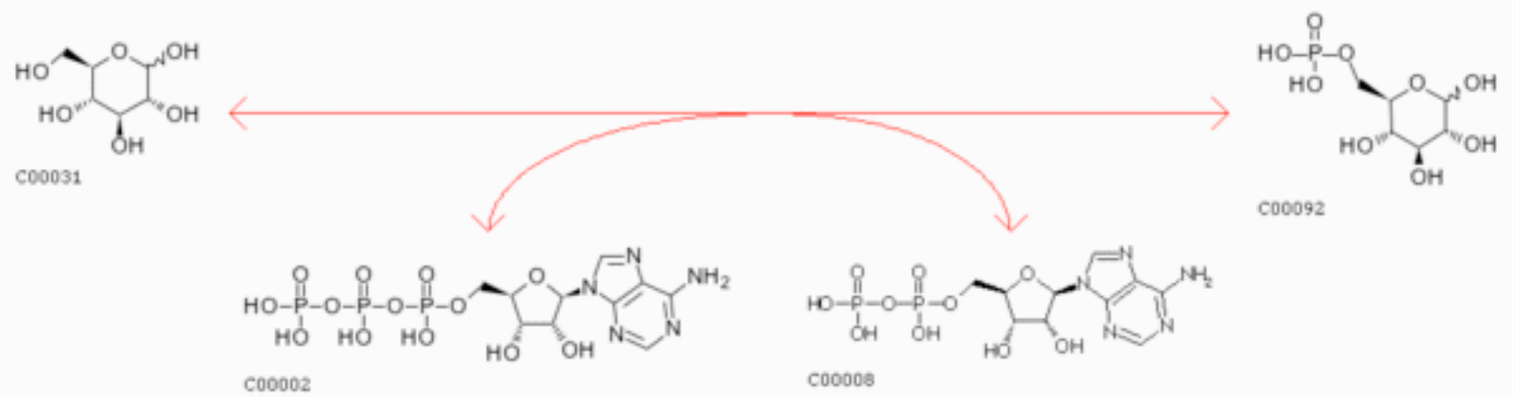
COMPOUND: C00092

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 Ino PATH: map01062 Bi PATH: ko02020 Two-component system 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

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

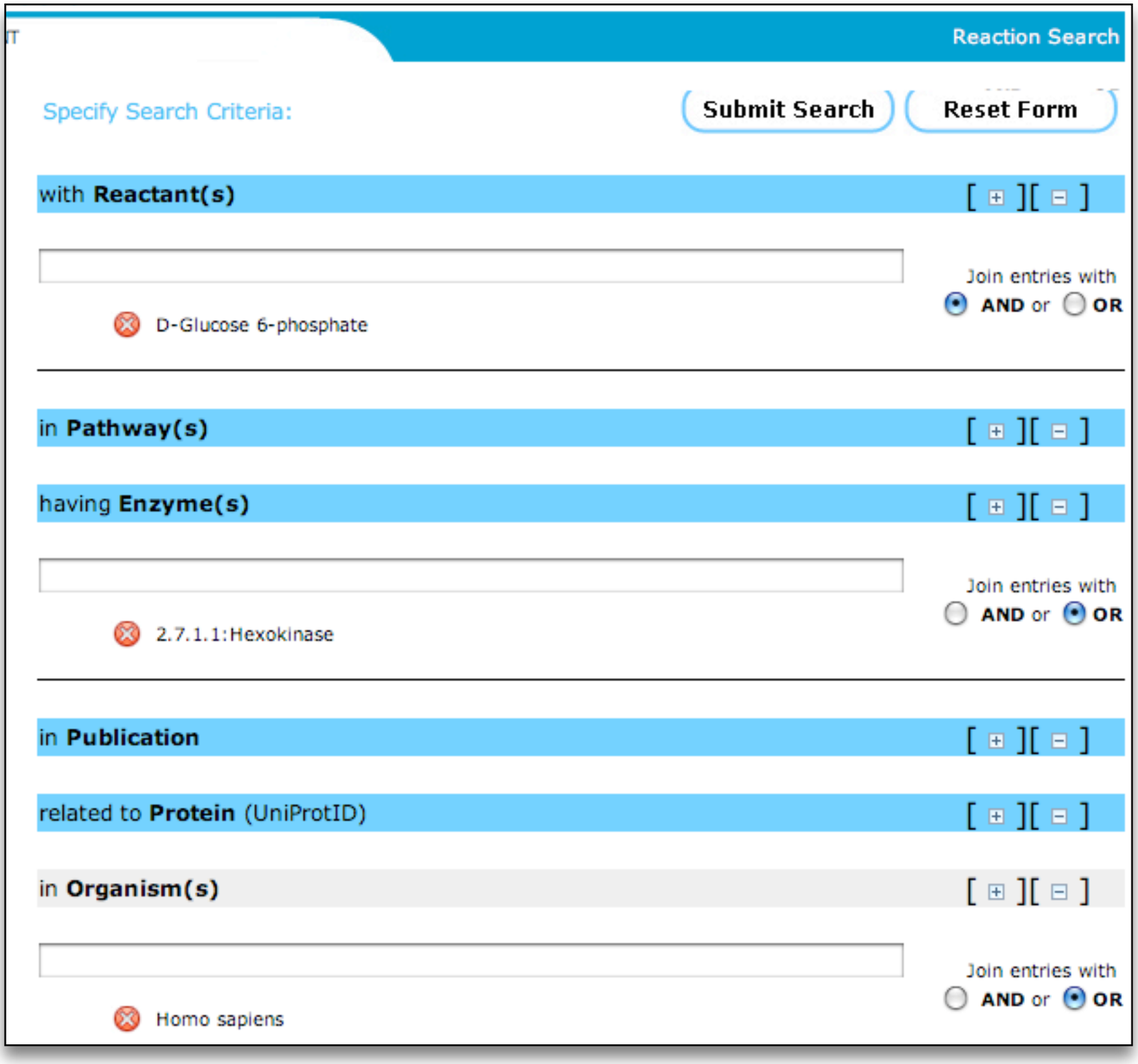
What is SABIO-RK? TOP

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



Suche in SABIO-RK

Reaction Search

Specify Search Criteria:

Submit Search | Reset Form

with **Reactant(s)**

D-Glucose 6-phosphate

in **Pathway(s)**

having **Enzyme(s)**

2.7.1.1:Hexokinase

in **Publication**

related to **Protein** (UniProtID)

in **Organism(s)**

Homo sapiens

Search Results

Total number of reactions found for specified search criteria: 2

Click here to view your search criteria

Modify Search

Kinetic Data Availability:

view Kinetic data available matching the search criteria

view Kinetic data available, but not matching all search criteria

No kinetic data available

Number of results per page: 10 Display

Show only reactions having kinetic data matching the search criteria ☑

Send Selected Reactions to SBML File

Reactions	Select Reaction(s) (De)Select All	Kinetic Data for this reaction (Click to View)	Enzyme EC#	Kinetic data for enzymes (Click to View)
ITP + D-Glucose <-> D-Glucose 6-phosphate + IDP	☐	view	2.7.1.1	view
D-Glucose + ATP <-> D-Glucose 6-phosphate + ADP	☐	view	2.7.1.1 2.7.1.2	view view

Pages: 1

Previous Next

Suche in SABIO-RK

Reaction Search

Specify Search Criteria:

Submit Search | Reset Form

with **Reactant(s)**

D-Glucose 6-phosphate

in **Pathway(s)**

having **Enzyme(s)**

2.7.1.1:Hexokinase

in **Publication**

related to **Protein** (UniProtID)

in **Organism(s)**

Homo sapiens

Search Results

Total number of reactions found for specified search criteria: 2

Click here to view your search criteria

Modify Search

Kinetic Data Availability:

view — Kinetic data available matching the search criteria

view — Kinetic data available, but not matching all search criteria

No kinetic data available

Number of results per page: 10 Display

Show only reactions having kinetic data matching the search criteria ☑

Send Selected Reactions to SBML File

Reactions	Select Reaction(s) (De)Select All	Kinetic Data for this reaction (Click to View)	Enzyme EC#	Kinetic data for enzymes (Click to View)
ITP + D-Glucose <-> D-Glucose 6-phosphate + IDP	☐	view	2.7.1.1	view
D-Glucose + ATP <-> D-Glucose 6-phosphate + ADP	☐	view	2.7.1.1 2.7.1.2	view view

Pages: 1

Previous Next

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

Nächste Woche: Modellierung größerer Systeme (ProMoT, SBML)