



Heidelberg Institute for
Theoretical Studies



SYCAMORE

<http://sycamore.eml.org>

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SYCAMORE

Outline

- motivation
- implementation
- main features
- interaction with other applications

SYCAMORE

**“SYstems biology’s Computational Analysis and
MOdeling Research Environment”**

Motivation

- to facilitate the set-up, simulation and analysis of new biochemical models, particularly by non-expert users
- facilitates building and modification of biochemical models
- view, analysis and refinement of models
- allows quick simulations
- interaction with other tools



SYCAMORE


Implementation features


- no installation required: web application
- database supported modelling: SABIO-RK
- one platform for different programs, including
 - Copasi for simulation & sensitivity analysis
 - JWS online for simulation & visualization
 - qPIPSA for parameter estimation

Sycamore Homepage

<http://sycamore.eml.org/>







Menu

- [User guide](#)
- [Use case](#)
- [Contact](#)
- [Imprint](#)

Links

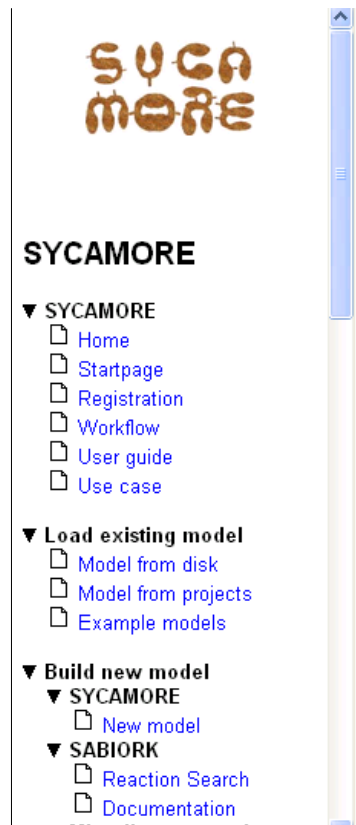
- [COPASI](#)
- [SABIO-RK](#)
- [webPIPSA](#)

SYCAMORE

SYCAMORE is a system that provides you with a facilitated access to a number of tools and methods in order to build models of biochemical systems, view, analyse and refine them, as well as perform quick simulations. SYCAMORE is not intended to substitute for expert simulation and modeling software packages, but might interact with those. It is rather intended to support and guide system biologists when doing computational research.

One important function of SYCAMORE is to allow you to build a draft model of your system of interest in such a way that kinetic expressions and parameters are as close to reality as possible. We want to emphasize that the resulting model still has a draft character and should not be taken as "the final model". However, setting up your model in such a way that parameters etc. are as close to reality as possible on the basis of literature data and computational parameter estimation methods should facilitate any parameter fitting methods that you want to employ later on.

Sycamore start screen



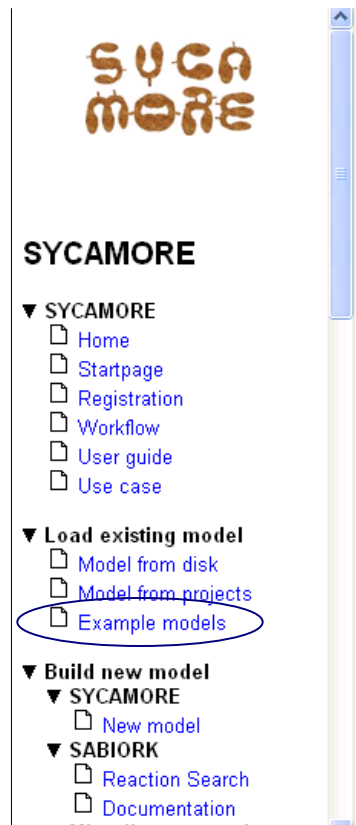
SYCAMORE

SYCAMORE allows you to build, view and edit models, to analyze and refine them, to perform simulations, sensitivity analysis and parameter estimations. To do so, you may start with one of the following options:

- Build a new model starting from scratch by defining reactions, metabolites, kinetic equations and parameters. [build new model](#)
- Build a new model with the support of SABIORK, a database that stores reactions and their corresponding kinetic parameters. [build SABIORK model](#)
- Load a SBML model from your hard disk. [load model from disk](#)
- Load a SBML model from projects. SYCAMORE offers the possibility to store complete and incomplete models in an internal database as your personal 'projects'. [load model from projects](#)
- Load an example model for testing of SYCAMORE. [load example model](#)
- Additionally, you may perform parameter estimations in order to determine unknown parameter values. [parameter estimation](#)

Sycamore start screen

Example models provided for testing



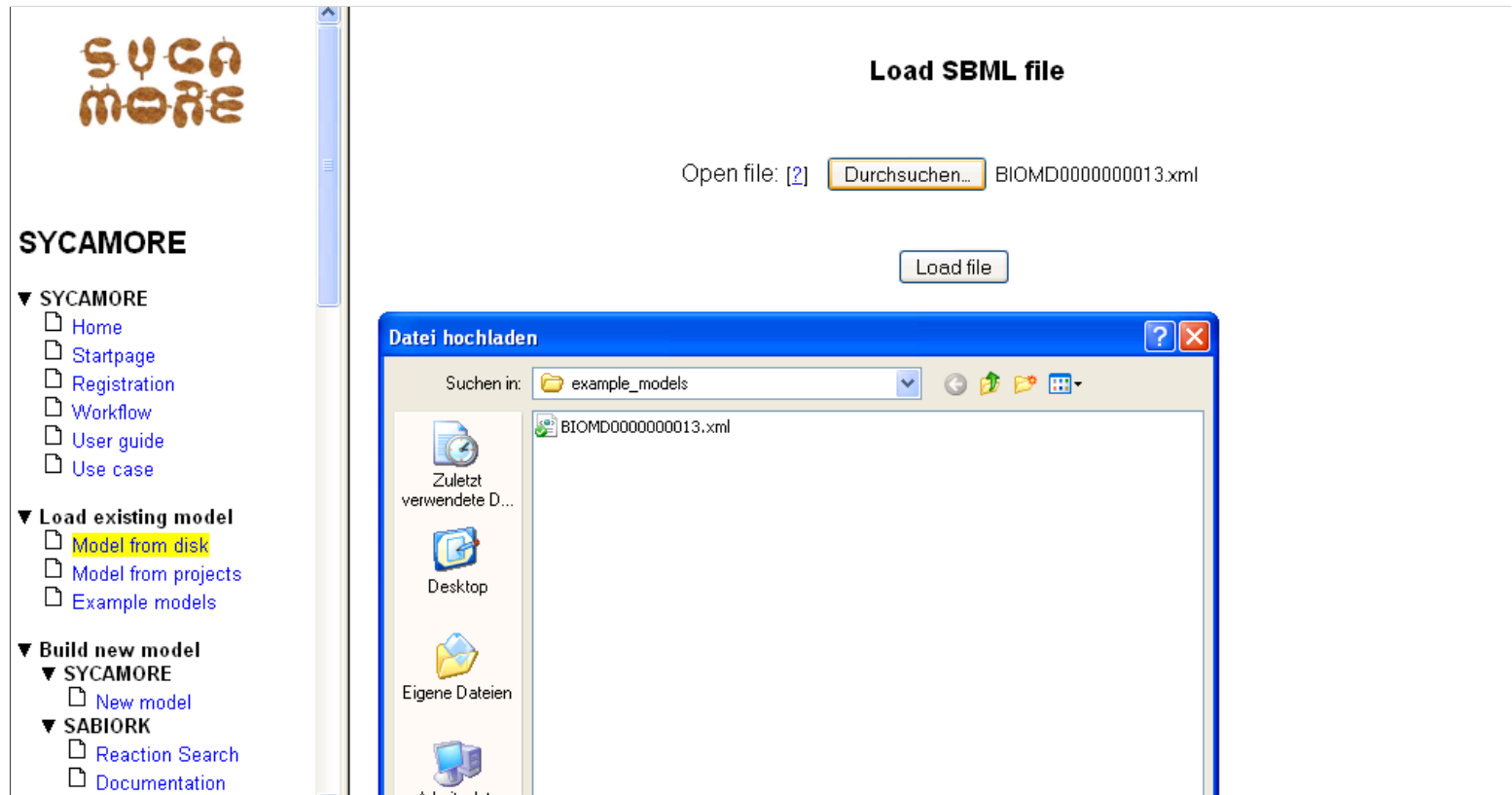
SYCAMORE

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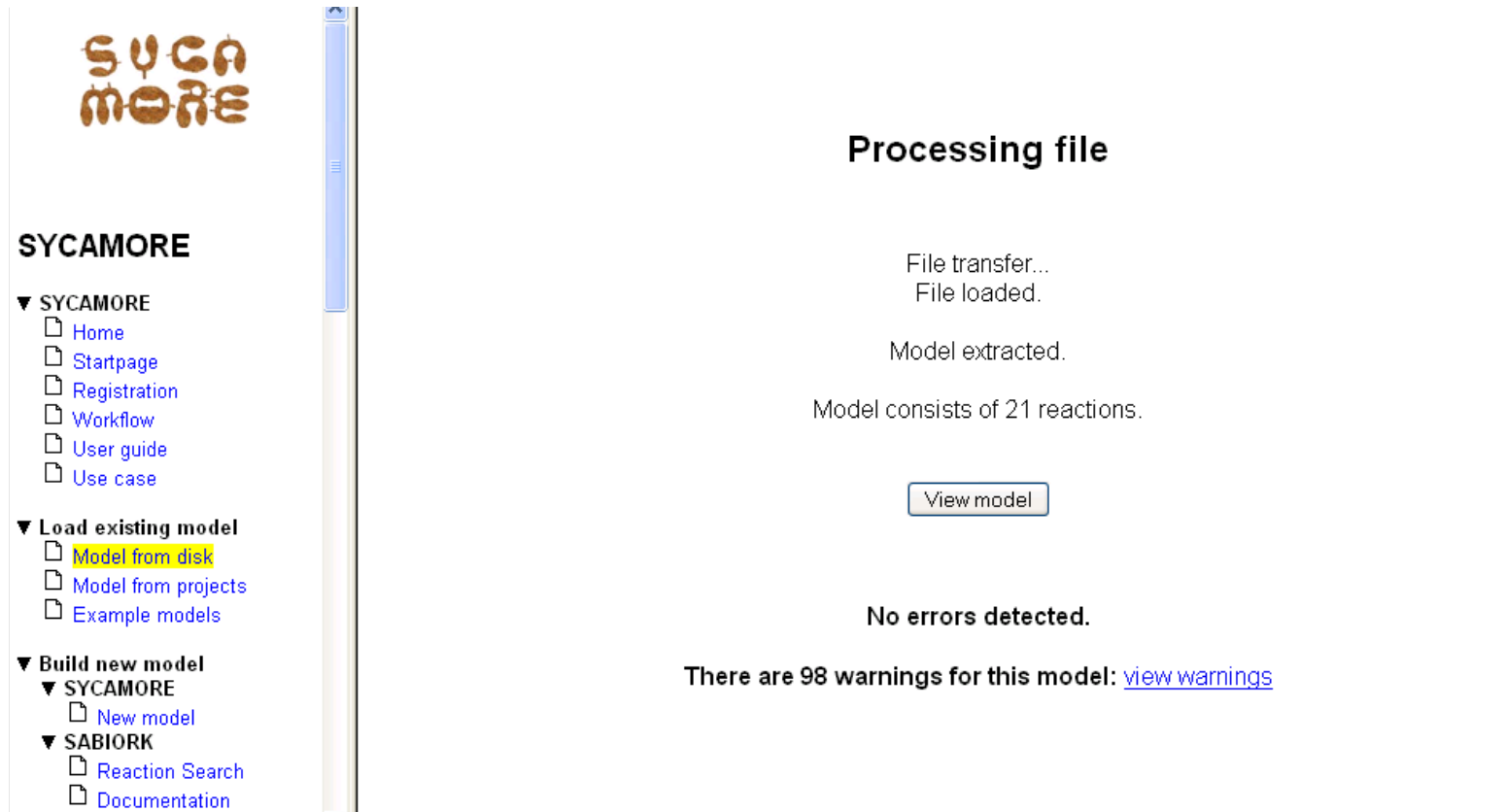
Model import

Upload of models (SBML format)



Model import

Model validation: <http://sbml.org/validator/> (F. Bergmann)



The screenshot displays the SYCAMORE web application interface. On the left is a navigation sidebar with the SYCAMORE logo at the top. Below the logo, the text 'SYCAMORE' is followed by a list of links: Home, Startpage, Registration, Workflow, User guide, and Use case. Under the heading 'Load existing model', the link 'Model from disk' is highlighted in yellow, followed by 'Model from projects' and 'Example models'. Under the heading 'Build new model', there is a sub-section for SYCAMORE with a 'New model' link, and a sub-section for SABIORK with 'Reaction Search' and 'Documentation' links. The main content area on the right is titled 'Processing file' and shows the progress of a file upload: 'File transfer...' and 'File loaded.' are followed by 'Model extracted.' and 'Model consists of 21 reactions.' A 'View model' button is present. At the bottom of the main area, it states 'No errors detected.' and 'There are 98 warnings for this model: [view warnings](#)'.

SYCAMORE

- ▼ SYCAMORE
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- ▼ Load existing model
 - Model from disk
 - Model from projects
 - Example models
- ▼ Build new model
 - ▼ SYCAMORE
 - New model
 - ▼ SABIORK
 - Reaction Search
 - Documentation

Processing file

File transfer...
File loaded.

Model extracted.

Model consists of 21 reactions.


[View model](#)

No errors detected.

There are 98 warnings for this model: [view warnings](#)

Model editing

Display of all model data



SYCAMORE

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 - ▼ SYCAMORE
 - New model
 - ▼ SABIORK
 - Reaction Search
 - Documentation

Model Poolman2004_CalvinCycle

Reactions

#	Name	Reaction	Reversible	Edit
0	J0	$\text{RuBP_ch} + \text{x_CO2} \Rightarrow 2 \text{PGA_ch}; \text{FBP_ch}, \text{SBP_ch}, \text{Pi_ch}, \text{x_NADPH_ch}$	false	edit
1	J1	$\text{GAP_ch} \Leftrightarrow \text{DHAP_ch}$	true	edit
2	J2	$\text{GAP_ch} + \text{DHAP_ch} \Leftrightarrow \text{FBP_ch}$	true	edit
3	J3	$\text{GAP_ch} + \text{F6P_ch} \Leftrightarrow \text{X5P_ch} + \text{E4P_ch}$	true	edit
4	J4	$\text{DHAP_ch} + \text{E4P_ch} \Leftrightarrow \text{SBP_ch}$	true	edit
5	J5	$\text{S7P_ch} + \text{GAP_ch} \Leftrightarrow \text{R5P_ch} + \text{X5P_ch}$	true	edit
6	J6	$\text{R5P_ch} \Leftrightarrow \text{Ru5P_ch}$	true	edit
7	J7	$\text{X5P_ch} \Leftrightarrow \text{Ru5P_ch}$	true	edit
8	J8	$\text{x_Pi_cyt} + \text{PGA_ch} \Rightarrow \text{x_PGA_cyt} + \text{Pi_ch}; \text{DHAP_ch}, \text{GAP_ch}$	false	edit
9	J9	$\text{x_Pi_cyt} + \text{GAP_ch} \Rightarrow \text{x_GAP_cyt} + \text{Pi_ch}; \text{PGA_ch}, \text{DHAP_ch}$	false	edit
10	J10	$\text{F6P_ch} \Leftrightarrow \text{G6P_ch}$	true	edit
11	J11	$\text{G6P_ch} \Leftrightarrow \text{G1P_ch}$	true	edit
12	J12	$\text{Pi_ch} + \text{ADP_ch} \Rightarrow \text{ATP_ch}$	false	edit
13	J13	$\text{Ru5P_ch} + \text{ATP_ch} \Rightarrow \text{RuBP_ch} + \text{ADP_ch}; \text{PGA_ch}, \text{Pi_ch}$	false	edit
14	J14	$\text{PGA_ch} + \text{ATP_ch} \Rightarrow \text{BPGA_ch} + \text{ADP_ch}$	false	edit

Model editing

Reactions including compounds, kinetic law and parameters

▼ Reactions

All reactions

J0

J1

J2

J3

J4

J5

J6

J7

J8

J9

J10

J11

J12

J13

J14

J15

J16

J17

J18

J19

J20

▼ Refine & analyze model

Completeness

Sensitivity analysis

Metannogen annotation

▼ Model simulation

Edit reaction J2

[guidance / manual](#)

Reaction [?] (* required information)

Name

J2

Equation [?]

GAP_ch + DHAP_ch <=> FBP_ch

Reversible

true

Compound

Stoich. factor*	Name	Role*	Init. amount	Init. concentr.	Unit [?]	Compartment	Boundary cond.	Delete
1	GAP_ch	substrate	0.01334			uVol	false	delete
1	DHAP_ch	substrate	0.29345			uVol	false	delete
1	FBP_ch	product	0.02776			uVol	false	delete

add new compound

 or add existing compound:

Kinetic law [?] (* required information)

Formula [?]

(Enter formula with space like 'a + b / d' instead of 'a+b/d')

F_Aldo_v * (DHAP_ch * GAP_ch - FBP_ch / q5)

User support: example I

Predefined kinetic law equations
(selection dependent on reaction equation)

▼ Reactions

☐ All reactions

☐ vgp

☐ vpglm

☐ vpgi

☐ vpfk

☐ vald

☐ vtpi

☐ vgapdh

☐ vpgk

☐ vpgm

☐ ven

☐ vpk

☐ vldh

☐ vck

☐ vadk

☐ vatpase

☒ vout

▼ Refine & analyze model

☐ Completeness

☐ Sensitivity analysis

☐ Metanngen annotation

▼ Model simulation

☐ Copasi

☐ JWS online

☐ Software launcher

▼ Parameter estimation

☐ Start

☐ User guide

Kinetic law [?] (* required information)

Formula [?]
(Enter formula with space like 'a + b / d'
instead of 'a+b/d')

kout * L&C

Parameter

Name	Role [?]	Value*	Unit [?]	Global [?]	Delete
kout	constant	0.2		false	delete

add new parameter or add global parameter: no global parameter defined

add new kinetic law:

Henri-Michaelis-Menten (irreversible)

Hill Cooperativity

Iso Uni Uni

Mass action (irreversible)

Mass action (reversible)

Reversible Hill

Reversible Michaelis-Menten

Substrate activation (irr)

Substrate inhibition (irr)

Substrate inhibition (rev)

Uni Uni

User support: example I

Predefined kinetic law equations

▼ Reactions

All reactions

vgp

vpglm

vpgi

vpfk

vald

vtpi

vgapdh

vpgk

vpgm

ven

vpk

vidh

vck

vadk

vatpase

vfout

▼ Refine & analyze model

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User guide

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▼ Save model

Assign formula and parameter variables for reaction vfout

The names and values of the parameter variables can be changed on the next page.

Iso Uni Uni (reversible)

Formula

$$V_f * (\text{substrate} - \text{product} / K_{eq}) / (\text{substrate} * (1 + \text{product} / K_{ii}) + K_{ms} * (1 + \text{product} / K_{mp}))$$

Compound

Compound name	Compound role	Name in formula
LAC	substrate	substrate
LACo	product	product

Note that the name in the formula will be automatically replaced by the compound name.

Parameter

Name	Name in formula	Value	Unit
Kms	Kms	1	mmol/ml
Kmp	Kmp	1	mmol/ml
Kii	Kii	1	mmol/ml

User support: example II

Annotation support (MIRIAM compliant)

▼ Model

Model description

Compounds

Global parameter

Rules

Function def.

Unit definitions

Annotations

Pathway map

▼ Compartments

All compartments

uVol

▼ Reactions

All reactions

J0

J1

J2

J3

J4

J5

J6

J7

J8

J9

J10

J11

J12

J13

J14

J15

compartments

reactions

compounds

kinetic laws

rules

function definitions

units

RDF annotation for reaction J0

⚠ The annotations were updated although the following error(s) were observed:

The id '00024' is not valid for KEGG Reaction (expected: 'Rid+\$').

#	Relationship	Resource	ID
0	is version of	Enzyme Nomenclature	4.1.1.39
1	is	KEGG Reaction	00024
2	- select -	- select -	
3	- select -	- select -	

add annotation rows

delete annotation values

update & save annotations

Online storage of models

(registration required)

J18
J19
J20

▼ Refine & analyze model

□ Completeness
□ Sensitivity analysis
□ Metannogen annotation

▼ Model simulation

□ Copasi
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□ Software launcher

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□ Start
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▼ Save model

□ View XML code
□ Save on disk
□ Save as project

► Resources

Registration
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Projects

#	Project name	Version	Created	Comment	Edit comment	Load project	Delete project
0	BIOMD0000000013.xml	1	2013-09-03		edit	load	delete

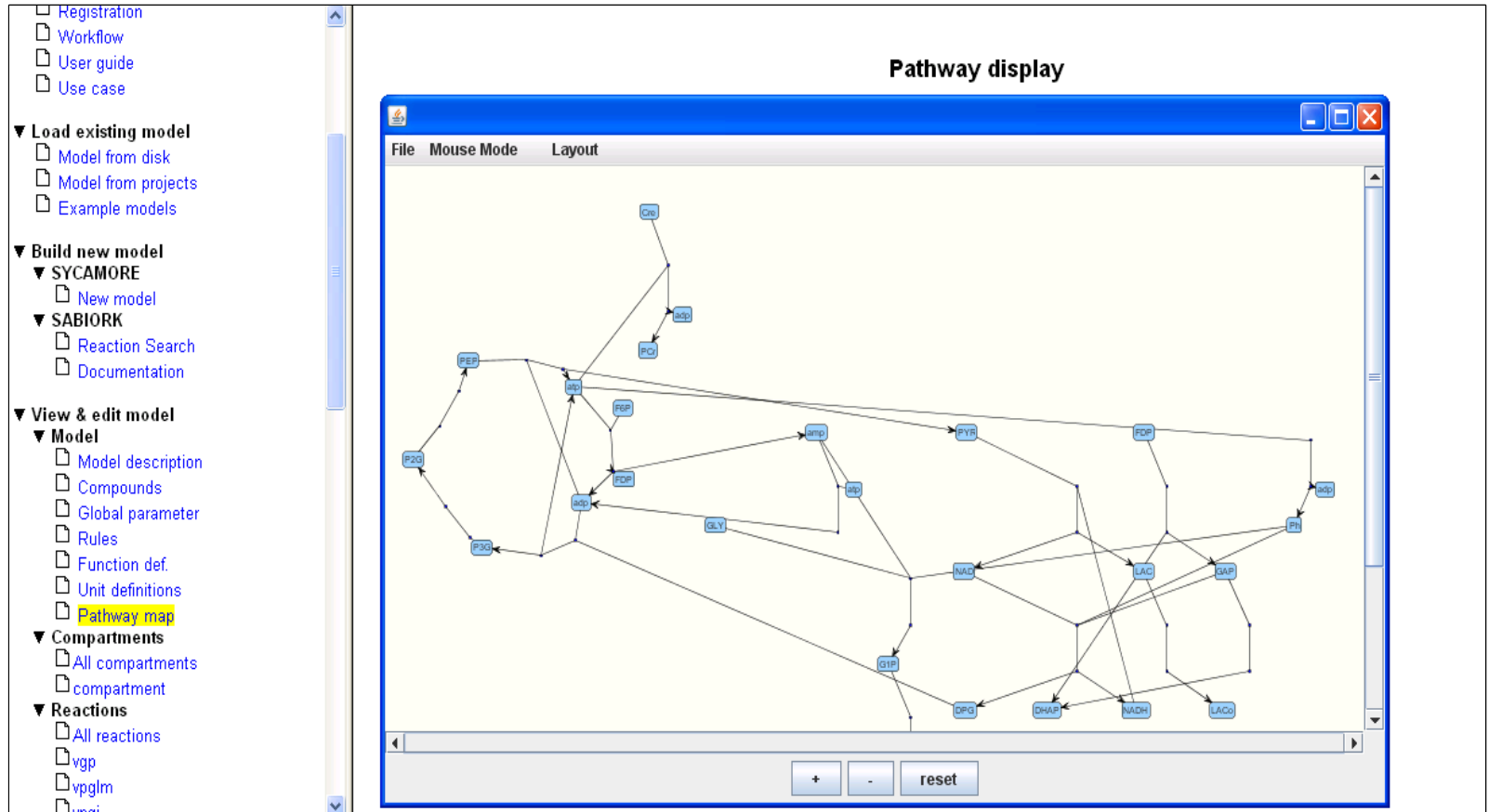
Save model as project:

Project name	Version	Comment
BIOMD0000000013.xml	1	

Save model as project

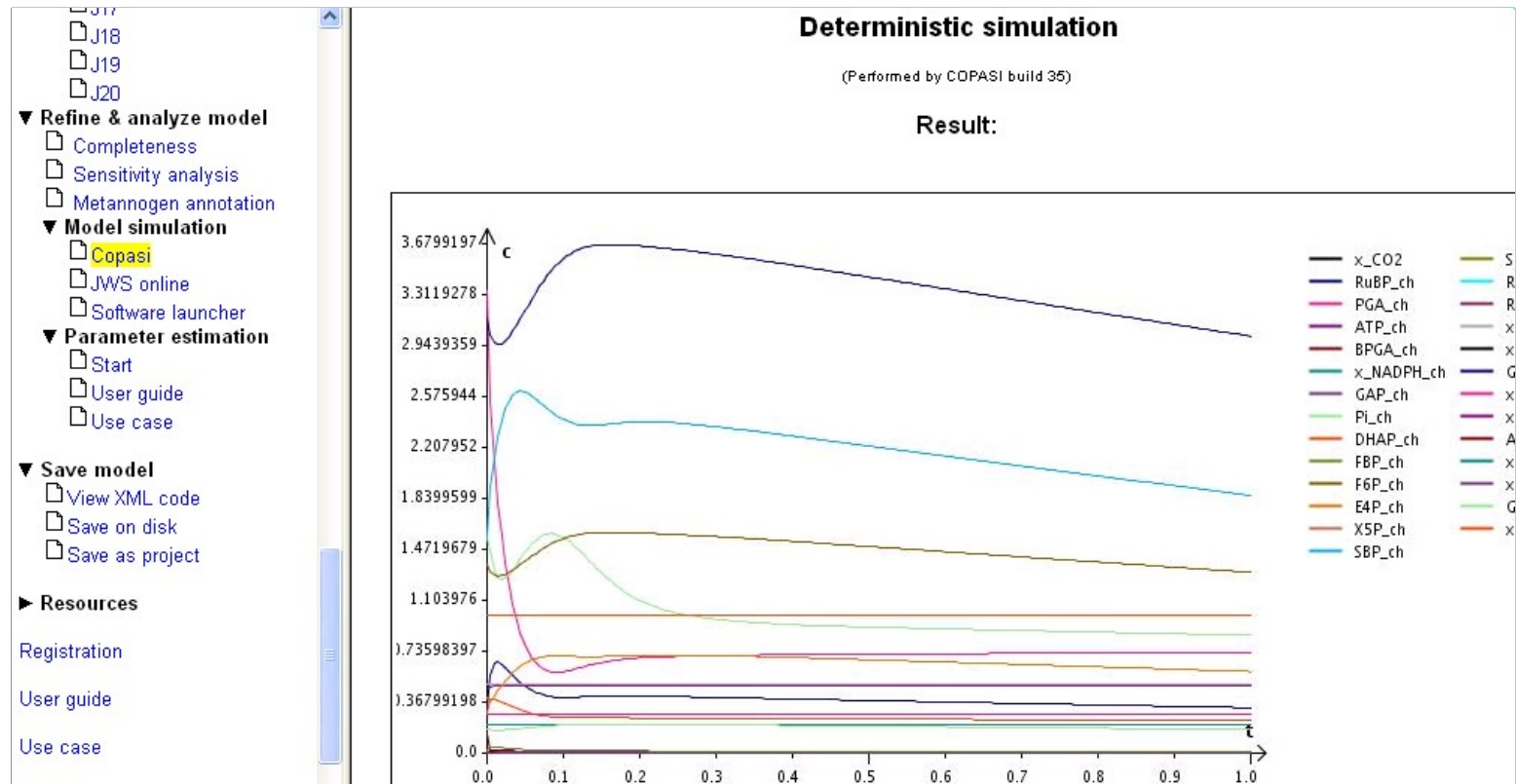
Pathway visualisation

(SBGN import/export/display in next release)



Model simulation

Time course simulation of metabolite concentrations (COPASI)



(J. Snoep <http://jjj.biochem.sun.ac.za/>)

▼ Refine & analyze model

- Completeness
- Sensitivity analysis
- Metatranscript annotation

▼ Model simulation

- Copasi
- JWS online**
- Software launcher

▼ Parameter estimation

- Start
- User guide
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▼ Save model

- View XML code
- Save on disk
- Save as project

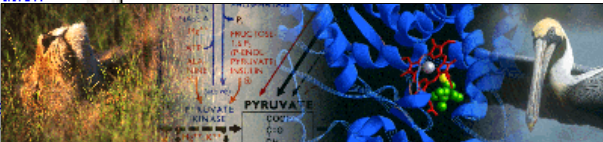
► Resources

- Registration
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JWS online model simulation

View and simulate model at JWS Online: [Model](#)

[Search](#) | [Upload](#) | [About](#) | [Help](#)




parameters

Name
Lighton
J0Rbcovm
J0Rbcokm
J0RbcokIPGA
J0RbcokIFBP
J0RbcokISBP
J0RbcokIPi
J0RbcokINADPH
J1TPIv
J1q4
J2FAlDnv

external variables

initial conditions

Schema



Sim State MCA Scan

Enter time period for plotting

Start End

Evaluate model

Save as SED-ML script

Select category to be plotted

Species Rates Other

Select species to be plotted

all none

RuBPch
PGAch

Sensitivity analysis

Find those parameters to which the concentrations of interest are most sensitive. These parameters are expected to be crucial for the models behaviour. (COPASI backend)

J11

J12

J13

J14

J15

J16

J17

J18

J19

J20

▼ Refine & analyze model

Completeness

Sensitivity analysis

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Start

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▼ Save model

View XML code

Save on disk

Save as project

► Resources

Scaled sensitivity analysis

value	(J0).Rbco_KIFBP	(J0).Rbco_KINADPH	(J0).Rbco_KiPGA	(J0).Rbco_KiPi	(J0).Rbco_KiSBP	(J0).Rbco_km	(J
0.530	-1000.290	-1021.640	-979.557	-1000.230	349.432	1152.640	
0.530	-1000.310	-1021.660	-979.552	-1000.230	349.470	1150.510	
1e-09	-1.050e-09	-1.373e-10	2.838e-10	3.919e-10	-1.524e-09	8.860e-10	
0.530	-1000.290	-1021.660	-979.557	-1000.230	349.219	1150.410	
0.550	-1000.440	-1023.000	-1047.480	-1000.250	469.181	1436.820	
0.490	6975.570	1413.600	-1168.910	-1019.490	-1354.480	358.339	
0.550	-1000.440	-1023.000	-1047.480	-1000.250	469.182	1436.820	
0.000	-1004.770	-996.931	-1361.620	-1000.000	-2362.470	11886.800	
0.166	2.862e-05	-0.003	-2.452e-06	-0.000	1.814e-05	0.004	
0.502	2.499e-05	-0.012	-9.960e-07	-0.000	1.018e-05	0.017	
0.550	-1000.440	-1023.000	-1047.500	-1000.250	469.200	1436.830	
0.550	-1000.440	-1023.000	-1047.480	-1000.250	469.184	1436.870	
0.499	2.540e-05	-0.013	-3.919e-07	-0.000	1.104e-05	0.018	
0.550	-1000.440	-1023.000	-1047.500	-1000.250	469.207	1436.850	
0.550	-1000.440	-1023.000	-1047.500	-1000.250	469.204	1436.840	
0.166	2.862e-05	-0.003	-2.452e-06	-0.000	1.814e-05	0.004	
0.090	-1990.560	-258.342	534.103	737.461	-2868.630	1667.370	
0.166	2.862e-05	-0.003	-2.452e-06	-0.000	1.814e-05	0.004	

Database supported modelling I

SABIO-RK: search for data

The screenshot displays the SABIO-RK Biochemical Reaction Kinetics Database search interface. On the left, a sidebar for SYCAMORE provides navigation options: SYCAMORE, Load existing model (Model from disk, Model from projects, Example models), Build new model (SYCAMORE: New model; SABIORK: Reaction Search, Documentation), and Miscellaneous tools. Below this is a View & edit model section with links for Model description, Compounds, Global parameter, and Rules.

The main content area features the SABIO-RK logo and a navigation bar with links: Home, Search, Web Services, News, Documentation, Publications, Statistics, Links, and About. The Search section includes a search bar with the text 'nadph', a magnifying glass icon, a Reset button, and a help icon. Below the search bar is an 'Advanced Search' button and a list of instructions: enter search term(s) as free text (like Google), press 'magnification glass' to start search, search results will be displayed below (scroll down !), select entries (mark checkboxes), if you want to export data, click the checkbox for each entry and finally click on the symbol in the upper right corner to proceed, and click button 'Send entries to SYCAMORE'.

On the right, the Filter Options panel allows filtering by Enzyme (Wildtype, Mutant, Recombinant), Kinetic Data (Rate Equation), Reaction (Transport Reaction), Environmental Conditions (pH: 0 - 14, Temperature: -10 C° - 115 C°), and Source (Direct Submission, Publication, BioModel, Entries inserted since: 14/10/2008).

At the bottom, there are buttons for Entry View, Reaction View, and Visual Search (beta). A summary line states: Total number of kinetic law entries found: 5193.

Database supported modelling I

SABIO-RK: data export

SYCAMORE

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 - ▼ SABIO-RK
 - Reaction Search
 - Documentation
 - Miscellaneous tools
- ▼ View & edit model
 - ▼ Model
 - Model description
 - Compounds
 - Global parameter
 - Rules
 - Function def.
 - Unit definitions

1 2 3 4 5 6 7 8 9 10 .. 347 Next

display 15 entries per page

Kinetic data	Reaction	Enzyme			Tissue	Organism	Parameter (besides concentration)	pH	Temperature	Add
		ECNumber	Protein	Variant						
▶	5,6,7,8-Tetrahydrofolate + NADP+ = H+ + Dihydrofolate + NADPH	1.5.1.3	P0ABQ4	wildtype	-	Escherichia coli	Kcat Km	15.0	7.0	<input checked="" type="checkbox"/>
▶	L-Arginine + NADPH + H+ + O2 = L-Citrulline + NADP+ + Nitric oxide	1.14.13.39		wildtype	epidermal cell	Aiptasia pallida	Km Vmax	25.0		<input type="checkbox"/>
▶	NADP+ + Isocitrate = CO2 + NADPH + 2-Oxoglutarate + H+	1.1.1.42	P33198	wildtype	heart	Sus scrofa	Km Vmax	25.0	7.4	<input type="checkbox"/>
▶	NADP+ + Isocitrate = CO2 + NADPH	1.1.1.42	P33198	mutant	heart	Sus scrofa	Km	25.0	7.4	<input type="checkbox"/>

add data to model

Search for reactions (scroll down to see the results), select kinetic data, click on 'entries to export' (upper right corner), then click button 'send data to SYCAMORE' and finally add the data to the model by clicking this button:

Database supported modelling II

SABIO-RK: data import into SYCAMORE

- J4
- J5
- J6
- J7
- J8
- J9
- J10
- J11
- J12
- J13
- J14
- J15
- J16
- J17
- J18
- J19
- J20
- reaction_0**
- ▼ Refine & analyze model
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- ▼ Save model

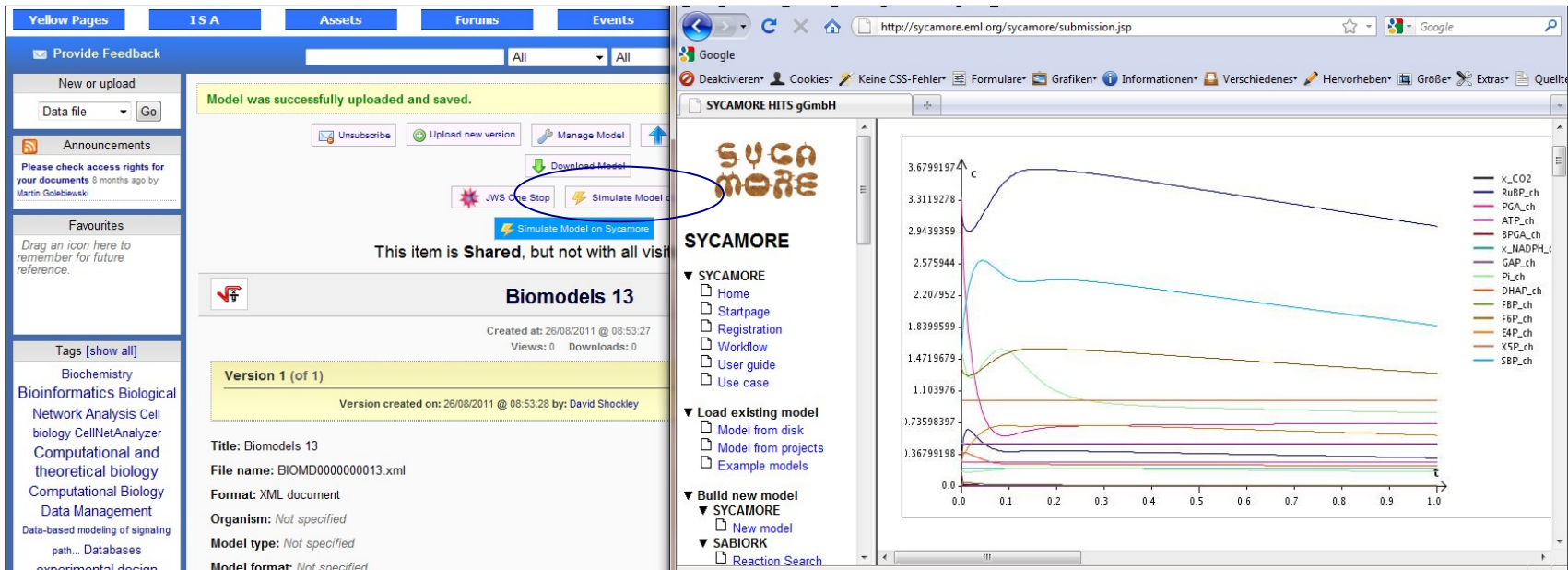
11	J11	G6P_ch <=> G1P_ch	true	edit
12	J12	Pi_ch + ADP_ch => ATP_ch	false	edit
13	J13	Ru5P_ch + ATP_ch => RuBP_ch + ADP_ch ; PGA_ch , Pi_ch	false	edit
14	J14	PGA_ch + ATP_ch => BPGA_ch + ADP_ch	false	edit
15	J15	ATP_ch + G1P_ch => x_Starch_ch + ADP_ch + Pi_ch ; PGA_ch , F6P_ch , FBP_ch	false	edit
16	J16	x_Starch_ch + Pi_ch => G1P_ch	false	edit
17	J17	FBP_ch => F6P_ch + Pi_ch	false	edit
18	J18	x_Pi_cyt + DHAP_ch => x_DHAP_cyt + Pi_ch ; PGA_ch , GAP_ch	false	edit
19	J19	x_NADPH_ch + BPGA_ch + x_Proton_ch => x_NADP_ch + GAP_ch + Pi_ch	false	edit
20	J20	SBP_ch => Pi_ch + S7P_ch	false	edit
21	reaction_0	Dihydrofolate + NADPH + H+ <=> NADP+ + 5,6,7,8-Tetrahydrofolate ; dihydrofolate reductase(Enzyme) wildtype DHFR	true	edit

Compounds

Name	Initial amount	Initial Concentration	Unit	Compartment	Boundary Condition	Edit
x_CO2	1.0	.	default	uVol	true	edit
RuBP_ch	0.33644	.	default	uVol	false	edit
PGA_ch	3.35479	.	default	uVol	false	edit
ATP_ch	0.49806	.	default	uVol	false	edit
BPGA_ch	0.14825	.	default	uVol	false	edit
x_NADPH_ch	0.21	.	default	uVol	true	edit
GAP_ch	0.01334	.	default	uVol	false	edit

Integration into VLN SEEK

Analysis of models stored in SEEK



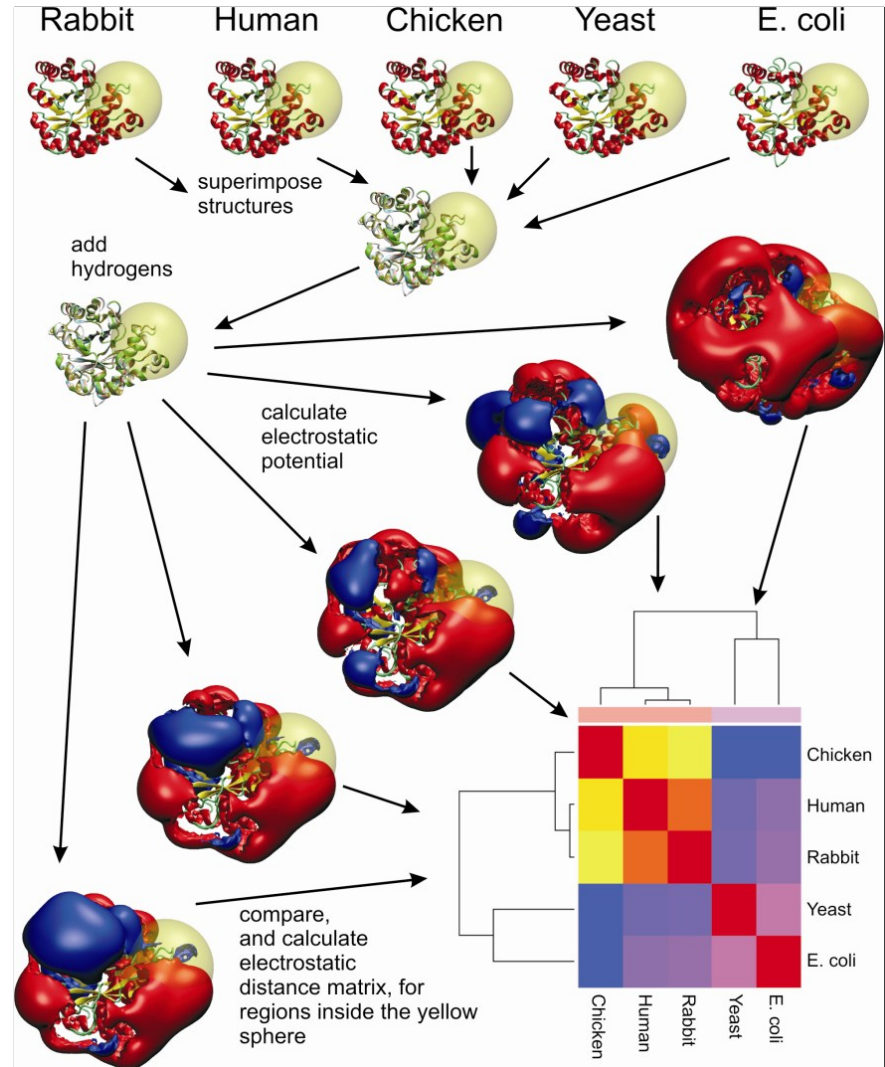
Parameter estimation: PIPSA

- Often, kinetic parameters for enzymes such as K_m or k_{cat}/K_m are not available from the desired species but have been measured for enzymes from other species
- The electrostatic potential is one of the key determinants of enzymatic catalysis
- PIPSA, **P**rotein **I**nteraction **P**roperty **S**imilarity **A**nalysis, can be used to aid the estimation of kinetic parameters, based on known parameters of similar species
- qPIPSA: UniProt ID of enzyme as starting point (SYCAMORE)
- webPIPSA: PDB files as starting point (Protein Data Bank structure file; pipsa.embl.org/pipsa/)
- qPIPSA: BMC Bioinformatics 2007, 8: 373
- webPIPSA: Nucleic Acid Research, doi:10.1093/nar/gkn181

Parameter estimation: PIPSA

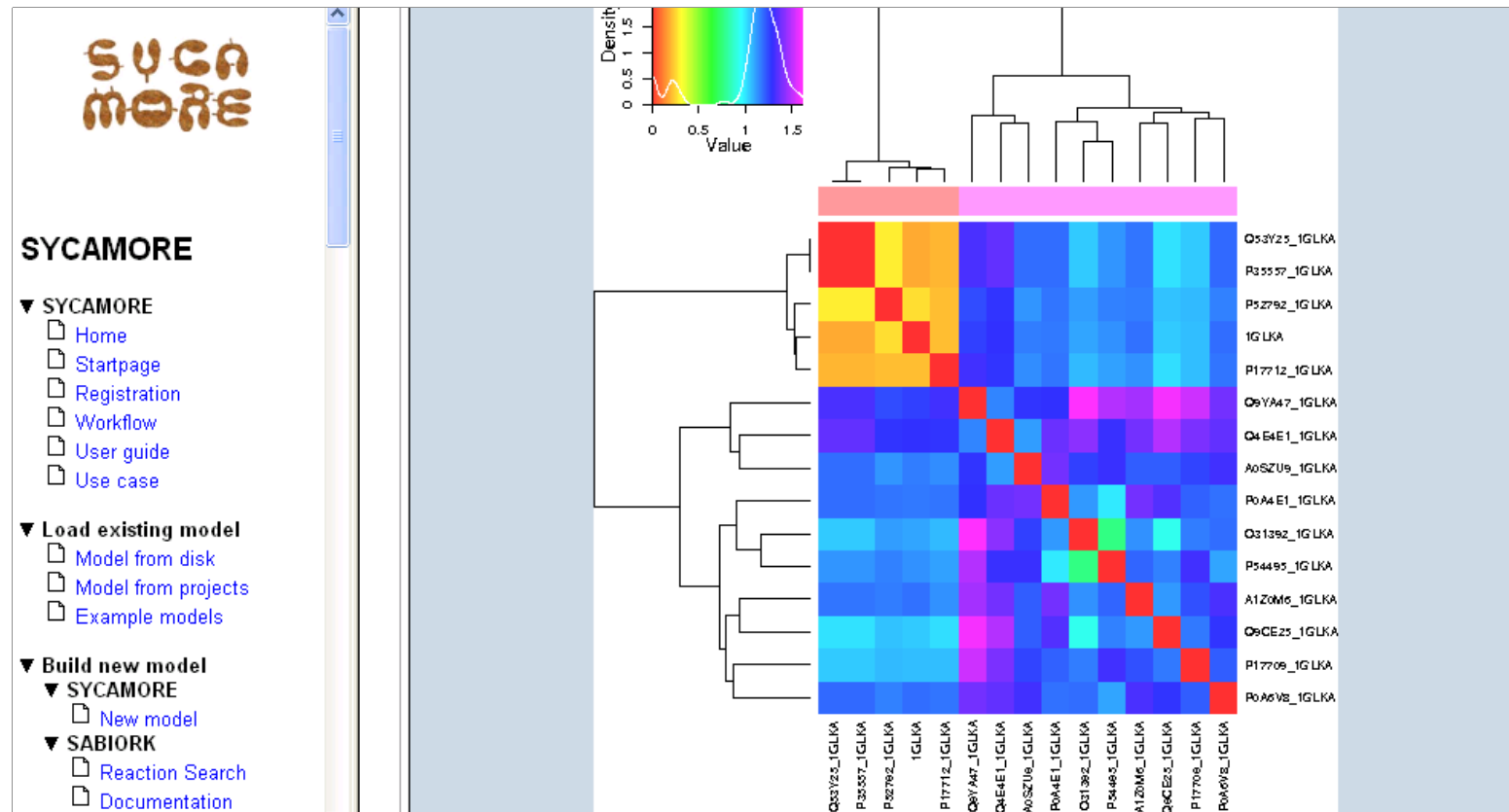
Schematic overview of the workflow employed in webPIPSA. The protein structures are a subset of the Triosephosphate Isomerase.

Output: heatmap, no numeric values



Parameter estimation: qPIPSA

Output: heatmap (no numerical values)



Summary features

- Model editing
- Loading, saving, storage of models
- Database supported modelling (SABIO-RK)
- Sensitivity analysis
- Pathway visualization
- Model simulation (COPASI, JWS online)
- Structure based parameter estimation (qPIPSA)

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