



U.S. Department of  
Health and Human  
Services



National Institutes  
of Health



National Heart, Lung,  
and Blood Institute

# QBT Quantitative Biology Tool

Integrative Computational Biology Lab,  
NHLBI, NIH

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ICSB 2008



# What distinguishes QBT from other SBML-compliant tools?

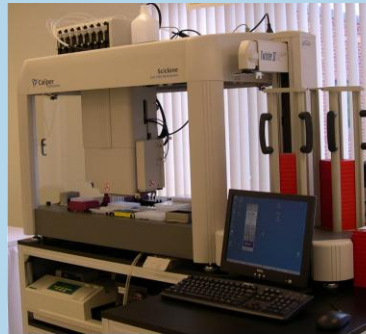
- Primarily a tool for non-computational biologists to construct, annotate and evaluate models.
- Designed to support projects with high-throughput data sets (microarrays, sequencing, GWAS, proteomics)
- Intelligent tools to access Ensembl (and other) annotation data
- Workgroup server
- API to add new data types and helper apps

# NHLBI Intramural Research

50 Principal Investigators  
in 5 centers

Genomics /  
Microarray Core  
2500 arrays/yr

Proteomics Core  
40 Projects /  
month



### ABI 4700 MALDI-TOF/TOF MS



A high-speed, high-sensitivity instrument with a sample autoloader that allows high throughput sample analysis...

### Ettan Gel Spot Handling Workstation



The workstation carries out automated gel spot-picking, in-gel digestion, and sample/matrix spotting onto MALDI-plates ...

### Finnigan FT-ICR LC-MS/MS



The Finnigan FT-ICR Mass Spectrometer displays very high mass resolution ( $>100,000$  at  $m/z=500$ ) and mass accuracy ( $<1-2$  ppm) and is valuable for differentiating structurally similar peptides...

### Finnigan ProteomeX workstation, an LC-MS/MS system



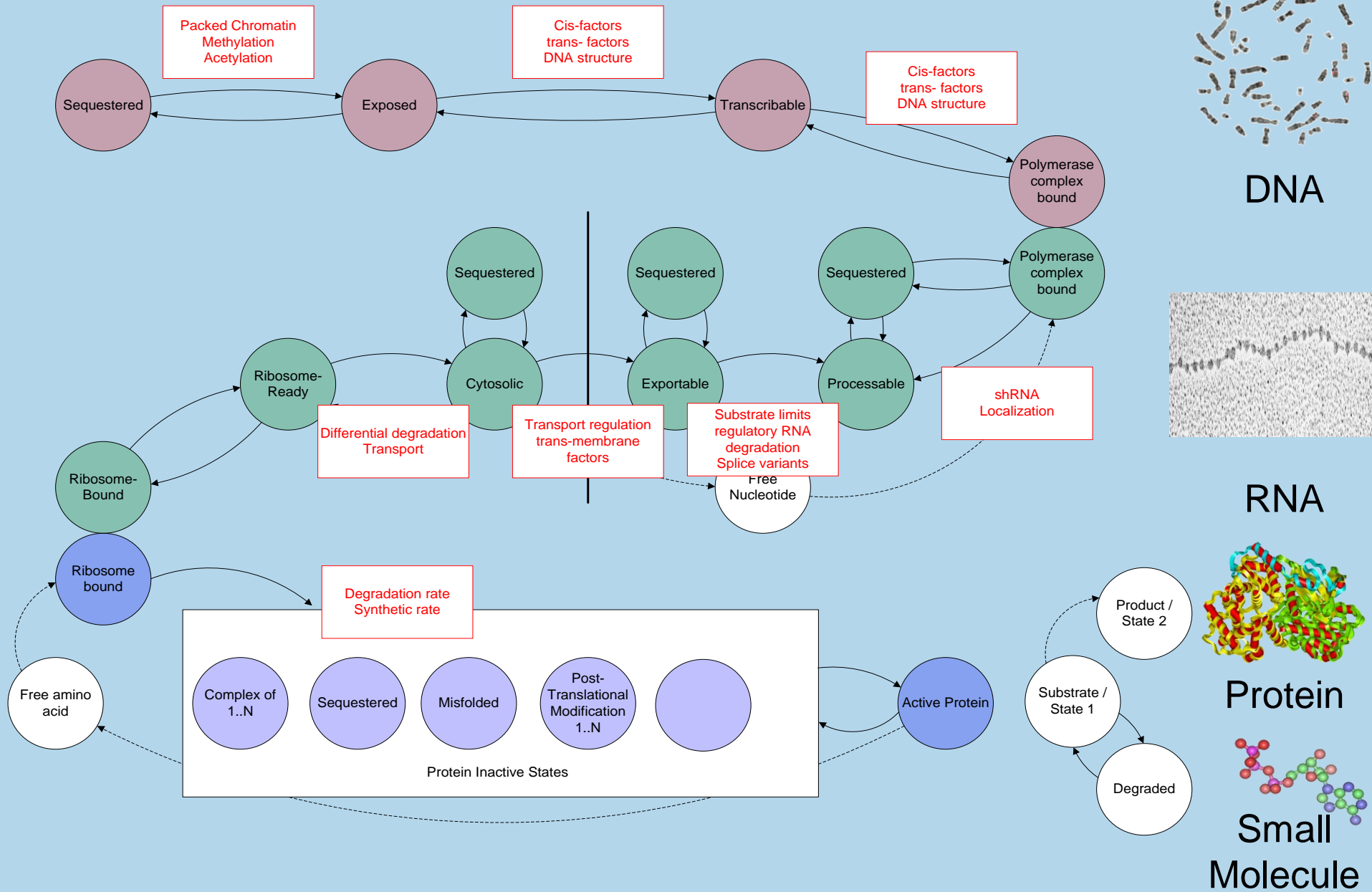
The system performs 1D- or 2D-LC/MS analysis which consists of a Surveyor Autosampler, two Surveyor LC pumps, and Deca XP plus ion-trap mass spectrometer. It uses BioWorks for database search.

### Shimadzu Axima MALDI TOF MS



The superior performance of the AXIMA-CFR™ plus with improved resolution and mass accuracy provides increased confidence in mass fingerprint for protein ID.

# Biologically relevant sites of regulation (far from exhaustive)



# Ontology-driven Model Editor

The screenshot displays the QBT Quantitative Biology Tool interface. The main window is titled "QBT Quantitative Biology Tool 200805300101" and features a menu bar with "File", "Edit", "Model", "Data", "Analyze", "Graph", "Tools", "Window", and "Help".

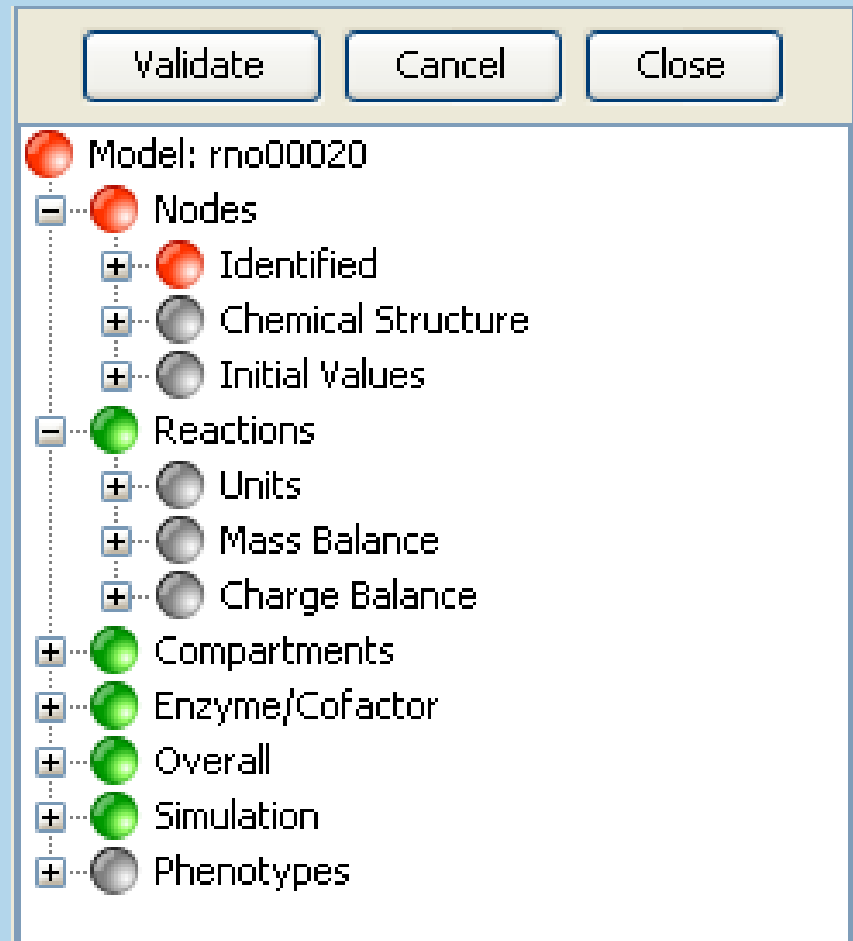
The interface is divided into several panels:

- Left Panel (QBT Explorer):** Shows a hierarchical tree structure with folders for "Data", "Models", "Analysis", "Literature", "Web Query", and "R Scripts". Under "Models", "RNOTCAV4" is selected, showing sub-items for "Nodes", "Edges", "Parameters", "Events", "Simulation", "Settings", and "Results-RNOTCAV4".
- Top Panel (Runtime):** Contains tabs for "mito1", "RNOTCAV4", "Settings", "Results-RNOTCAV4", and "Graphical Results".
- Central Canvas:** Displays a diagram of a mitochondrial membrane. The membrane is represented by a green band, with the "Intermembrane Space" above it and the "Matrix" below it. Three complexes are shown: "Complex I" (blue oval), "Complex III" (brown oval with a "P" above it), and "Complex IV" (blue oval). A blue arrow points to the membrane.
- Right Panel (Palette):** Titled "Biochemistry", it contains various shapes representing biological entities: "Small Molecule" (oval), "Protein" (rectangle), "Receptor" (inverted triangle), "Ion Channel" (rectangle with a vertical bar), "Gene" (rectangle), "RNA" (trapezoid), "Small Ion" (circle), "Other" (triangle), "Phenotype" (trapezoid), and "Compartment" (rectangle).
- Bottom Panel (Log Window):** Shows the text "Jacobian not requested".

A context menu is open over the diagram, listing the following actions: "Open", "Edit", "Format", "Copy", "Paste", "Delete", "Identify this for searching", "Find Related Reactions", "Find Related Pathways" (highlighted), "Find Related Processes", and "Search PubChem".

# Editor features

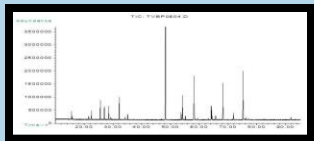
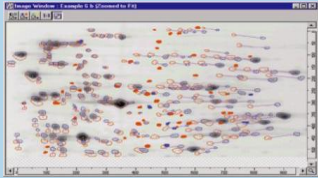
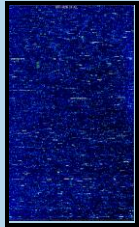
- Nested models
- User defined shape, color, etc.
- SBGN mode
- Images as nodes
- Ontology-driven model checker w/suggested fixes



# Import data. QBT ontology relates searchable entities with associated queries. (e.g. identify enzyme activity)

The screenshot displays the QBT Quantitative Biology Tool interface. The main window shows a table with columns for various biological parameters and numerical values. The table is titled 'Flux Balance Analysis:'. The columns include 'TrimProtei...', 'NCBI Gen...', 'EC Number', 'BrainAveN', 'HeartAveN', 'KidneyAveN', 'LungAveN', 'B1', 'B2', 'B3', 'B4', 'B5', and 'B6'. The rows contain numerical data for various identifiers like 'IPI00212015', 'IPI00214665', etc.

TrimProtei...	NCBI Gen...	EC Number	BrainAveN	HeartAveN	KidneyAveN	LungAveN	B1	B2	B3	B4	B5	B6
IPI00212015	24158	1.3.99.3	0.945556451	1.004024575	1.020056477	1.030362497	14.695802	14.6978786	14.7024687	15.2771669	14.6886411	14.7050676
IPI00214665	24159	2.3.3.8	1.008602774	0.990553647	0.993346553	1.007497027	16.2887709	16.2812512	16.5480514	16.2019111	16.4133545	16.5623736
IPI00327244	24170		1.010553197	1.02687508	0.981354283	0.98121744	14.9708814	14.8102314	15.0064436	15.0836925	14.9702484	15.0477791
IPI00192626	24171		1.019157364	1.003929842	0.976593584	1.00031921	15.551335	15.4983952	15.684924	15.0524627	15.2732415	15.490858
IPI00331983	24172	1.1.1.1	1.073197492	0.982230097	1.032765524	0.911806887	17.1978011	16.9717947	17.1754206	15.9613536	17.1188575	16.7169456
IPI00191740	24177		1.019719542	0.978260191	0.98155685	1.020463417	15.2634272	14.6083006	14.8767871	14.7823522	15.5051902	15.4855403
IPI00209744	24179		0.997449012	0.990433857	1.032214589	0.979902542	14.8125141	14.9600413	14.8618314	14.6313667	14.2432324	15.0858385
IPI00210351	24183	2.7.4.3	1.036008842	0.989567726	1.003985442	0.97043799	15.6462495	15.5053418	15.8130054	15.3093943	15.6741551	15.6698375
IPI00230857	24184	2.7.4.3	0.967439899	0.986766011	1.019281022	1.026513068	15.0230231	14.8496158	15.0091538	15.0370324	15.0257972	14.8592611
IPI00212844	24185	2.7.11.1	0.953476105	1.004168271	1.021348198	1.021007425	15.8607727	16.0864136	15.5665569	16.7349839	15.9785923	16.1066871
IPI00191737	24186		0.987669263	1.005834493	0.968800989	1.037695255	15.288693	15.6019584	15.6381403	15.7525551	15.5114082	15.5272701
IPI00231734	24189	4.1.2.13	1.074276974	1.011175151	0.986067007	0.928480868	16.6243781	16.5934152	16.8725201	16.2462944	16.667024	16.9183296
IPI00231736	24191	4.1.2.13	1.062772518	0.995802361	0.978990207	0.962434913	16.1945689	16.1196605	16.3635308	15.6384476	16.2274324	16.2674191
IPI00327516	24197	3.1.3.1	0.99046433	1.017929882	1.003931832	0.988091852	15.628611	15.1866066	15.2637517	15.1913041	15.2763424	15.4444152
IPI00188859	24205		1.001248299	1.005345095	0.996517977	0.996888629	15.2151344	15.050298	15.1815518	14.9067513	15.0515273	15.2009473
IPI00203532	24206	3.4.19.1	1.033361107	0.996412675	1.011225913	0.959000305	16.2198668	16.3185754	16.5992268	16.0648939	16.5204017	15.9991082
IPI00206600	24207		0.973886503	1.016038502	0.978777605	1.03129739	13.432148	13.5542673	13.6982507	14.0830851	13.6927983	13.6245036
IPI00326305	24211	3.6.3.9	1.029064065	0.970810937	1.027240871	0.972884127	16.1556648	15.9612729	15.9771657	15.4448736	16.0638383	16.1336965
IPI00205693	24212	3.6.3.9	1.051288056	0.97764751	0.996586665	0.97447777	16.2646672	16.1428138	15.9828993	15.4054038	16.2587907	16.1952544
IPI00231451	24213	3.6.3.9	1.057218208	0.983276662	0.989248187	0.970256943	16.3250159	16.1530423	16.0988162	15.5021608	16.2551271	16.2699398
IPI00203440	24214		1.005200012	1.008554069	1.010455151	0.975790768	16.1330154	15.9953784	15.9149725	15.9455544	16.1679749	15.6641152
IPI00194875	24215	3.6.3.8	1.025789344	0.99663349	0.990832728	0.986744438	15.5197982	15.3713583	15.5551115	15.172165	15.4484661	15.599497
IPI00231316	24215	3.6.3.8	1.026948362	1.001230147	0.985507528	0.986313962	15.3504723	15.2181962	15.3103201	14.9996963	15.3035373	15.3718445
IPI00365705	24216		1.036433416	0.99666753	1.006461692	0.960437362	16.0656025	15.848909	15.7967669	15.4235199	15.9337947	15.86312
IPI00324094	24218	3.6.3.4	1.098315836	0.997651227	0.993561147	1.025629265	13.7803271	13.8985242	13.688218	13.8844808	14.3517447	13.8601081
IPI00209973	24235		0.990320366	1.048939882	0.972515321	0.988224431	13.0981355	12.955683	13.2493685	13.2812252	13.0690473	12.8305945
IPI00365582	24240		0.987464489	1.020326228	0.977231177	1.014978107	15.2557403	15.3286646	16.0699028	15.5968977	15.0289763	15.4845695
IPI00211711	24241		1.011344328	1.03732309	0.981754774	0.969577808	15.7515201	15.9923378	15.3936835	15.7995254	15.6098531	15.4617083
IPI00231955	24244		1.100055023	0.955327294	1.000283651	0.944334032	18.0944415	18.0065328	18.3323665	16.5280662	17.9324412	18.1256005
IPI00211185	24245	2.7.11.17	1.070588839	0.979654083	0.971055816	0.978701263	16.8362829	16.6214602	16.7562067	15.7963877	16.6634517	16.7273957
IPI00212226	24246	2.7.11.17	1.083738486	0.961183595	0.973923935	0.981153984	17.1431241	16.9407522	17.1234094	15.8890957	16.958038	17.0434605
IPI00231742	24248	1.1.1.1.6	0.962280645	0.963215851	0.98328492	1.091218584	14.4490256	14.4225321	14.5178372	14.4752521	14.48397	14.4857942
IPI00214299	24250	4.2.1.22	0.973554499	1.151200157	0.930046805	0.945198539	14.7964359	14.5980534	14.7183893	16.6121642	14.8209219	14.7385576
IPI00189627	24258		0.997917821	1.027369626	0.978201569	0.996510983	16.4213602	16.422492	16.1631088	16.4024207	16.0660452	16.0233143
IPI00210280	24267	2.1.1.6	1.019681772	0.990405821	1.006188315	0.983724092	15.2795119	15.1605353	15.14136478	14.8377854	15.1815884	15.3462483
IPI00325847	24268	1.16.3.1	0.968195178	1.035128517	1.000085369	0.996590936	14.727652	14.8922257	14.6969835	15.0722933	14.7068136	14.61004
IPI00327713	24269	3.4.17.1	0.968930808	1.024593134	0.972707152	1.033768907	14.544964	14.7260949	14.4273232	15.0473414	14.6910291	14.6805175
IPI00193131	24282		0.964726983	1.035846266	1.008879609	0.990547142	19.0358059	18.9230252	18.9052963	19.3456826	19.3054504	19.019408
IPI00190771	24284		1.018695491	0.986882937	1.007567646	0.986853876	16.8043067	16.5151313	16.539317	16.1521166	16.6790932	16.6055785



# Pathways rank-ordered by representation in data set (KEGG, GO [then Reactome])

QBT Quantitative Biology Tool 200801291616

File Edit Model Window Help

QBT Expl... Runtime

MassSpecSurvey080620(CSV) Rank related pathways-MassSpecSurvey080620(CSV)

Data Source

MassSpecSurvey080620(CSV)

TrimProteinID

NCBI GeneID

EC Number

B1

B2

B3

Recommended Linking Method

(to connect data to pathways' enzymes)

EC Number

Link column EC Number

Species R. norvegicus

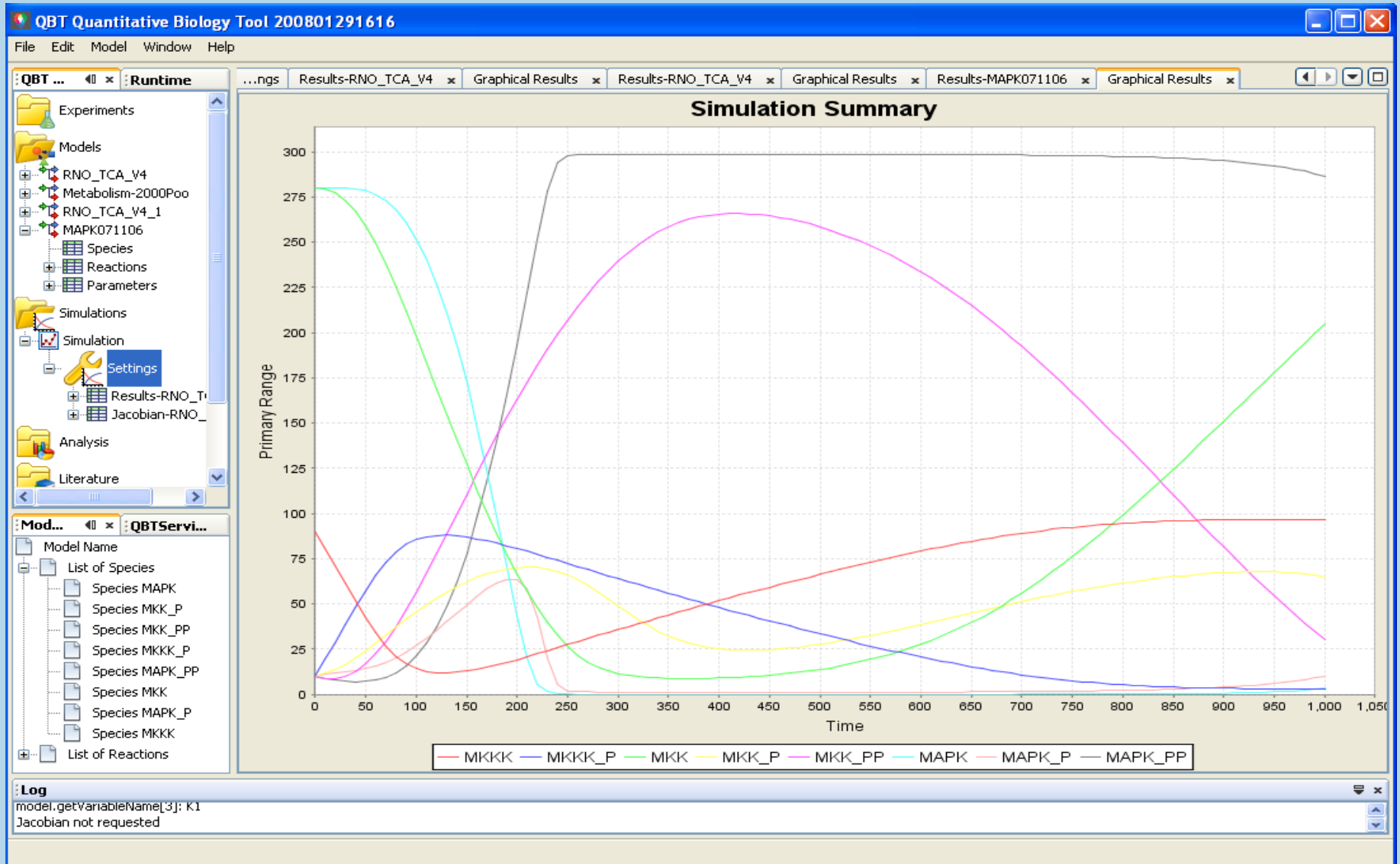
Apply Selections

Show Matching EC Numbers

Rank Related Pathways

Pathway	Source Database	Type	Pathway ID	Proteins in Pathway	Mapped From...	Fraction Mapped	p-value
Valine, leucine and isoleucine degradation	KEGG	Metabolic	rno00280	26.0	21.0	0.810	4.73e-06
Insulin signaling pathway	KEGG	Signaling	rno04910	33.0	21.0	0.640	0.00223
PPAR signaling pathway	KEGG	Signaling	rno03320	23.0	18.0	0.780	4.53e-05
Glycolysis / Gluconeogenesis	KEGG	Metabolic	rno00010	25.0	17.0	0.680	0.00151
Propanoate metabolism	KEGG	Metabolic	rno00640	19.0	16.0	0.840	1.42e-05
Fatty acid metabolism	KEGG	Metabolic	rno00071	20.0	16.0	0.800	5.92e-05
Glycine, serine and threonine metabolism	KEGG	Metabolic	rno00260	29.0	16.0	0.550	0.0403
Purine metabolism	KEGG	Metabolic	rno00230	41.0	16.0	0.390	0.543
GnRH signaling pathway	KEGG	Signaling	rno04912	16.0	15.0	0.940	5.36e-07
Butanoate metabolism	KEGG	Metabolic	rno00650	21.0	15.0	0.710	0.00104
MAPK signaling pathway	KEGG	Signaling	rno04010	15.0	14.0	0.930	1.34e-06
Pyruvate metabolism	KEGG	Metabolic	rno00620	18.0	14.0	0.780	0.000268
Adipocytokine signaling pathway	KEGG	Signaling	rno04920	15.0	13.0	0.870	3.14e-05
Calcium signaling pathway	KEGG	Signaling	rno04020	17.0	13.0	0.760	0.000559
Glycan structures - biosynthesis 1	KEGG	Signaling	rno01030	45.0	13.0	0.290	0.942
Gap junction	KEGG	Signaling	rno04540	12.0	12.0	1.00	0.00
Long-term depression	KEGG	Signaling	rno04730	13.0	12.0	0.920	8.33e-06
VEGF signaling pathway	KEGG	Signaling	rno04370	14.0	12.0	0.860	7.31e-05
beta-Alanine metabolism	KEGG	Metabolic	rno00410	18.0	12.0	0.670	0.00701
Tyrosine metabolism	KEGG	Metabolic	rno00350	20.0	12.0	0.600	0.0254
Tryptophan metabolism	KEGG	Metabolic	rno00380	28.0	12.0	0.430	0.246

# Basic simulation / data player



# Simple Flux Analysis across experimental conditions

QBT Quantitative Biology Tool 200801291616

File Edit Model Window Help

QBT ... Runtime MAPK071106 x Species-MAPK071106 x Settings x Results-MAPK071106 x Graphical Results x MassSpecSurvey080620(CSV) x Flux Balance Analysis: x

Experiments

- Data 1
- Data 2
- MassSpecSurvey080620

Models

- RNO\_TCA\_V4
- Metabolism-2000Poo
- RNO\_TCA\_V4\_1
- MAPK071106
- Species
- Reactions
- Parameters

Simulations

- Simulation
- Settings
- Results-RNO\_T...
- Jacobian-RNO\_...

Model

RNO\_TCA\_V4

Use model kinetics  
 Use only mass action kinetics  
 Add mass action kinetics as needed

Data Source

MassSpecSurvey080620(CSV)

TrimProteinID

NCBI GeneID

EC Number

B1

B2

B3

Recommended Linking Method

(to match your data to model's enzymes)

EC Number

Link Column EC Number

Apply Selections

Flux Analysis Results

Type	Name	Link	Base Flux/Qty	BrainAveN	HeartAveN	KidneyAveN	LungAveN
Input	CoA		-4.00	1.01	0.995	1.00	0.997
Input	(S)-Malate		-2.00	1.03	1.01	0.981	0.980
Input	Succinate		-3.00	0.987	0.997	1.01	1.00
Input	Citrate		-4.00	1.01	1.00	0.996	0.993
Input	Pyruvate		-1.00	0.966	0.952	1.03	1.05
Input	Enzyme N6-(dihy...		-1.00	0.994	1.02	1.00	0.987
Intermediate	Isocitrate		-2.00	1.02	1.00	0.999	0.979
Intermediate	2-Oxoglutarate		1.00	1.04	1.01	0.998	0.958
Intermediate	Thiamin diphosph...		0.00	1.00	1.00	1.00	1.00
Intermediate	Oxalosuccinate		0.00	1.00	1.00	1.00	1.00
Intermediate	Oxaloacetate		3.00	1.04	0.983	1.00	0.969
Intermediate	3-Carboxy-1-hyd...		0.00	1.00	1.00	1.00	1.00
Intermediate	Enzyme N6-(lipoyl...		2.78e-17	-2.07e+14	6.06e+14	6.95e+13	-4.69e+14
Output	[Dihydropolylisi...		1.00	1.00	1.00	1.00	1.00
Output	CO2		4.00	0.989	1.01	0.993	1.01
Output	cis-Aconitate		2.00	1.00	1.00	1.00	1.00
Output	Succinyl-CoA		2.00	0.990	0.989	1.01	1.01
Output	Acetyl-CoA		2.00	1.02	1.00	0.992	0.986
Output	Phosphoenolpyru...		1.00	0.917	1.02	0.974	1.09
Output	Fumarate		2.00	0.998	1.01	1.00	0.990
Protein	succinate---CoA li...	6.2.1.5	1.00	0.997	1.01	1.00	0.994
Protein	succinate---CoA li...	6.2.1.4	1.00	0.984	0.968	1.03	1.02
Protein	isocitrate dehydr...	1.1.1.41	1.00	1.04	1.01	0.998	0.958
Protein	isocitrate dehydr...		1.00	1.00	1.00	1.00	1.00
Protein	phosphoenolpyru...	4.1.1.32	1.00	0.917	1.02	0.974	1.09
Protein	ATP citrate synth...	2.3.3.8	1.00	1.01	0.991	0.993	1.01
Protein	dihydropolyl deh...	1.8.1.4	1.00	0.994	1.02	1.00	0.987
Protein	malate dehydrog...	1.1.1.37	1.00	1.04	1.01	0.976	0.973
Protein	citrate (5i)-synth...	2.3.3.1	1.00	1.03	1.01	0.991	0.964
Protein	pyruvate carbox...	6.4.1.1	1.00	0.966	0.952	1.03	1.05
Protein	succinate dehydr...	1.3.5.1	1.00	0.981	1.01	1.01	0.993
Protein	fumarate hydrat...	4.2.1.2	1.00	1.01	1.01	0.986	0.987
Protein	aconitate hydrat...		1.00	1.00	1.00	1.00	1.00

Log

Selected model file location: I:\Documents and Settings\BillingE\My Documents\QBT\RNO\_TCA\_V4.xml

# Novel aspects of QBT

- Use of ontology to manage new data types and user interactions
- Ability to add new data types and methods through API (add owl content and jar)
- Ability to associate helper applications
- Database access includes aggregator functions to combine user data with Ensembl and other sites' data
- Interactive access to R environment

# Availability:

2008: Intramural (Beta)

3/2009: General Availability

## Acknowledgements

### Laboratory of Cardiac Energetics

John Legato

Robert Balaban

Vinodh Chandrasekaran

Thor Johnson

Durga Penmatsa

### Laboratory of Kidney and Electrolyte Metabolism

Vinay Kumar

Mark Knepper

### Laboratory of Computational Biophysics

Bernard Brooks

Richard Pastor