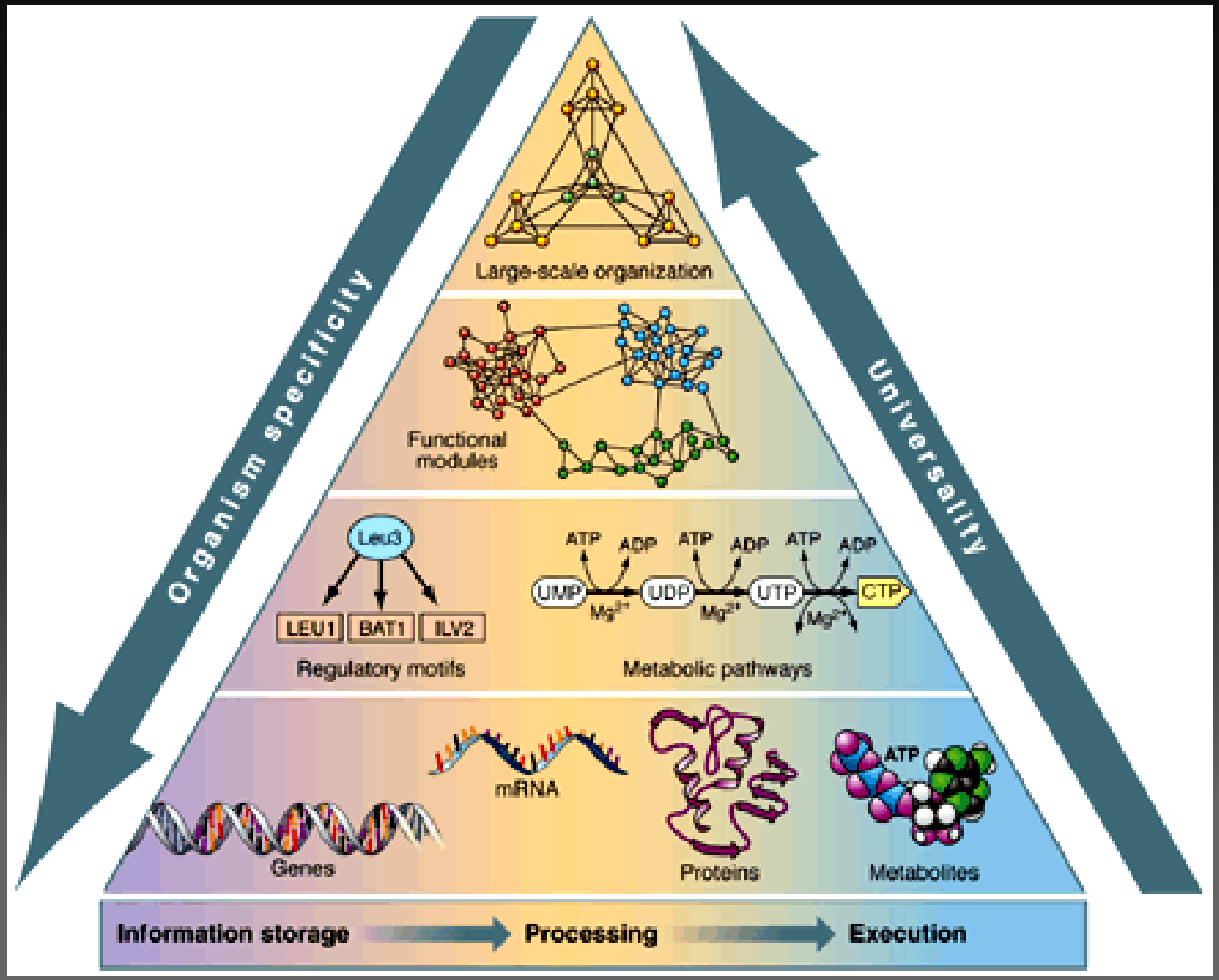
Higher-order systems

Part L

Higher-order systems

- Modeling and reconstructing molecular pathways
- Protein interaction information
- Higher-order systems

Higher-order systems

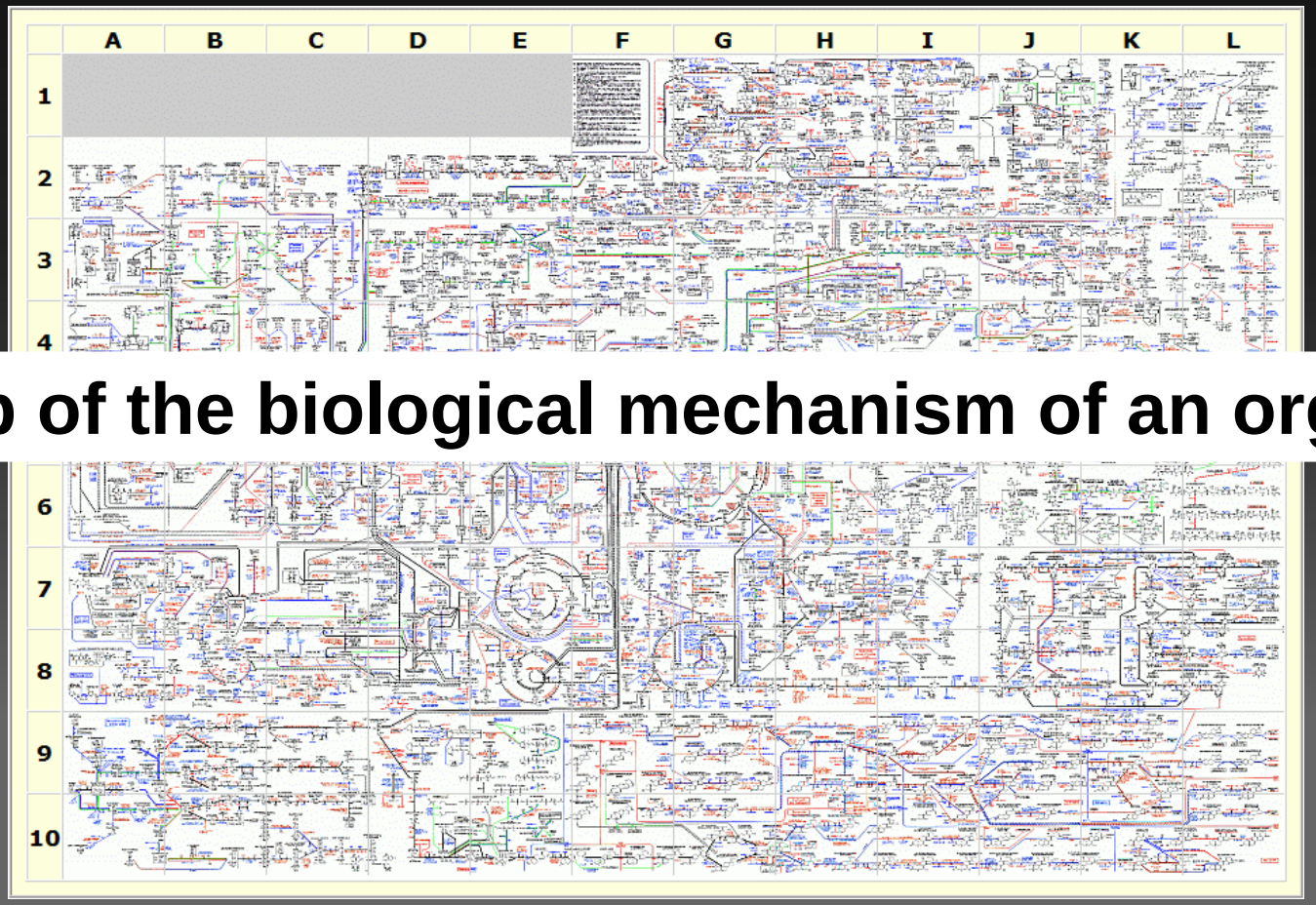


Molecular pathways

- What is molecular pathways
- Types of molecular pathways
- Why study pathways and networks
- What information is needed
- Inferring pathways and networks
- Pathway and cellular simulations

Molecular pathways

- What is molecular pathways



A map of the biological mechanism of an organism

Metabolic Pathways *ExPASy,http://www.expasy.org/cgi-bin/show_thumbnails.pl,*

Molecular pathways

- What is molecular pathways
- Types of molecular pathways
- Why study pathways and networks
- What information is needed
- Inferring pathways and networks
- Pathway and cellular simulations

Molecular pathways

- Types of molecular pathways (networks)

- **Metabolic Pathways**
  - is a series of chemical reactions occurring within a cell. In each pathway a principal chemical is modified by chemical reactions. These reactions are accelerated, more accurately catalyzed, by enzymes. Dietary minerals, vitamins and other cofactors are often needed by the enzyme to perform its task

- **Metabolic network**
  - is the complete set of metabolic and physical processes that determine the physiological and biochemical properties of a cell. As such, these networks comprise the chemical reactions of metabolism as well as the regulatory interactions that guide these reactions.

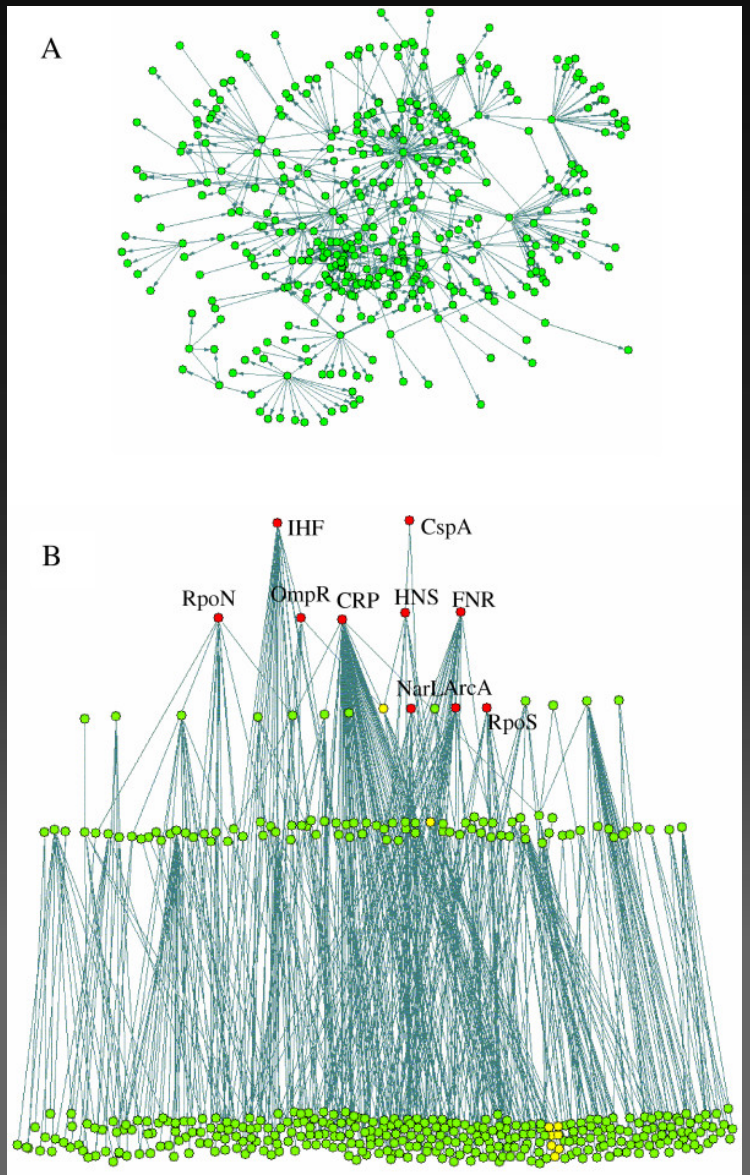
- **Signal Transduction Pathways**
  - Signal transduction is the study of how cells control their own and each others' behaviors through chemical signals

- **Regulatory Pathways (Gene Regulatory Network)**
  - is a collection of DNA segments in a cell which interact with each other (indirectly through their RNA and protein expression products) and with other substances in the cell, thereby governing the rates at which genes in the network are transcribed into mRNA.

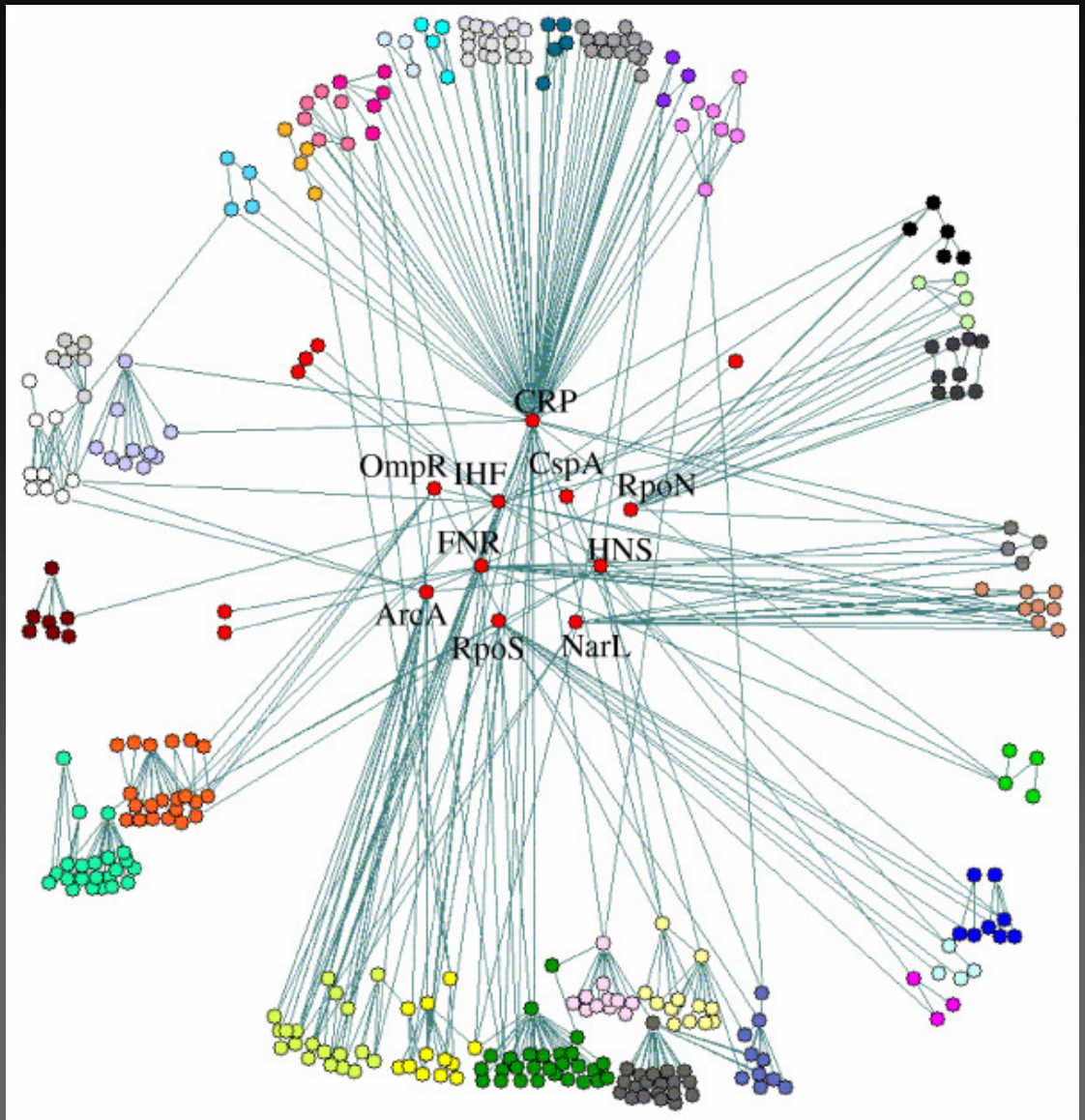
Molecular pathways

- Pathway diagrams
- Graphical modelers
- Pathway databases
- Pathway representation

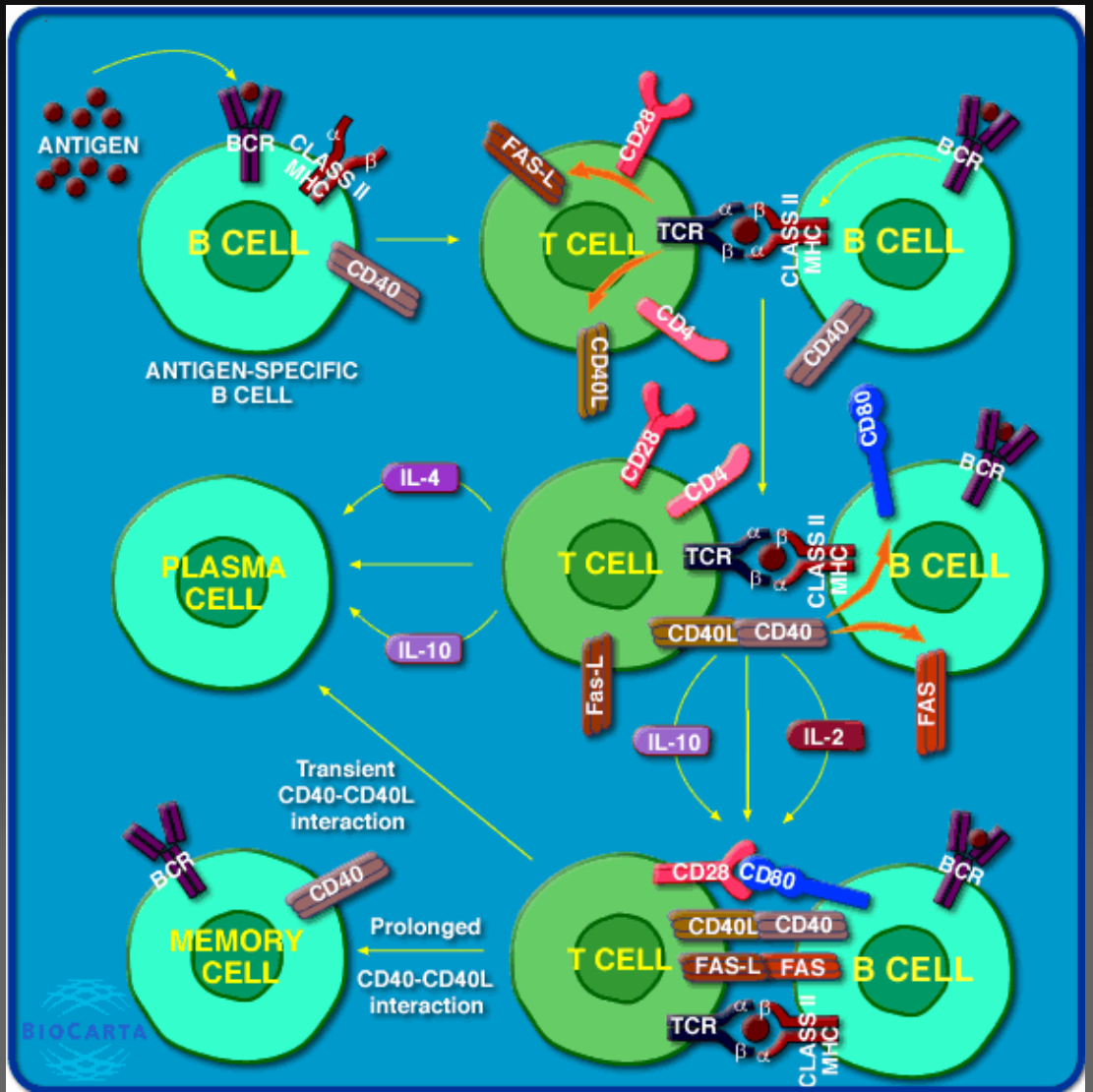
Pathway diagrams



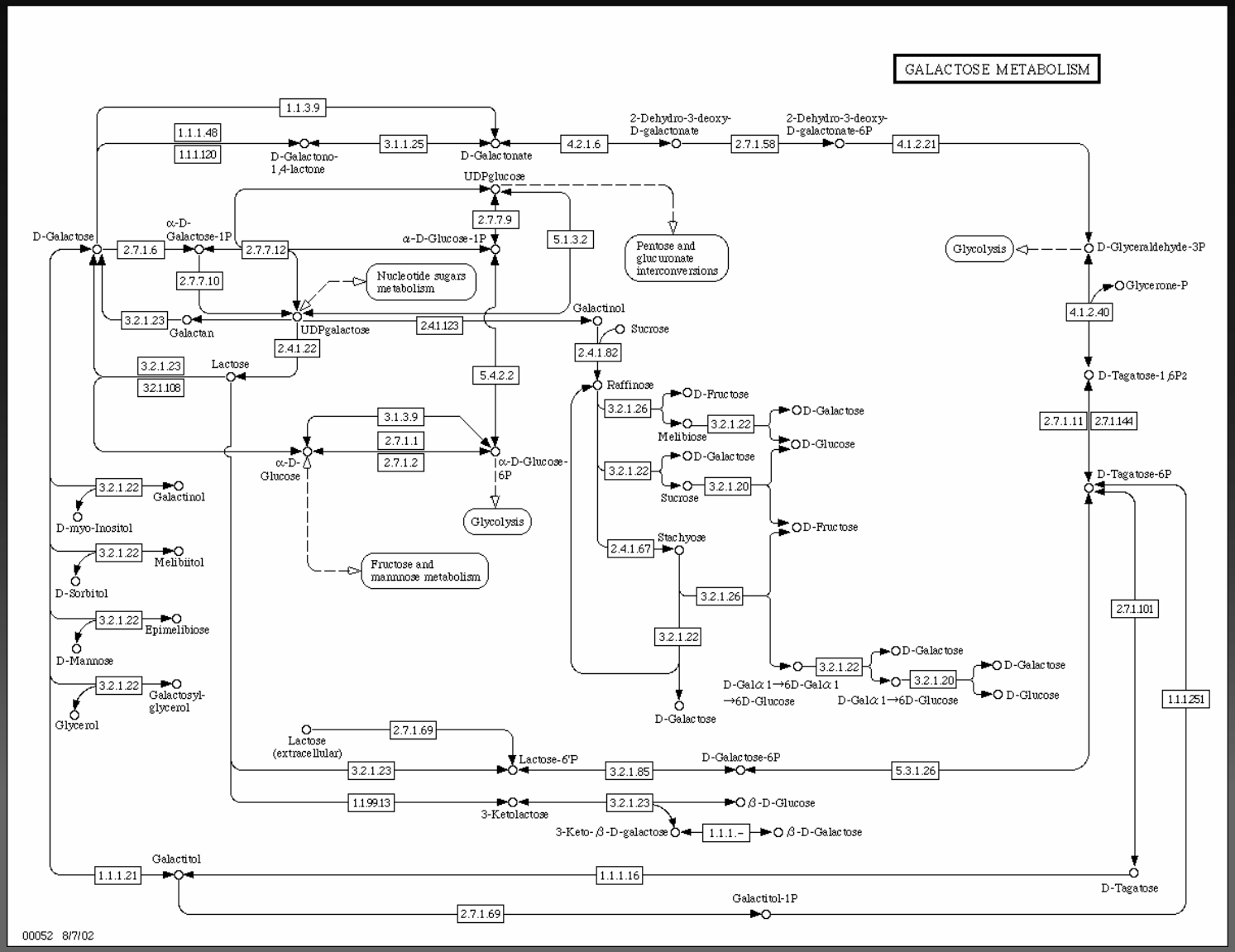
Pathway diagrams



Pathway diagrams



Pathway diagrams



Pathway diagrams

- Static Images of Pathways
  - BPC [2001] (Biochemical Pathway Chart)
    - A poster-liked handmade static image that describes the metabolic pathways and cellular / molecular processes.
  - BioCarta [2001]
    - A database that store the pathway information with static image format. Can be browsed by categories and searched by keywords. Hosted by a commercial company.
  - KEGG [2001] (Kyoto Encyclopedia of Genes and Genomes)
    - A database that specially focuses on storing metabolic pathways information. All proteins are categorized in their functions by EC (Enzyme Classification) Number system.
  - BRITE [2001] (Biomolecular Relations in Information Transmission Expression)
    - It is a binary relation search engine based on KEGG database. It can search the binary interaction between genes, proteins, or other biological molecules.

Pathway diagrams

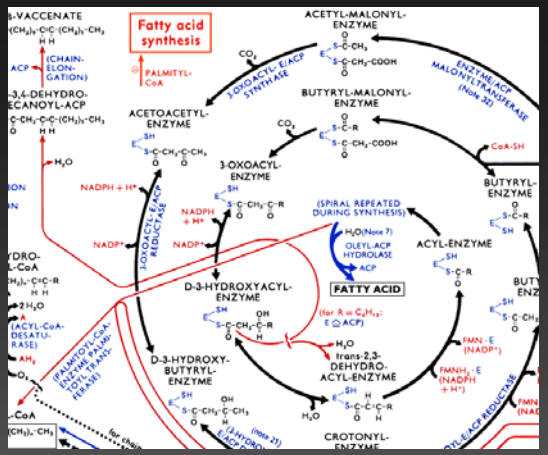
- Dynamic Images of Pathways
  - BioCyc [2002]
    - This is a database that contains metabolic pathway information for 260 species. It presents a pathway chart dynamically.
  - STKE (Signal Transduction Knowledge Environment)
    - This is the site hosted by Science Magazine. It collects pathways related to signal transduction and is searchable by keywords.

Molecular pathways

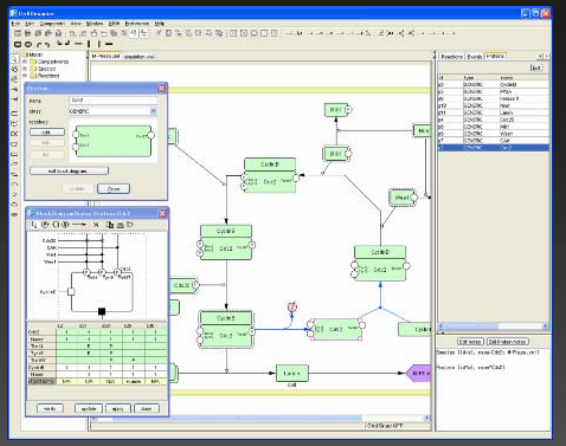
- Pathway diagrams
- Graphical modelers
- Pathway repositories
- Pathway representation

Graphical modelers

- What is the Graphical modeler?



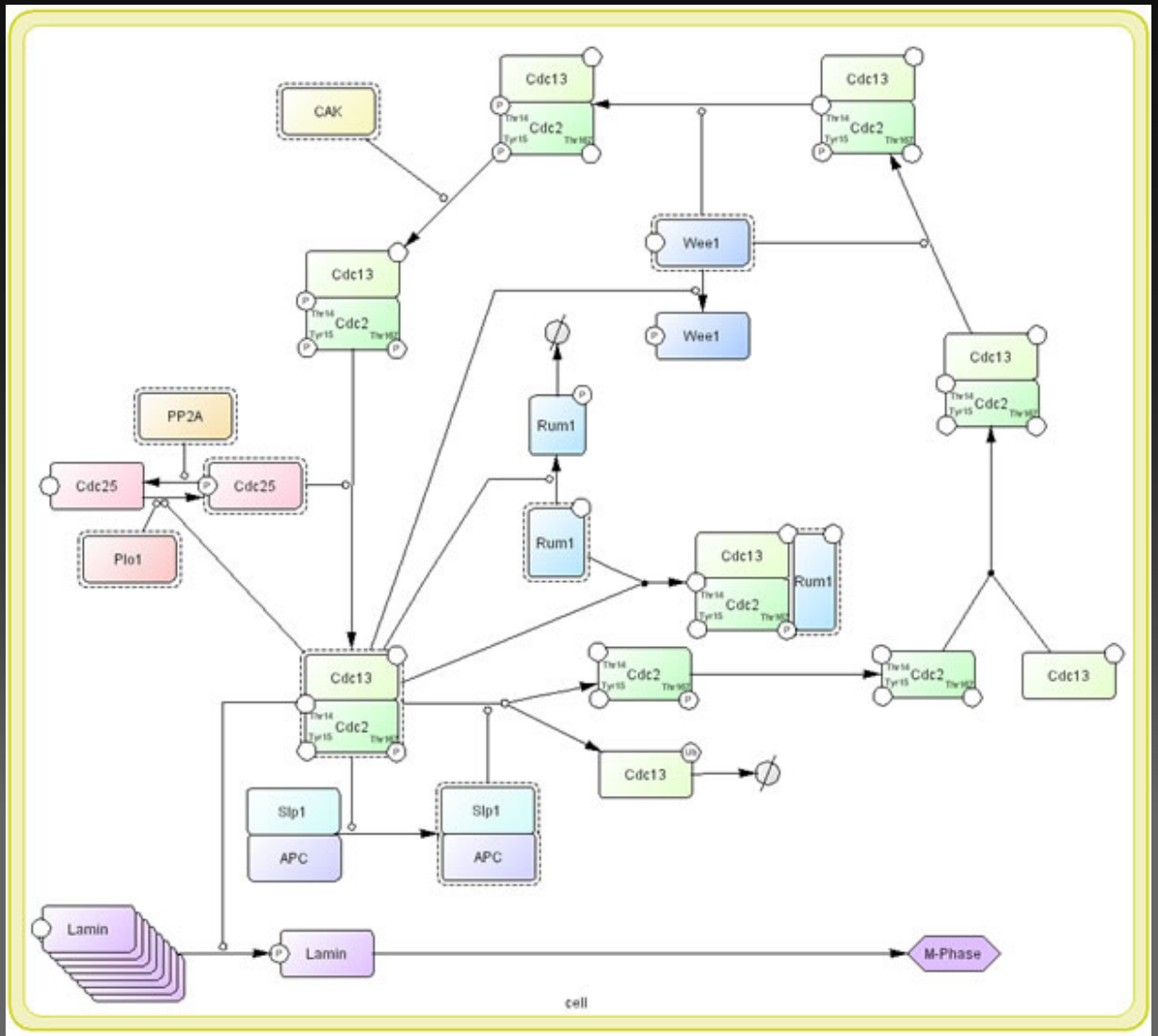




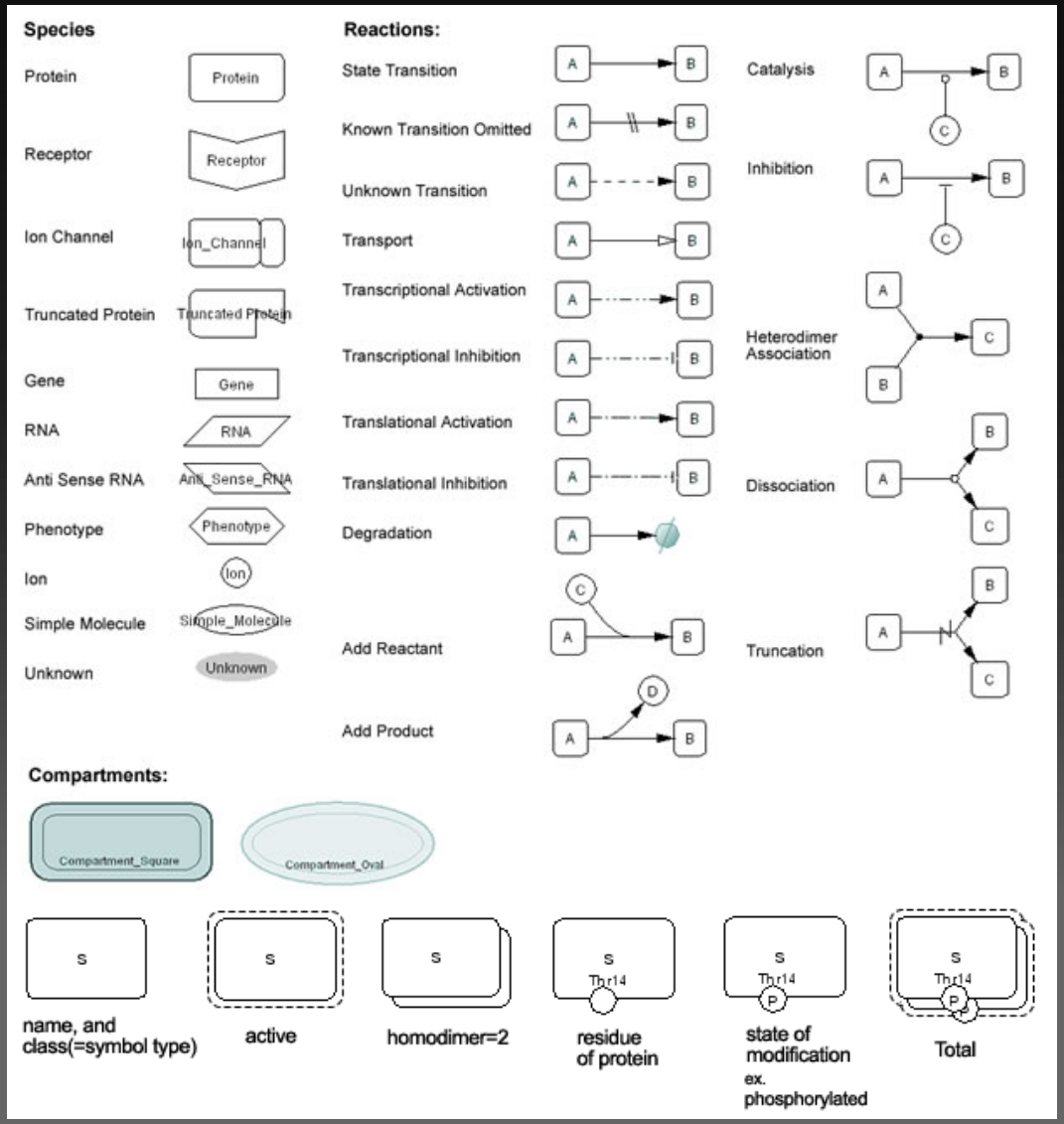
Human-readable Pathways

Machine-readable Pathways

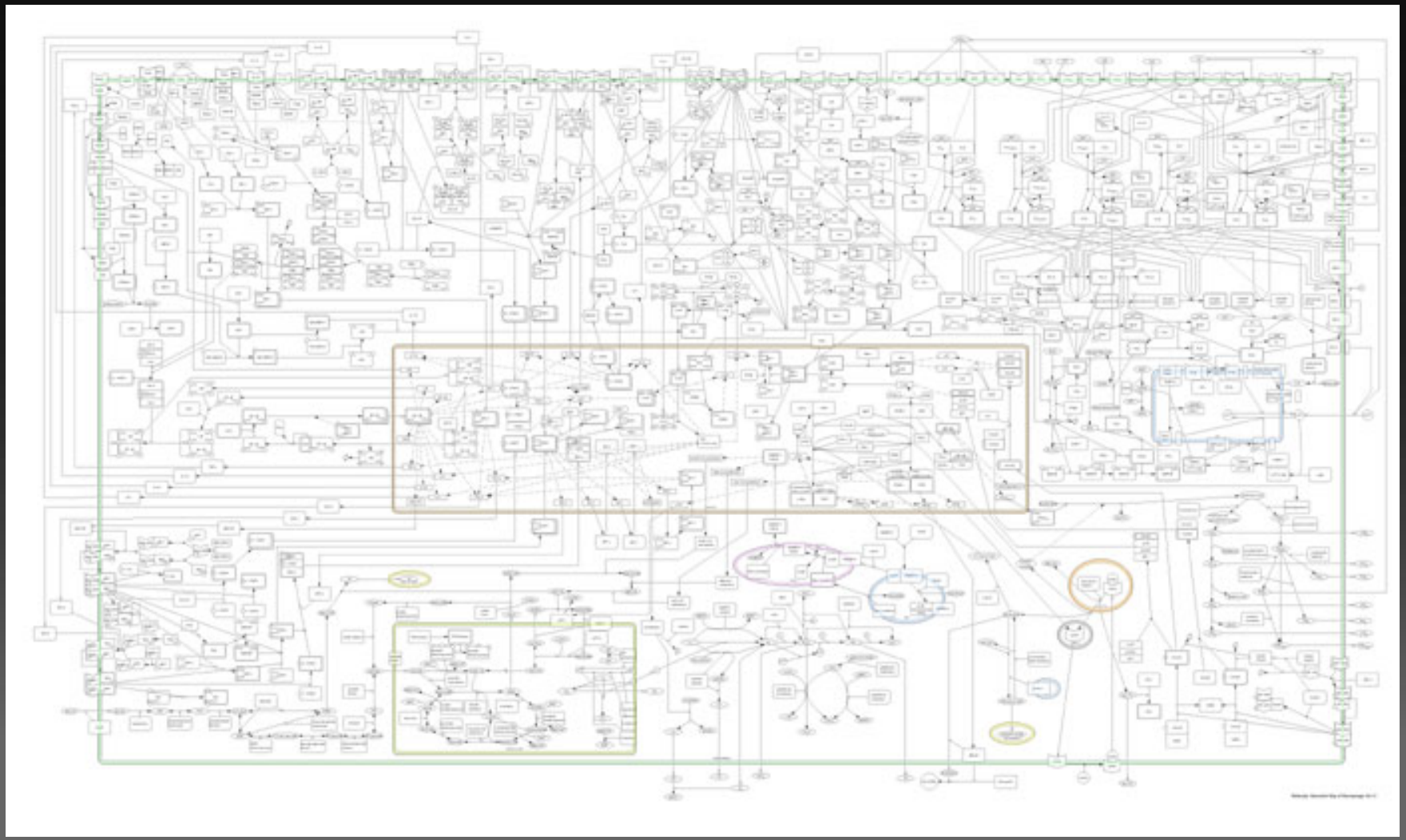
Graphical modelers



Graphical modelers



Graphical modelers



Graphical modelers





















Pathway repositories

- EcoCyc/BioCyc/MetaCyc
- Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY DB
- BioCarta
- BioModels database

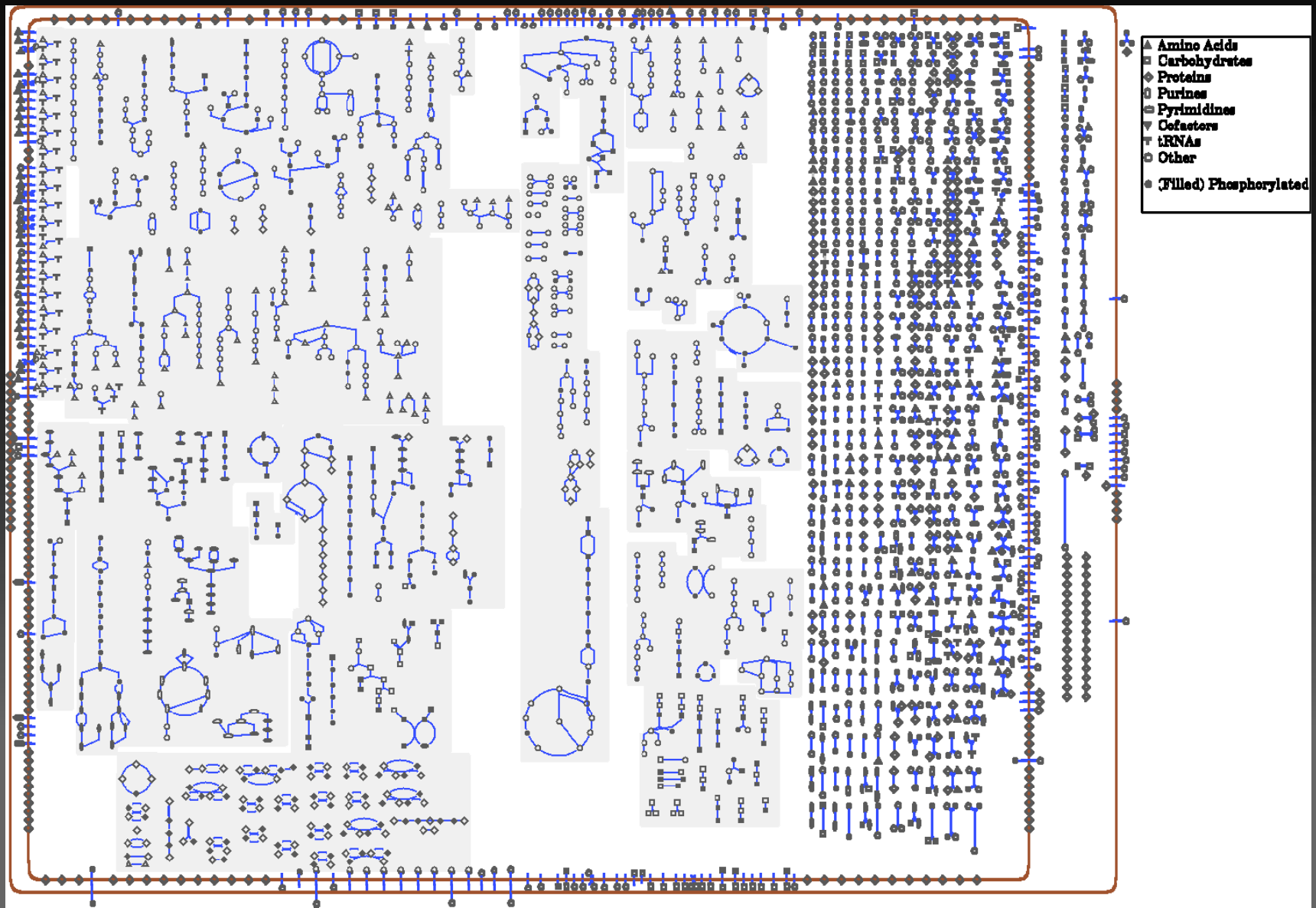
EcoCyc database (ecocyc.org)

- EcoCyc is a scientific database for the bacterium *Escherichia coli* K-12 MG1655. The EcoCyc project performs literature-based curation of the entire genome, and of transcriptional regulation, transporters, and metabolic pathways.

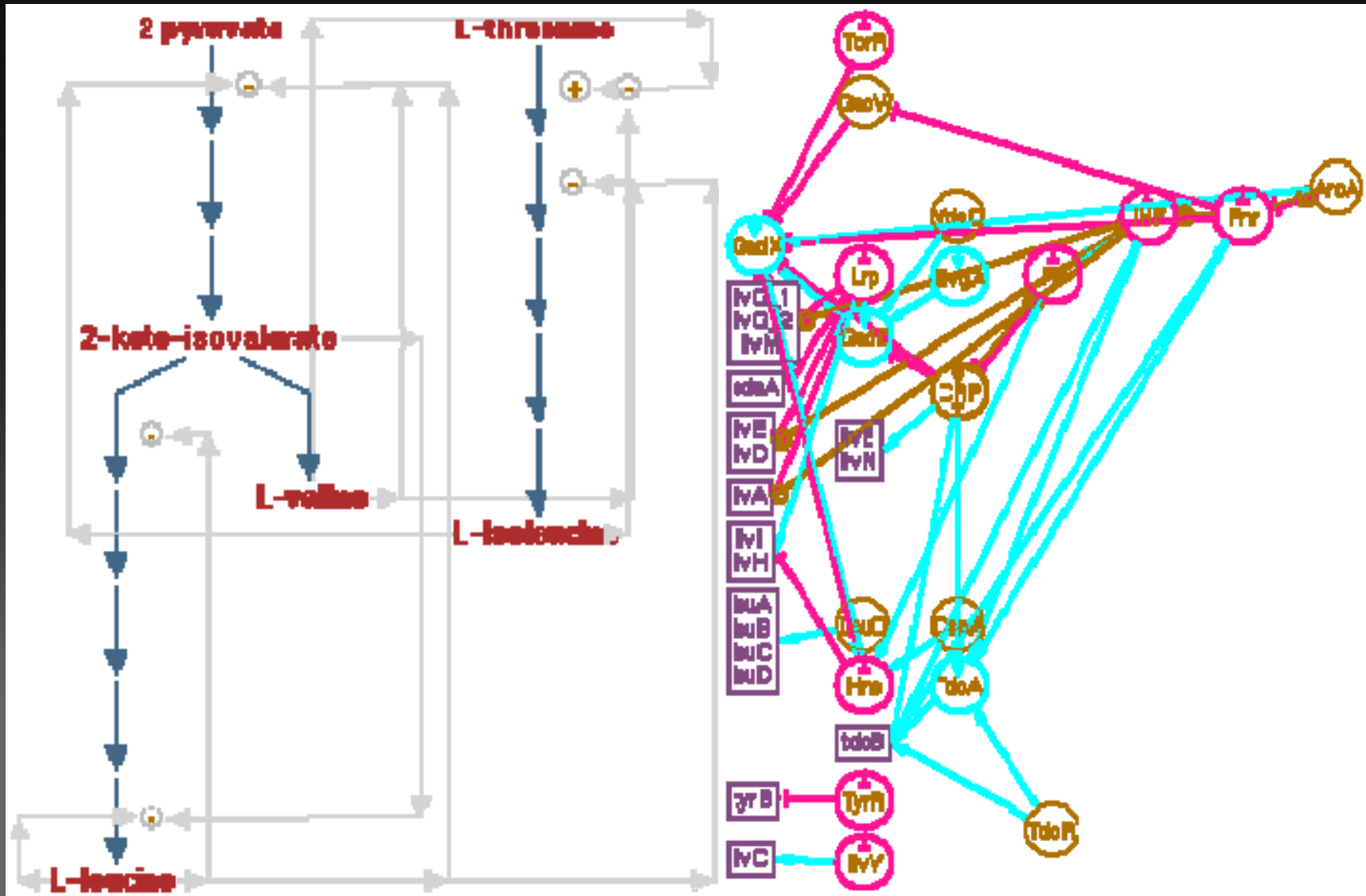
- Encompasses >791 chemical compounds in >744 noted biochemical reactions

- Pathway was compiled via literature information extraction and extensive manual curation
  - System allows for users to indicate evidence of pathway annotations
  - Curation is done collaboratively with numerous experts outside of EcoCyc

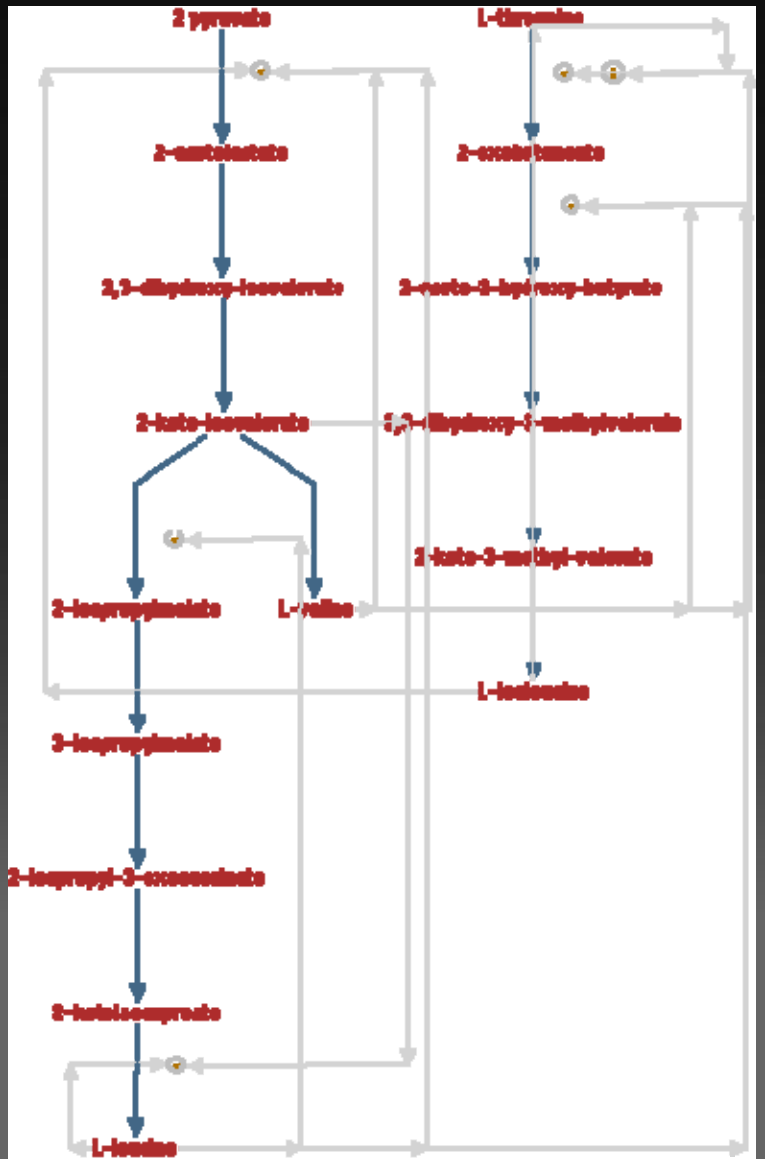
EcoCyc database (ecocyc.org)



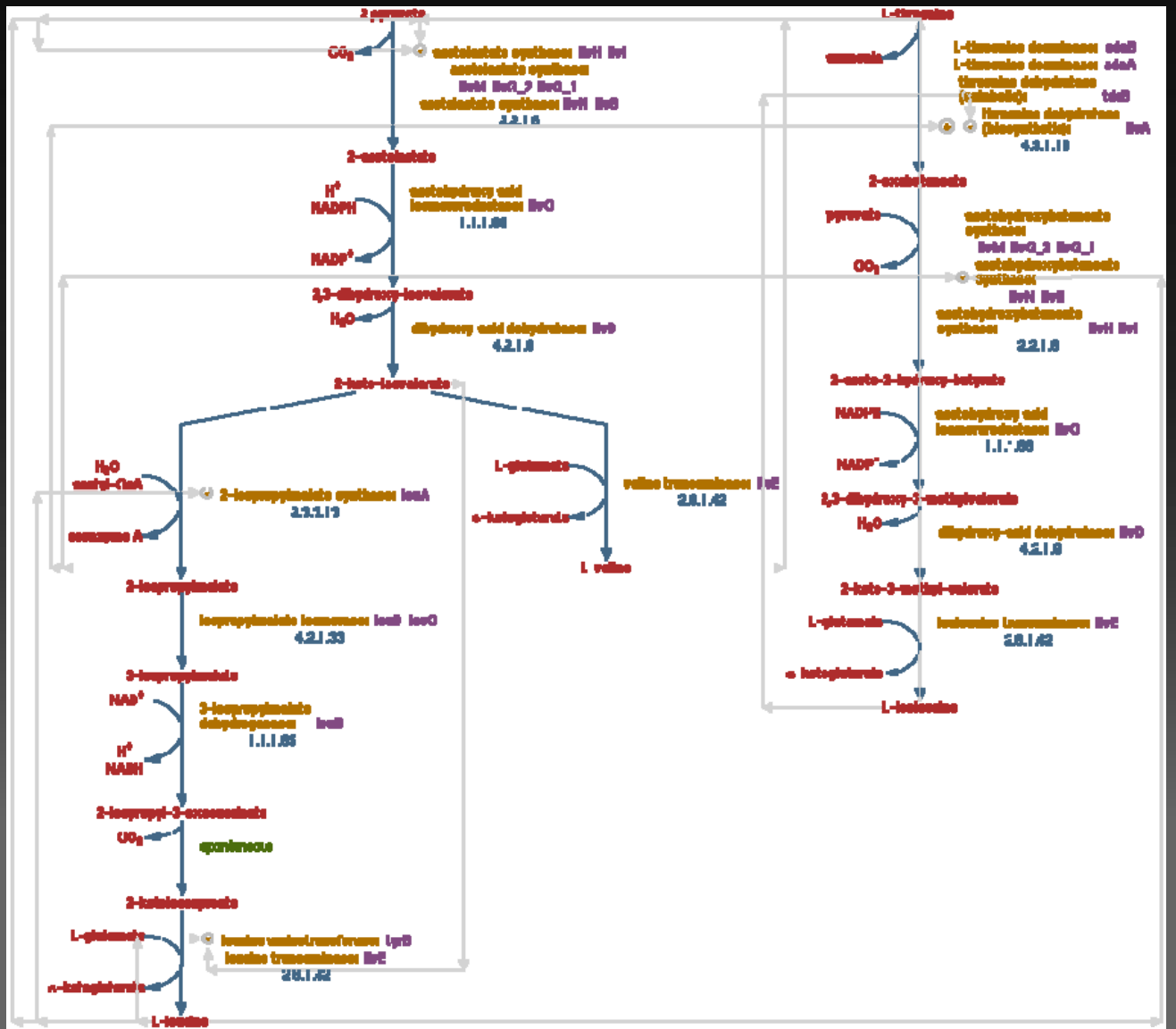
EcoCyc database (ecocyc.org)



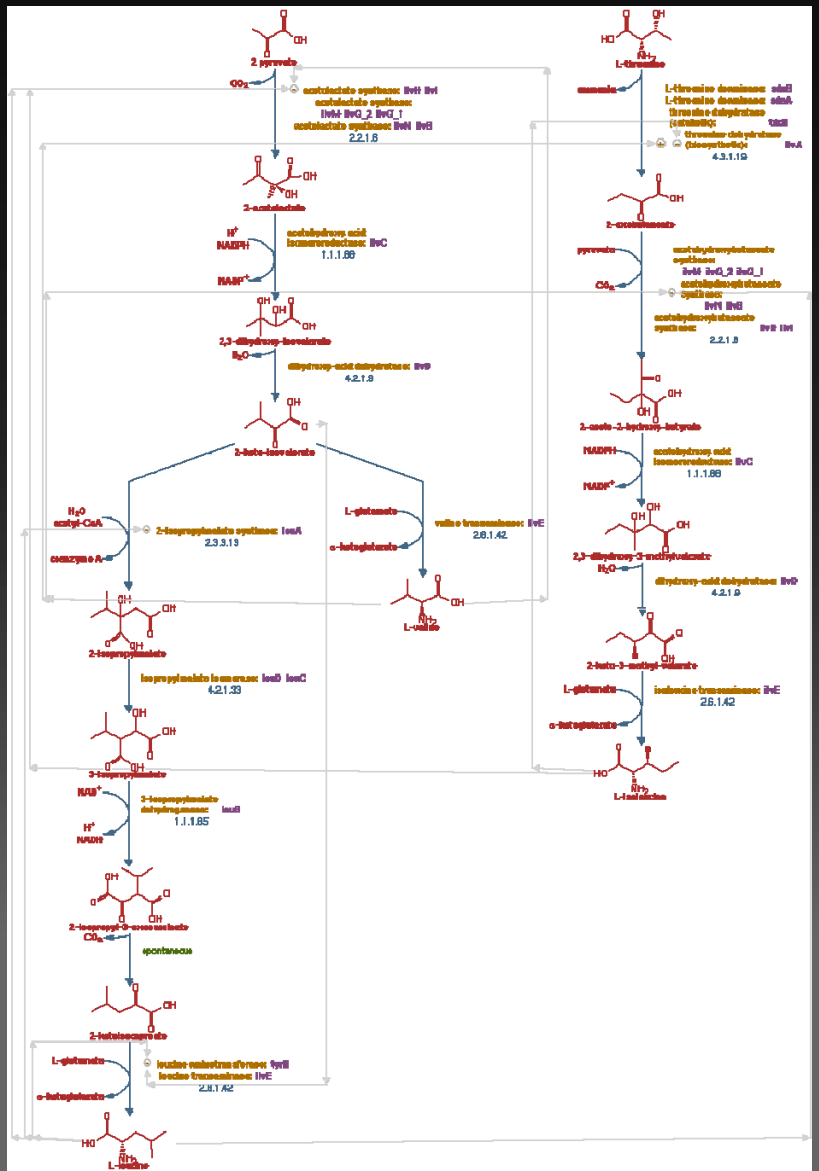
EcoCyc database (ecocyc.org)



EcoCyc database (ecocyc.org)

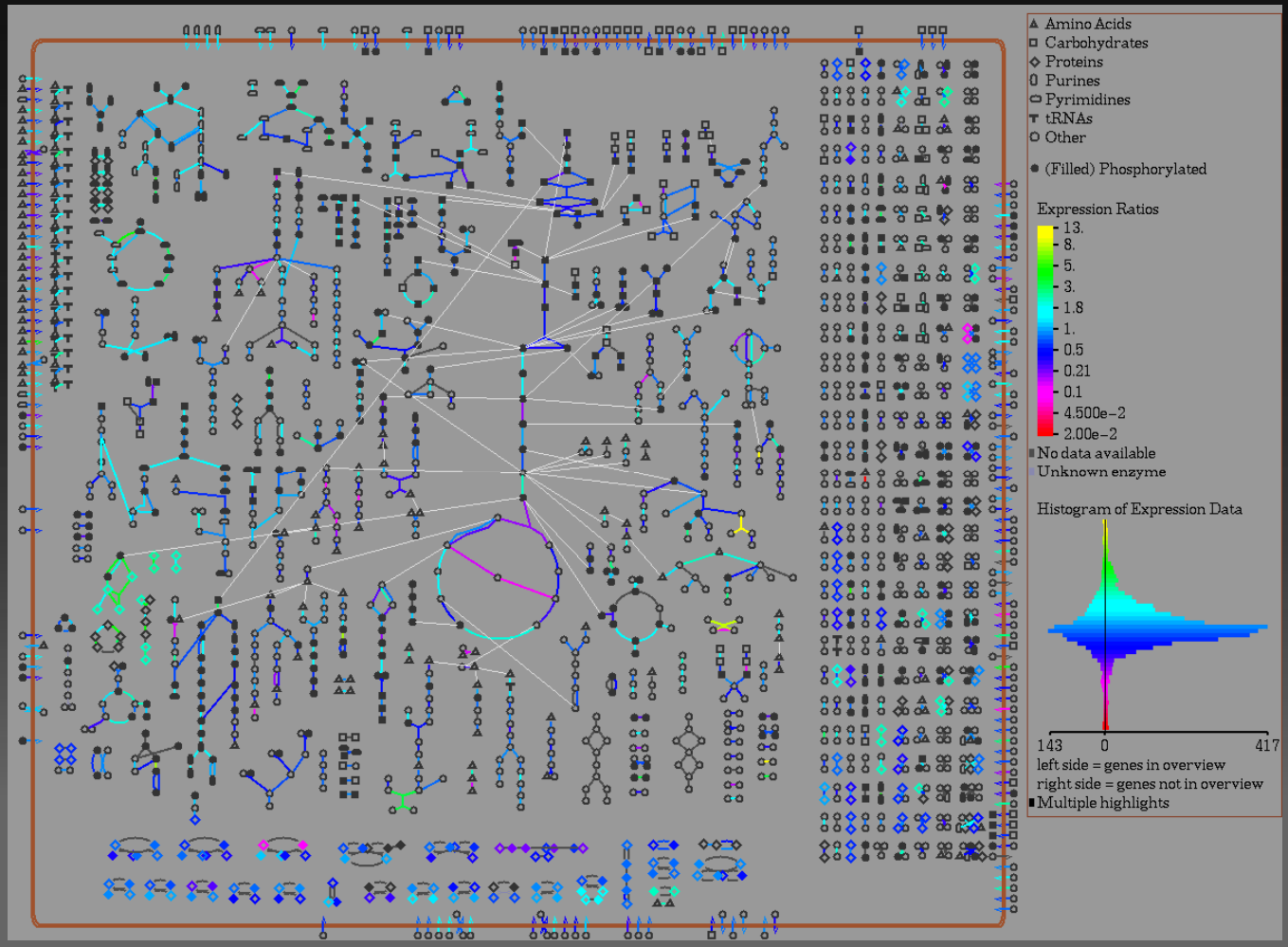


EcoCyc database (ecocyc.org)



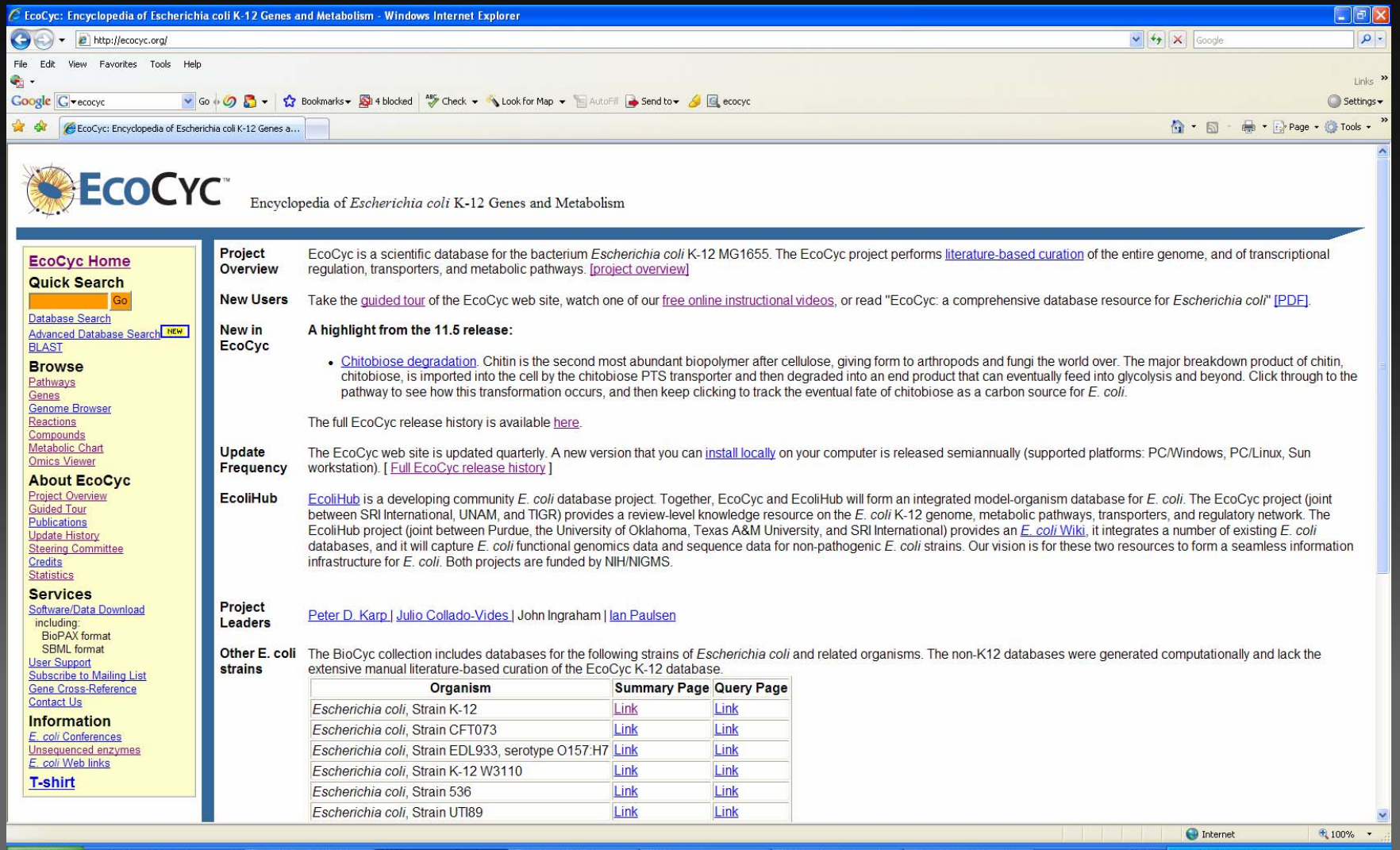
EcoCyc database (ecocyc.org)

Single gene expression experiment:



Time series gene expression animation: http://biocyc.org/expr-examples/animation.html

EcoCyc database (ecocyc.org)



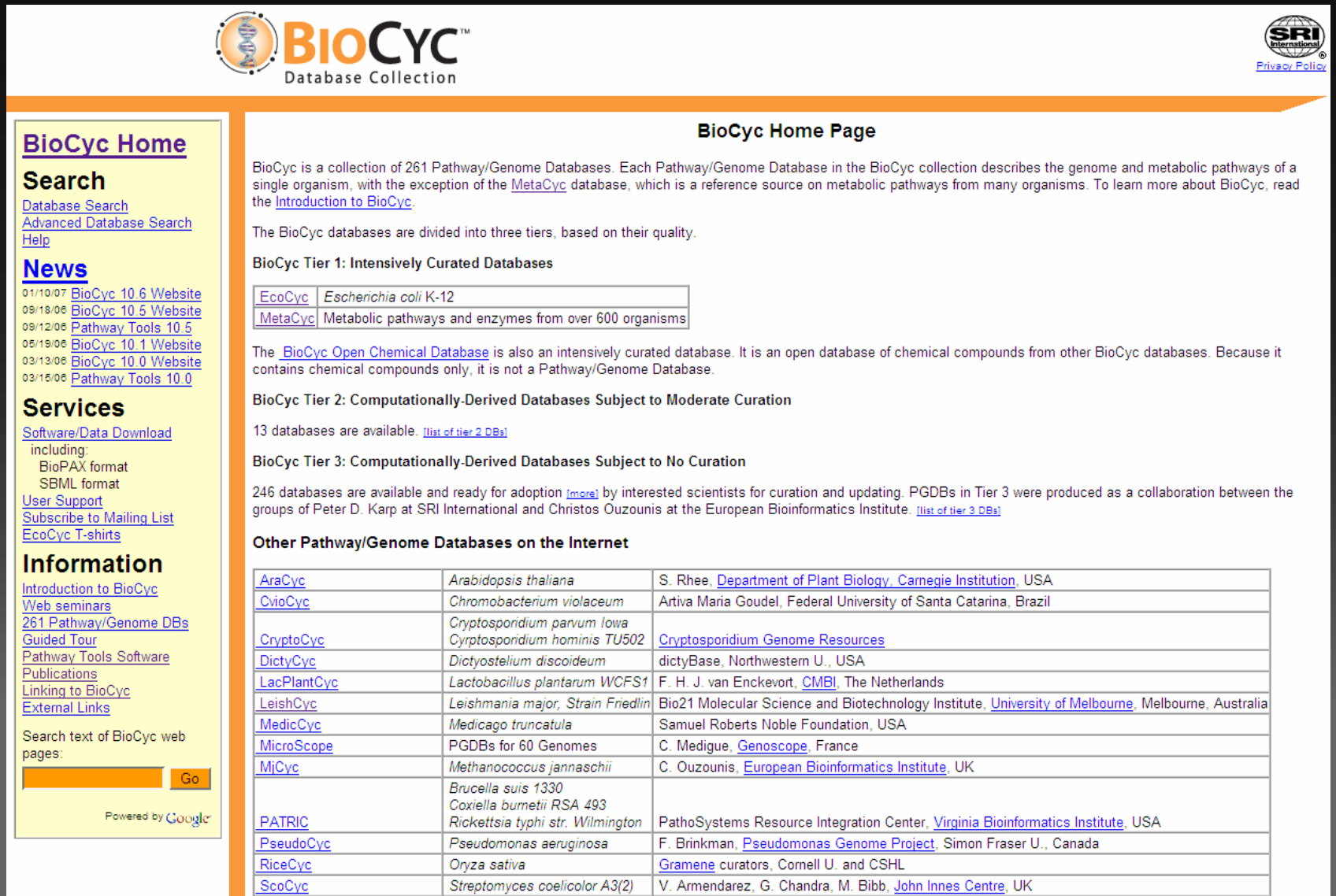
BioCyc database (biocyc.org)

- Pathway/genome database (PGDB) for organisms with completely sequenced genomes

- >260 full genomes/pathways deposited
- Species-specific pathways are inferred form MetaCyc

- Query/navigation/pathway creation support through the Pathway Tools software suite

BioCyc database (biocyc.org)



BioCyc Database Collection

Privacy Policy

BioCyc Home

Search

Database Search
Advanced Database Search
Help

News

01/10/07 BioCyc 10.6 Website
09/18/06 BioCyc 10.5 Website
09/12/06 Pathway Tools 10.5
05/19/06 BioCyc 10.1 Website
03/13/06 BioCyc 10.0 Website
03/15/06 Pathway Tools 10.0

Services

Software/Data Download
including:
BioPAX format
SBML format
User Support
Subscribe to Mailing List
EcoCyc T-shirts

Information

Introduction to BioCyc
Web seminars
261 Pathway/Genome DBs
Guided Tour
Pathway Tools Software
Publications
Linking to BioCyc
External Links

Search text of BioCyc web pages:

Go

Powered by Google

BioCyc Home Page

BioCyc is a collection of 261 Pathway/Genome Databases. Each Pathway/Genome Database in the BioCyc collection describes the genome and metabolic pathways of a single organism, with the exception of the MetaCyc database, which is a reference source on metabolic pathways from many organisms. To learn more about BioCyc, read the Introduction to BioCyc.

The BioCyc databases are divided into three tiers, based on their quality.

BioCyc Tier 1: Intensively Curated Databases

EcoCyc	*Escherichia coli* K-12
MetaCyc	Metabolic pathways and enzymes from over 600 organisms

The BioCyc Open Chemical Database is also an intensively curated database. It is an open database of chemical compounds from other BioCyc databases. Because it contains chemical compounds only, it is not a Pathway/Genome Database.

BioCyc Tier 2: Computationally-Derived Databases Subject to Moderate Curation

13 databases are available. [list of tier 2 DBs]

BioCyc Tier 3: Computationally-Derived Databases Subject to No Curation

246 databases are available and ready for adoption [more] by interested scientists for curation and updating. PGDBs in Tier 3 were produced as a collaboration between the groups of Peter D. Karp at SRI International and Christos Ouzounis at the European Bioinformatics Institute. [list of tier 3 DBs]

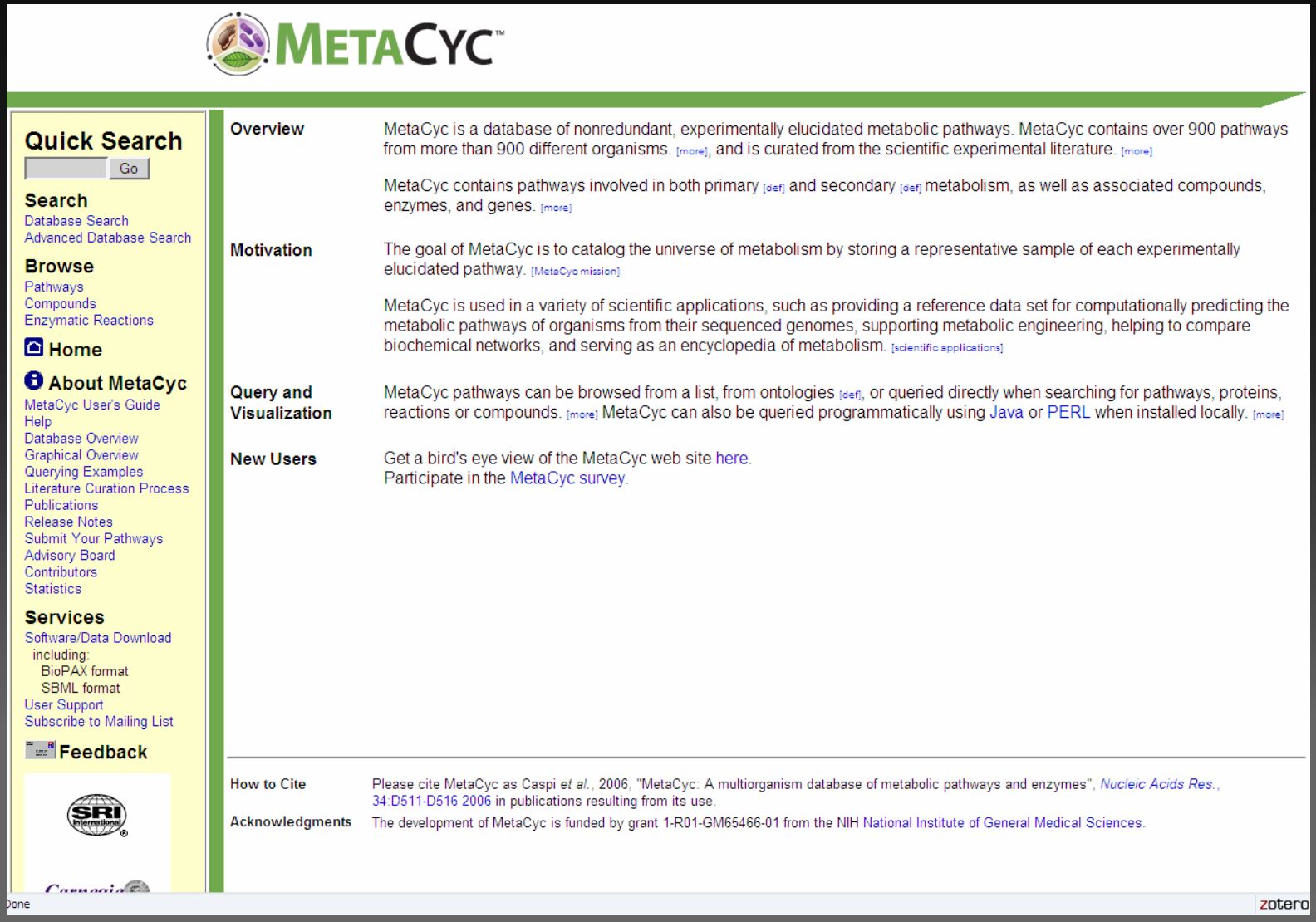
Other Pathway/Genome Databases on the Internet

AraCyc	*Arabidopsis thaliana*	S. Rhee, Department of Plant Biology, Carnegie Institution, USA
CvioCyc	*Chromobacterium violaceum*	Artiva Maria Goudel, Federal University of Santa Catarina, Brazil
CryptoCyc	*Cryptosporidium parvum Iowa* *Cyrptosporidium hominis TU502*	Cryptosporidium Genome Resources
DictyCyc	*Dictyostelium discoideum*	dictyBase, Northwestern U., USA
LacPlantCyc	*Lactobacillus plantarum WCFS1*	F. H. J. van Enckevort, CMBI, The Netherlands
LeishCyc	*Leishmania major, Strain Friedlin*	Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Melbourne, Australia
MedicCyc	*Medicago truncatula*	Samuel Roberts Noble Foundation, USA
MicroScope	PGDBs for 60 Genomes	C. Medigue, Genoscope, France
MjCyc	*Methanococcus jannaschii*	C. Ouzounis, European Bioinformatics Institute, UK
PATRIC	*Brucella suis 1330* *Coxiella burnetii RSA 493* *Rickettsia typhi str. Wilmington*	PathoSystems Resource Integration Center, Virginia Bioinformatics Institute, USA
PseudoCyc	*Pseudomonas aeruginosa*	F. Brinkman, Pseudomonas Genome Project, Simon Fraser U., Canada
RiceCyc	*Oryza sativa*	Gramene curators, Cornell U. and CSHL
ScoCyc	*Streptomyces coelicolor A3(2)*	V. Armendarez, G. Chandra, M. Bibb, John Innes Centre, UK

MetaCyc database (metacyc.org)

- Non-redundant reference database for metabolic pathways, reactions, enzymes and compounds
- >900 pathways from >900 species (mostly plants and microorganisms)
- Curation through experimental verification and manual literature review

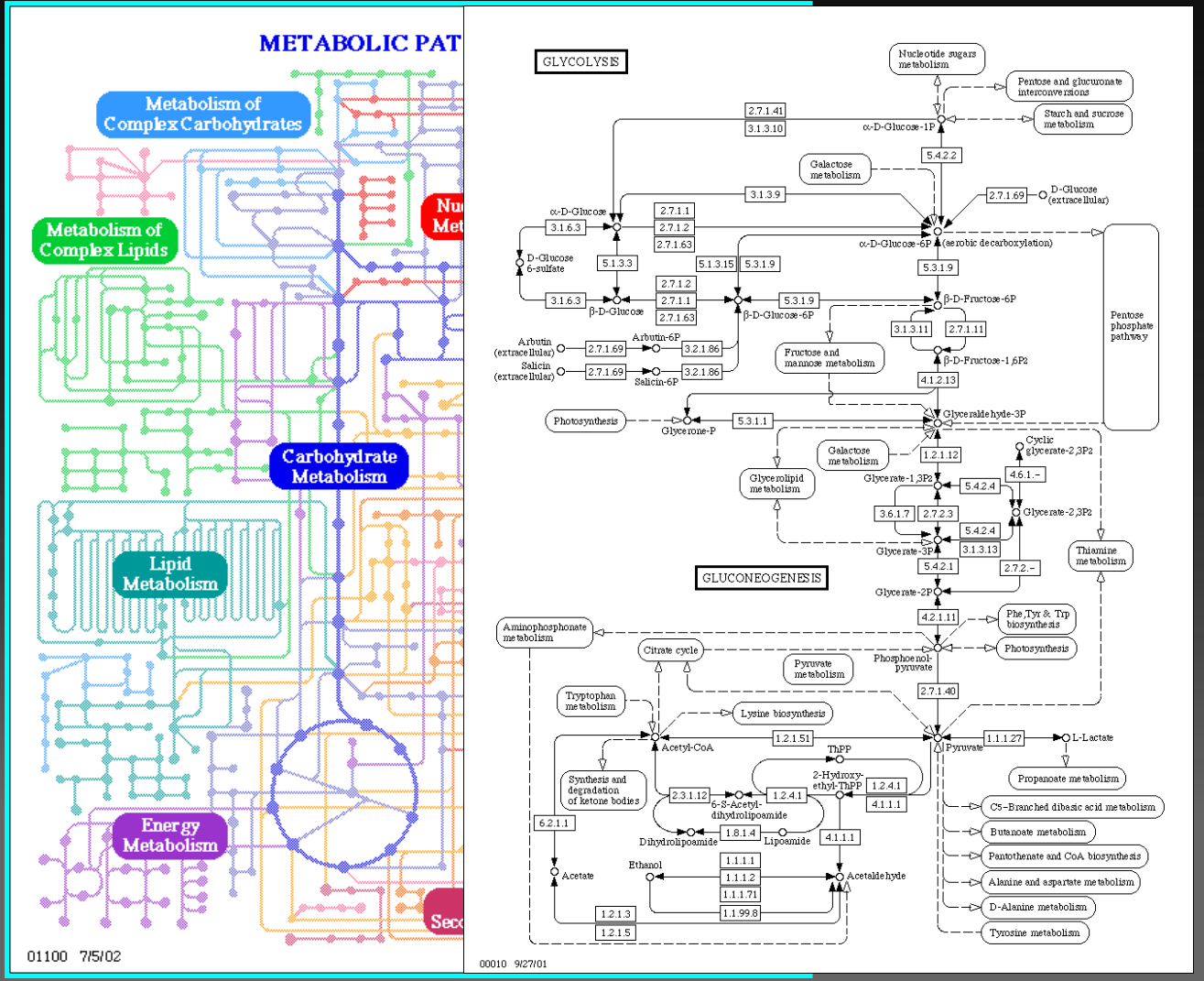
MetaCyc database (metacyc.org)



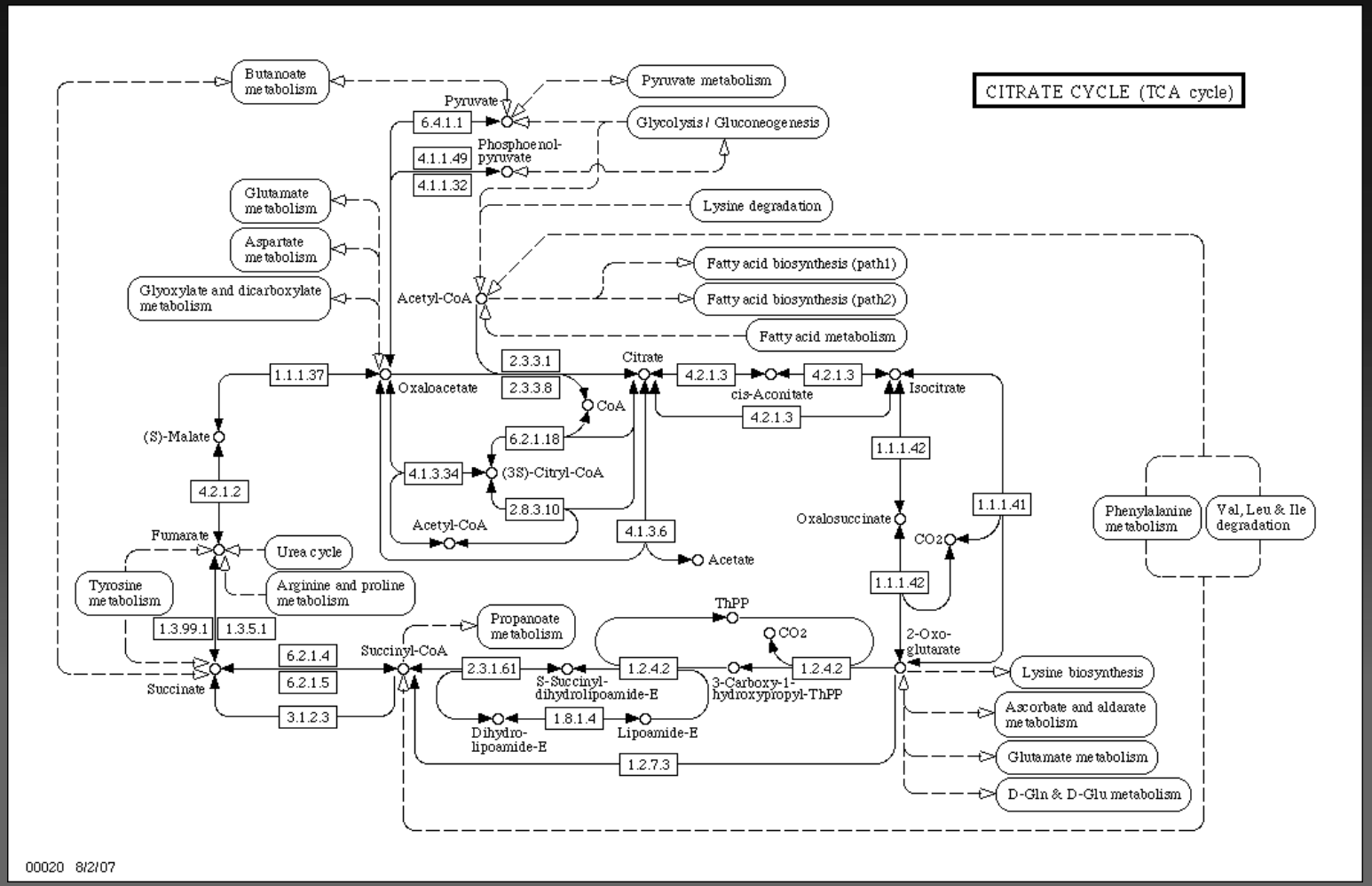
KEGG PATHWAY database (kegg.com)

- Consolidated set of databases that cover genomics (GENE), chemical compounds (LIGAND) and reaction networks (PATHWAY)
- Broad focus on metabolics, signal transduction, disease, etc.
- Species-specific views available (but networks are static across all organisms)

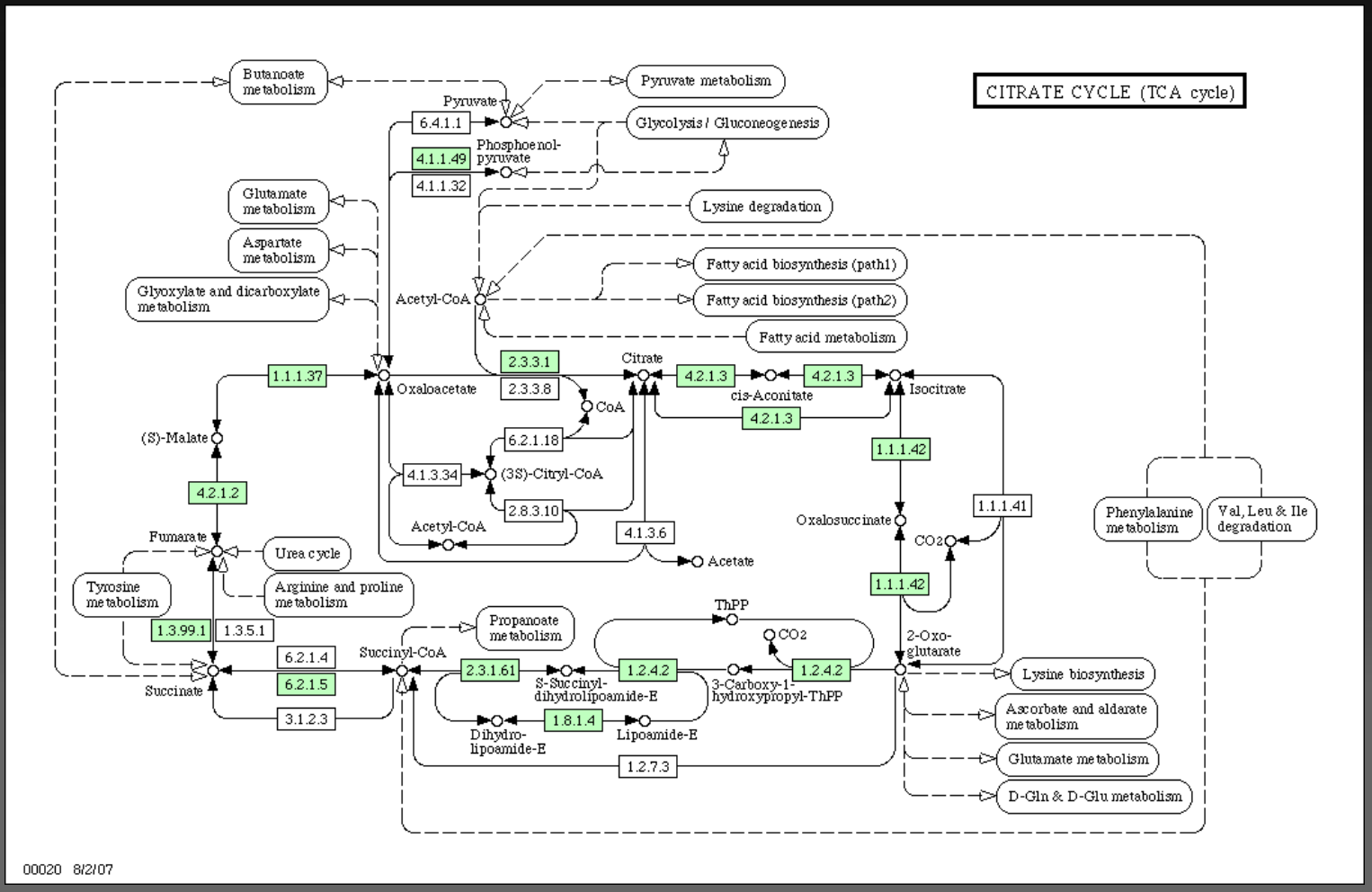
KEGG PATHWAY database



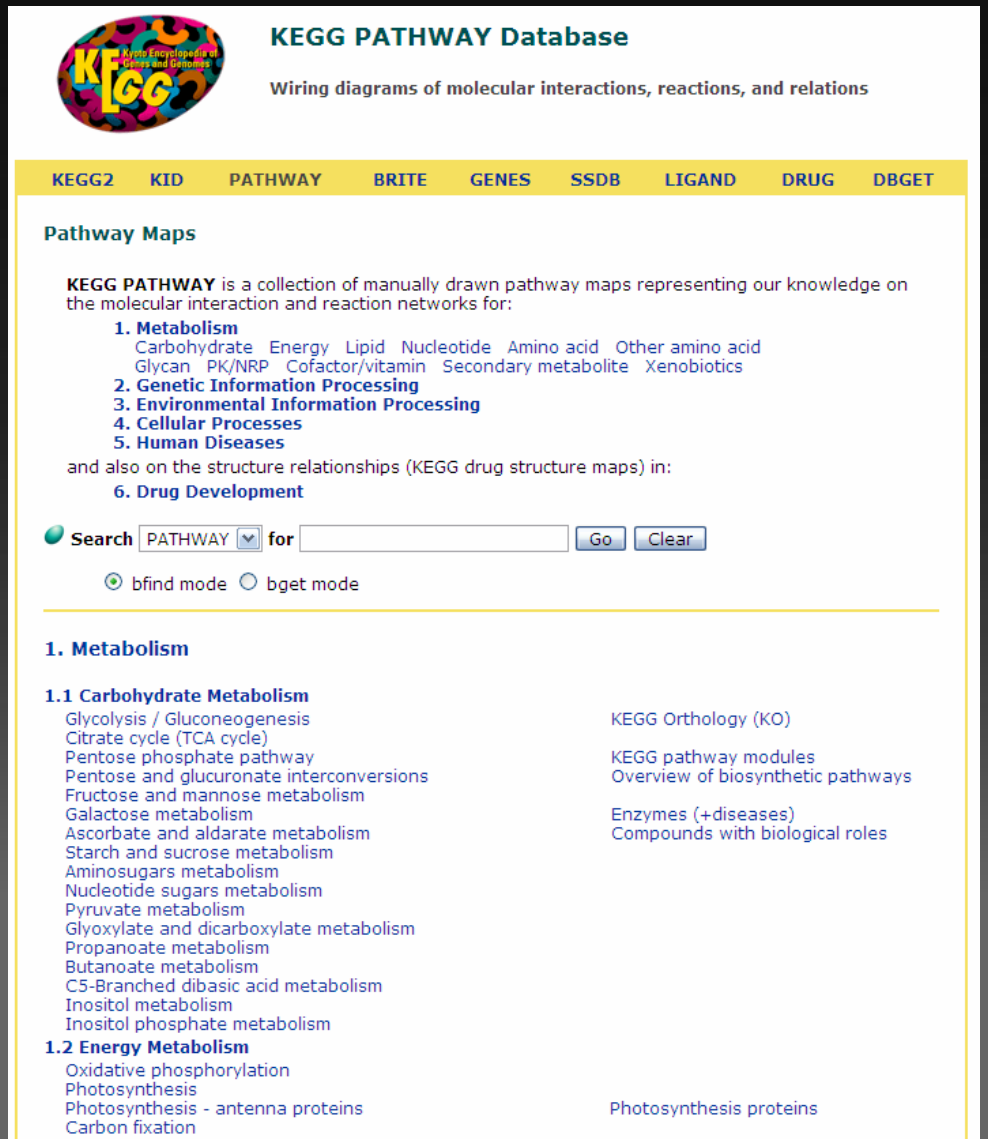
KEGG PATHWAY database



KEGG


CITRATE CYCLE (TCA cycle)
Butanoate metabolism
Pyruvate metabolism
Pyruvate
6.4.1.1
Glycolysis / Gluconeogenesis
4.1.1.49
Phosphoenol-pyruvate
4.1.1.32
Glutamate metabolism
Lysine degradation
Aspartate metabolism
Glyoxylate and dicarboxylate metabolism
Acetyl-CoA
Fatty acid biosynthesis (path1)
Fatty acid biosynthesis (path2)
Fatty acid metabolism
2.3.3.1
2.3.3.8
Citrate
4.2.1.3
4.2.1.3
cis-Aconitate
Isocitrate
1.1.1.37
Oxaloacetate
CoA
4.2.1.3
(S)-Malate
6.2.1.18
1.1.1.42
4.1.3.34
(3S)-Citryl-CoA
4.2.1.2
2.8.3.10
1.1.1.41
Oxalosuccinate
Acetyl-CoA
4.1.3.6
Fumarate
Urea cycle
CO2
Acetate
Phenylalanine metabolism
Val, Leu & Ile degradation
Tyrosine metabolism
Arginine and proline metabolism
1.1.1.42
ThPP
1.3.99.1
1.3.5.1
Propanoate metabolism
CO2
2-Oxo-glutarate
6.2.1.4
Succinyl-CoA
2.3.1.61
1.2.4.2
1.2.4.2
Lysine biosynthesis
6.2.1.5
S-Succinyl-dihydrolipoamide-E
3-Carboxy-1-hydroxypropyl-ThPP
Succinate
3.1.2.3
1.8.1.4
Ascorbate and aldarate metabolism
Dihydro-lipoamide-E
Lipoamide-E
Glutamate metabolism
1.2.7.3
D-Gln & D-Glu metabolism
00020 8/2/07

KEGG PATHWAY database



KEGG PATHWAY Database

Wiring diagrams of molecular interactions, reactions, and relations

KEGG2 KID PATHWAY BRITE GENES SSDB LIGAND DRUG DBGET

Pathway Maps

KEGG PATHWAY is a collection of manually drawn pathway maps representing our knowledge on the molecular interaction and reaction networks for:

1. **Metabolism**
   Carbohydrate Energy Lipid Nucleotide Amino acid Other amino acid
   Glycan PK/NRP Cofactor/vitamin Secondary metabolite Xenobiotics
2. **Genetic Information Processing**
3. **Environmental Information Processing**
4. **Cellular Processes**
5. **Human Diseases**

and also on the structure relationships (KEGG drug structure maps) in:

6. **Drug Development**

Search PATHWAY **for** Go Clear

bfind mode bget mode

1. Metabolism

1.1 Carbohydrate Metabolism

Glycolysis / Gluconeogenesis
Citrate cycle (TCA cycle)
Pentose phosphate pathway
Pentose and glucuronate interconversions
Fructose and mannose metabolism
Galactose metabolism
Ascorbate and aldarate metabolism
Starch and sucrose metabolism
Aminosugars metabolism
Nucleotide sugars metabolism
Pyruvate metabolism
Glyoxylate and dicarboxylate metabolism
Propanoate metabolism
Butanoate metabolism
C5-Branched dibasic acid metabolism
Inositol metabolism
Inositol phosphate metabolism

KEGG Orthology (KO)

KEGG pathway modules
Overview of biosynthetic pathways

Enzymes (+diseases)
Compounds with biological roles

1.2 Energy Metabolism

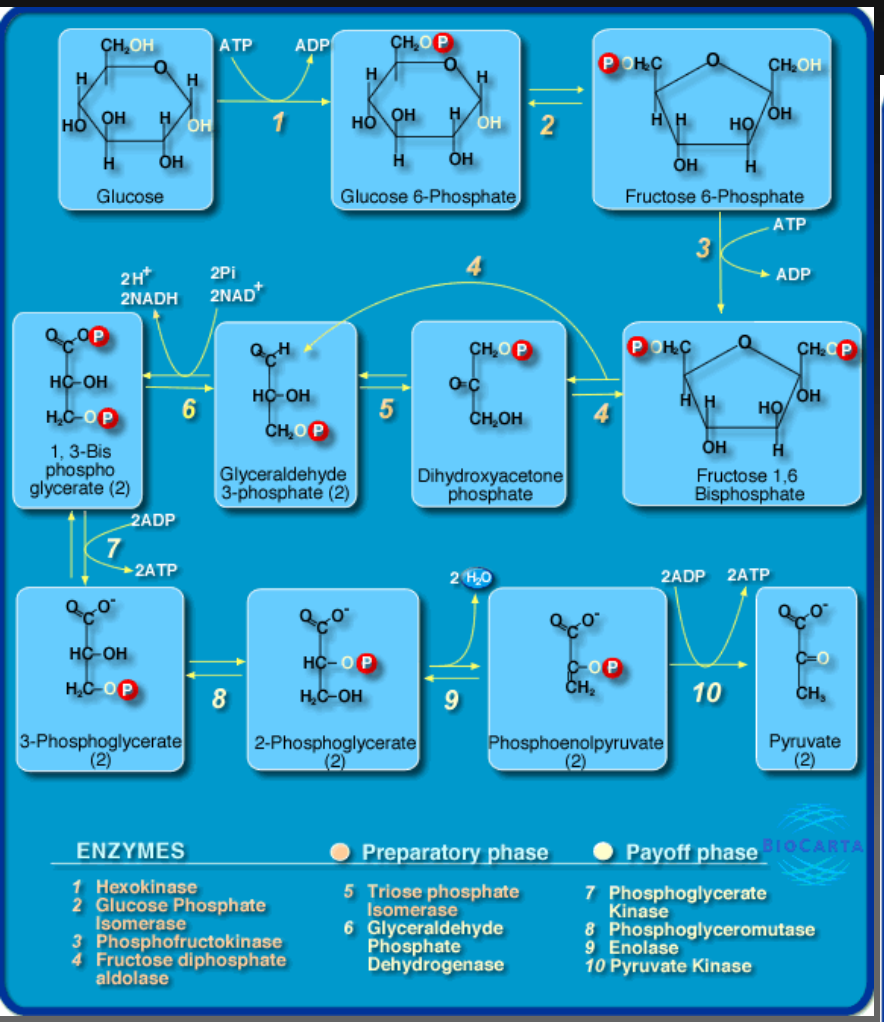
Oxidative phosphorylation
Photosynthesis
Photosynthesis - antenna proteins
Carbon fixation

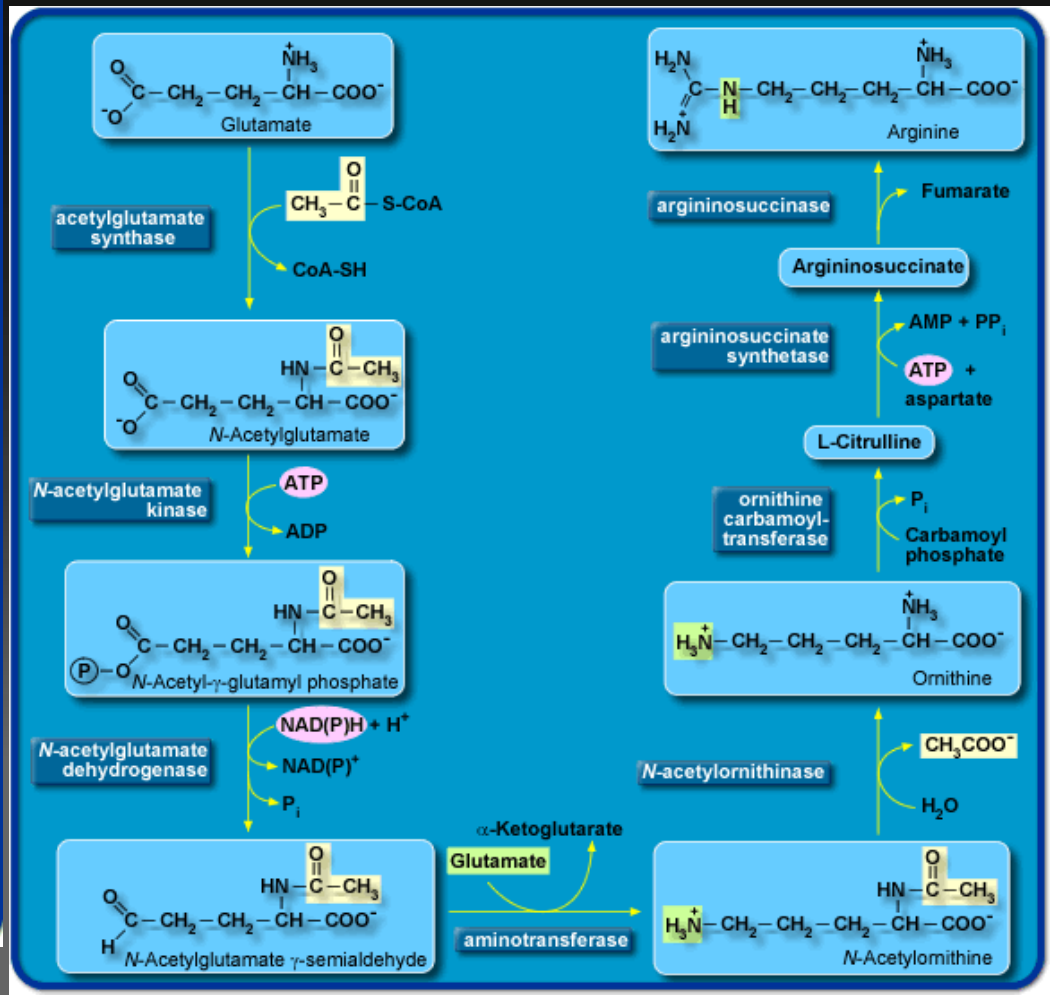
Photosynthesis proteins

BioCarta database (biocarta.com)

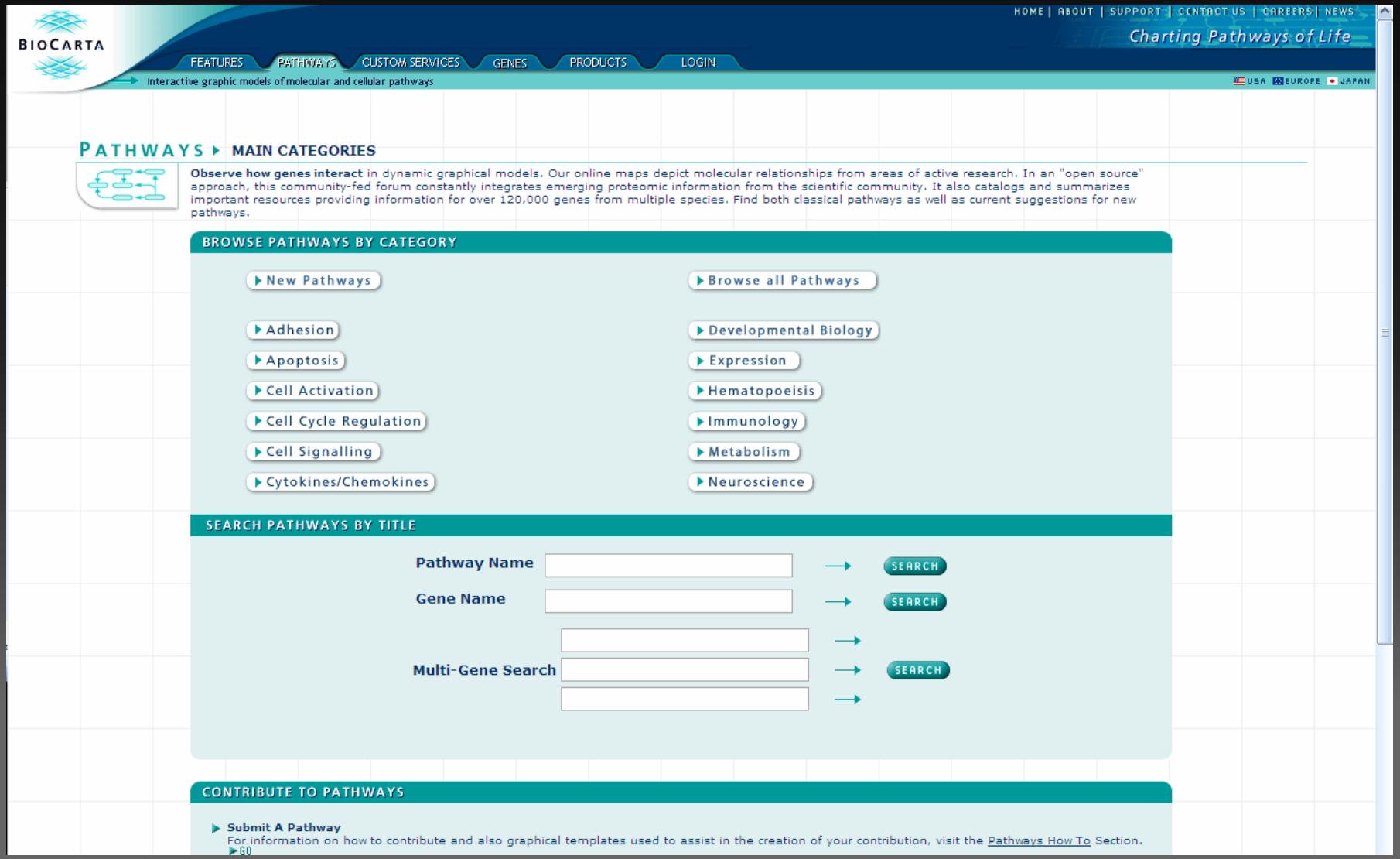
- Corporate-owned, publicly-curated pathway database
- Series of interactive, “cartoon” pathway maps
- Predominantly human and mouse pathways
- Contains 160,000 gene entries and 355 pathways

BioCarta database





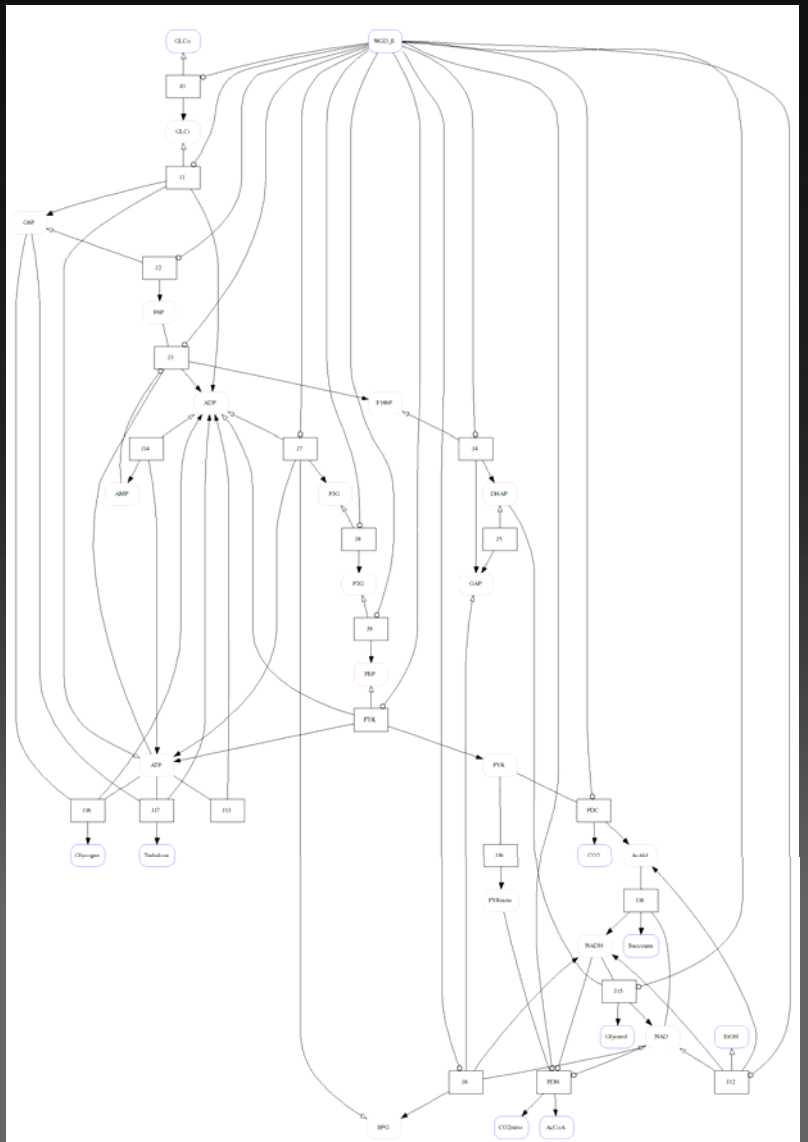
BioCarta database



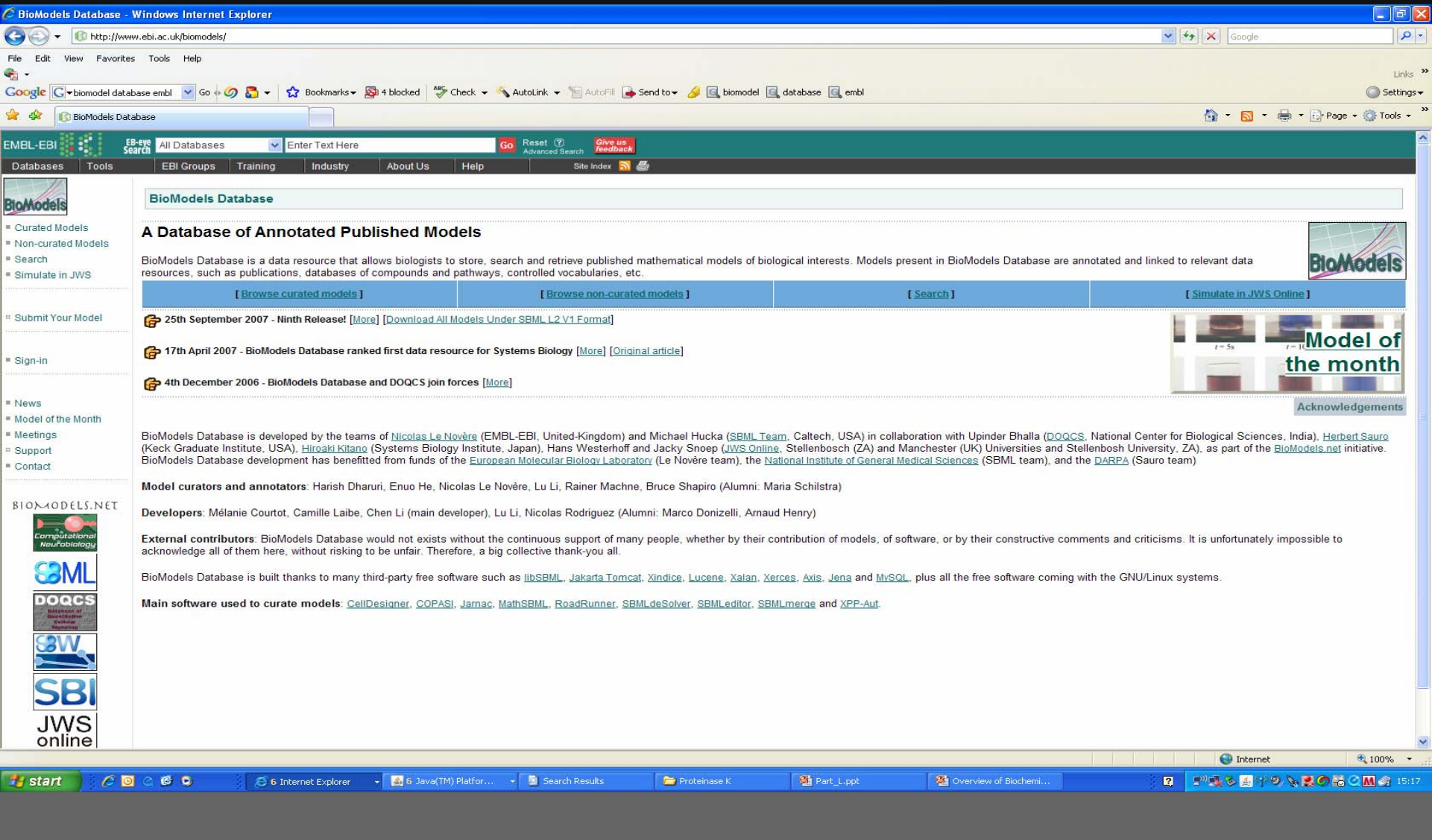
BioModels database

- Database for published, quantitative models of biochemical processes
- All models/pathways curated manually, compliant with MIRIAM
- Models can be output in SBML format for quantitative modeling
- Release: 25/September/2007
  - Models:192,
  - Species:10484
  - Reactions:12482
  - Cross-references:7985

BioModels database



BioModels database



Comparison of pathway databases

	MetaCyc/ BioCyc	KEGG PATHWAYS	BioCarta	BioModels
Curation	Manual and automated	Automated	Manual	Manual
Size	~621+ pathways	~289 reference pathways	~355 pathways	~126 models
Nomenclature	EC, GO	EC, KO	None	GO
Organism coverage	~500 species	Various	Primarily human and mouse	~475 species
Visuals	Species-specific custom	Reference and species-specific	Animated, cartoonish	Non-standardized
Primary usage	PGDB, computational biology	PGDB, pathway comparisons	Human pathways, disease	Simulations, modeling

Pathway Databases

- Other metabolic pathway databases

Metabolic Pathways of Biochemistry



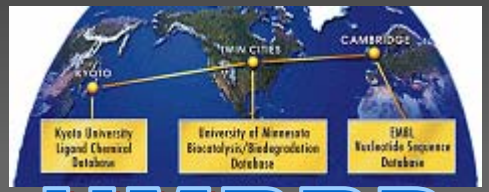
P. D. S.
Pathway Database System

PATIKA

NCGR
PathDB

Reactome

BRENDA



UMBBD

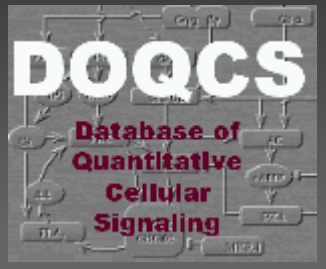
NetBiochem

Pathway Databases

- Some signaling transduction pathway databases













Pathway Databases

- Some gene regulatory network databases

DBTBS

TRANSFAC

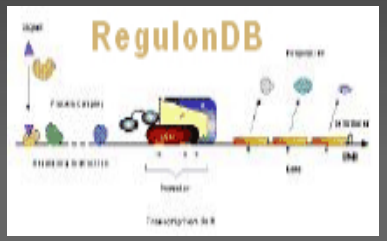
SPAD

PROkaryotIC Database Of Gene Regulation

TRRD 4.x
Transcription Regulatory Region Database
Institute of Cytology and Genetics
Novosibirsk, Russia

COMPEL





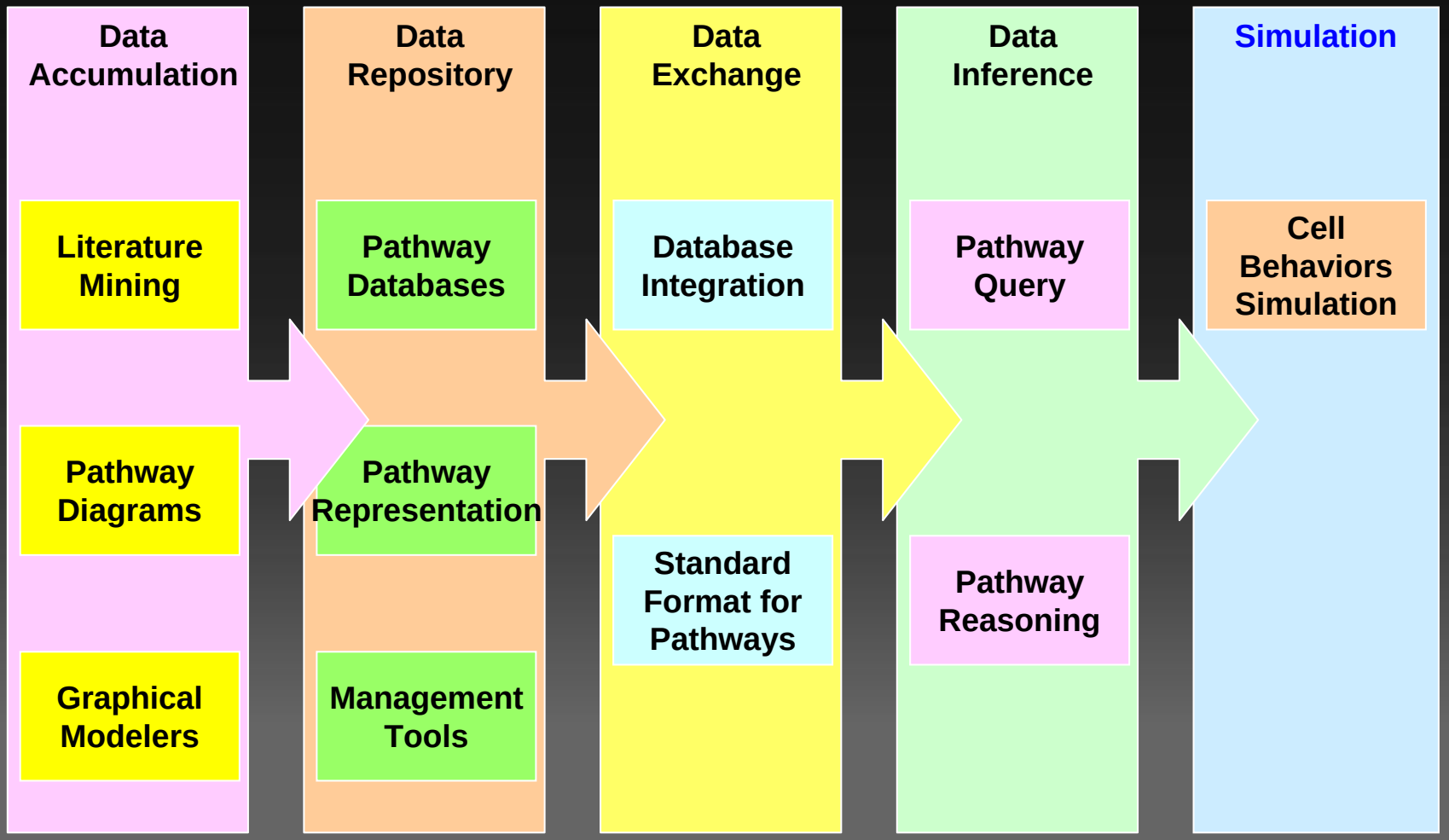
Higher-order systems

- What is molecular pathways
- Types of molecular pathways
- Why study pathways and networks
- What information is needed
- Inferring pathways and networks
- Pathway and cellular simulations

Why study pathways and networks

- **To understand the mechanism of organism**
  - guidance for biologists to design experiments.
  - helps pharmacist to design drugs easier.
  - understand the difference of mechanism between species.
- **Enable us to do the simulation (systems biology)**
  - saves time and money for biologists to do experiments.
  - predicts the behaviors by a special treatment for an organism.
- **Towards synthetic biology**
  - combines science and engineering in order to design and build novel biological functions and systems

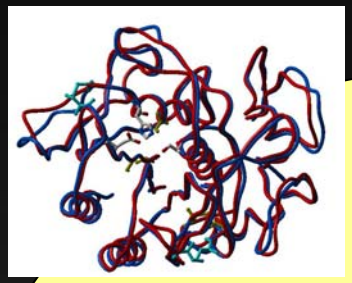
Why study pathways and networks

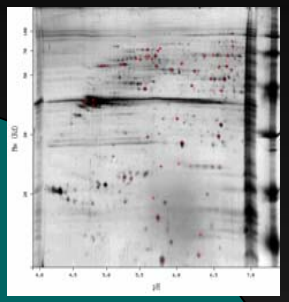


Higher-order systems

- What is Biochemical Pathways
- Types of Biochemical Pathways
- Why Pathway Studies is Important
- What information is needed
- Inferring pathways and networks
- Pathway and cellular simulations

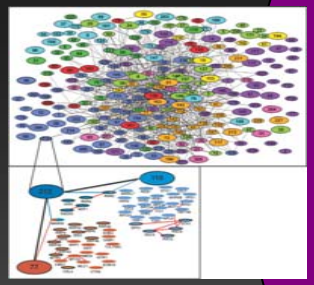
Information needed





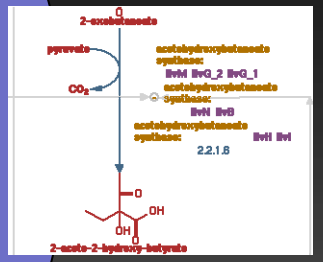
Structural genomics

Proteomics

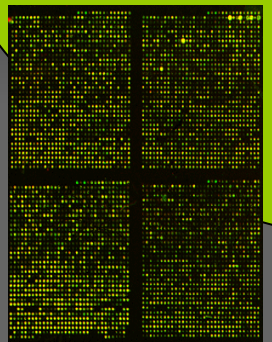


Interactionics

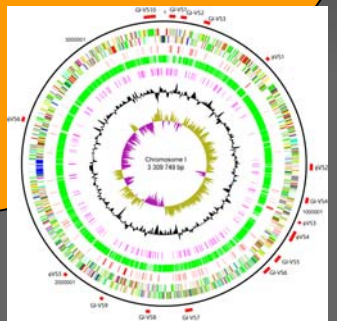
Metabolomics



Transcriptomics



Genomics



Information needed

- **Genomics data:**
- **Transcriptomics data:**
- **Proteomics data:**
- **Metabolomics data:**
- **Interactiomics data:**
- **Other experimental data:**
  - Any experiment, high-throughput or otherwise, in which data values are assigned to **genes**, **proteins**, **reactions**, **metabolites** or **reaction flux data (fluxomics)** can be viewed in a pathway context.

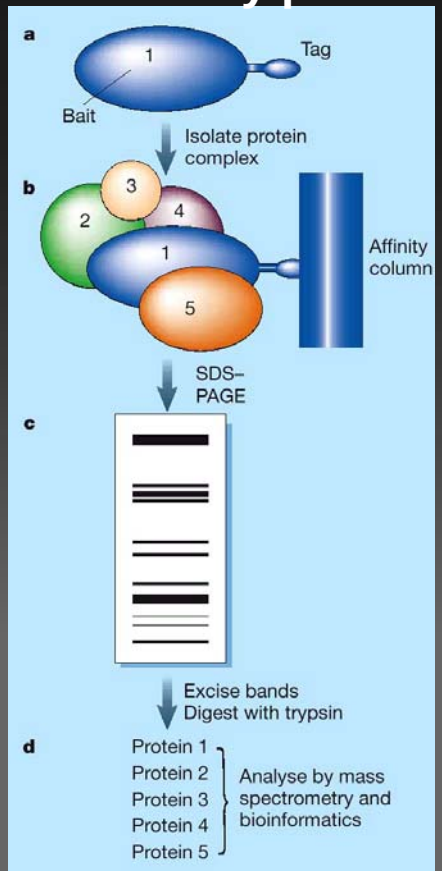
Information needed

- Interactiomics
  - Co-immunoprecipitation
  - Fluorescence resonance energy transfer (FRET)
  - Label transfer
  - Tandem affinity purification (TAP)
  - Two-hybrid screening
  - Chemical crosslinking
  - Dual Polarisation Interferometry (DPI)
  - Protein-protein docking
  - Static Light Scattering (SLS)
  - Chemical crosslinking followed by MS

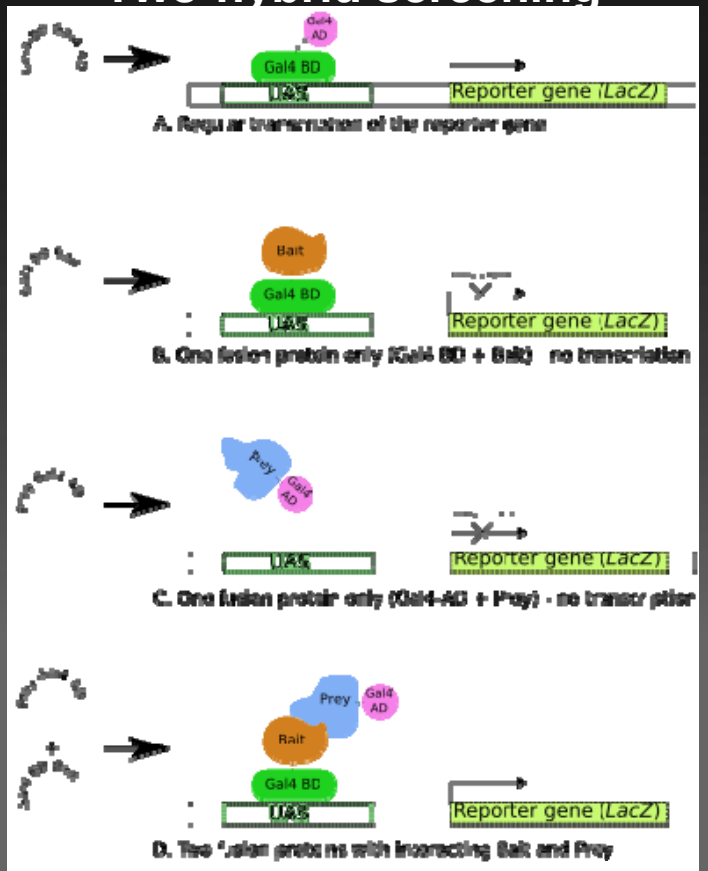
Information needed

- Interactiomics

TAP- Tandem affinity purification



Two-hybrid screening



Higher-order systems

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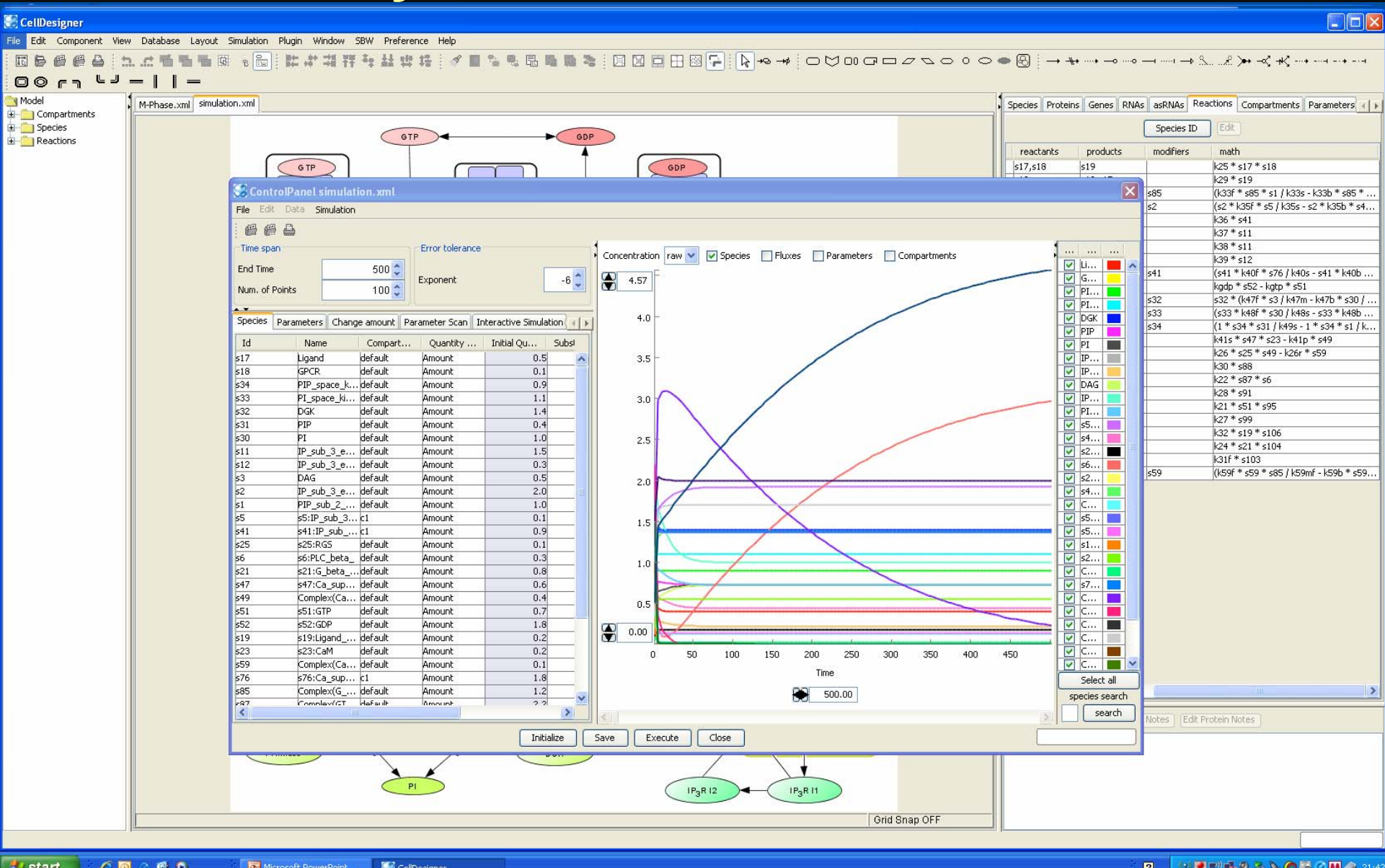
Inferring pathways and networks

- Experimental methods
  - Proteomics
  - Transcriptomics
  - Yeast two-hybrid assay
  - Mutants – knockout / Rescue - overexpression
- Computational methods
  - Database-driven protein-protein interactions
  - Expression clustering techniques
  - Literature-mining for specified interactions

Higher-order systems

- What is Biochemical Pathways
- Types of Biochemical Pathways
- Why Pathway Studies is Important
- What information is needed
- Methods of inferring pathways and networks
- Pathway and cellular simulations

Pathway and cellular simulations



Towards synthetic biology

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RESEARCH ARTICLES

Genome Transplantation in Bacteria: Changing One Species to Another

Carole Lartigue, John I. Glass,* Nina Alperovich, Rembert Pieper, Prashanth P. Parmar, Clyde A. Hutchison, III, Hamilton O. Smith, J. Craig Venter

As a step toward propagation of synthetic genomes, we completely replaced the genome of a bacterial cell with one from another species by transplanting a whole genome as naked DNA. Intact genomic DNA from *Mycoplasma mycoides* large colony (LC), virtually free of protein, was transplanted into *Mycoplasma capricolum* cells by polyethylene glycol–mediated transformation. Cells selected for tetracycline resistance, carried by the *M. mycoides* LC chromosome, contain the complete donor genome and are free of detectable recipient genomic sequences. These cells that result from genome transplantation are phenotypically identical to the *M. mycoides* LC donor strain as judged by several criteria.

The J. Craig Venter Institute, Rockville, MD 20850, USA.

* To whom correspondence should be addressed. E-mail: jglass@jcvi.org

It has been known ever since Oswald Avery's pioneering experiments with pneumococcal transformation more than

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