Моделирование метаболических путей

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Метаболи́зм (от греч. μεταβολή — «превращение, изменение»), — набор химических реакций, которые протекают в живом организме и способствуют поддержанию жизни.

Метаболический путь – совокупность метаболических реакций

Метаболиты – субстраты и продукты, участвующие в реакциях

Цели и задачи метаболического моделирования

Научные задачи:

•систематизация накопленных экспериментальных данных

•исследование механизмов клеточной регуляции в сложных биохимических системах

•объяснение экспериментально установленных фактов и предсказание новых ещё не выявленных внутриклеточных явлений

Биоинженерные задачи:

•разработка новых лекарств

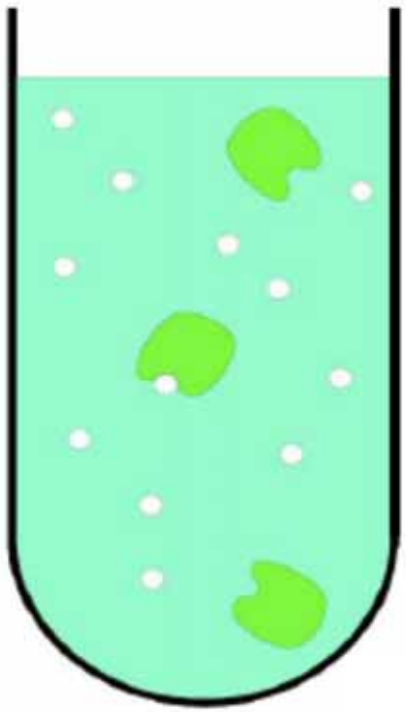
•оптимизация получения необходимых веществ из бактериальных клеток и других организмов

•разработка новых штаммов с наперед заданными свойствами

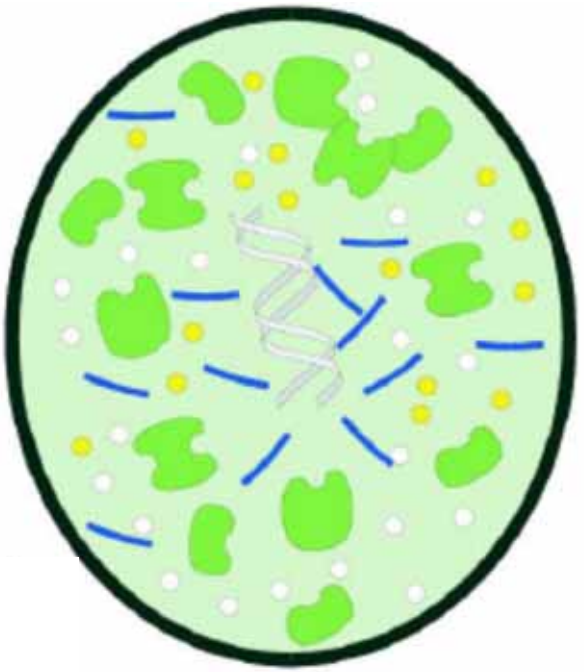
•оптимизация уже существующих промышленных штаммов

Уровни исследования метаболических реакций

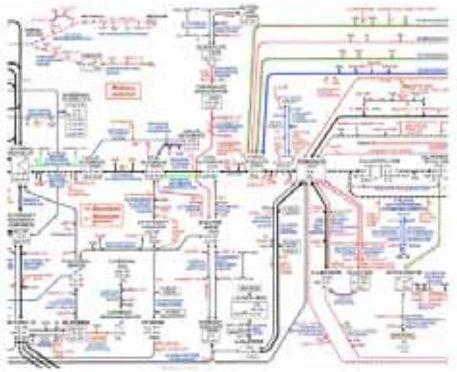
In vitro

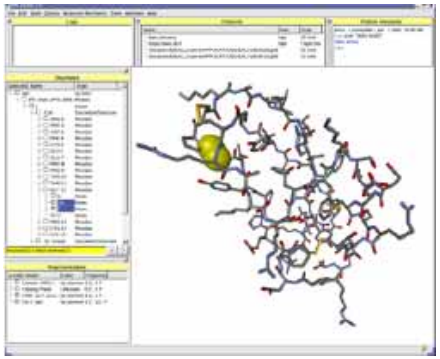


In vivo

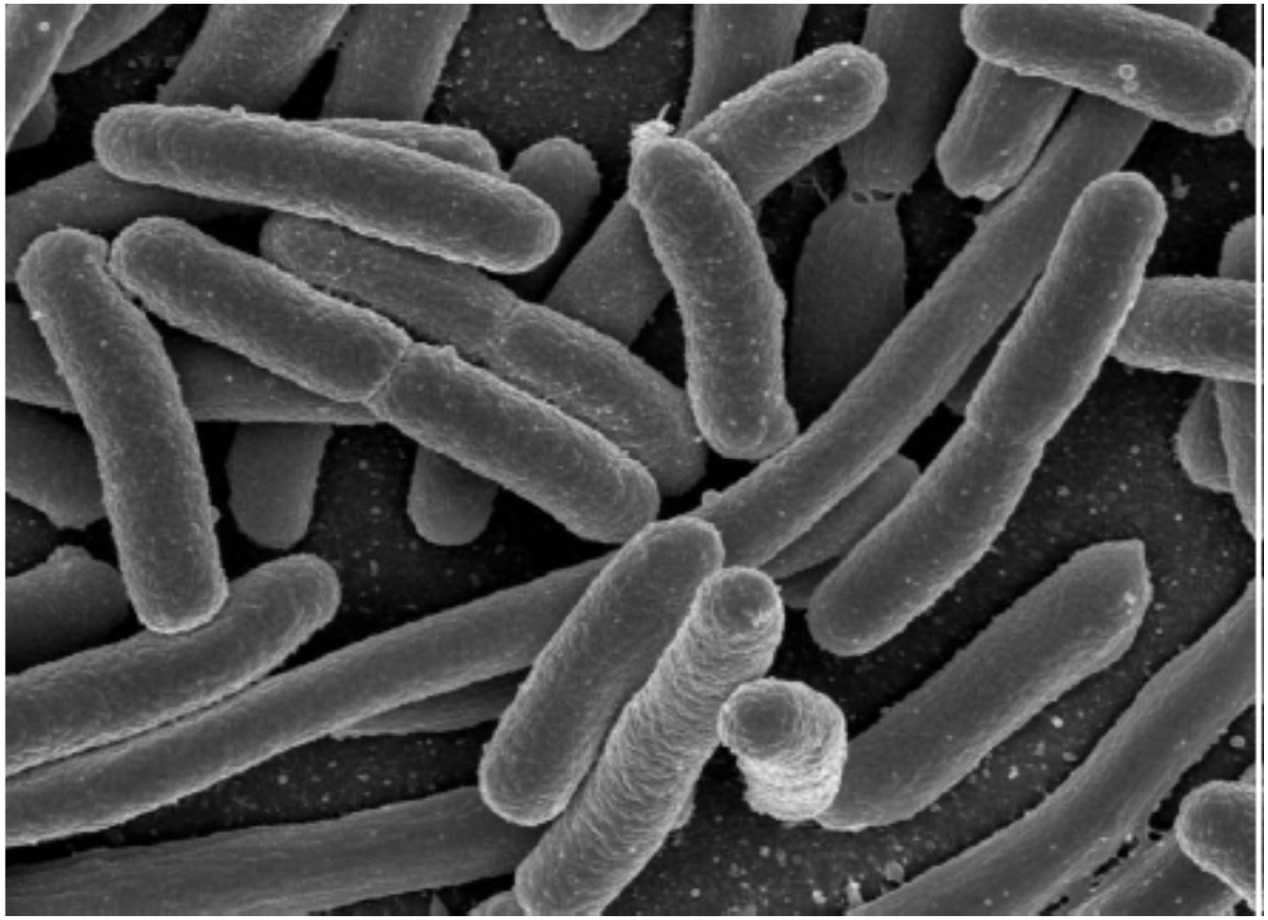


In silico





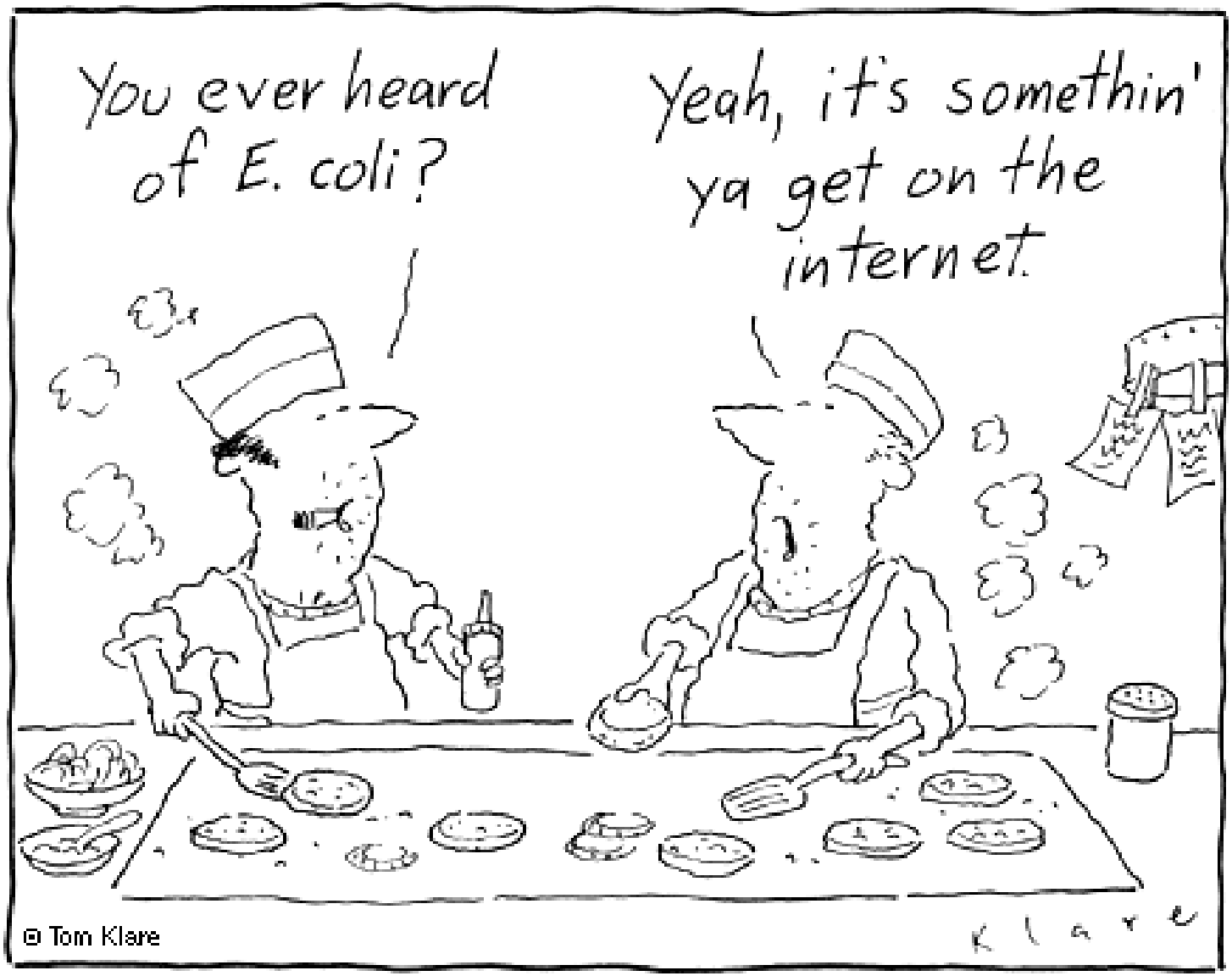
Моделирование метаболических путей *Escherichia coli*



http://www3.niaid.nih.gov/NR/rdonlyres/49477C30-0513-47BE-88FC-17974CB1F952/0/e_coli.jpg)

Escherichia coli – удобный объект для моделирования клеточного метаболизма

Электронная клетка: миф или реальность?



Теоретические подходы и концепции метаболического моделирования

Классический системный подход

1. выделить элементарные единицы системы
2. охарактеризовать все значимые взаимодействия между единицами
3. организовать единицы как иерархию взаимодействующих модулей
4. описать состояние каждой единицы и каждого взаимодействия количественно

W. Wiechert and R. Takors. Validation of Metabolic Models: Concepts, Tools, and Problems, pages 277–320. Horizon Scientific Press (Horizon Bioscience), 2004.

Данные для верификации метаболической модели

1. Многие (но не все) внутриклеточные концентрации метаболитов могут быть измерены.
2. Активности ферментов могут быть определены из клеточных экстрактов.
3. В стационарном состоянии большинство метаболических потоков может быть определено с помощью изотопа ^{13}C.
4. Кинетические константы многих реакций измерены и собраны в базы данных.

W. Wiechert and R. Takors. Validation of Metabolic Models: Concepts, Tools, and Problems, pages 277–320. Horizon Scientific Press (Horizon Bioscience), 2004.

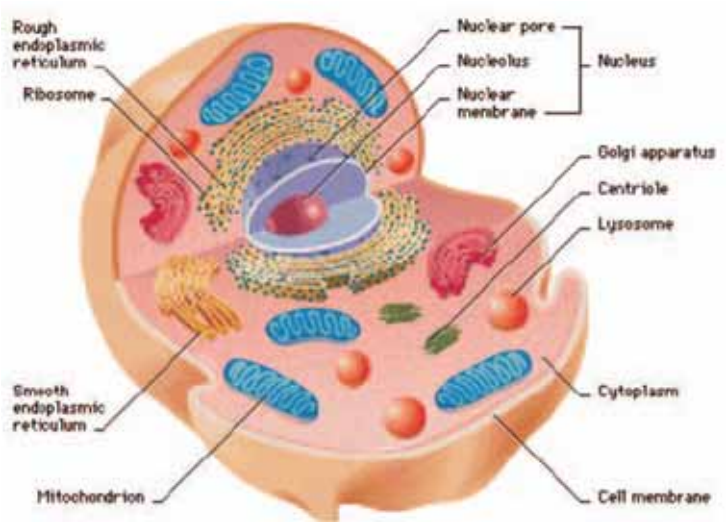
Количественные знания ограничены

1. Существует большая разница между дискретными данными, получаемыми в экспериментах и непрерывными физиологическими процессами.
2. Технические ограничения (несовершенство приборов).
3. Данные о некоторых клеточных процессах отсутствуют.
4. Данные собираются для разных штаммов, разных организмов, в разных экспериментальных условиях.

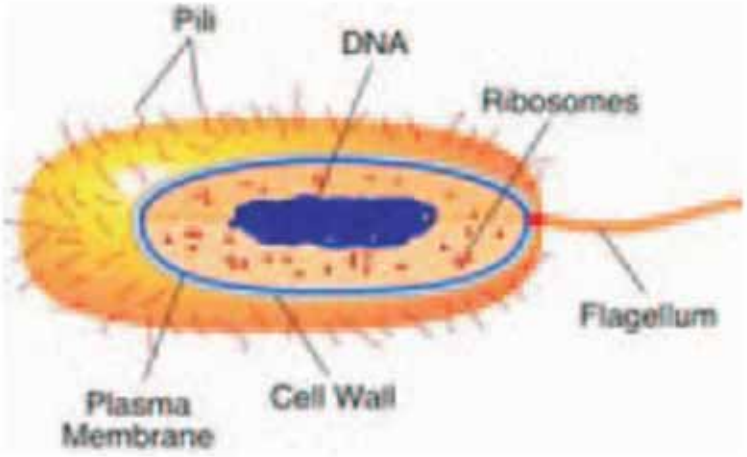
W. Wiechert and R. Takors. Validation of Metabolic Models: Concepts, Tools, and Problems, pages 277–320. Horizon Scientific Press (Horizon Bioscience), 2004.

Разные уровни сложности организации клеток

Клетка эукариот



Клетка прокариот



Клеточные процессы локализованы в разных компартментах

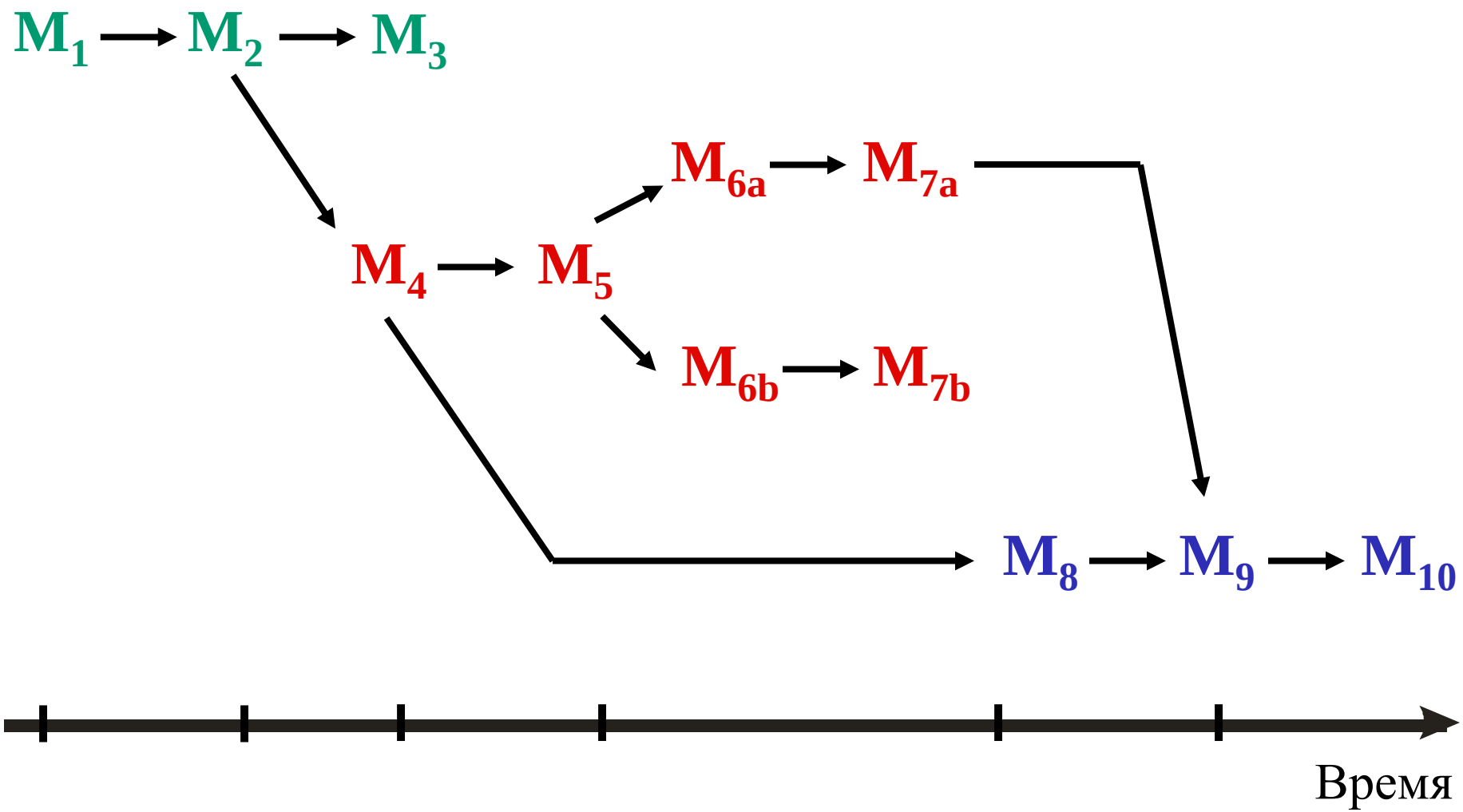
Все процессы протекают в одном компартменте

Как строятся метаболические модели

1. Метаболическая реакция добавляется, убирается или заменяется на другую.
2. Механизм реакции усложняется, упрощается, заменяется другим.
3. Неизвестные кинетические параметры оцениваются с помощью фитирования.

W. Wiechert and R. Takors. Validation of Metabolic Models: Concepts, Tools, and Problems, pages 277–320. Horizon Scientific Press (Horizon Bioscience), 2004.

Эволюция модели



W. Wiechert and R. Takors. Validation of Metabolic Models: Concepts, Tools, and Problems, pages 277–320. Horizon Scientific Press (Horizon Bioscience), 2004.

Типы метаболических моделей

кинетические модели – системы ОДУ

- (~10-50 уравнений, ~100-500 параметров)
- описание отдельных метаболических путей
- решение модели – динамическое поведение метаболитов во времени

стехиометрические модели – системы линейных алгебраических уравнений

- (~100-1000 уравнений)
- описание метаболизма целой клетки
- решение модели – стационарное распределение метаболических потоков

“The simplest living cell is so complex that supercomputer models may never simulate its behavior perfectly.
But even imperfect models could shake the foundations of biology.”

W.Wayt Gibbs. Scientific American, 2001

«Простейшая клетка настолько сложна, что даже моделирование на суперкомпьютерах никогда не воспроизведет ее поведение в совершенстве. Но даже несовершенные модели могут потрясти основы биологии.»

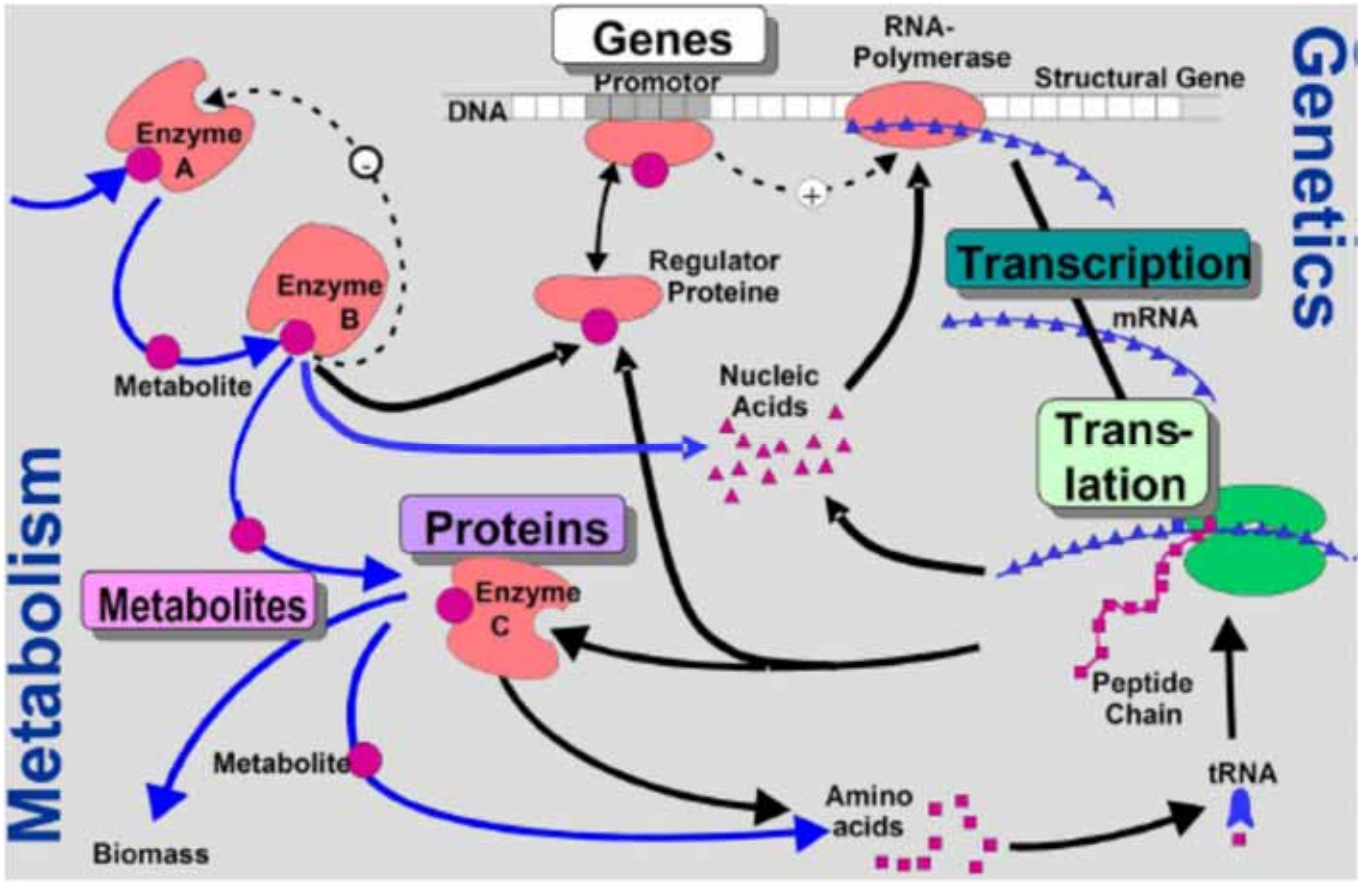
Кинетические модели

- построение схемы метаболического пути

- вывод уравнений скорости (по типу Михаэлиса-Ментен) для каждой реакции и объединение в систему дифференциальных уравнений (ОДУ)

- подбор параметров по экспериментальным данным

Escherichia coli



720 метаболических процессов
436 метаболитов
540 ферментов

Figure from Ermir Qeli
Information Visualization Techniques for Metabolic Engineering
Dissertation zur Erlangung des akademischen Grades Doktor der Naturwissenschaften (Dr. rer. nat)

Описание метаболизма включает:
мембранные транспортные процессы,
центральные катаболические пути,
биосинтетические пути (продукция всех компонент биомассы),
использование альтернативных источников углерода

Метаболические пути *Escherichia coli*

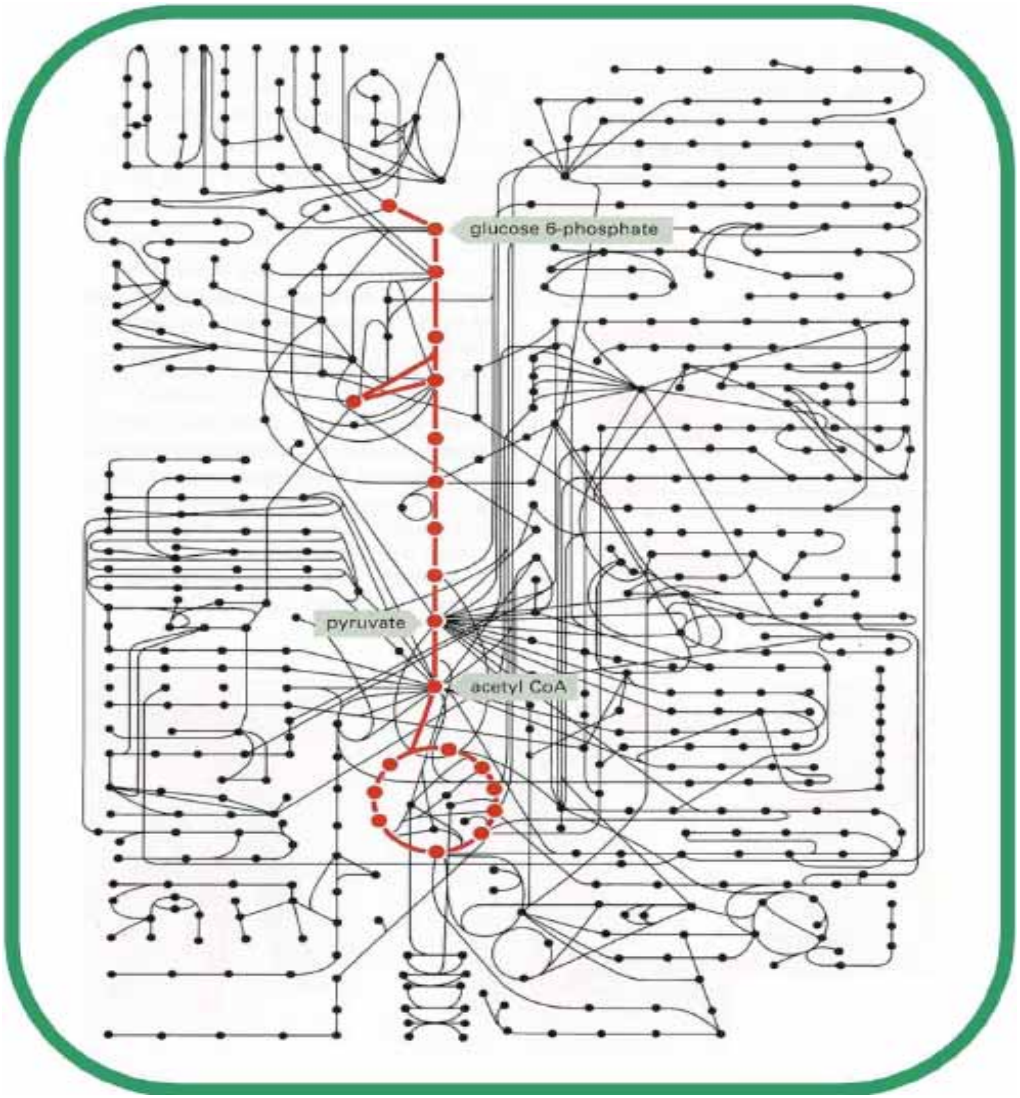


Figure from Ermir Qeli
Information Visualization Techniques for Metabolic Engineering
Dissertation zur Erlangung des akademischen Grades Doktor der Naturwissenschaften (Dr. rer. nat)

Красным цветом выделены центральные метаболические пути

Центральные метаболические пути

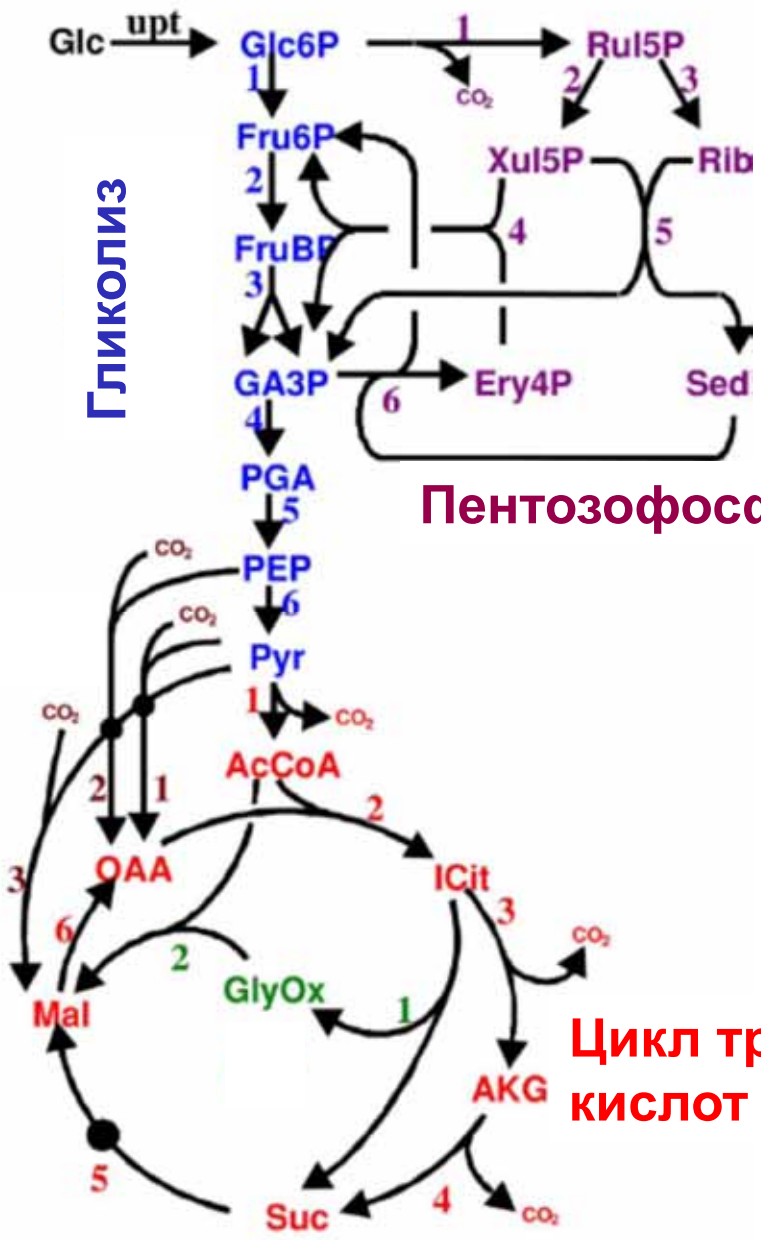
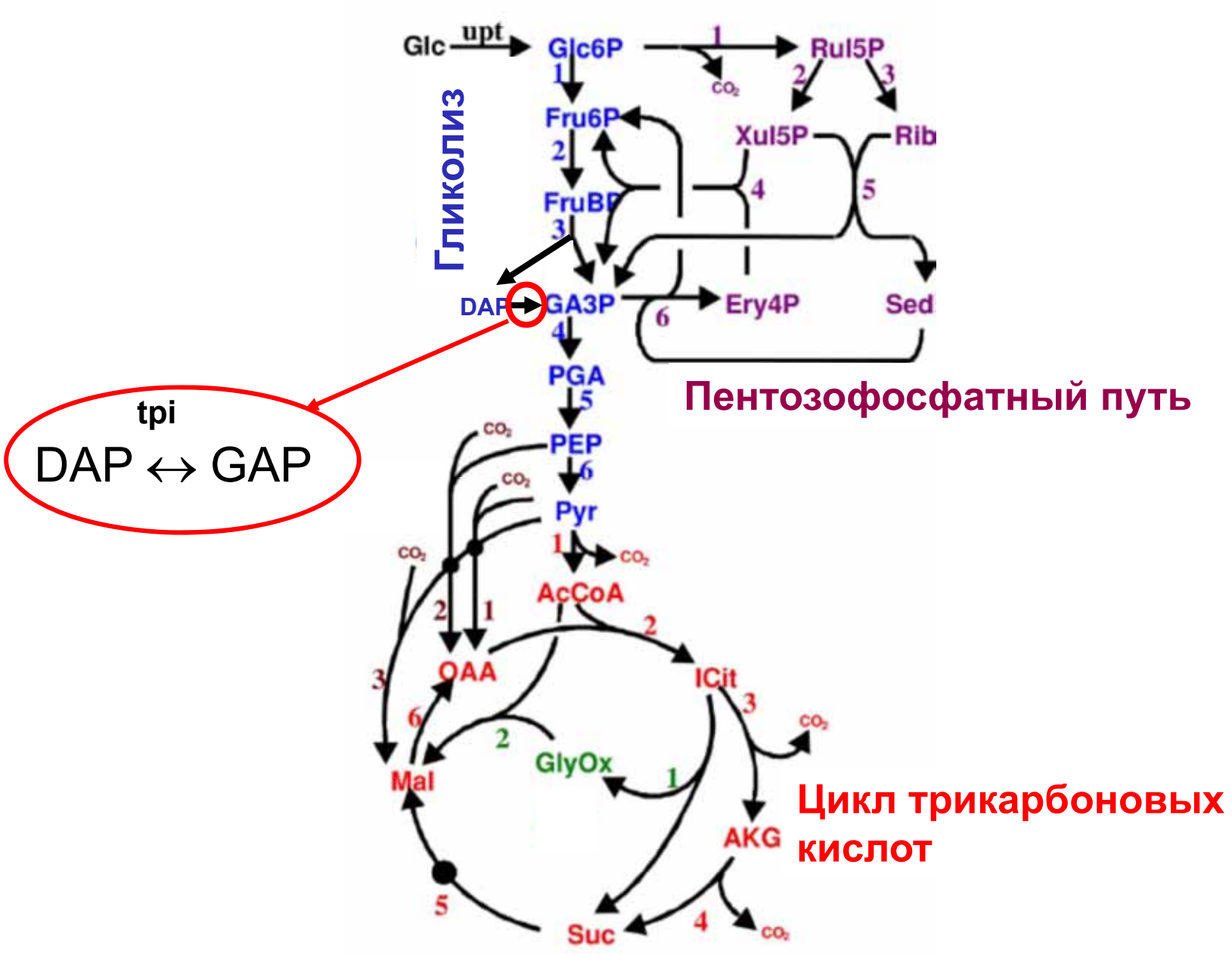
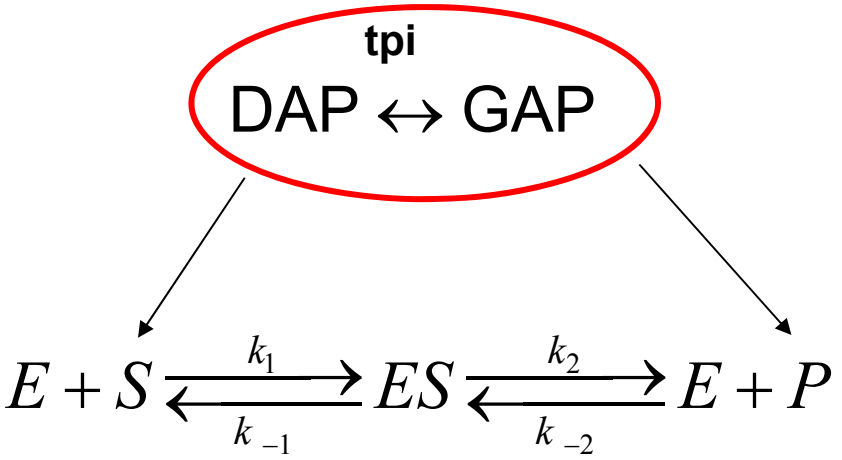


Figure from Ermir Qeli
Information Visualization Techniques for Metabolic Engineering
Dissertation zur Erlangung des akademischen Grades Doktor der Naturwissenschaften (Dr. rer. nat)

Центральные метаболические пути

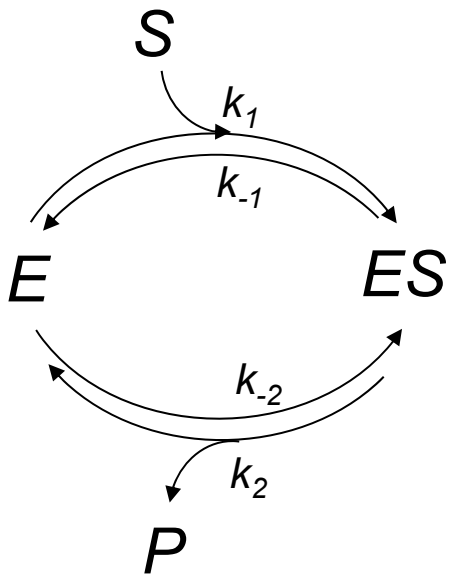


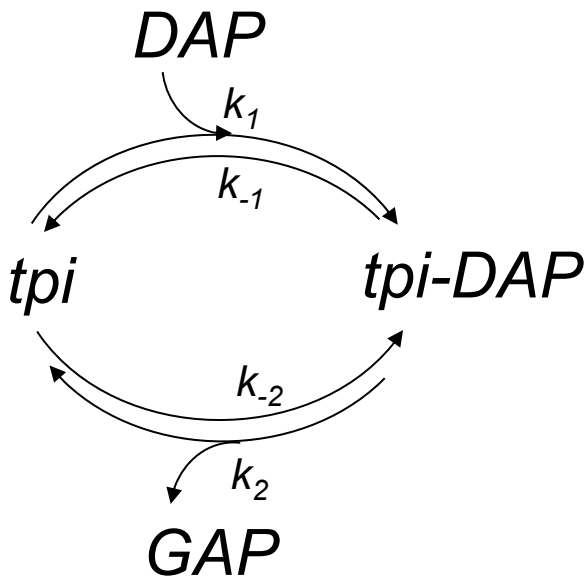
Вывод уравнения скорости



Кинетическая схема взаимодействия субстрата и продукта с ферментом

Каталитический цикл фермента





Вывод уравнения скорости

Кинетическая схема взаимодействия субстрата и продукта с ферментом:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} E + P$$

Соответствующая система дифференциальных уравнений:

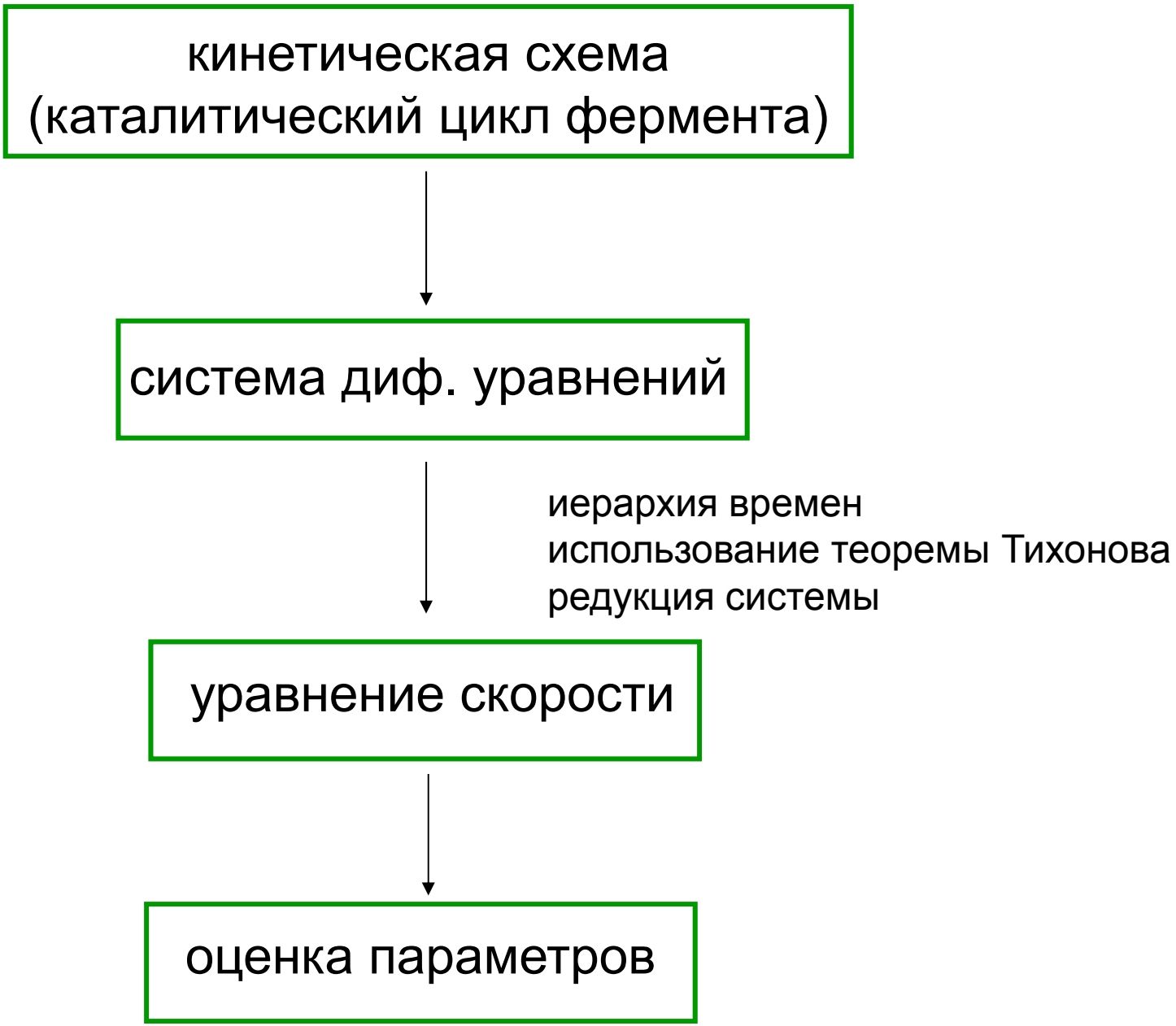
$$\left.\begin{aligned} \frac{dS}{dt} &= -k_1 \cdot S \cdot E + k_{-1} \cdot ES \\ \frac{dP}{dt} &= k_2 \cdot ES - k_{-2} \cdot E \cdot P \end{aligned}\right\}$$ медленные переменные

$$\left.\begin{aligned} \frac{dE}{dt} &= -k_1 \cdot S \cdot E + k_{-1} \cdot ES + k_2 \cdot ES - k_{-2} \cdot E \cdot P \\ \frac{dES}{dt} &= k_1 \cdot S \cdot E - k_{-1} \cdot ES - k_2 \cdot ES + k_{-2} \cdot E \cdot P \end{aligned}\right\}$$ быстрые переменные

Уравнение скорости:

$$\frac{dP}{dt} = -\frac{dS}{dt} = V = E_0 \frac{k_2 \frac{S}{K_m^S} - k_{-2} \frac{P}{K_m^P}}{1 + \frac{S}{K_m^S} + \frac{P}{K_m^P}}$$

Описание ферментативной реакции



Уравнения скорости для триозофосфат изомеразы (tpi)

tpi

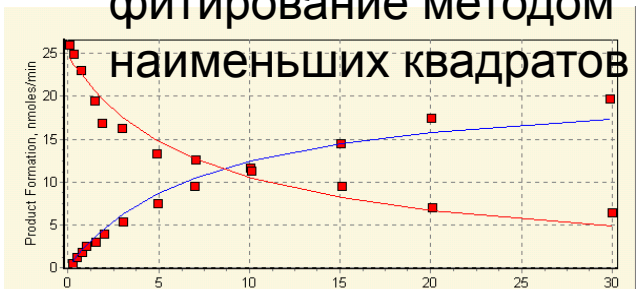
DAP ↔ GAP

$$V = E_0 \frac{k_2 \frac{C_{DAP}}{K_m^{DAP}} - k_{-2} \frac{C_{GAP}}{K_m^{GAP}}}{1 + \frac{C_{DAP}}{K_m^{DAP}} + \frac{C_{GAP}}{K_m^{GAP}}}$$

Определение констант:

эксперимент

фитирование методом наименьших квадратов



литература
базы данных

$K_m^{DAP} = 2.3$ mM

$K_m^{GAP} = 1.5$ mM

$k_2 = 45000$ 1/min,

$k_{-2} = 520000$ 1/min

константы Михаэлиса для субстрата и продукта

каталитические константы для прямой и обратной реакций (число оборотов фермента)

экспериментально измеряемые константы

Вывод системы уравнений

В общем случае

Уравнения, описывающие изменения во времени каждого метаболита:

$$\frac{dC_j}{dt} = \sum V_{ij} - \mu C_j$$

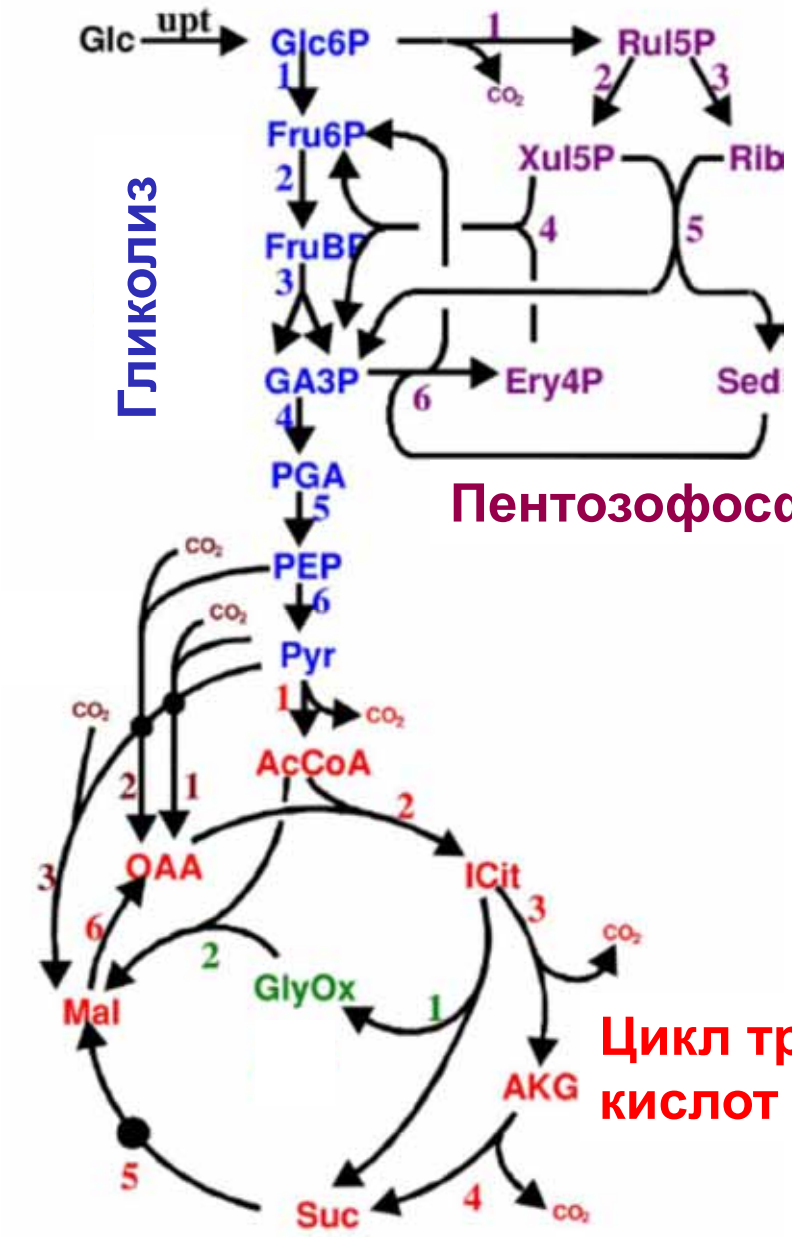
C_j – концентрация j-го метаболита

V_{ij} – скорость образования или распада j-го метаболита в i-той реакции

μC_j – уменьшение концентрации за счет клеточного роста

Моделирование центрального метаболизма *E.coli*

Manfred Rizzi et al,
Institute of Biochemical Engineering,
University of Stuttgart, Germany

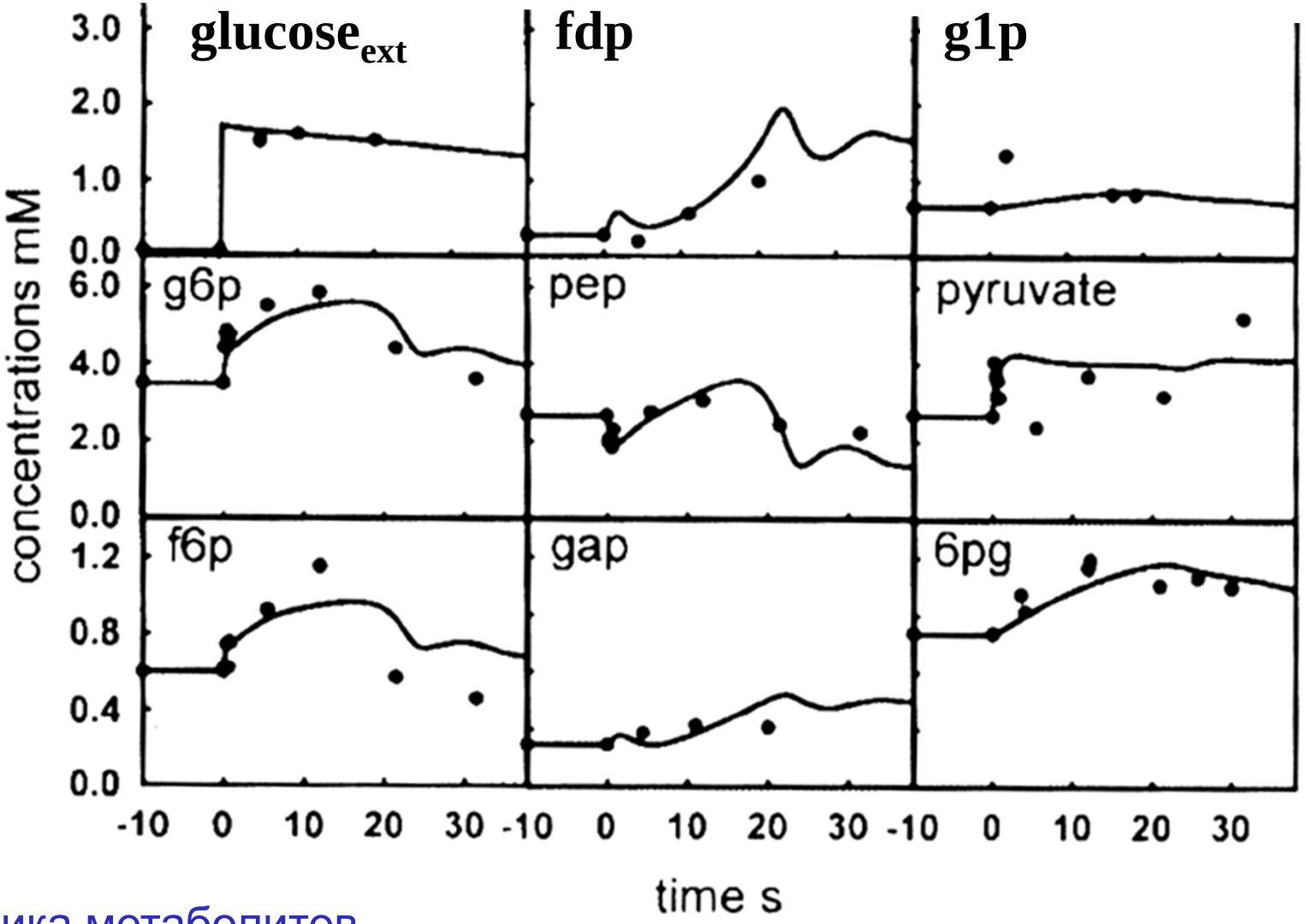


Пентозофосфатный путь

1. Вывод уравнения скорости для каждого фермента.
2. Объединение в систему уравнений для всего пути.
3. Оценка параметров.

Цикл трикарбоновых кислот

Результаты фитирования модели



Кинетика метаболитов.
Точки – экспериментальные данные
Линии – результаты численного счета

Manfred Rizzi et al,
Institute of Biochemical Engineering,
University of Stuttgart, Germany

Результаты моделирования

•Описана экспериментально наблюдаемая динамика (в том числе и колебательный процесс).

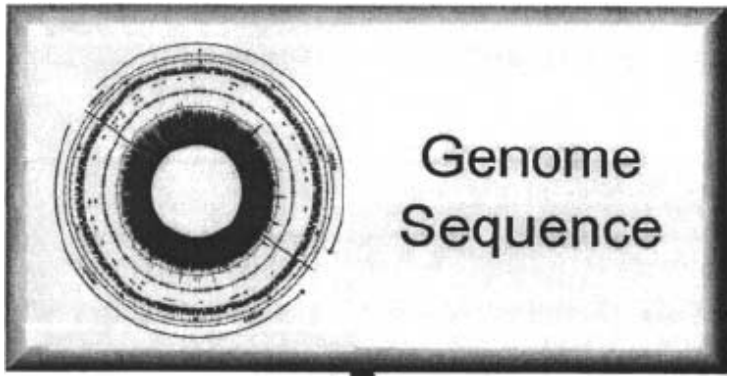
•Показано, что поглощение глюкозы в основном контролируется двумя системами: транспортной (PTS) и ее ингибиторами.

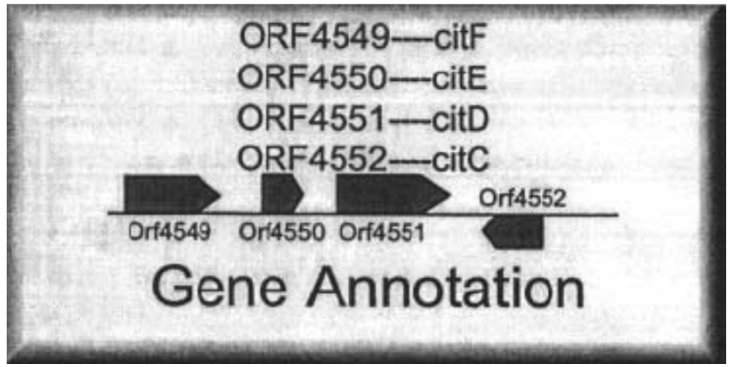
Manfred Rizzi et al,
Institute of Biochemical Engineering,
University of Stuttgart, Germany

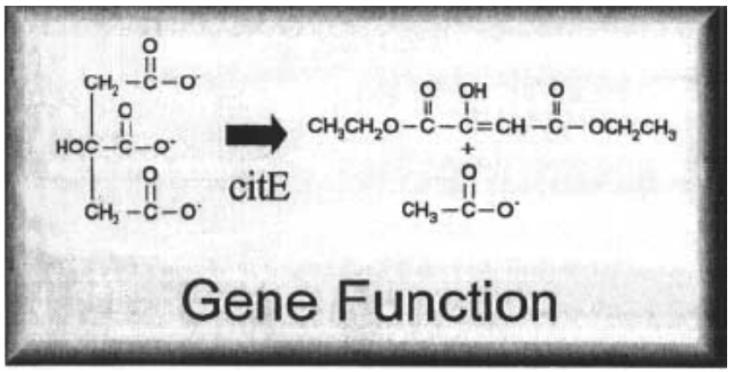
Использование баз данных для построения метаболических моделей

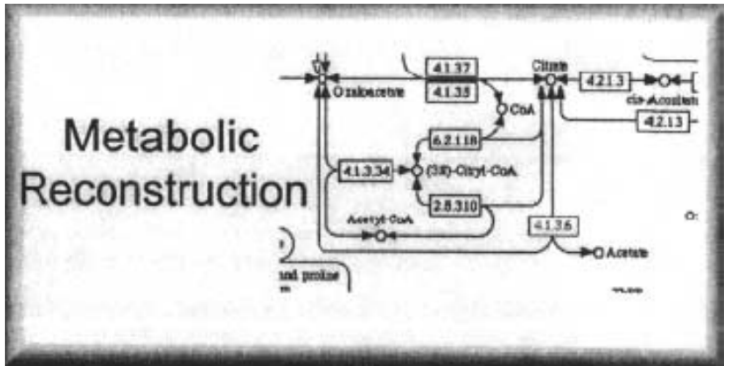
От генома до фенотипа

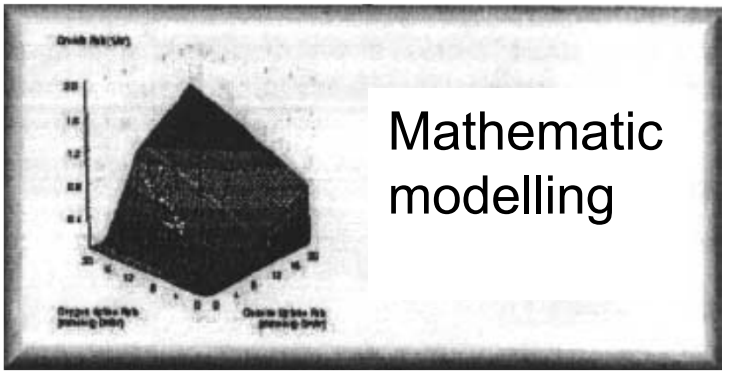
J. Edwards, M. Covert and B. Palsson
Environmental Microbiology (2002) **4**(3), 133–140

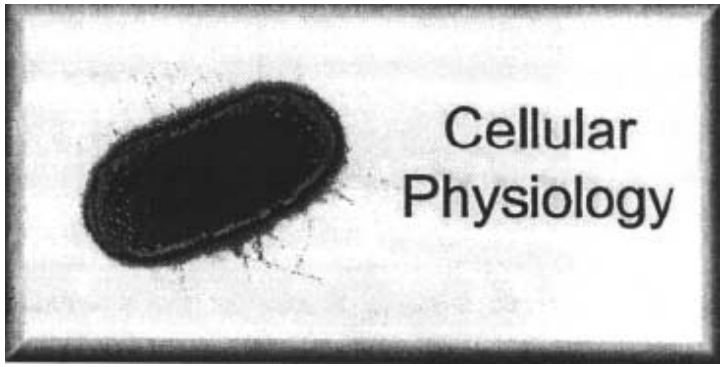












Построение метаболических моделей

Основные шаги:

- Определили последовательность генов (эксперимент)
- Выделили интересующий ген (эксперимент)
- Определили аминокислотную последовательность (базы данных)
- Определили белок (базы данных)
- Определили метаболическую реакцию (базы данных)
- Внесли в схему метаболических путей (моделирование)
- Получили картину метаболических путей (моделирование)

Базы данных по базам данным

Русскоязычный ресурс

Молекулярно-биологические базы данных

http://www.jcbi.ru/baza/index.shtml

Англоязычный ресурс

NCBI Центр биотехнологической информации

http://www.ncbi.nlm.nih.gov/

Молекулярно-биологические базы данных

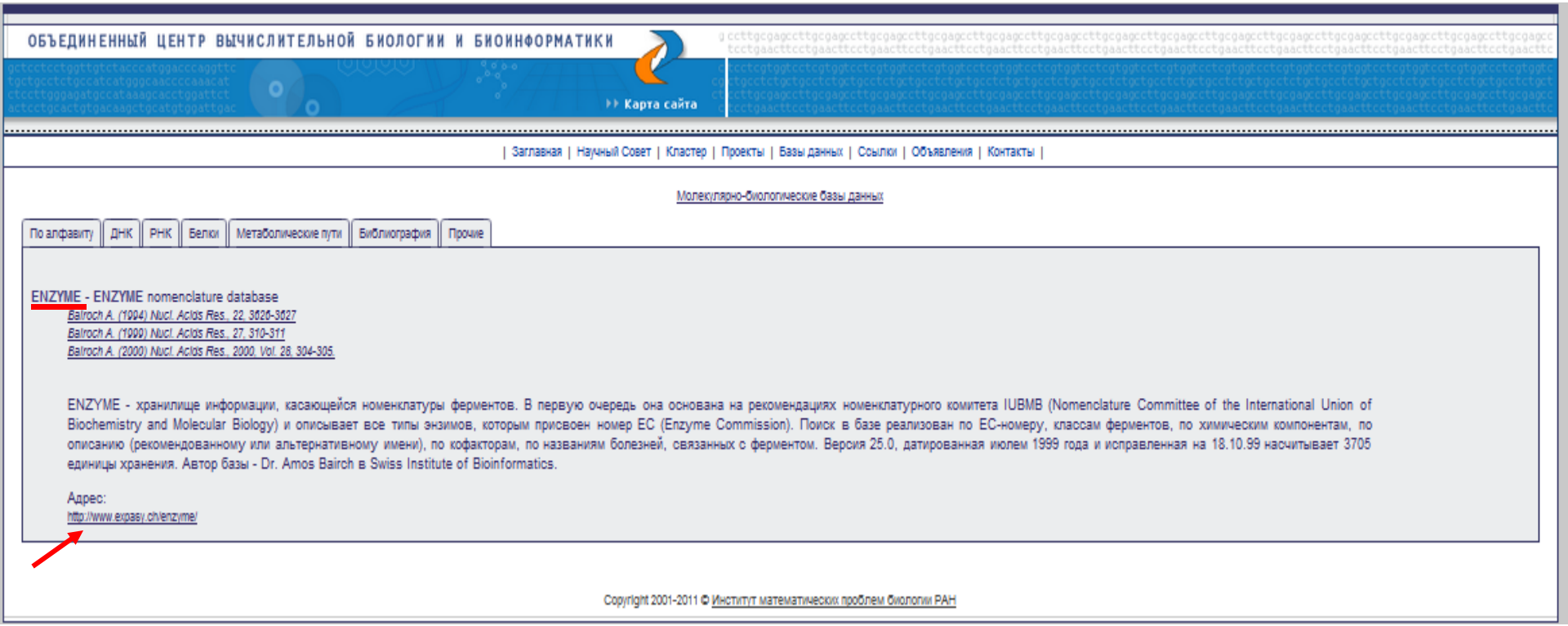
Молекулярно-биологические базы данных

По алфавиту | ДНК | РНК | Белки | Метаболические пути | Библиография | Прочие

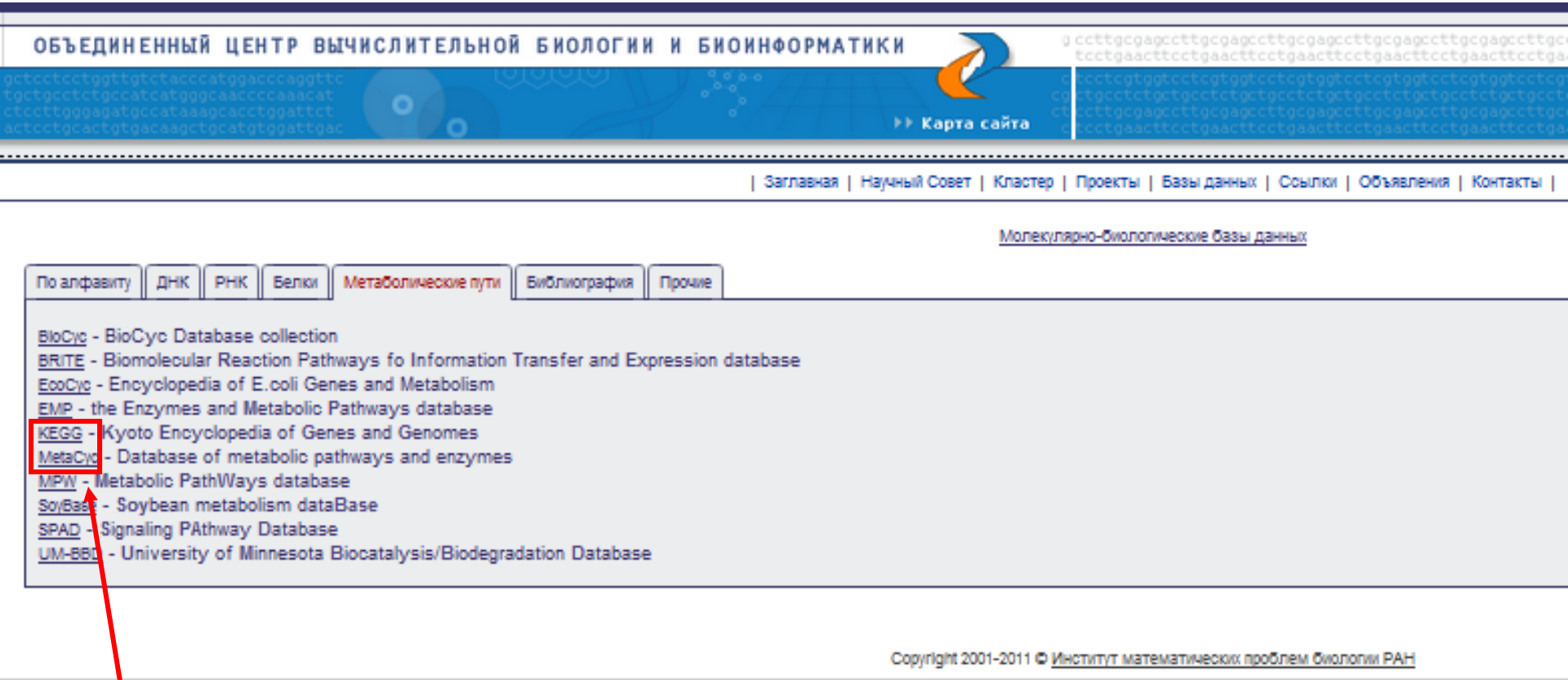
1D-структуры | 2D-структуры | 3D-структуры | Семейства | Домены | Мотивы | >>

AARSDB - AminoAcyl-tRNASynthetases DataBase
ASTRAL - The ASTRAL Compendium for Sequence and Structure Analysis
BioImage - Biological Images for scientific research
BioMagResBank [BMRB] - repository for data from NMR on proteins, peptides, and nucleic acids
Blocks - most highly conserved regions of proteins
BRENDA - enzyme database
CE - Databases and Tools for 3-D Protein Structure Comparison and Alignment
CluSTr - a database of clusters of SWISS-PROT+TrEMBL proteins
COG - the database of Clusters of Ortologous Groups of proteins
DaliDD - Dali Domain Dictionary
DIP - Database of Interacting Proteins
DOMO - protein domain database
DSSP - Dictionary of Secondary Structure of Proteins
ENZYME - ENZYME nomenclature database
FSSP - Fold classification based on Structure-Structure alignment of Proteins
GEO - Gene Expression Omnibus
GTOP - Genomes TO Protein structures and functions
Histones - Histone sequence database
HSSP - Homology-derived Secondary Structure of Proteins
HUGE - Human Unidentified Gene-Encoded large protein database
InParanoid - Eukaryotic Ortholog Groups Database
IProClass - an integrated, comprehensive and annotated Protein Classification database
ISSD - Integrated Sequence-Structure Database
Kabat - Kabat database of sequences of proteins of immunological interest
Klotho - biochemical compounds declarative database
LGIC - Ligand Gated Ion Channel subunit database
LIGAND - LIGAND chemical database for enzyme reactions
MEROPS - Peptidase database
MetaFam - a comprehensive protein family resource
MMDB - Molecular Modelling DataBase
MSD - Macromolecular Structure Database
OWL - Composite Protein Sequence Database
PALI - a database of Phylogeny and ALIgnment of homologous protein structures
PDB - Brookhaven Protein DataBank
PFAM - Protein families database of alignments and HMMs
PIR - Protein Information Resource
PIR-ALN - database of Protein sequence ALIgNments
PMD - Protein Mutant Database
Predictome - a database of putative functional links between proteins
PRINTS - database of protein family fingerPRINTS
ProDom - Protein Domain families database
PROSITE - PROtein SITEs and patterns dictionary
ProtRepeatsDB
Rebase - Restriction Enzyme dataBASE
SBASE - protein domain library
SCOP - Structural Classification Of Proteins
SWISS-2DPAGE
SWISS-PROT - the protein sequence data bank
The Homeodomain Resource
TIGRFAMs - a protein family resource for the functional identification of proteins
trEMBL - EMBL protein-coding DNA sequence features translated into peptide sequences
UniProt - the Universal Protein knowledgebase

Молекулярно-биологические базы данных



Молекулярно-биологические базы данных

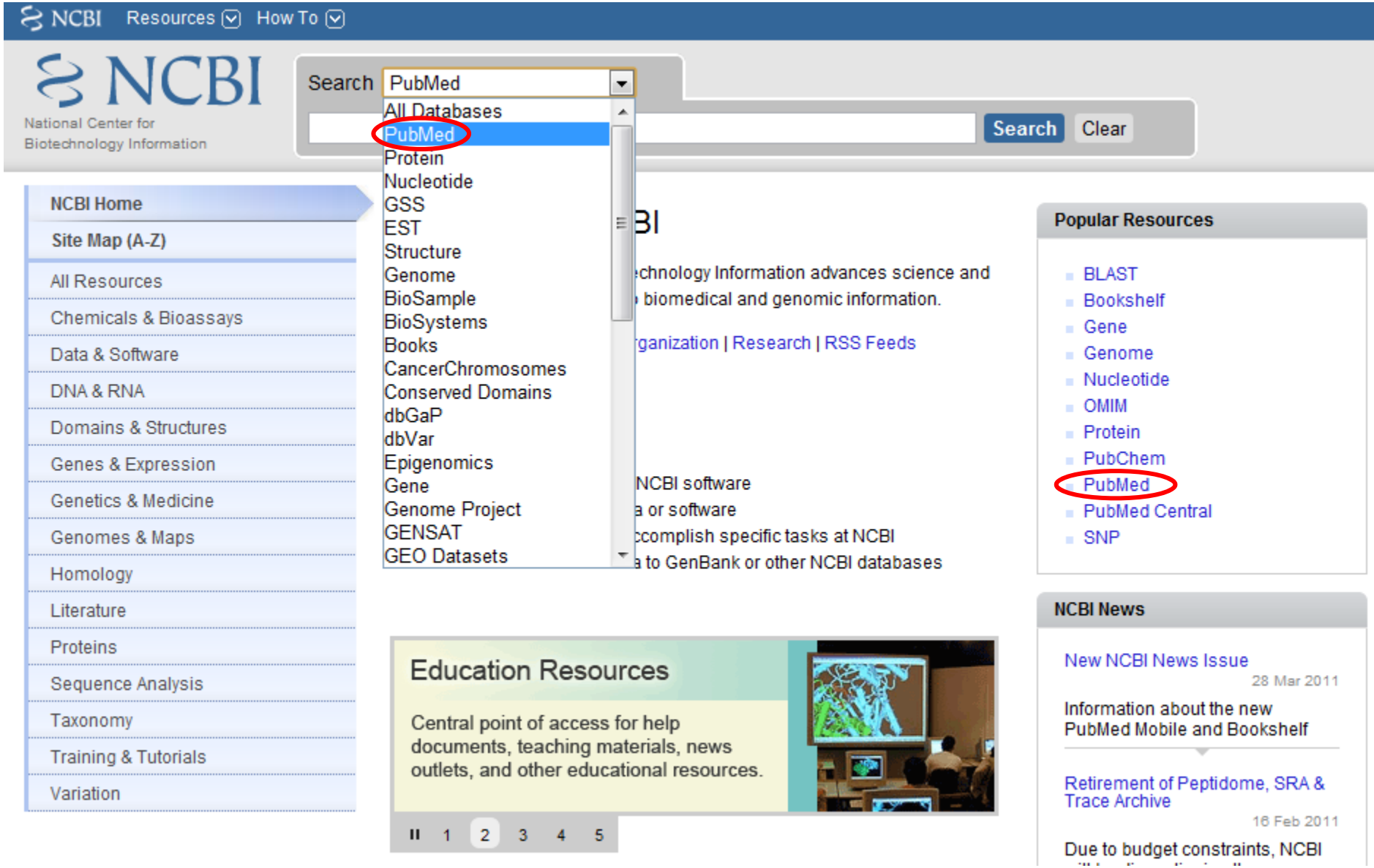


Можно использовать для построения метаболических моделей

NCBI Центр биотехнологической информации

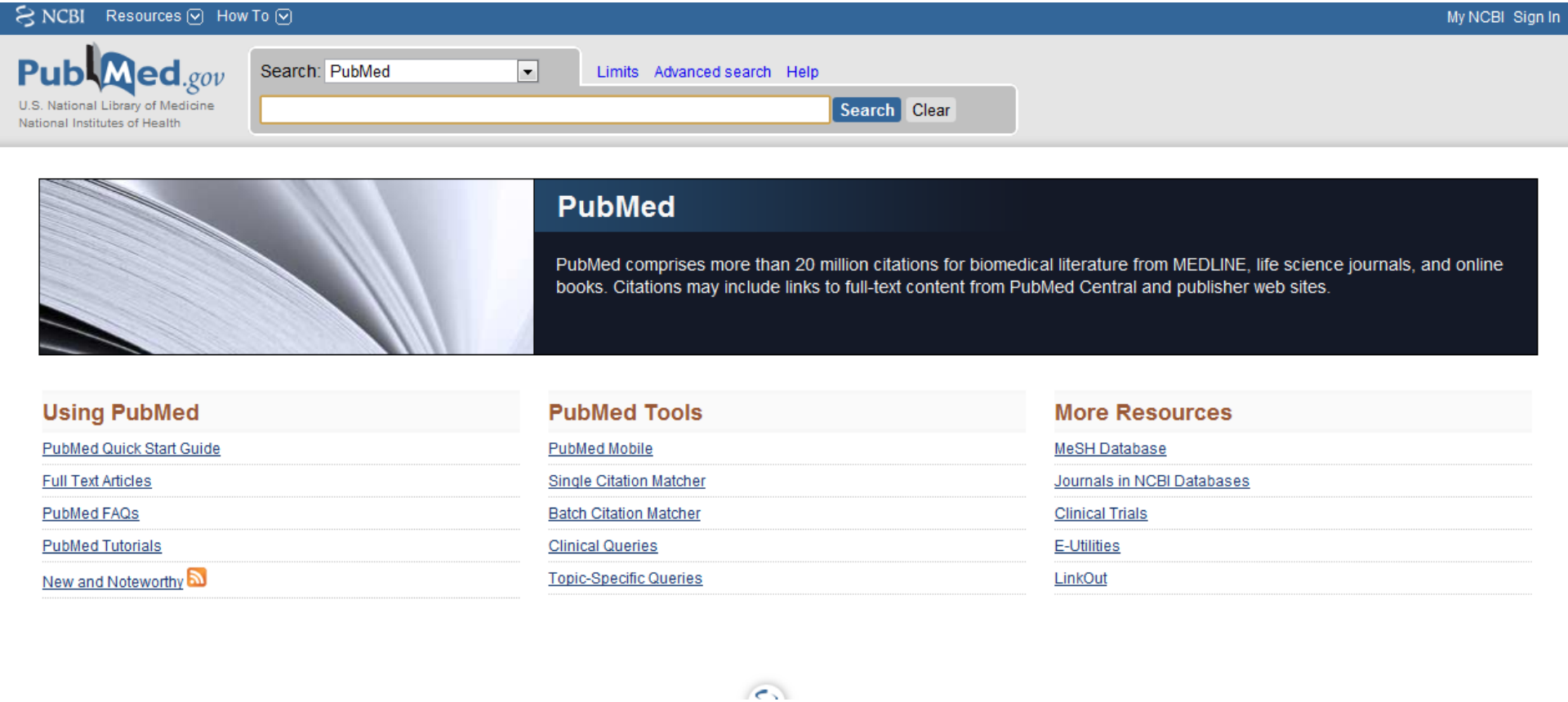
http://www.ncbi.nlm.nih.gov/

англоязычный ресурс

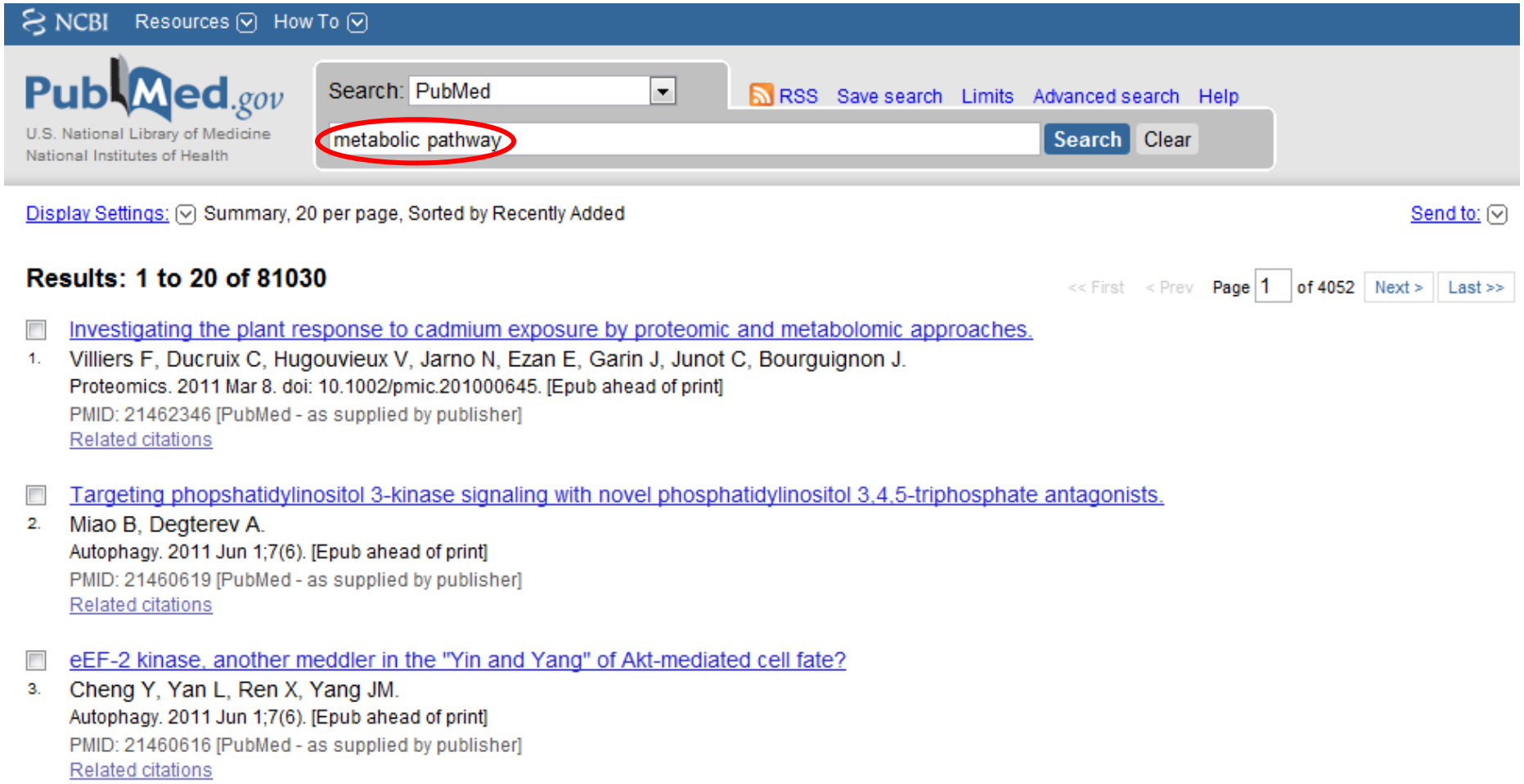


База данных по публикациям в биологии и медицине

http://www.ncbi.nlm.nih.gov/pubmed/

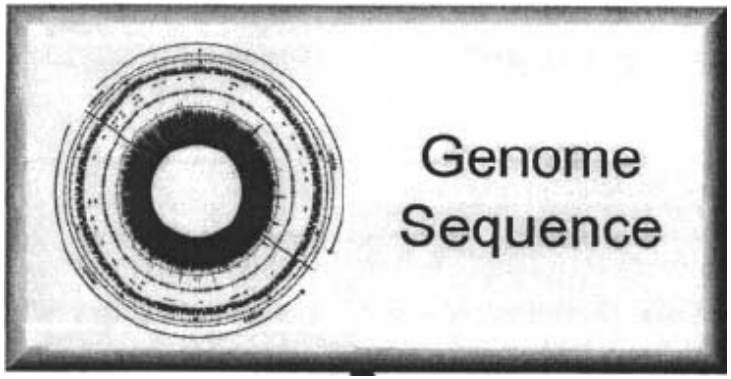


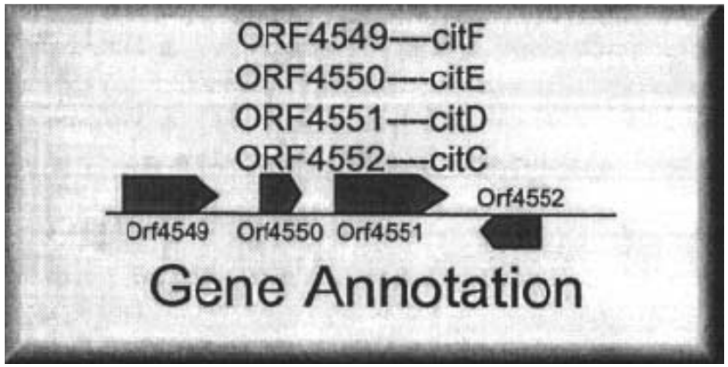
База данных по публикациям в биологии и медицине

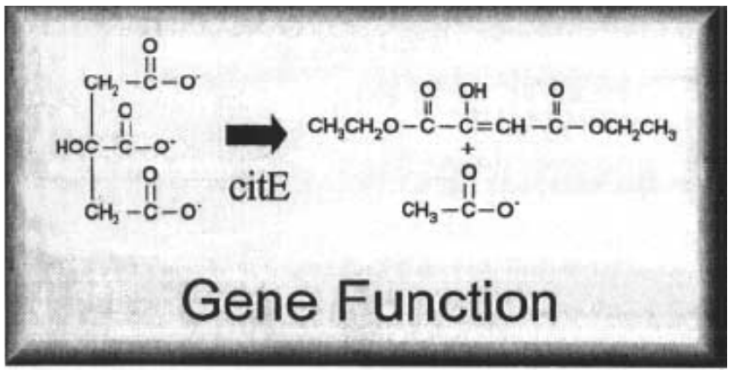


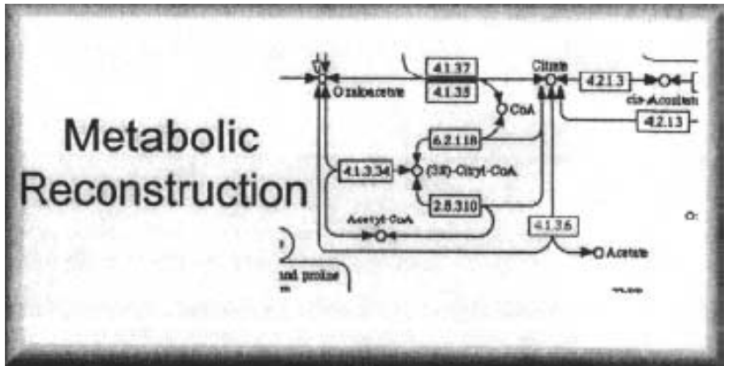
81030 ссылок на ключевые слова “metabolic pathway”

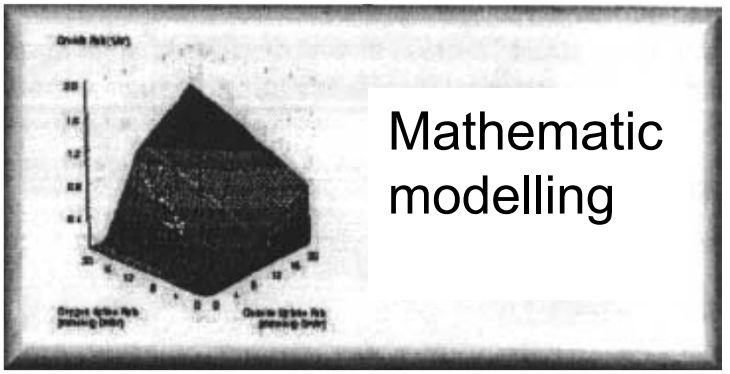
От генома до фенотипа

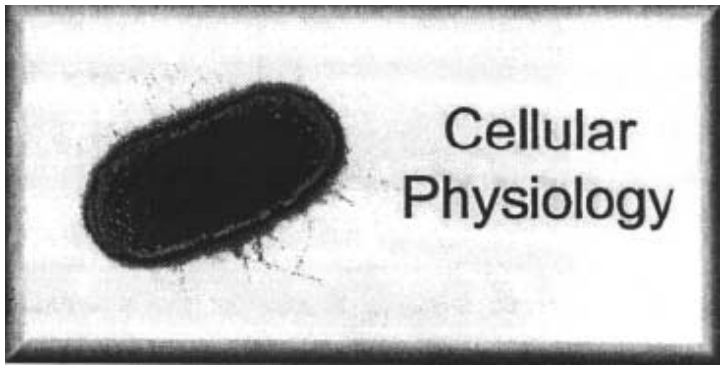










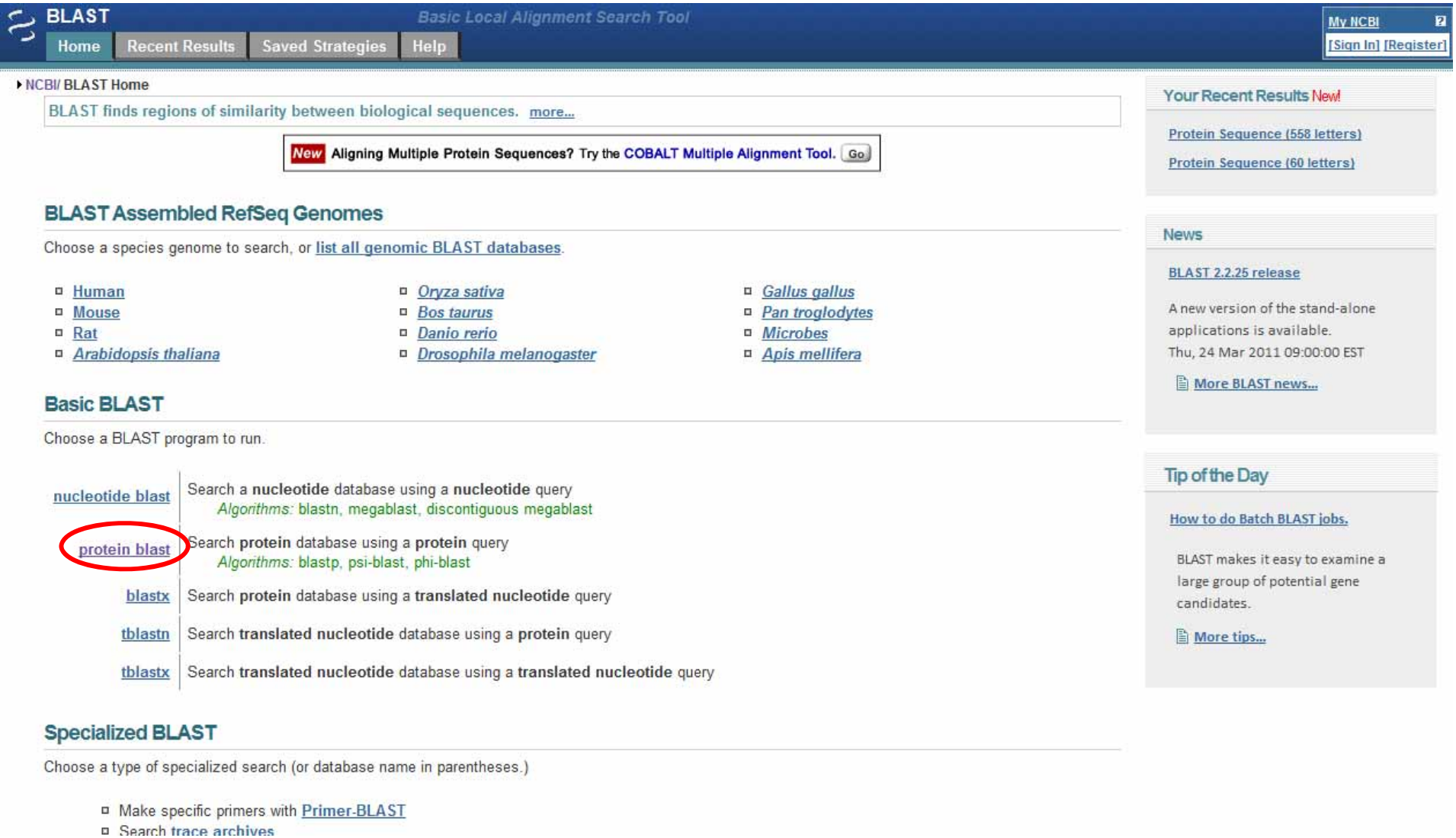


Пример аминокислотной последовательности

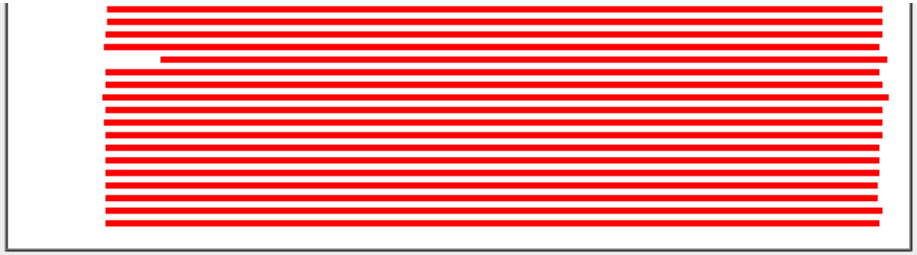
MAALTRDPQFQKLQQWYREHRSELNLRRLFDANKDRFNHFSLTLNTNHGHILVDYSKNLV
TEDVMRMLVDLAKSRGVEAARERMFNGEKINYTEGRAVLHVALRNRSNTPILVDGKDVMP
EVNKVLDKMKSFCQRVRSGDWKGYTGKTITDVINIGIGGSDLGPLMVTEALKPYSSGGPR
VWYVSNIDGTHIAKTLAQLNPESSLFIIASKTFTTQETITNAETAKEWFLQAAKDPSAVA
KHFVALSTNTTKVKEFGIDPQNMFEFWDWVGGRYSLWSAIGLSIALHVGFDNFEQLLSGA
HWMDQHFRTTPLEKNAPVLLALLGIWYINCFGCETHAMLPYDQYLHRFAAYFQQGDMESN
GKYITKSGTRVDHQTGPIVWGEPGTNGQHAFYQLIHQGTKMIPCDFLIPVQTQHPIRKGL
HHKILLANFLAQTEALMRGKSTEEARKELQAAGKSPEDLERLLPHKVFEGNRPTNSIVFT
KLTPFMLGALVAMYEHKIFVQGIIWDINSFDQWGVELGKQLAKKIEPELDGSAQVTSHDA
STNGLINFIKQQREARVQ

BLAST База данных по сравнению последовательностей

http://blast.ncbi.nlm.nih.gov/Blast.cgi



BLAST База данных по сравнению последовательностей



▼ Descriptions

Legend for links to other resources: U UniGene E GEO G Gene S Structure M Map Viewer PubChem BioAssay

Sequences producing significant alignments:

Accession	Description	Max score	Total score	Query coverage	E value	Links
AAP36518.1	Homo sapiens glucose phosphate isomerase [synthetic construct]	1169	1169	100%	0.0	
NP_000166.2	glucose-6-phosphate isomerase isoform 2 [Homo sapiens] >sp|P06	1169	1169	100%	0.0	U G M
1JLH_A	Chain A, Human Glucose-6-Phosphate Isomerase >pdb|1JLH|B Cha	1167	1167	100%	0.0	S
AAF22645.1	sperm antigen-36 [Homo sapiens]	1167	1167	100%	0.0	
1IAT_A	Chain A, Crystal Structure Of Human Phosphoglucose IsomeraseNE	1166	1166	99%	0.0	S
AAA36368.1	neuroleukin [Homo sapiens] >gb|AAB36062.1| glucose phosphate i	1165	1165	100%	0.0	G
NP_001126984.1	glucose-6-phosphate isomerase [Pongo abelii] >sp|Q5R4E3.3|G6PI	1158	1158	100%	0.0	G M
Q4R591.3	RecName: Full=Glucose-6-phosphate isomerase; Short=GPI; AltNar	1155	1155	100%	0.0	
NP_001075538.1	glucose-6-phosphate isomerase [Oryctolagus cuniculus] >sp|Q9N1	1100	1100	100%	0.0	U G M
NP_999495.1	glucose-6-phosphate isomerase [Sus scrofa] >sp|P08059.3|G6PI_I	1099	1099	100%	0.0	U G M
1N8T_A	Chain A, The Crystal Structure Of Phosphoglucose Isomerase From	1098	1098	99%	0.0	S
1G98_A	Chain A, Crystal Structure Analysis Of Rabbit Phosphoglucose Isom	1098	1098	100%	0.0	S
1GZD_A	Chain A, Crystal Structure Of Pig Phosphoglucose Isomerase >pdb|	1098	1098	99%	0.0	S
NP_001171651.1	glucose-6-phosphate isomerase isoform 1 [Homo sapiens] >dbj|BA	1097	1097	100%	0.0	U G M
BAG56947.1	unnamed protein product [Homo sapiens]	1096	1096	100%	0.0	G

Определили фермент, соответствующий выбранной последовательности:
glucose-6-phosphate isomerase

Базы данных по метаболическим путям

KEGG Pathway Database:
http://www.genome.jp/kegg/pathway.html

MetaCyc:
http://metacyc.org/

KEGG База данных по метаболическим путям

KEGG PATHWAY Database

Wiring diagrams of molecular interactions, reactions, and relations

KEGG2 PATHWAY BRITE MODULE DISEASE DRUG GENES GENOME LIGAND DBGET

Select prefix: map | Organism

Enter keywords: | Go | Help

Pathway Maps

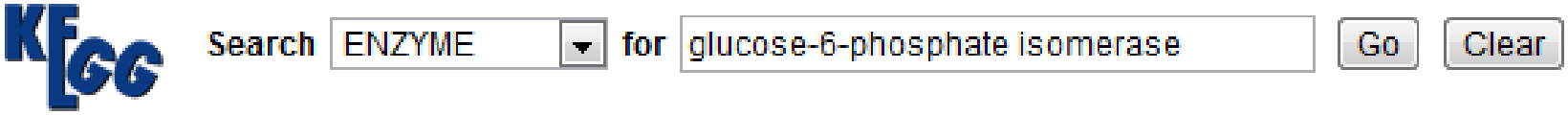
KEGG PATHWAY is a collection of manually drawn pathway maps (see new maps, change history, and last updates) representing our knowledge on the molecular interaction and reaction networks for:

- **0. Global Map**
- **1. Metabolism**
  - Carbohydrate Energy Lipid Nucleotide Amino acid Other amino acid Glycan
  - Cofactor/vitamin Terpenoid/PK Other secondary metabolite Xenobiotics Overview
- **2. Genetic Information Processing**
- **3. Environmental Information Processing**
- **4. Cellular Processes**
- **5. Organismal Systems**
- **6. Human Diseases**

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

- **7. Drug Development**

KEGG База данных по метаболическим путям



Database: ENZYME - Search term: glucose-6-phosphate isomerase (Total 1 hit)

5.3.1.9

glucose-6-phosphate isomerase; phosphohexose isomerase; phosphohexomutase; oxoisomerase; hexosephosphate isomerase; phosphosaccharomutase; phosphoglucoisomerase; phosphohexoisomerase; phosphoglucose isomerase; glucose phosphate isomerase; hexose pho • • •

DBGET integrated database retrieval system

KEGG База данных по метаболическим путям

KEGG

ENZYME: 5.3.1.9

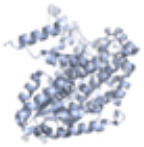
Help

Entry	EC 5.3.1.9 Enzyme
Name	glucose-6-phosphate isomerase; phosphohexose isomerase; phosphohexomutase; oxoisomerase; hexosephosphate isomerase; phosphosaccharomutase; phosphoglucoisomerase; phosphohexoisomerase; phosphoglucose isomerase; glucose phosphate isomerase; hexose phosphate isomerase; D-glucose-6-phosphate ketol-isomerase
Class	Isomerases; Intramolecular oxidoreductases; Interconverting aldoses and ketoses, and related compounds BRITE hierarchy
Sysname	D-glucose-6-phosphate aldose-ketose-isomerase
Reaction(IUBMB)	D-glucose 6-phosphate = D-fructose 6-phosphate [RN:R00771]
Reaction(KEGG)	R00771 > R02740 R03321; (other) R02739 Show all
Substrate	D-glucose 6-phosphate [CPD:C00092]
Product	D-fructose 6-phosphate [CPD:C00085]
Comment	Also catalyses the anomerization of D-glucose 6-phosphate.
Pathway	ec00010 Glycolysis / Gluconeogenesis ec00030 Pentose phosphate pathway ec00500 Starch and sucrose metabolism ec00520 Amino sugar and nucleotide sugar metabolism ec01100 Metabolic pathways ec01110 Biosynthesis of secondary metabolites ec01120 Microbial metabolism in diverse environments
Orthology	K01810 glucose-6-phosphate isomerase K06859 glucose-6-phosphate isomerase, archaeal K13810 transaldolase / glucose-6-phosphate isomerase
Genes	HSA: 2821(GPI) PTR: 455941(GPI) PON: 100174006(GPI) MCC: 717980

All links

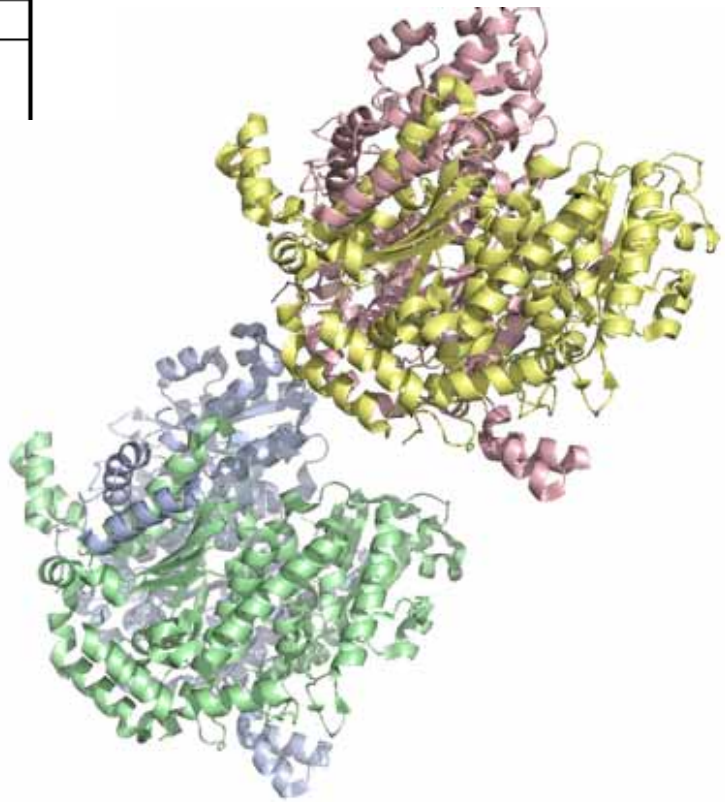
- Ontology (5)
  - KEGG BRITE (5)
- Pathway (8421)
  - KEGG PATHWAY (5587)
  - KEGG MODULE (2834)
- Disease (1)
  - OMIM (1)
- Chemical substance (5)
  - KEGG COMPOUND (5)
- Chemical reaction (14)
  - KEGG ENZYME (1)
  - KEGG REACTION (5)
  - KEGG RPAIR (4)
  - KEGG RCLASS (4)
- Genome (3)
  - KEGG GENOME (3)
- Gene (2209)
  - KEGG ORTHOLOGY (3)
  - KEGG GENES (1494)
  - KEGG DGENES (27)
  - KEGG EGENES (450)
  - KEGG MGENES (235)
- Protein sequence (6112)
  - UniProt (3930)
  - PRF (180)
  - RefSeq(pep) (1868)
  - PDBSTR (126)
  - PMD (8)
- DNA sequence (4921)
  - RefSeq(nuc) (1843)
  - GenBank (1541)
  - EMBL (1537)
- 3D Structure (64)
  - PDB (64)
- Protein domain (11)
  - InterPro (7)
  - Pfam (3)
  - PROSITE(DOC) (1)
- Literature (5)
  - PubMed (5)
- Enzyme (4)
  - BRENDA (1)
  - EXPASY-ENZYME (1)
  - EXPLORENZ (1)
  - IUBMB (1)
- All databases (21775)

KEGG База данных по метаболическим путям

	HPRD: 01394 Ensembl: ENSG00000105220 UniProt: P06744 B4DG39
Structure	PDB: 1IAT 1JIQ 1JLH 1IRI 1NUH Thumbnails  Jmol
Position	19q13.1
AA seq	558 aa AA seq DB search MAALTRDPQFQKLQQWYREHRSELNLRRLFDANKDRFNHFSLTLNTNHGHILVDYSKNLV

KEGG Homo sapiens (human) : 2821 5 PDB structures

PDB:1IAT	PDB:1JIQ	PDB:1JLH	PDB:1IRI	PDB:1NUH
1.62 Å	1.90 Å	2.10 Å	2.40 Å	2.51 Å
SO4 BME			E4P	SO4 PA5
Jmol	Jmol	Jmol	Jmol	Jmol



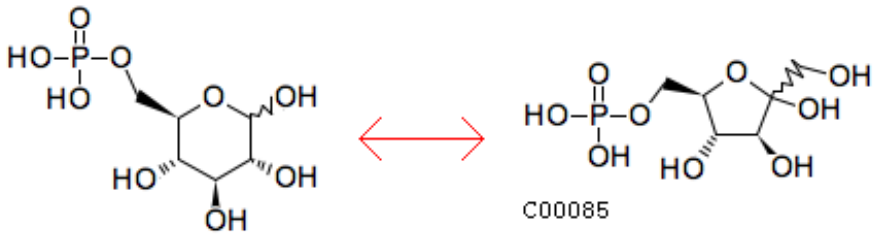
Определили структуру белка

KEGG База данных по метаболическим путям

KEGG

REACTION: R00771

Help

Entry	R00771 Reaction
Name	D-glucose-6-phosphate aldose-ketose-isomerase
Definition	D-Glucose 6-phosphate <=> D-Fructose 6-phosphate
Equation	C00092 <=> C00085
	 C00092 C00085
RPair	RP01093 C00085_C00092 main
Enzyme	5.3.1.9

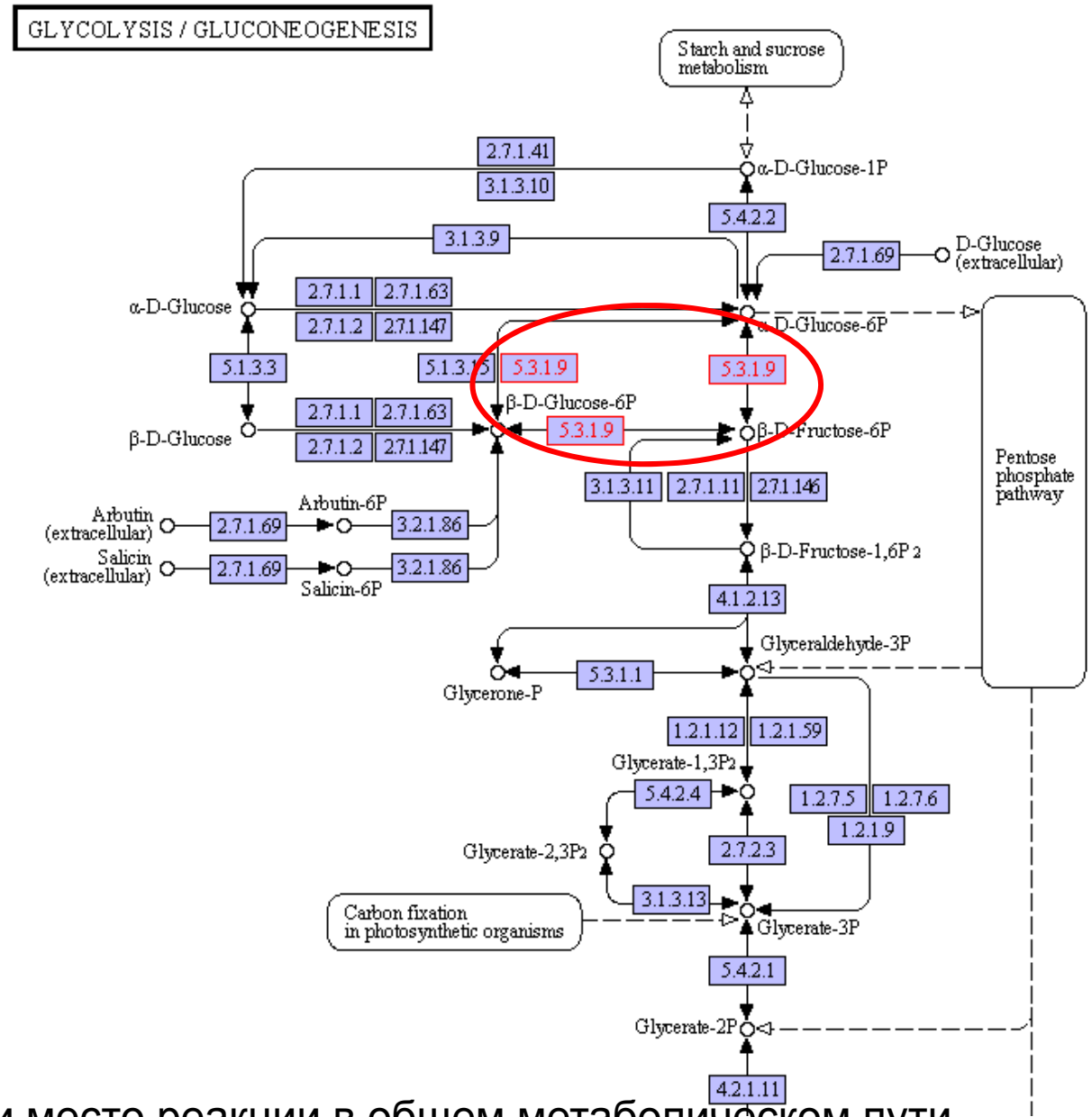
All links

Ontology (2)
KEGG BRITE (2)
Chemical substance (2)
KEGG COMPOUND (2)
Chemical reaction (3)
KEGG ENZYME (1)
KEGG RPAIR (1)
KEGG RCLASS (1)
All databases (7)

DBGET integrated database retrieval system

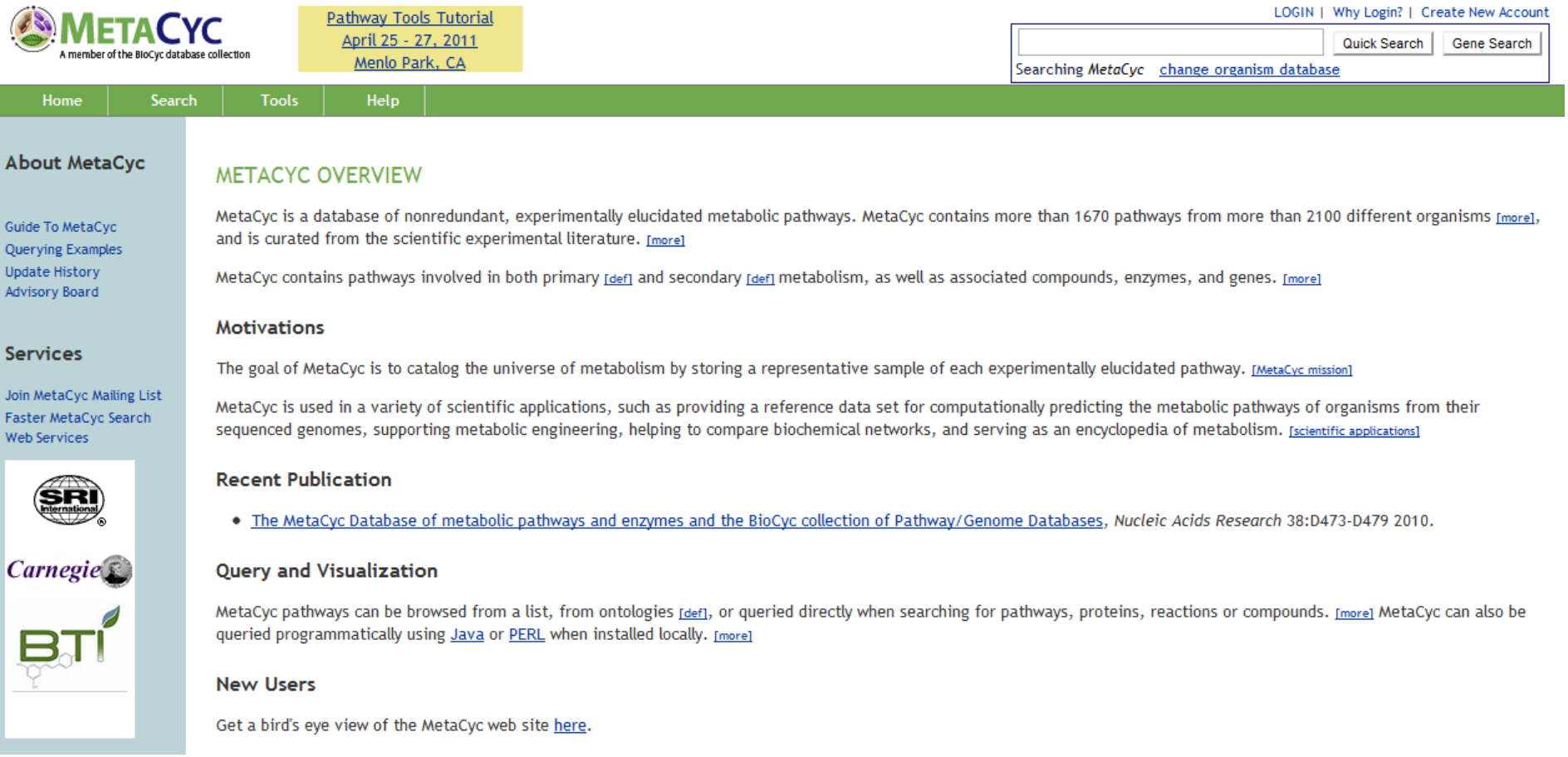
Определили метаболическую реакцию

KEGG База данных по метаболическим путям



Определили место реакции в общем метаболическом пути

MetaCyc База данных по метаболическим путям



MetaCyc База данных по метаболическим путям

Search Results for **glucose-6-phosphate isomerase**
using database *MetaCyc* what is this?

Alternative searches:
- Full text search for **glucose-6-phosphate isomerase** on all pages in this database using Google

Proteins (12) | Gene Ontology Terms (1) | Reactions (1)

Proteins Gene/Gene Product pages contain: chromosomal location of gene; depiction of its operon; link to genome browser; detailed summaries and citations; subunit structure (for protein complexes); cofactors, activators, and inhibitors (for enzymes), depiction of regulon (for transcriptional regulators), protein features.

- **glucose 6-phosphate isomerase** - *Mycoplasma pneumoniae*
- **glucose-6-phosphate isomerase** - *Bifidobacterium bifidum*
- **glucose-6-phosphate isomerase** - *Lactobacillus fermentum*
- **glucose-6-phosphate isomerase** - *Lactococcus lactis*
- **glucose-6-phosphate isomerase** - *Pisum sativum* (polypeptide)
- **glucose-6-phosphate isomerase** - *Pisum sativum* (protein complex)
- **glucose-6-phosphate isomerase** - *Saccharomyces cerevisiae*
- **glucose-6-phosphate isomerase** - *Spinacia oleracea*
- **glucose-6-phosphate isomerase** - *Thermotoga maritima*
- glucosamine-6-phosphate deaminase *(2-amino-2-deoxy-D-**glucose-6-phosphate** ketol **isomerase** (deaminating))* - *Escherichia coli*
- phosphoglucose isomerase *(**glucose-6-phosphate isomerase**)* - *Escherichia coli*
- phosphoglucose isomerase *(**glucose-6-phosphate isomerase**)* - *Pyrococcus furiosus*

Gene Ontology Terms GO term pages contain: Parent and child terms, and lists of matching gene products. Note that only those terms that have one or more associated genes in the selected organism (or that have children with one or more associated genes) are listed.

Molecular Function

- Class: GO:0004347 - glucose-6-phosphate isomerase activity

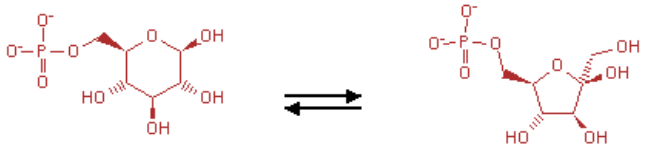
Reactions Reaction pages contain: reaction equation with chemical structures, links to all enzymes that catalyze the reaction, and all pathways in which the reaction participates.

- B-D-glucose-6-phosphate = D-fructose-6-phosphate *(**glucose-6-phosphate isomerase**)*

Определили реакцию

MetaCyc База данных по метаболическим путям

In Pathway: sorbitol biosynthesis I , starch biosynthesis , sucrose degradation IV , sucrose degradation III , heterolactic fermentation , gluconeogenesis I , formaldehyde oxidation I , glycolysis V (Pyrococcus) , glycolysis III , glycolysis I , GDP-mannose biosynthesis , Bifidobacterium shunt , homolactic fermentation , mannitol cycle , gluconeogenesis II (*Methanobacterium thermoautotrophicum*)



β-D-glucose-6-phosphate

D-fructose-6-phosphate

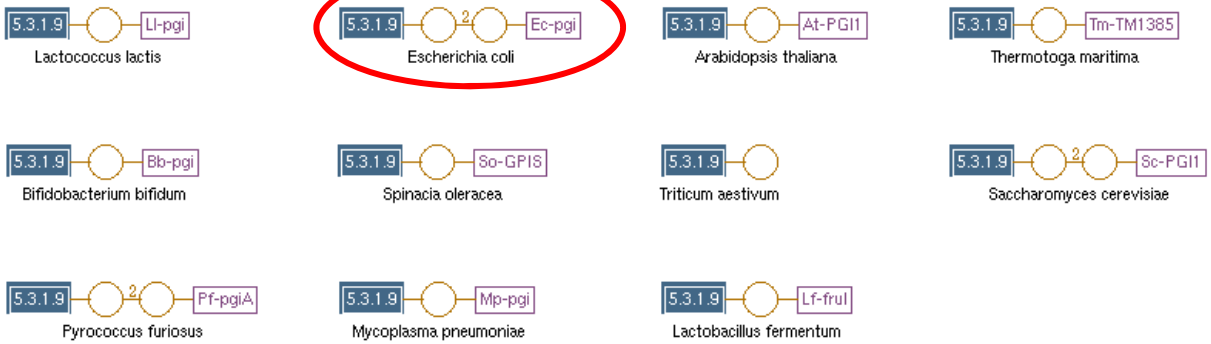
The reaction direction shown, that is, A + B <==> C + D versus C + D <==> A + B, is in accordance with the Enzyme Commission system.

Enzyme Commission Primary Name for this Reaction: glucose-6-phosphate isomerase

Enzyme Commission Synonyms for this Reaction: phosphohexose isomerase, phosphohexomutase, oxoisomerase, hexosephosphate isomerase, phosphosaccharomutase, phosphoglucoisomerase, phosphohexoisomerase, phosphoglucose isomerase, glucose phosphate isomerase, hexose phosphate isomerase, D-glucose-6-phosphate ketol-isomerase

$\Delta G^{0'}$ (kcal/mol): 0.4 KCAL/MOLE [Stryer88]

Gene-Reaction Schematic:



Unification Links: BRENDA:5.3.1.9 , ENZYME:5.3.1.9 , ExplorEnz:5.3.1.9 , KEGG:R00771

Relationship Links: UniProt:RELATED-TO:O25781 , UniProt:RELATED-TO:O61113 , UniProt:RELATED-TO:O82058 , UniProt:RELATED-TO:O82059 , UniProt:RELATED-TO:O83488 , UniProt:RELATED-TO:O84382 , UniProt:RELATED-TO:P06744 , UniProt:RELATED-TO:P06745 , UniProt:RELATED-TO:P08059 , UniProt:RELATED-TO:P0A6T1 , UniProt:RELATED-TO:P12341 , UniProt:RELATED-TO:P12709 , UniProt:RELATED-TO:P13375 , UniProt:RELATED-TO:P13376 , UniProt:RELATED-TO:P13377 , UniProt:RELATED-TO:P18240 , UniProt:RELATED-TO:P28718 , UniProt:RELATED-TO:P29333 , UniProt:RELATED-TO:P34796 , UniProt:RELATED-TO:P34797 , UniProt:RELATED-TO:P42862 , UniProt:RELATED-TO:P42863 , UniProt:RELATED-TO:P49105 , UniProt:RELATED-TO:P50309 , UniProt:RELATED-TO:P52983 , UniProt:RELATED-TO:P54240 , UniProt:RELATED-TO:P54242 , UniProt:RELATED-TO:P78033 , UniProt:RELATED-TO:P78917 , UniProt:RELATED-TO:P81181 , UniProt:RELATED-TO:Q7LZP0 , UniProt:RELATED-TO:Q9JSS6 , UniProt:RELATED-TO:Q9JTW1 , UniProt:RELATED-TO:Q9PMD4 , UniProt:RELATED-TO:Q9RMC1 , UniProt:RELATED-TO:Q9SB57 , UniProt:RELATED-TO:Q9X670 , UniProt:RELATED-TO:Q59000 , UniProt:RELATED-TO:Q59088

Выбрали интересующий организм

MetaCyc База данных по метаболическим путям

Enzymatic reaction of: phosphoglucose isomerase

Synonyms: glucose-6-phosphate isomerase, D-glucose-6-phosphate-ketol-isomerase

ß-D-glucose-6-phosphate <=> D-fructose-6-phosphate

The reaction direction shown, that is, A + B <==> C + D versus C + D <==> A + B, is in accordance with the direction of enzyme catalysis.

This reaction is reversible. [Ishii07]

In Pathways: gluconeogenesis I , glycolysis I , GDP-mannose biosynthesis

Summary:
The equilibrium constant for the reaction is 0.30 [Ishii07].

Citations: [Klungsoyr64]

Inhibitors (Competitive): phosphoenolpyruvate [Ogawa07]

Inhibitors (Unknown Mechanism): 6-phospho-D-gluconate [Schreyer80]

K_M for D-fructose-6-phosphate: 78 µM [Ogawa07]

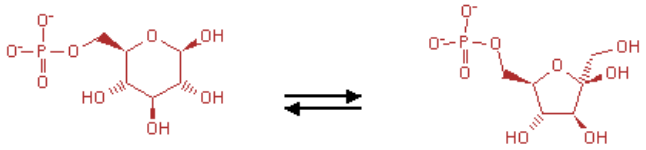
K_M for ß-D-glucose-6-phosphate: 1018 µM [Ogawa07]

$pH_{(opt)}$: 8 [Schreyer80]

Определили кинетические константы для уравнения скорости для *E.coli*

MetaCyc База данных по метаболическим путям

In Pathway: sorbitol biosynthesis I , starch biosynthesis , sucrose degradation IV , sucrose degradation III , heterolactic fermentation , gluconeogenesis I , formaldehyde oxidation I , glycolysis V (Pyrococcus) , glycolysis III , glycolysis I , GDP-mannose biosynthesis , Bifidobacterium shunt , homolactic fermentation , mannitol cycle , gluconeogenesis II (*Methanobacterium thermoautotrophicum*)



β-D-glucose-6-phosphate D-fructose-6-phosphate

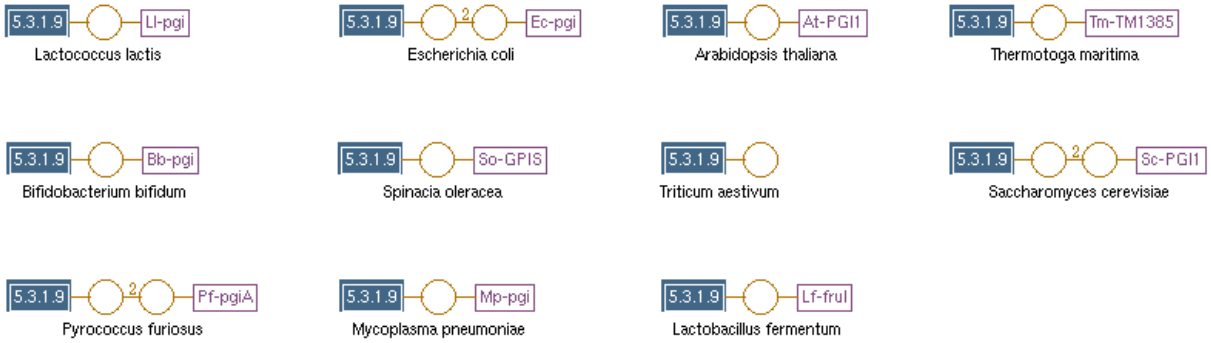
The reaction direction shown, that is, A + B <==> C + D versus C + D <==> A + B, is in accordance with the Enzyme Commission system.

Enzyme Commission Primary Name for this Reaction: glucose-6-phosphate isomerase

Enzyme Commission Synonyms for this Reaction: phosphohexose isomerase, phosphohexomutase, oxoisomerase, hexosephosphate isomerase, phosphosaccharomutase, phosphoglucoisomerase, phosphohexoisomerase, phosphoglucose isomerase, glucose phosphate isomerase, hexose phosphate isomerase, D-glucose-6-phosphate ketol-isomerase

$\Delta G^{0'}$ (kcal/mol): 0.4 KCAL/MOLE [Stryer88]

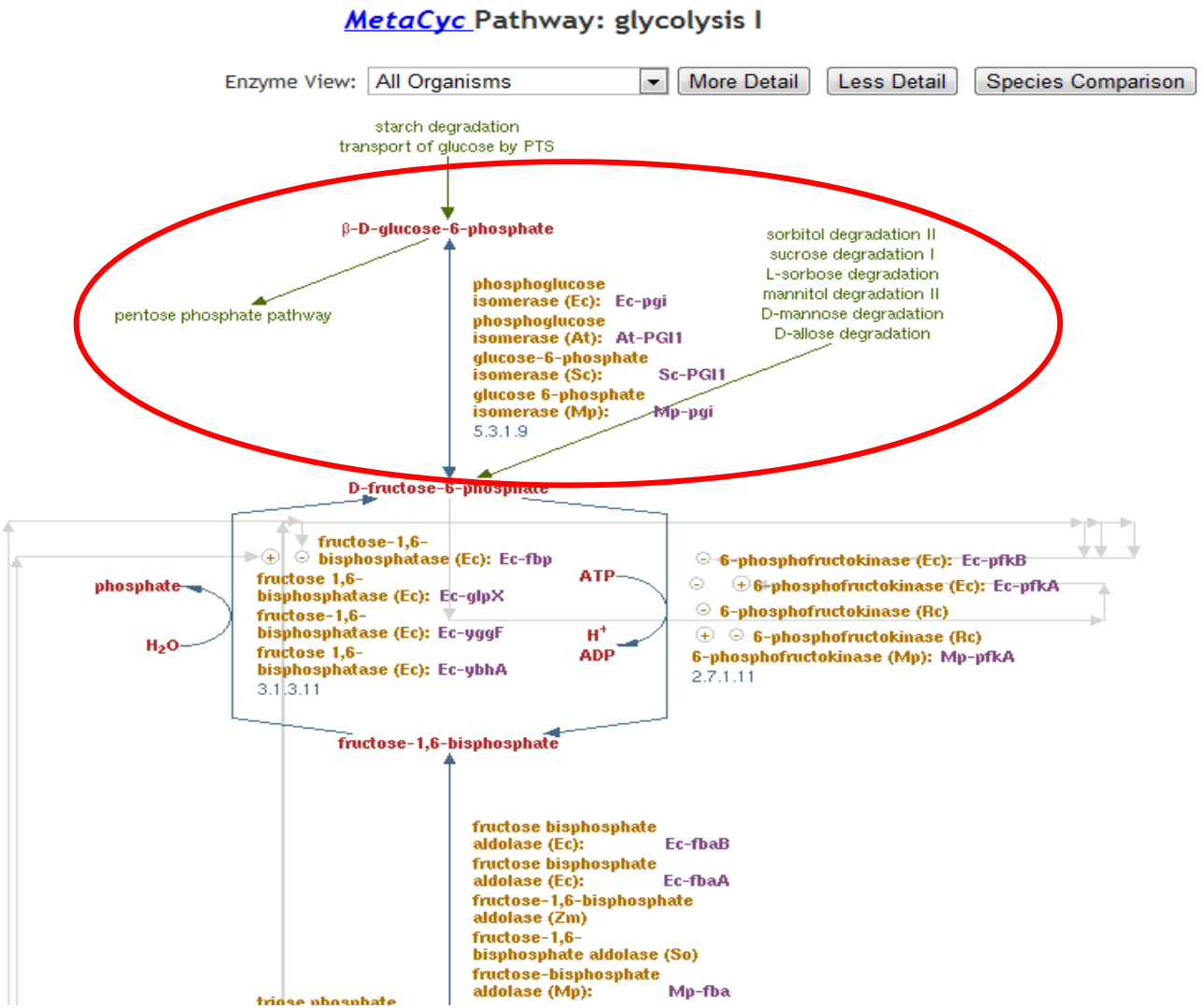
Gene-Reaction Schematic:



Unification Links: BRENDA:5.3.1.9 , ENZYME:5.3.1.9 , ExplorEnz:5.3.1.9 , KEGG:R00771

Relationship Links: UniProt:RELATED-TO:O25781 , UniProt:RELATED-TO:O61113 , UniProt:RELATED-TO:O82058 , UniProt:RELATED-TO:O82059 , UniProt:RELATED-TO:O83488 , UniProt:RELATED-TO:O84382 , UniProt:RELATED-TO:P06744 , UniProt:RELATED-TO:P06745 , UniProt:RELATED-TO:P08059 , UniProt:RELATED-TO:P0A6T1 , UniProt:RELATED-TO:P12341 , UniProt:RELATED-TO:P12709 , UniProt:RELATED-TO:P13375 , UniProt:RELATED-TO:P13376 , UniProt:RELATED-TO:P13377 , UniProt:RELATED-TO:P18240 , UniProt:RELATED-TO:P28718 , UniProt:RELATED-TO:P29333 , UniProt:RELATED-TO:P34796 , UniProt:RELATED-TO:P34797 , UniProt:RELATED-TO:P42862 , UniProt:RELATED-TO:P42863 , UniProt:RELATED-TO:P49105 , UniProt:RELATED-TO:P50309 , UniProt:RELATED-TO:P52983 , UniProt:RELATED-TO:P54240 , UniProt:RELATED-TO:P54242 , UniProt:RELATED-TO:P78033 , UniProt:RELATED-TO:P78917 , UniProt:RELATED-TO:P81181 , UniProt:RELATED-TO:Q7LZP0 , UniProt:RELATED-TO:Q9JSS6 , UniProt:RELATED-TO:Q9JTW1 , UniProt:RELATED-TO:Q9PMD4 , UniProt:RELATED-TO:Q9RMC1 , UniProt:RELATED-TO:Q9SB57 , UniProt:RELATED-TO:Q9X670 , UniProt:RELATED-TO:Q59000 , UniProt:RELATED-TO:Q59088

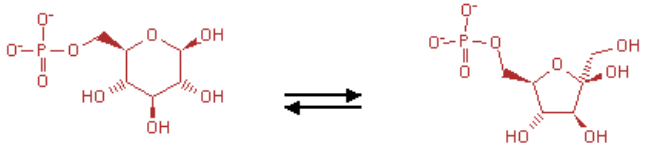
MetaCyc База данных по метаболическим путям



Определили место реакции в метаболическом пути

MetaCyc База данных по метаболическим путям

In Pathway: sorbitol biosynthesis I , starch biosynthesis , sucrose degradation IV , sucrose degradation III , heterolactic fermentation , gluconeogenesis I , formaldehyde oxidation I , glycolysis V (Pyrococcus) , glycolysis III , glycolysis I , GDP-mannose biosynthesis , Bifidobacterium shunt , homolactic fermentation , mannitol cycle , gluconeogenesis II (*Methanobacterium thermoautotrophicum*)



β-D-glucose-6-phosphate

D-fructose-6-phosphate

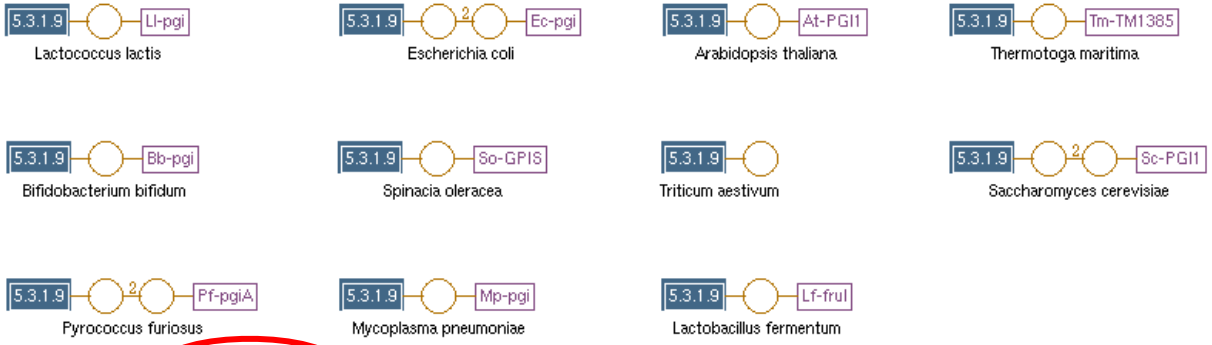
The reaction direction shown, that is, A + B <==> C + D versus C + D <==> A + B, is in accordance with the Enzyme Commission system.

Enzyme Commission Primary Name for this Reaction: glucose-6-phosphate isomerase

Enzyme Commission Synonyms for this Reaction: phosphohexose isomerase, phosphohexomutase, oxoisomerase, hexosephosphate isomerase, phosphosaccharomutase, phosphoglucoisomerase, phosphohexoisomerase, phosphoglucose isomerase, glucose phosphate isomerase, hexose phosphate isomerase, D-glucose-6-phosphate ketol-isomerase

$\Delta G^{0'}$ (kcal/mol): 0.4 KCAL/MOLE [Stryer88]

Gene-Reaction Schematic:



Unification Links: BRENDA:5.3.1.9 , ENZYME:5.3.1.9 , ExplorEnz:5.3.1.9 , KEGG:R00771

Relationship Links: UniProt:RELATED-TO:O25781 , UniProt:RELATED-TO:O61113 , UniProt:RELATED-TO:O82058 , UniProt:RELATED-TO:O82059 , UniProt:RELATED-TO:O83488 , UniProt:RELATED-TO:O84382 , UniProt:RELATED-TO:P06744 , UniProt:RELATED-TO:P06745 , UniProt:RELATED-TO:P08059 , UniProt:RELATED-TO:P0A6T1 , UniProt:RELATED-TO:P12341 , UniProt:RELATED-TO:P12709 , UniProt:RELATED-TO:P13375 , UniProt:RELATED-TO:P13376 , UniProt:RELATED-TO:P13377 , UniProt:RELATED-TO:P18240 , UniProt:RELATED-TO:P28718 , UniProt:RELATED-TO:P29333 , UniProt:RELATED-TO:P34796 , UniProt:RELATED-TO:P34797 , UniProt:RELATED-TO:P42862 , UniProt:RELATED-TO:P42863 , UniProt:RELATED-TO:P49105 , UniProt:RELATED-TO:P50309 , UniProt:RELATED-TO:P52983 , UniProt:RELATED-TO:P54240 , UniProt:RELATED-TO:P54242 , UniProt:RELATED-TO:P78033 , UniProt:RELATED-TO:P78917 , UniProt:RELATED-TO:P81181 , UniProt:RELATED-TO:Q7LZP0 , UniProt:RELATED-TO:Q9JSS6 , UniProt:RELATED-TO:Q9JTW1 , UniProt:RELATED-TO:Q9PMD4 , UniProt:RELATED-TO:Q9RMC1 , UniProt:RELATED-TO:Q9SB57 , UniProt:RELATED-TO:Q9X670 , UniProt:RELATED-TO:Q59000 , UniProt:RELATED-TO:Q59088

BRENDA База данных по белкам

http://www.brenda-enzymes.info/index.php4

PDB База данных по структуре белков

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CRYSTAL STRUCTURE OF HUMAN PHOSPHOGLUCOSE ISOMERASE/NEUROLEUKIN/AUTOCRINE MOTILITY FACTOR/MATURATION FACTOR

1IAT

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DOI:10.2210/pdb1iat/pdb

Primary Citation

The crystal structure of human phosphoglucose isomerase at 1.6 A resolution: implications for catalytic mechanism, cytokine activity and haemolytic anaemia.

Read, J., Pearce, J., Li, X., Muirhead, H., Chirgwin, J., Davies, C.

Journal: (2001) J.Mol.Biol. **309:** 447-463

PubMed: 11371164
DOI: 10.1006/jmbi.2001.4680
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PubMed Abstract:

Phosphoglucose isomerase (PGI) is a multifunctional protein, which, inside the cell, functions as a housekeeping enzyme of glycolysis and gluconeogenesis and, outside the cell, exerts wholly unrelated cytokine properties. We have determined the structure of human PGI to a resolution...
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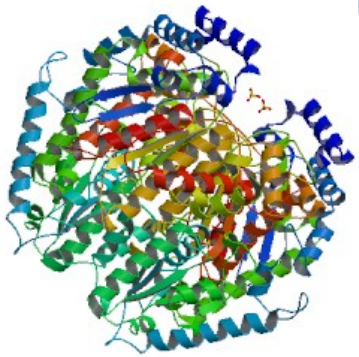
Molecular Description Hide

Classification: Isomerase
Structure Weight: 63369.64

Molecule: PHOSPHOGLUCOSE ISOMERASE
Polymer: 1 **Type:** polypeptide(L) **Length:** 557
Chains: A

Biological Assembly



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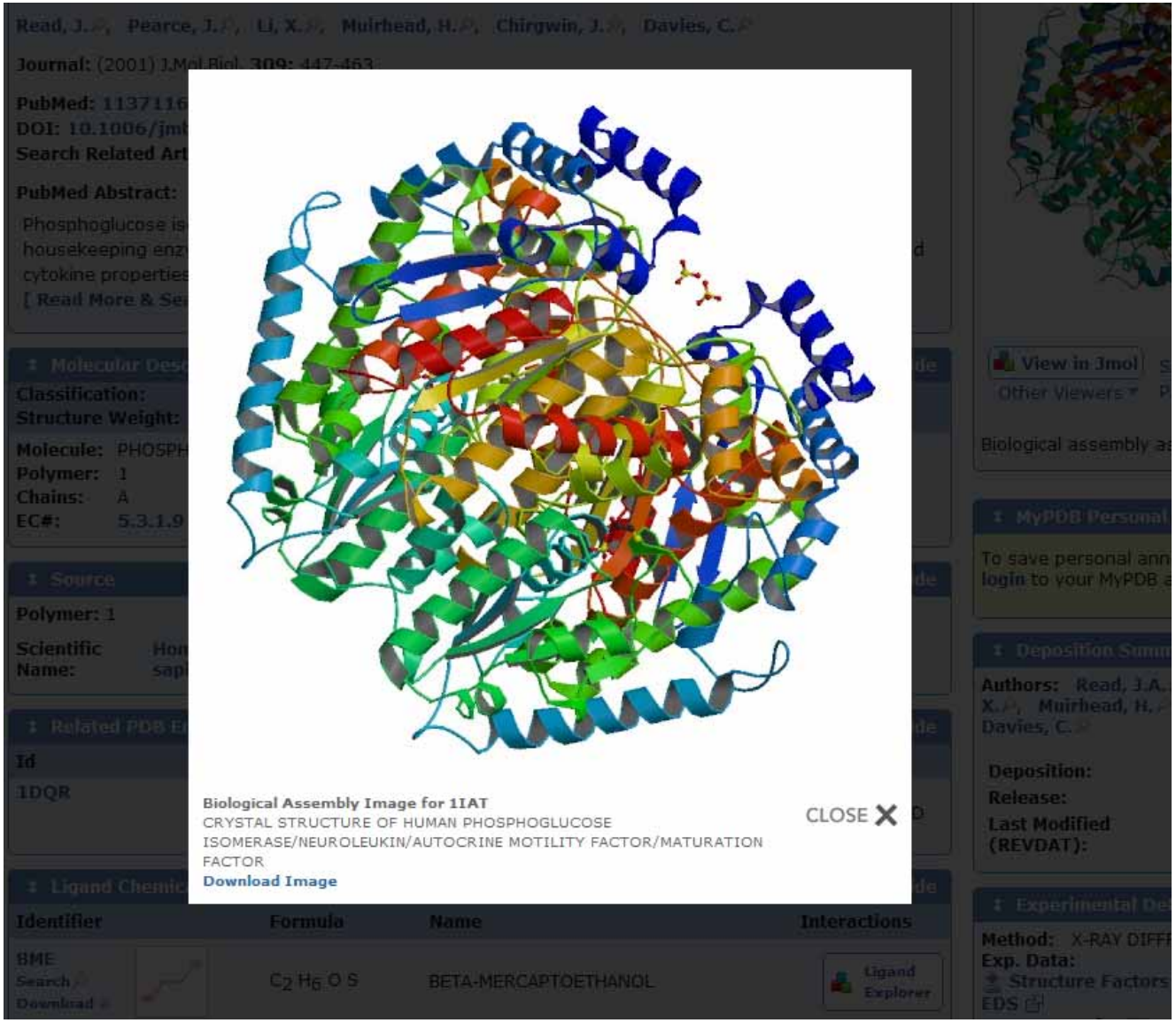
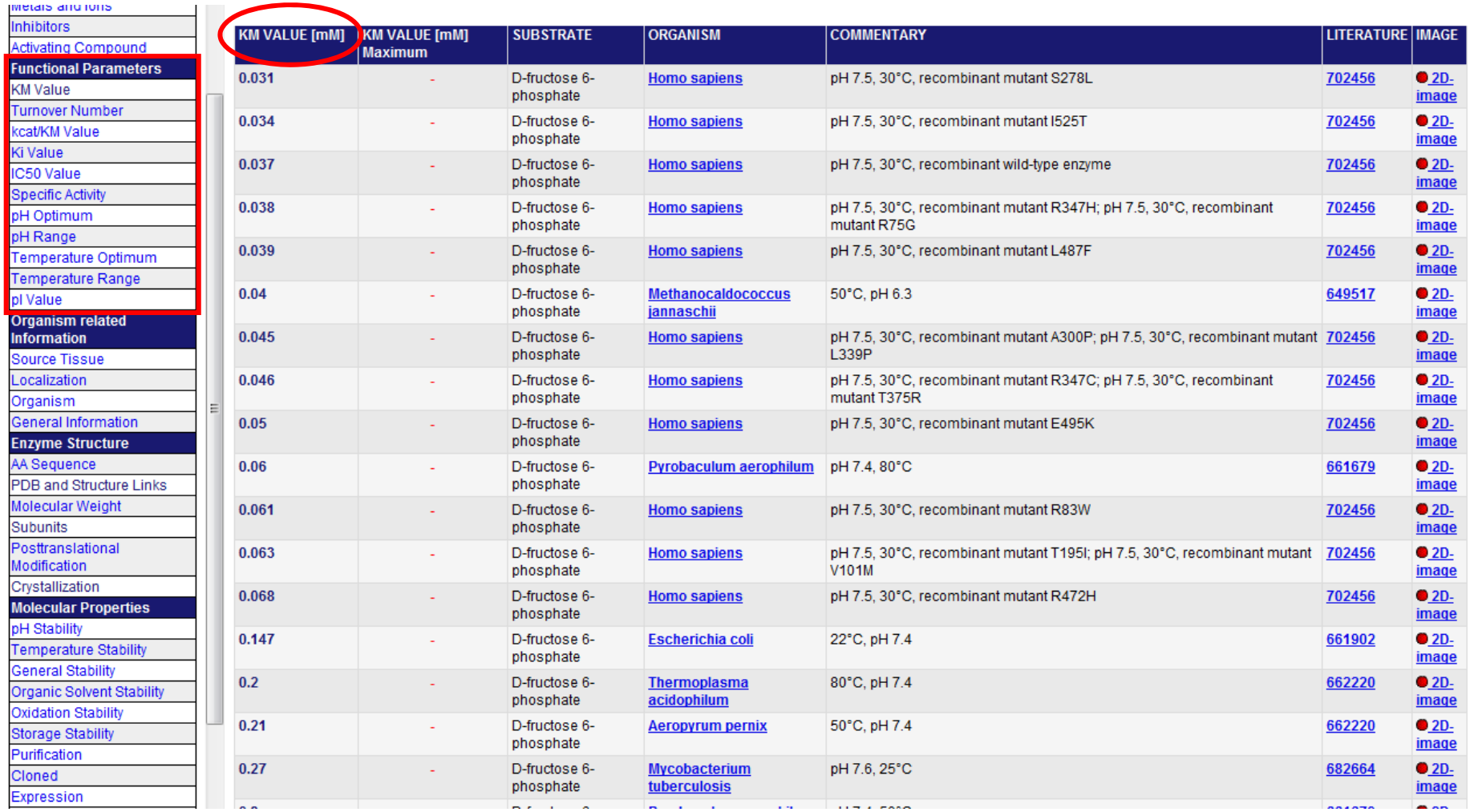
Biological assembly assigned by authors

PDB База данных по структуре белков



BRENDA База данных по белкам



Metals and Ions
Inhibitors
Activating Compound
Functional Parameters
KM Value
Turnover Number
kcat/KM Value
Ki Value
IC50 Value
Specific Activity
pH Optimum
pH Range
Temperature Optimum
Temperature Range
pI Value
Organism related Information
Source Tissue
Localization
Organism
General Information
Enzyme Structure
AA Sequence
PDB and Structure Links
Molecular Weight
Subunits
Posttranslational Modification
Crystallization
Molecular Properties
pH Stability
Temperature Stability
General Stability
Organic Solvent Stability
Oxidation Stability
Storage Stability
Purification
Cloned
Expression

KM VALUE [mM]	KM VALUE [mM] Maximum	SUBSTRATE	ORGANISM	COMMENTARY	LITERATURE	IMAGE
0.031	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant S278L	702456	2D-image
0.034	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant I525T	702456	2D-image
0.037	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant wild-type enzyme	702456	2D-image
0.038	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant R347H; pH 7.5, 30°C, recombinant mutant R75G	702456	2D-image
0.039	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant L487F	702456	2D-image
0.04	-	D-fructose 6-phosphate	Methanocaldococcus jannaschii	50°C, pH 6.3	649517	2D-image
0.045	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant A300P; pH 7.5, 30°C, recombinant mutant L339P	702456	2D-image
0.046	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant R347C; pH 7.5, 30°C, recombinant mutant T375R	702456	2D-image
0.05	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant E495K	702456	2D-image
0.06	-	D-fructose 6-phosphate	Pyrobaculum aerophilum	pH 7.4, 80°C	661679	2D-image
0.061	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant R83W	702456	2D-image
0.063	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant T195I; pH 7.5, 30°C, recombinant mutant V101M	702456	2D-image
0.068	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant R472H	702456	2D-image
0.147	-	D-fructose 6-phosphate	Escherichia coli	22°C, pH 7.4	661902	2D-image
0.2	-	D-fructose 6-phosphate	Thermoplasma acidophilum	80°C, pH 7.4	662220	2D-image
0.21	-	D-fructose 6-phosphate	Aeropyrum pernix	50°C, pH 7.4	662220	2D-image
0.27	-	D-fructose 6-phosphate	Mycobacterium tuberculosis	pH 7.6, 25°C	682664	2D-image

Определили кинетические константы для уравнения скорости

База данных по публикациям в биологии и медицине

Effects of inherited mutations on catalytic activity and structural stability of human glucose-6-phosphate isomerase expressed in Escherichia coli

Lin, H.; Kao, Y.; Chen, S.; Meng, M.; *Biochim. Biophys. Acta* 1794, 315-323 (2009)

Data extracted from this reference:

Cloned(Commentary)

Commentary	Organism
expression of wild-type and mutant enzymes in Escherichia coli strain DF2145	Homo sapiens

Engineering

Amino acid exchange	Commentary	Organism
A300P	the mutation may affect the folding efficiency of the enzyme protein, the mutant shows reduced expression level and barely detectable activity	Homo sapiens
E495K	the mutation may affect the folding efficiency of the enzyme protein, the mutant shows reduced expression level and barely detectable activity; the mutation weakens network bonding of the enzyme	Homo sapiens
H389R	the mutation at or near the active site highly affects the catalytic efficiency of the enzyme, the mutant shows barely detectable activity	Homo sapiens
I525T	the mutation decreases the enzyme tolerance to heat or SDS by mechanisms of decreasing packing efficiency; the mutation destabilizes the ternary structure of the enzyme	Homo sapiens

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Biochim Biophys Acta. 2009 Feb;1794(2):315-23. Epub 2008 Nov 21.

Effects of inherited mutations on catalytic activity and structural stability of human glucose-6-phosphate isomerase expressed in Escherichia coli.

Lin HY, Kao YH, Chen ST, Meng M.

Graduate Institute of Biotechnology, National Chung Hsing University, Taichung, Taiwan 40227, Republic of China.

Abstract

Glucose-6-phosphate isomerase (GPI), a homodimeric enzyme, catalyzes the interconversion between glucose-6-phosphate and fructose-6-phosphate. In mammals, it can also act as an autocrine motility factor, neuroleukin, and maturation factor. Deficiency of the enzymatic activity in red blood cells causes nonspherocytic hemolytic anemia in human. To gain a more complete understanding of the molecular basis for the hemolytic anemia due to the GPI-deficiency, the wild-type enzyme and sixteen genetic variants were expressed in Escherichia coli and functionally characterized. Conclusions are as follows: (1) mutations usually have negative influences on catalytic parameters, particularly k(cat), as well as structure stability; (2) mutations at or close to the active site, including R273H, H389R, and S278L, cause great damage to the catalytic function, yet

Related citations

Erythrocyte pyruvate kinase- and glucose phosphate isomerase de [Biophys Chem. 1997]

Expression and enzymatic characterization of human glucose pho [Blood Cells Mol Dis. 1998]

Molecular basis of neurological dysfunction coupled with haemolytic ana [Hum Genet. 1998]

Review Glucose-6-phosphate isomerase d [Baillieres Best Pract Res Clin Haematol. 20...]

Review Red cell glycolytic enzyme disorders Cardiovasc Hematol Disord Drug Targets. 200...]

Нашли ссылки на сходные публикации