

Моделирование метаболических путей

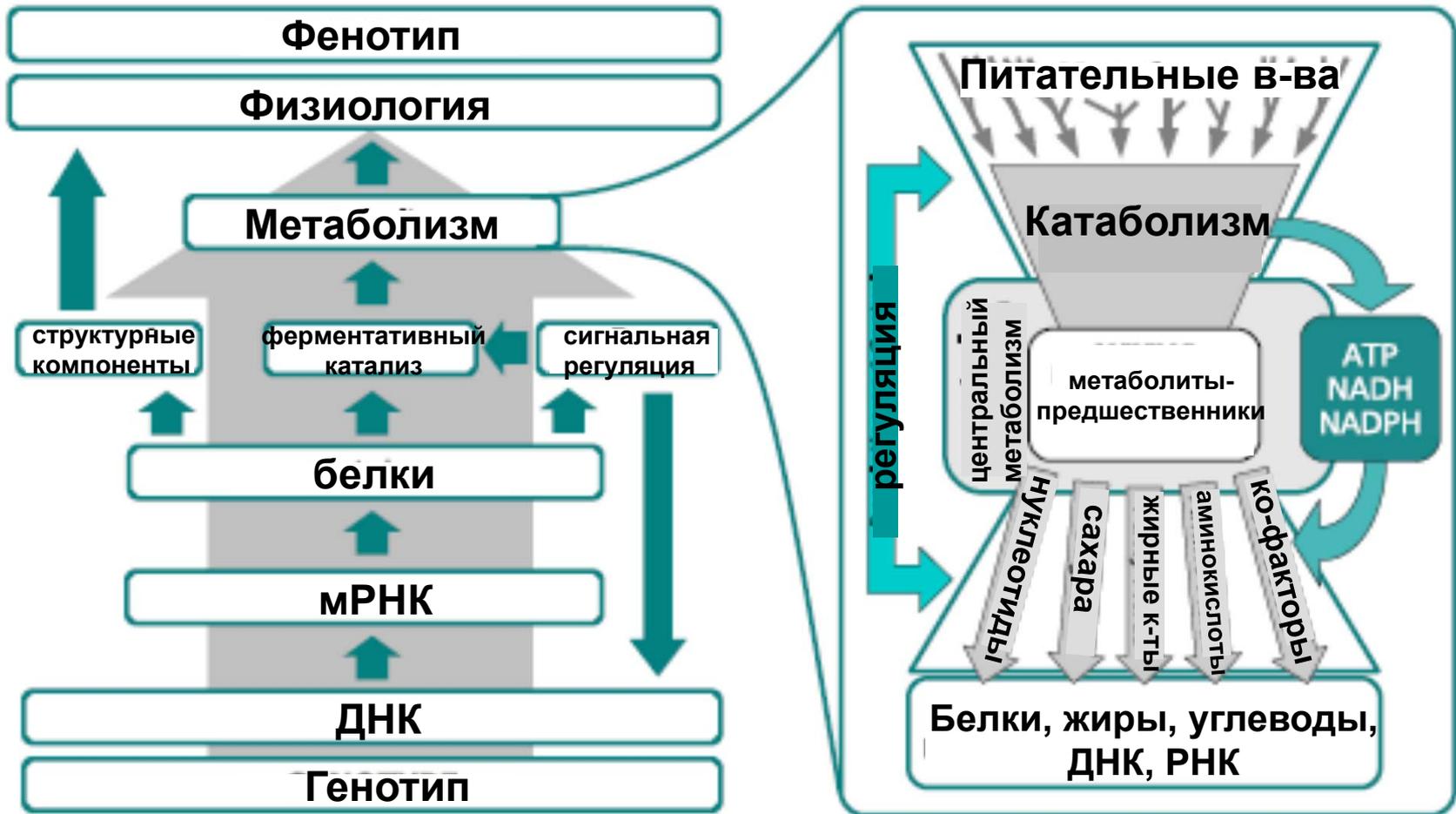
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Биологического ф-та МГУ

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

Метаболический путь — совокупность метаболических реакций

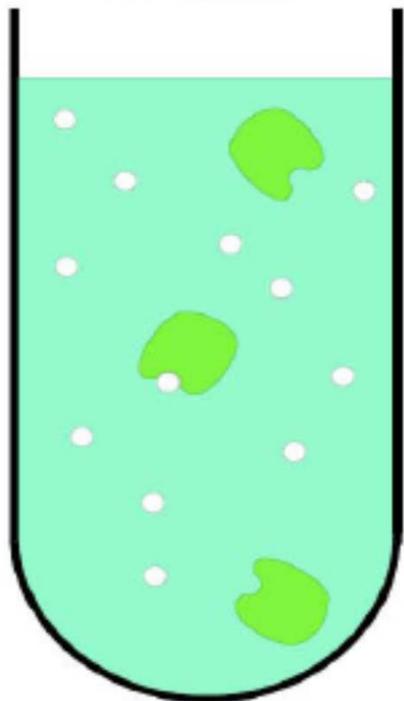
Метаболиты — субстраты и продукты, участвующие в реакциях

Организация клеточного метаболизма



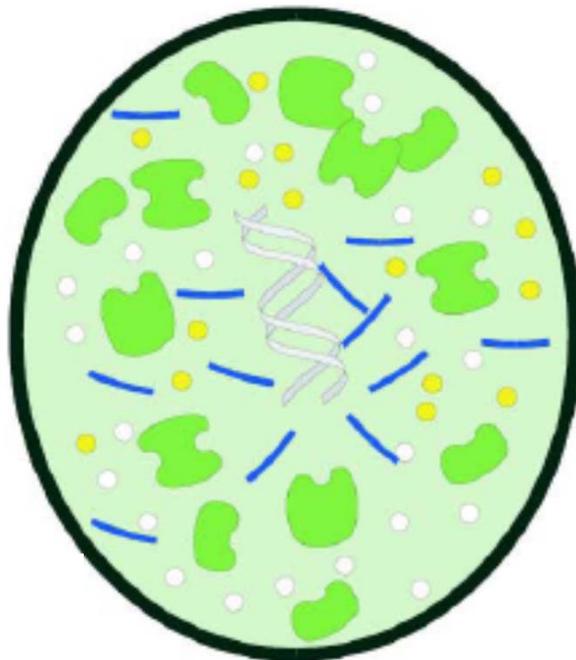
Уровни исследования метаболических реакций

In vitro



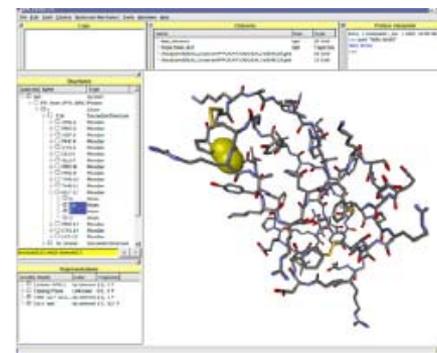
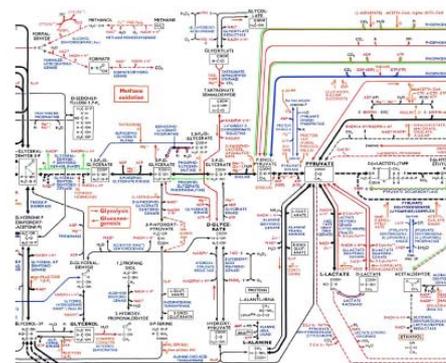
свойства отдельных
метаболитов и их
динамика

In vivo



описание
характеристик
метаболизма клетки
в целом

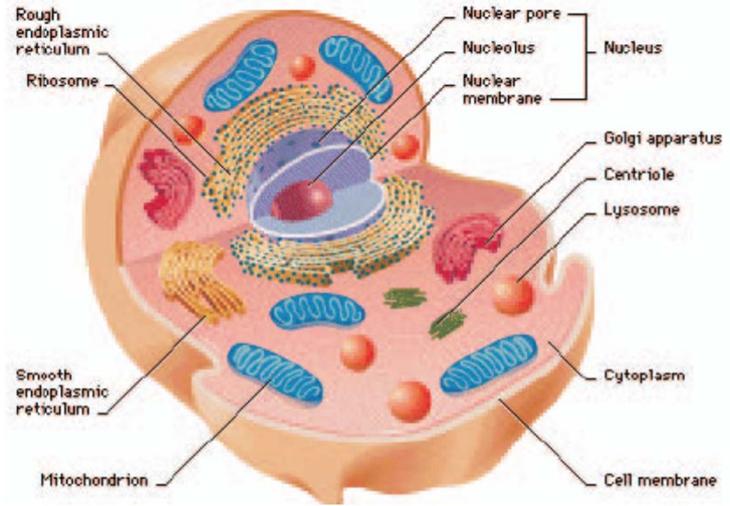
In silico



построение
«электронной
клетки»

Разные уровни сложности организации клеток

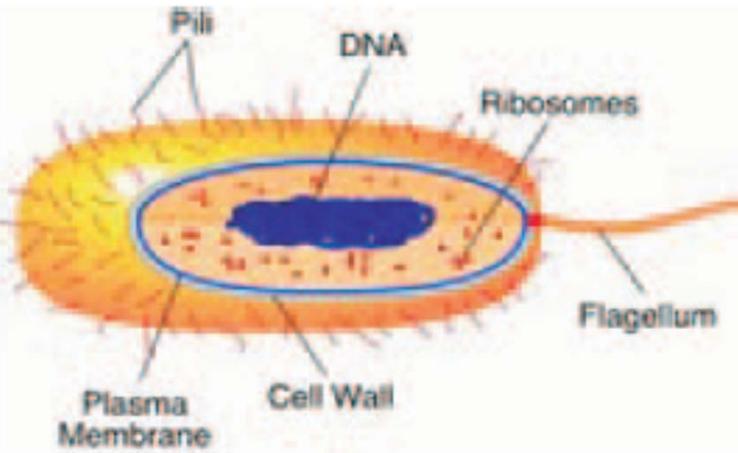
Клетка эукариот



Клеточные процессы локализованы в разных компартментах

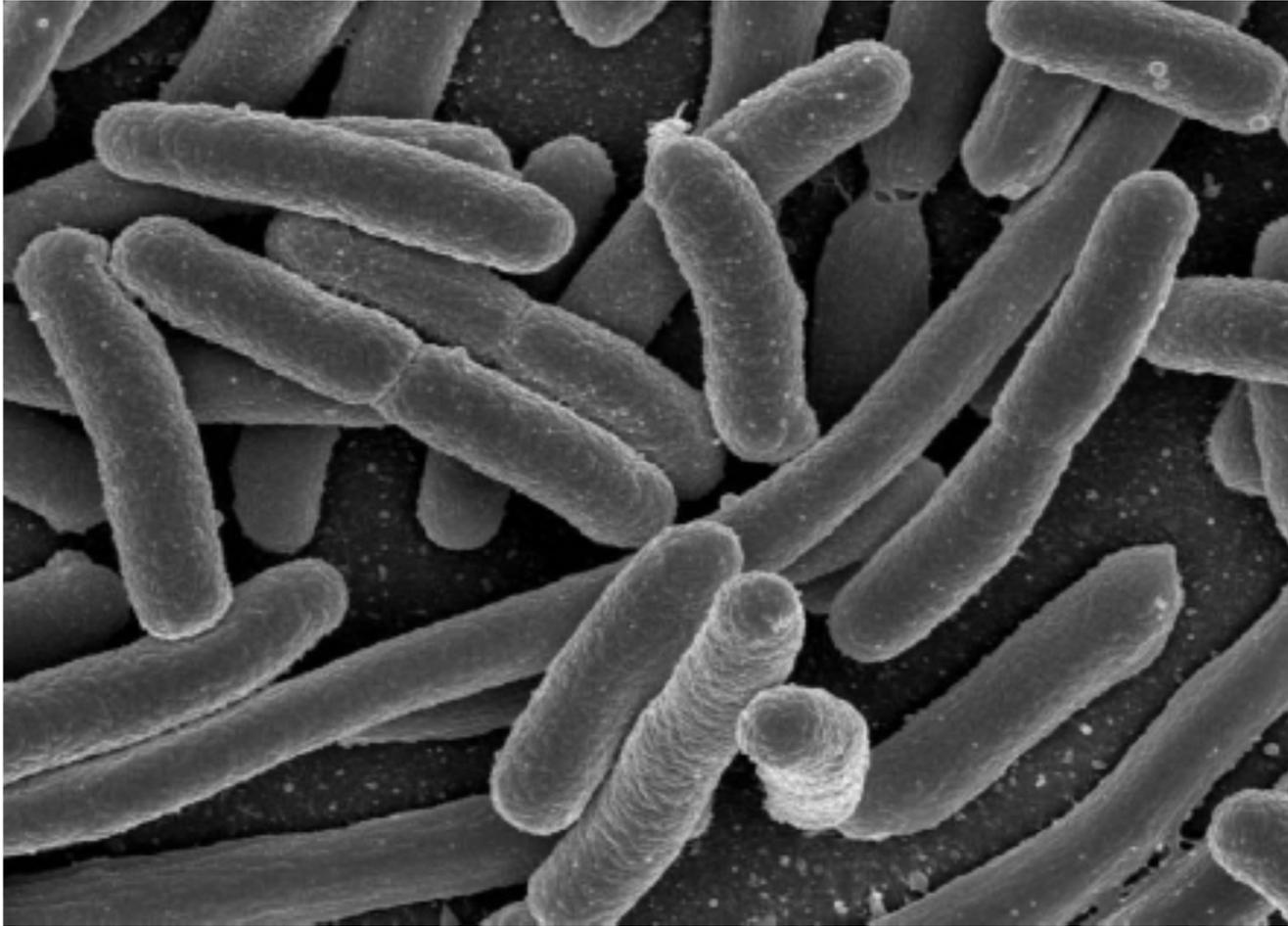
Первые модели – модели клеток прокариот

Клетка прокариот



Все процессы протекают в одном компартменте

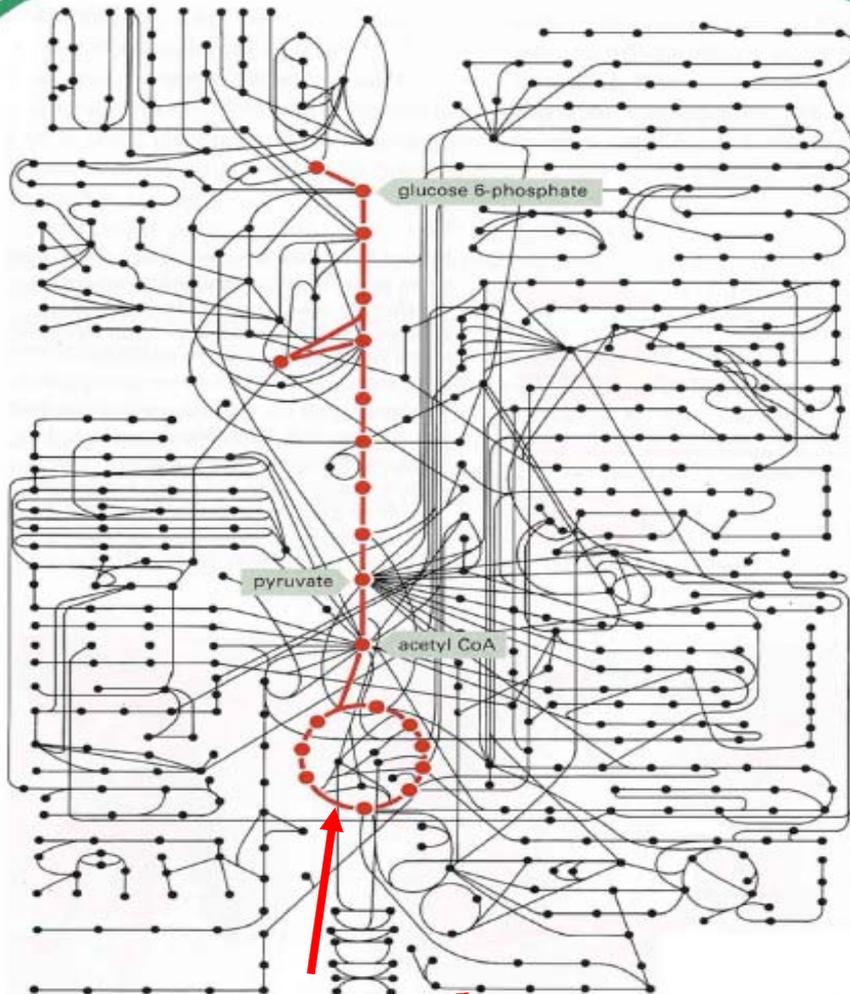
Escherichia coli



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

Escherichia coli – удобный объект для моделирования
клеточного метаболизма

Метаболические пути *Escherichia coli*



центральные метаболические пути

720 метаболических процессов
436 метаболитов
540 ферментов

**Описание метаболизма
включает:**

- мембранные транспортные процессы
- центральные катаболические пути
- биосинтетические пути (продукция всех компонент биомассы)
- использование различных источников углерода

Представление метаболических путей

Центральные метаболические пути

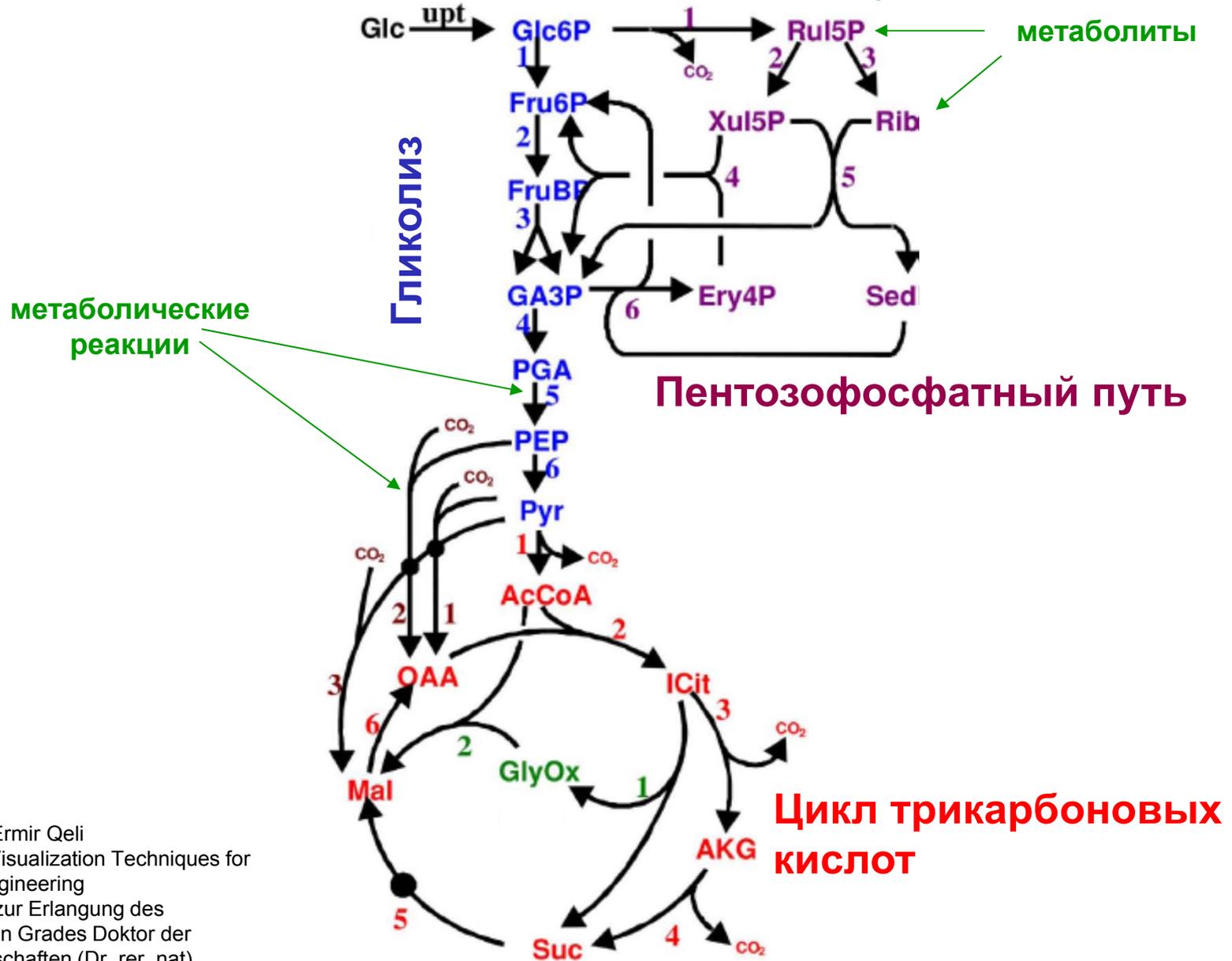


Figure from Ermir Qeli
Information Visualization Techniques for
Metabolic Engineering
Dissertation zur Erlangung des
akademischen Grades Doktor der
Naturwissenschaften (Dr. rer. nat)

Цели и задачи метаболического моделирования

Научные задачи:

- исследование механизмов клеточной регуляции в сложных биохимических системах
- объяснение экспериментально установленных фактов и предсказание новых ещё не выявленных внутриклеточных явлений
- систематизация накопленных экспериментальных данных

Биоинженерные задачи:

- оптимизация получения необходимых веществ из бактериальных клеток и других организмов
- разработка новых штаммов с наперед заданными свойствами
- разработка новых лекарств

Построение метаболической модели:

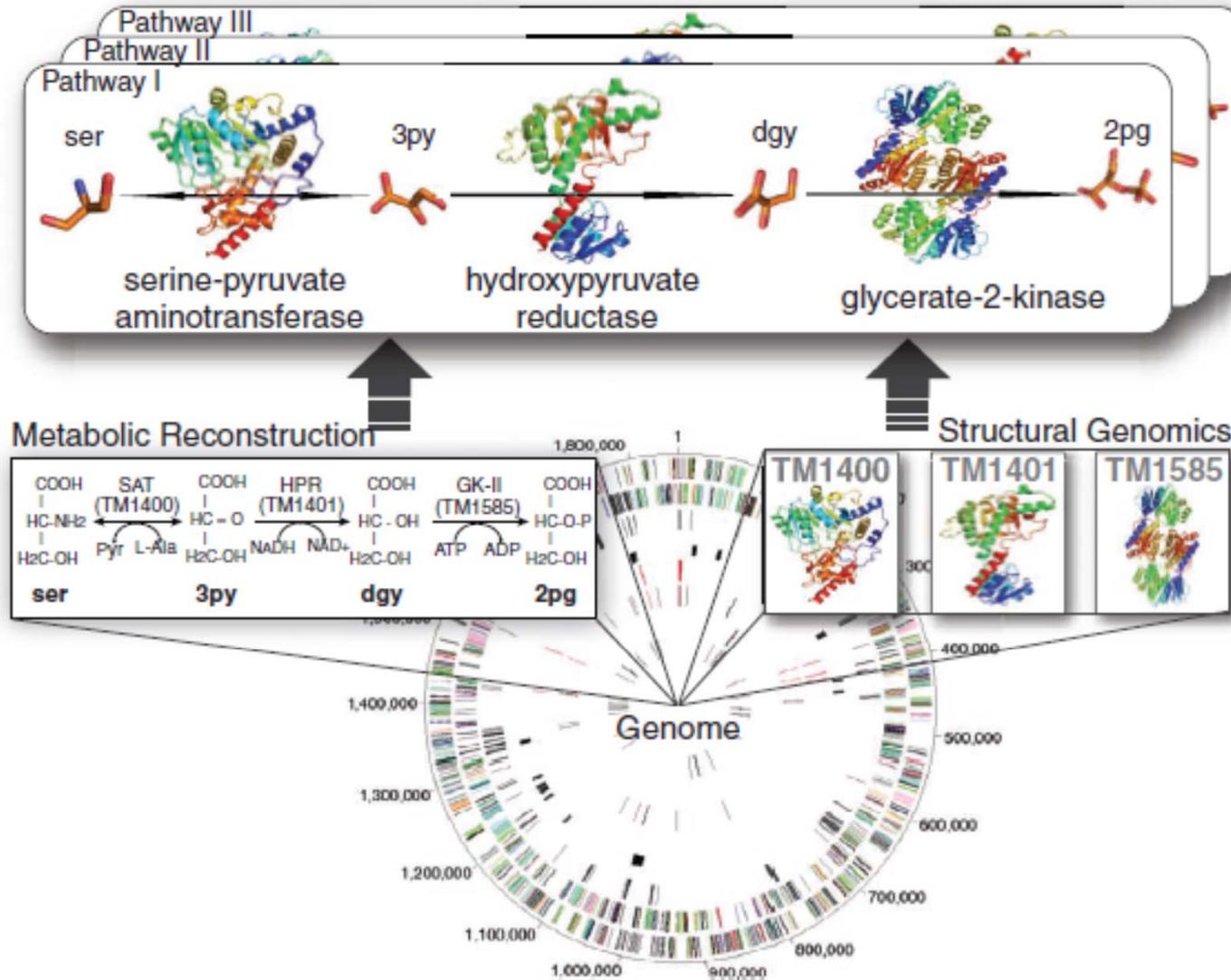
реконструкция метаболических путей:

построение общей схемы метаболических путей

математическое описание:

вывод уравнений скорости и построение системы уравнений в соответствии с метаболической картой

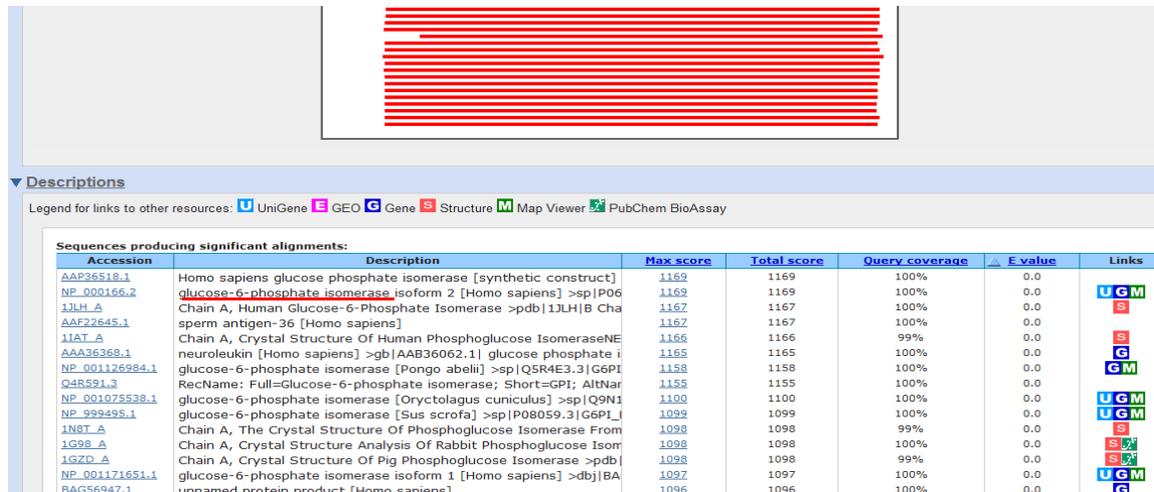
Реконструкция метаболических путей



Пример аминокислотной последовательности

MAALTRDPQFQKLQQWYREHRSELNLRRLFDANKDRFNHFSLTNTNHHGHILVDYSKNLVTEDVMRMLVDLAKSRGVEAA
RERMFNGEKINYTEGRAVLHVALRNRSNTPILVDGKDVMPVNVKVLDDKMKSFQQRVRSQDWKGYTGKTITDVINIGIGGSD
LGPLMVTEALKPYSSGGPRVWYVSNIDGTHIAKTLAQLNPESLFIASKTFTTQETITNAETAKEWFLQAAKDPSAVA
KHFVALSTNTTKVKEFGIDPQNMFEFWDWVGGRYSLWSAIGLSIALHVGFDNFEQLLSGAHWMDQHFRTTPLEKNAPVLL
ALLGIWYINCFGCETHAMLPYDQYLHRFAAYFQQGDMESNGKYITKSGTRVDHQTGPVWGEPTNGQHAFYQLIHQGT
KMIPCDLIPVQTQHPIRKGLHHKILLANFLAQTEALMRGKSTEEARKELQAAGKSPEDLERLLPHKVFEGNRPTNSIVFT
KLTPFMLGALVAMYEHKIFVQGIWDINSFDQWGVELGKQLAKKIEPELDGSAQVTSHDASTNGLINFIKQQREARVQ

BLAST База данных по сравнению последовательностей



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	UGM
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	
NP_001126984.1	glucose-6-phosphate isomerase [Pongo abelii] >sp Q5R4E3.3 G6PI	1158	1158	100%	0.0	GM
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	UGM
NP_999495.1	glucose-6-phosphate isomerase [Sus scrofa] >sp P08059.3 G6PI_	1099	1099	100%	0.0	UGM
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	100%	0.0	S
NP_001171651.1	glucose-6-phosphate isomerase isoform 1 [Homo sapiens] >dbj BA	1097	1097	100%	0.0	UGM
BAG56947.1	unnamed protein product [Homo sapiens]	1096	1096	100%	0.0	G

фермент, соответствующий выбранной последовательности

glucose-6-phosphate isomerase

реакция, катализируемая ферментом



определение всех реакций метаблического пути

Геном

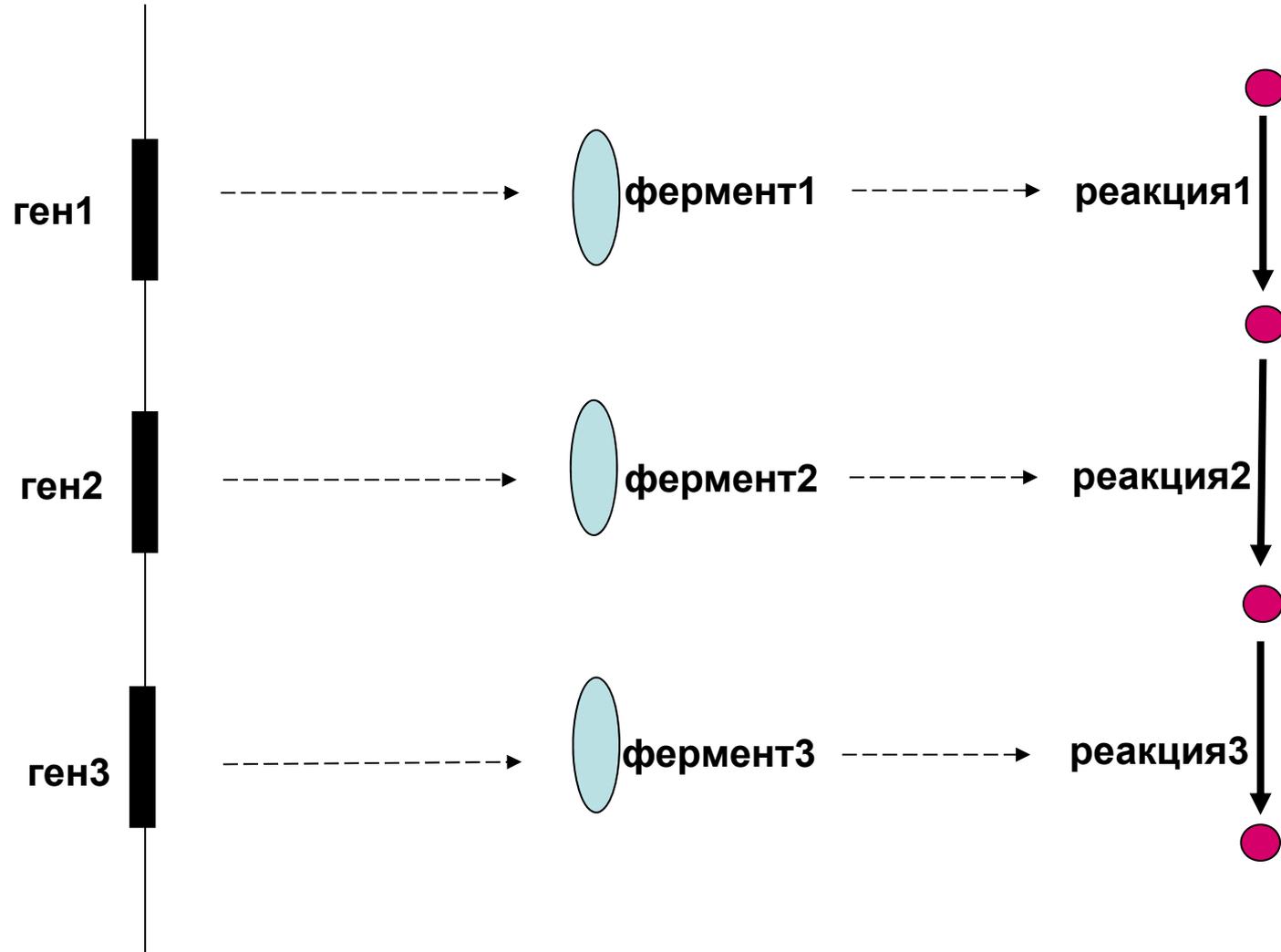
(совокупность генов)

Протеом

(совокупность белков)

Метаболом

(совокупность
метаболических реакций)



Молекулярно-биологические базы данных

русскоязычный ресурс

ОБЪЕДИНЕННЫЙ ЦЕНТР ВЫЧИСЛИТЕЛЬНОЙ БИОЛОГИИ И БИОИНФОРМАТИКИ



» Карта сайта

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[Молекулярно-биологические базы данных](#)

[По алфавиту](#) | [ДНК](#) | [РНК](#) | [Белки](#) | [Метаболические пути](#) | [Библиография](#) | [Прочие](#)

[BioCyc](#) - BioCyc Database collection
[BRITe](#) - Biomolecular Reaction Pathways fo Information Transfer and Expression database
[EcoCyc](#) - Encyclopedia of E.coli Genes and Metabolism
[EMP](#) - the Enzymes and Metabolic Pathways database
[KEGG](#) - Kyoto Encyclopedia of Genes and Genomes
[MetaCyc](#) - Database of metabolic pathways and enzymes
[MPW](#) - Metabolic PathWays database
[SoiBase](#) - Soybean metabolism dataBase
[SPAD](#) - Signaling PAtHway Database
[UM-BBD](#) - University of Minnesota Biocatalysis/Biodegradation Database

NCBI Центр биотехнологической информации

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

англоязычный ресурс

The screenshot displays the NCBI website interface. At the top, there is a navigation bar with 'NCBI Resources' and 'How To' dropdown menus. Below this is the NCBI logo and the text 'National Center for Biotechnology Information'. A search bar is present with a dropdown menu currently showing 'PubMed' selected, and other options like 'All Databases', 'Protein', 'Nucleotide', 'GSS', 'EST', 'Structure', 'Genome', 'BioSample', 'BioSystems', 'Books', 'CancerChromosomes', 'Conserved Domains', 'dbGaP', 'dbVar', 'Epigenomics', 'Gene', 'Genome Project', 'GENSAT', and 'GEO Datasets'. To the right of the search bar are 'Search' and 'Clear' buttons. On the left side, there is a vertical navigation menu with items such as 'NCBI Home', 'Site Map (A-Z)', 'All Resources', 'Chemicals & Bioassays', 'Data & Software', 'DNA & RNA', 'Domains & Structures', 'Genes & Expression', 'Genetics & Medicine', 'Genomes & Maps', 'Homology', 'Literature', 'Proteins', 'Sequence Analysis', 'Taxonomy', 'Training & Tutorials', and 'Variation'. In the center, there is a main content area with a heading 'NCBI' and a paragraph: 'Biotechnology Information advances science and... biomedical and genomic information.' Below this is a link for 'Organization | Research | RSS Feeds'. On the right side, there are two sections: 'Popular Resources' with a list of links including 'BLAST', 'Bookshelf', 'Gene', 'Genome', 'Nucleotide', 'OMIM', 'Protein', 'PubChem', 'PubMed', 'PubMed Central', and 'SNP'; and 'NCBI News' with a link for 'New NCBI News Issue' dated '28 Mar 2011' and another link for 'Retirement of Peptidome, SRA & Trace Archive' dated '16 Feb 2011'. At the bottom, there is an 'Education Resources' section with the text 'Central point of access for help documents, teaching materials, news outlets, and other educational resources.' and a small image of a person at a computer. A navigation bar at the very bottom shows a series of numbered buttons from 1 to 5, with '2' being the active page.

KEGG База данных по метаблическим путям



KEGG PATHWAY Database

Wiring diagrams of molecular interactions, reactions, and relations

KEGG2 PATHWAY BRITZ 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



Search

ENZYME



for

glucose-6-phosphate isomerase

Go

Clear

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



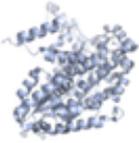
ENZYME: 5.3.1.9

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	HS: 2821 (GPI) PTR: 455941 (GPI) PON: 100174006 (GPI) MCC: 717980

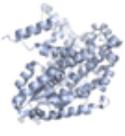
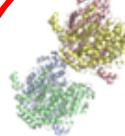
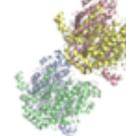
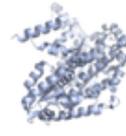
All links
Ontology (5) KEGG BRITE (5)
Pathway (8421) KEGG PATHWAY (5587) KEGG MODULE (2834)
Disease (1) OMIM (1)
Chemical substance (5) KEGG COMPOUND (5)
Chemical reaction (14) KEGG ENZYME (1) KEGG REACTION (5) KEGG RPAIR (4) KEGG RCLASS (4)
Genome (3) KEGG GENOME (3)
Gene (2209) KEGG ORTHOLOGY (3) KEGG 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)

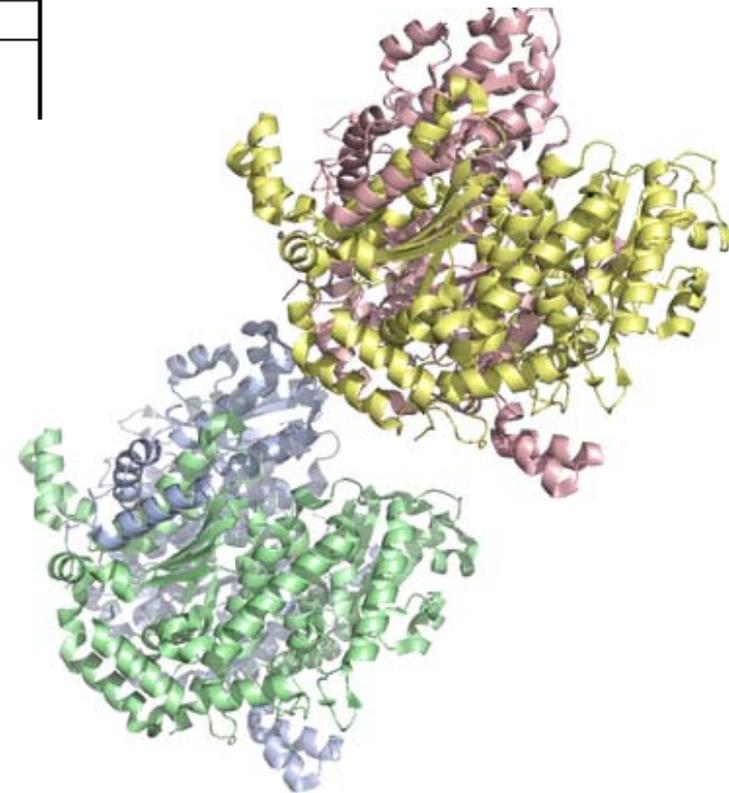
KEGG База данных по метаболическим путям

	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 MAALTRDPQFQKLQQWYREHRSELNLRRLFDANKDRFNHFSLTLNTHGHILVDYSKNLV



KEGG Homo sapiens (human) : 2821 5 PDB structures

 PDB:1IAT 1.62 Å S04 BME Jmol	 PDB:1JIQ 1.90 Å Jmol	 PDB:1JLH 2.10 Å Jmol	 PDB:1IRI 2.40 Å E4P Jmol	 PDB:1NUH 2.51 Å S04 PA5 Jmol
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Определили структуру белка

KEGG База данных по метаболическим путям



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	
	<p>C00092</p> <p>C00085</p>	
RPair	RP01093 C00085_C00092 main	
Enzyme	5.3.1.9	

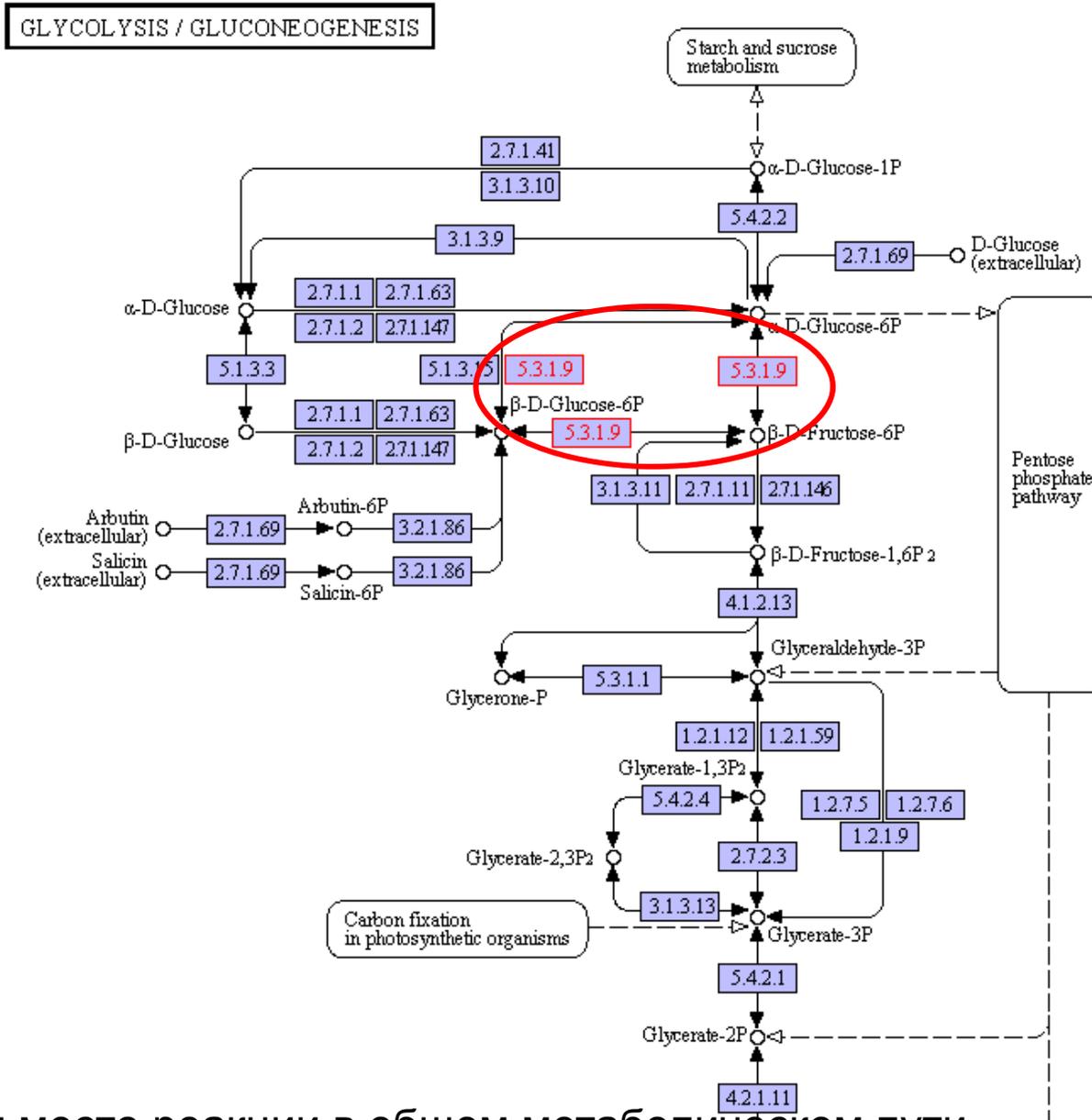
All links

[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



[Pathway Tools Tutorial](#)
April 25 - 27, 2011
Menlo Park, CA

[LOGIN](#) | [Why Login?](#) | [Create New Account](#)

<input type="text"/>	<input type="button" value="Quick Search"/>	<input type="button" value="Gene Search"/>
Searching <i>MetaCyc</i> change organism database		

[Home](#) | [Search](#) | [Tools](#) | [Help](#)

About MetaCyc

[Guide To MetaCyc](#)
[Querying Examples](#)
[Update History](#)
[Advisory Board](#)

Services

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[Web Services](#)



[Carnegie](#)



METACYC OVERVIEW

MetaCyc is a database of nonredundant, experimentally elucidated metabolic pathways. MetaCyc contains more than 1670 pathways from more than 2100 different organisms [\[more\]](#), and is curated from the scientific experimental literature. [\[more\]](#)

MetaCyc contains pathways involved in both primary [\[def\]](#) and secondary [\[def\]](#) metabolism, as well as associated compounds, enzymes, and genes. [\[more\]](#)

Motivations

The goal of MetaCyc is to catalog the universe of metabolism by storing a representative sample of each experimentally elucidated pathway. [\[MetaCyc mission\]](#)

MetaCyc is used in a variety of scientific applications, such as providing a reference data set for computationally predicting the metabolic pathways of organisms from their sequenced genomes, supporting metabolic engineering, helping to compare biochemical networks, and serving as an encyclopedia of metabolism. [\[scientific applications\]](#)

Recent Publication

- [The MetaCyc Database of metabolic pathways and enzymes and the BioCyc collection of Pathway/Genome Databases](#), *Nucleic Acids Research* 38:D473-D479 2010.

Query and Visualization

MetaCyc pathways can be browsed from a list, from ontologies [\[def\]](#), or queried directly when searching for pathways, proteins, reactions or compounds. [\[more\]](#) MetaCyc can also be queried programmatically using [Java](#) or [PERL](#) when installed locally. [\[more\]](#)

New Users

Get a bird's eye view of the MetaCyc web site [here](#).

MetaCyc База данных по метаболическим путям

Search Results for **glucose-6-phosphate isomerase** using database *MetaCyc* [what is this?](#)

[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.

- [β-D-glucose-6-phosphate = D-fructose-6-phosphate \(glucose-6-phosphate isomerase\)](#)

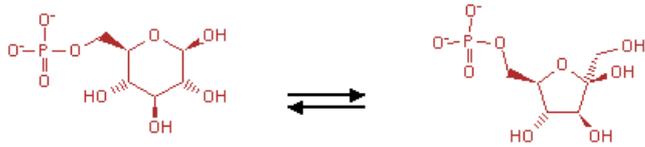
Alternative searches:

- [Full text search](#) for glucose-6-phosphate isomerase on all pages in this database using [Google](#)

Определили реакцию

MetaСус 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, $A + B \rightleftharpoons C + D$ versus $C + D \rightleftharpoons A + B$, 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

ΔG° (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:Q9S857](#), [UniProt:RELATED-TO:Q9X670](#), [UniProt:RELATED-TO:Q59000](#), [UniProt:RELATED-TO:Q59088](#)

BRENDA База данных по белкам

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

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- Enzyme Nomenclature**
- EC number
- Recommended Name
- Reaction
- Reaction Type
- Pathway
- Systematic Name
- Synonyms
- CAS Registry Number
- Enzyme-Ligand Interactions**
- Substrate/Product
- Natural Substrates
- Cofactor
- Metals and Ions
- Inhibitors
- Activating Compound
- Functional Parameters**
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- 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

BRENDA
The Comprehensive Enzyme Information System
EC 5.3.1.9 - Glucose-6-phosphate isomerase

Information on EC 5.3.1.9 - Glucose-6-phosphate isomerase:

Mark a special word or phrase in this record:

Select one or more organisms in this record:

- All organisms
- Aeropyrum pernix
- Apis mellifera
- Arabidopsis thaliana
- Archaeoglobus fulgidus

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EC NUMBER	COMMENTARY
5.3.1.9	-

RECOMMENDED NAME	GeneOntology No.
Glucose-6-phosphate isomerase	GO:0004347

REACTION	REACTION DIAGRAM	COMMENTARY	ORGANISM	LITERATURE
D-Glucose 6-phosphate = D-fructose 6-phosphate		-	-	-
D-Glucose 6-phosphate = D-fructose 6-phosphate		push-pull mechanism of ring opening in which H388 breaks the O5-C1 bond by donating a proton, and simultaneously, K518 abstracts a proton from the C1 hydroxyl group	Mus musculus	662633
D-Glucose 6-phosphate = D-fructose 6-phosphate		mechanism is based on an enediol intermediate	Pyrococcus furiosus	662637
D-Glucose 6-phosphate = D-fructose 6-phosphate		multistep catalytic mechanism, model including catalytically active amino acids	Oryctolagus cuniculus	663346

PDB База данных по структуре белков

<http://www.rcsb.org/pdb/explore/explore.do?job=summary&pdbId=1iat>

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Summary **Sequence** Annotations Seq. Similarity 3D Similarity Literature Biol. & Chem. Methods Geometry Links

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

DOI:10.2210/pdb1iat/pdb

Primary Citation

The crystal structure of human phosphoglucose isomerase at 1.6 Å 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

Classification: Isomerase

Structure Weight: 63369.64

Molecule: PHOSPHOGLUCOSE ISOMERASE

Polymer: 1 Type: polypeptide(L)

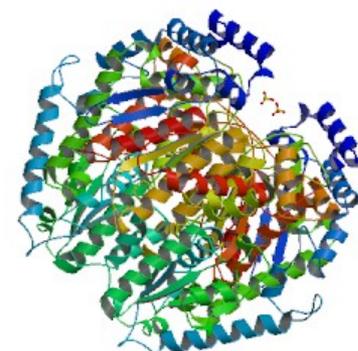
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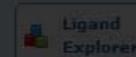
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Read, J. P., Pearce, J. P., Li, X. P., Muirhead, H. P., Chirgwin, J. P., Davies, C. P.
Journal: (2001) J.Mol.Biol. 309: 447-463
PubMed: 1137116
DOI: 10.1006/jmb.2001.2500
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PubMed Abstract:
Phosphoglucose is a housekeeping enzyme with cytokine properties. [Read More & See]

↓ Molecular Description
Classification:
Structure Weight:
Molecule: PHOSPH
Polymer: 1
Chains: A
EC#: 5.3.1.9

↓ Source
Polymer: 1
Scientific Name: Hon sapi

↓ Related PDB Entries
Id
1DQR

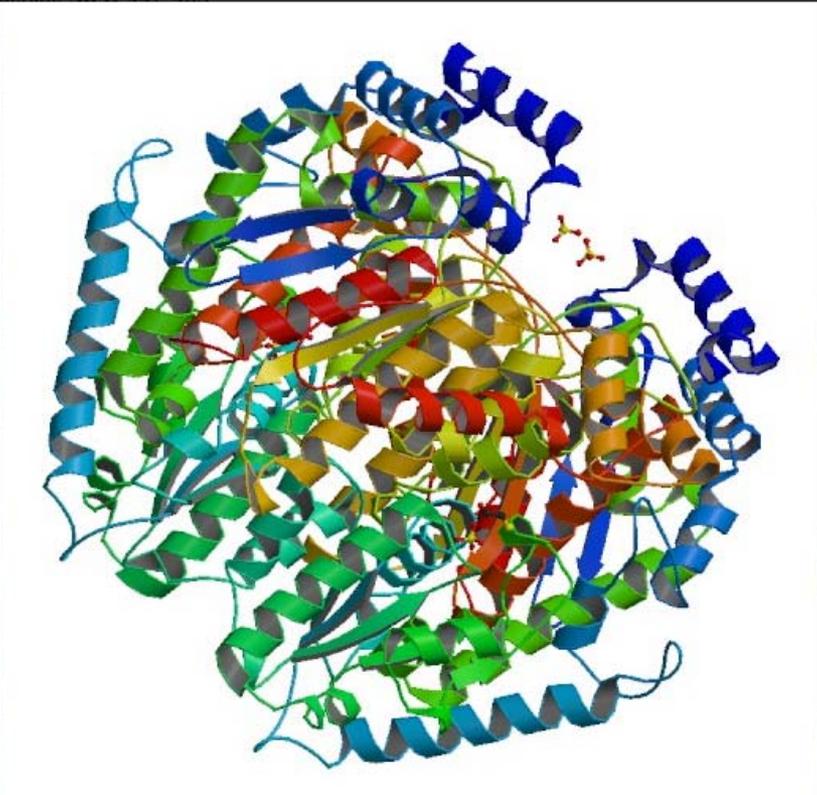
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Other Viewers *
Biological assembly as

↓ MyPDB Personal
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↓ Deposition Summary
Authors: Read, J.A., X. P., Muirhead, H. P., Davies, C. P.
Deposition:
Release:
Last Modified (REVDAT):

↓ Experimental Data
Method: X-RAY DIFFRACTION
Exp. Data:
Structure Factors
EDS 

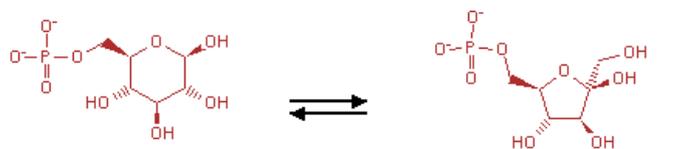


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β -D-glucose-6-phosphate

D-fructose-6-phosphate

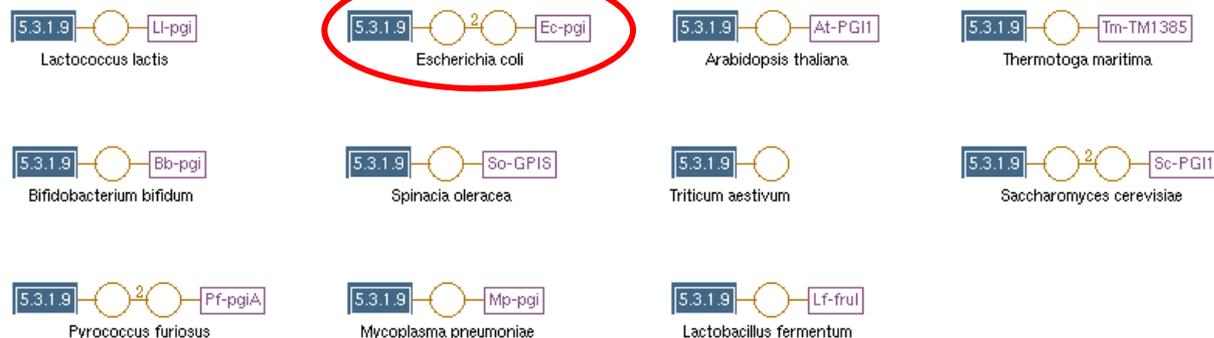
The reaction direction shown, that is, $A + B \rightleftharpoons C + D$ versus $C + D \rightleftharpoons A + B$, is in accordance with the Enzyme Commission system.

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ΔG° (kcal/mol): 0.4 KCAL/MOLE [[Stryer88](#)]

Gene-Reaction Schematic: [?](#)



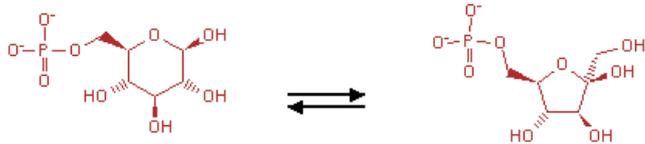
Unification Links: [BRENDA:5.3.1.9](#), [ENZYME:5.3.1.9](#), [ExplorEnz:5.3.1.9](#), [KEGG:R00771](#)

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Выбрали интересующий организм

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ΔG° (kcal/mol): 0.4 KCAL/MOLE [[Stryer88](#)]

Gene-Reaction Schematic: [?](#)

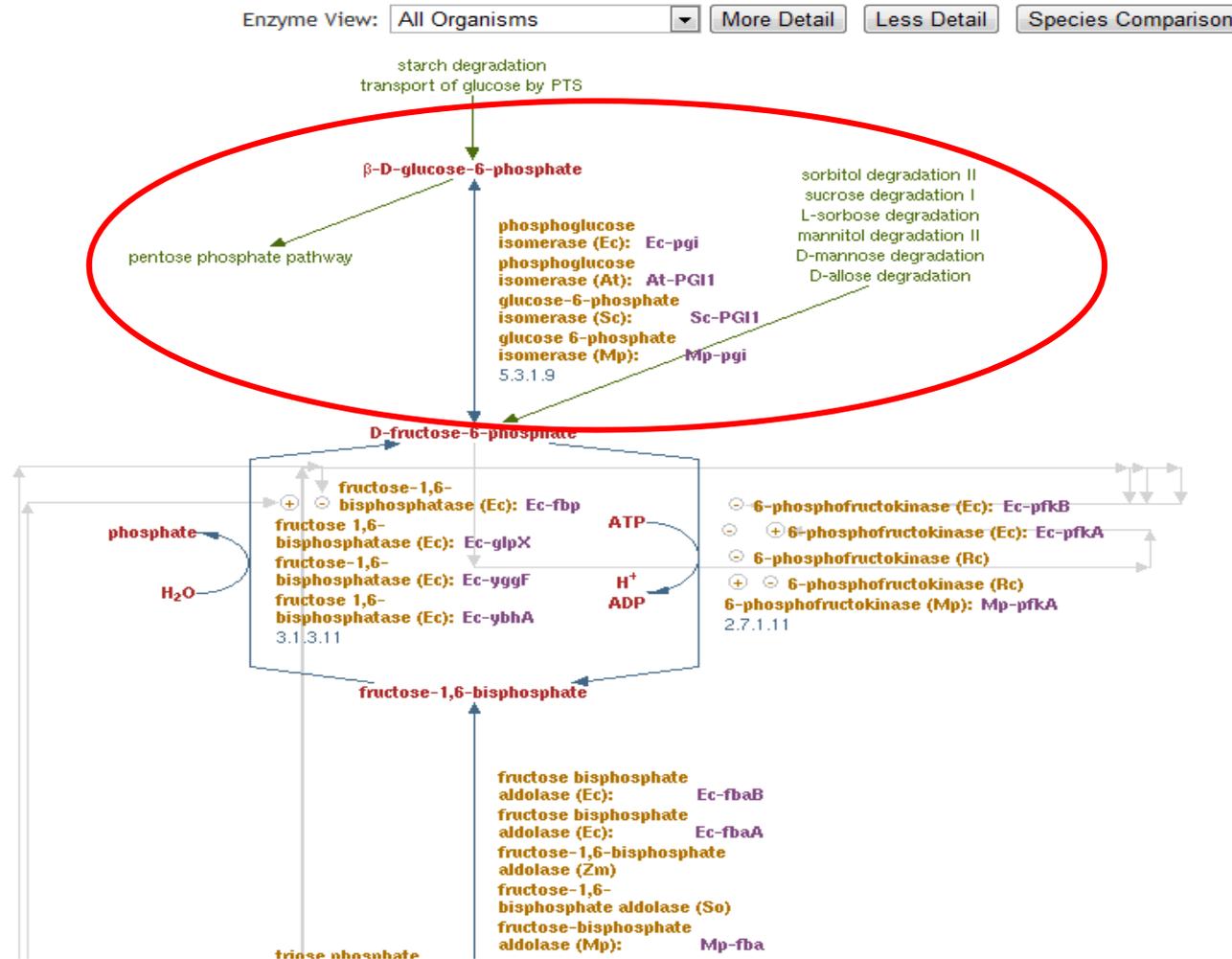


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MetaCyc База данных по метаболическим путям

MetaCyc Pathway: glycolysis I



Определили место реакции в метаболическом пути

Построение метаболической модели

“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.»

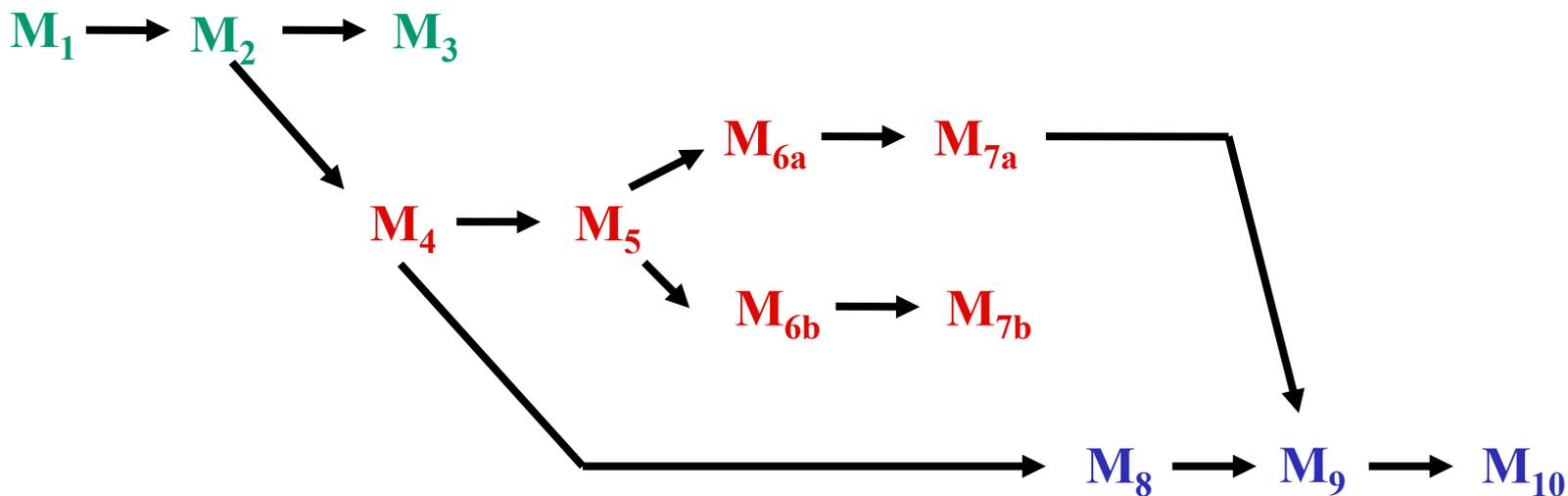
Теоретические подходы и концепции метаболического моделирования

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

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.



Типы метаболических моделей

кинетические модели – системы ОДУ

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

стехиометрические (потоковые) модели – системы линейных алгебраических уравнений

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

Представление скорости реакции

В соответствии с законом действующих масс

(скорость реакции пропорциональна вероятности столкновения реагентов, а вероятность в свою очередь пропорциональна концентрации реагентов с учетом молекулярности реакции)



$$v = k_1 S_1 S_2 - k_{-1} P^2 = v_+ - v_-$$

v - общая скорость реакции

v_+ - скорость прямой реакции

v_- - скорость обратной реакции

В общем виде:

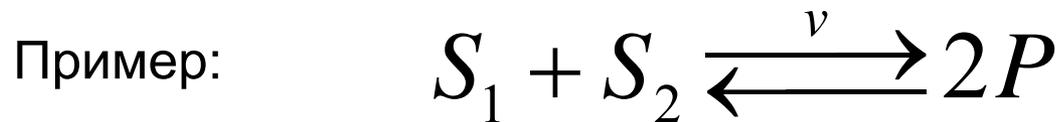
$$v = v_+ - v_- = k_+ \prod_i S_i^{m_i} - k_- \prod_j P_j^{m_j}$$

m_i и m_j соответствуют молекулярности S_i и P_j

Скорость реакции может быть выражена как через **концентрации** реагирующих веществ, так и в виде баланса **скоростей** прямых и обратных реакций.

Стехиометрические коэффициенты

Стехиометрические коэффициенты обозначают пропорции субстратов и продуктов, участвующих в реакции.



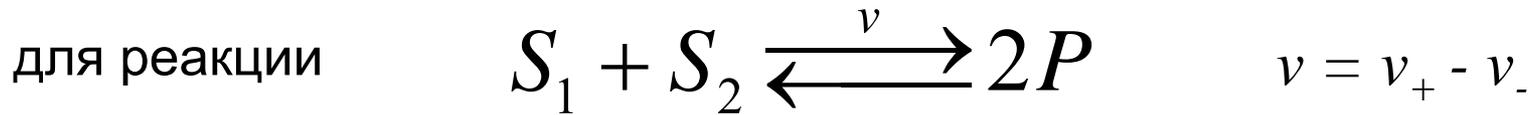
Стехиометрические коэффициенты для S_1 , S_2 и P : -1, -1 и 2.

Набор стехиометрических коэффициентов не единственен:

если считать, что для получения одного моля используется по половине моля каждого субстрата S_1 и S_2 , можно записать: -1/2, -1/2 и 1;

или если изменить направление реакции, тогда можно записать: 1, 1 и -2.

ОДУ для одной и нескольких реакций



имеем ОДУ:

$$\frac{dS_1}{dt} = \frac{dS_2}{dt} = -v$$

$$\frac{dP}{dt} = 2v$$

убыль субстрата S_1 со скоростью v сопровождается убылью субстрата S_2 с той же скоростью и удвоенной скоростью увеличения концентрации продукта P

Для метаболической сети, состоящей из m метаболитов и r реакций, динамика системы описывается системой m уравнений.

Уравнения наз. уравнениями баланса, поскольку рассматривается баланс между синтезом и распадом метаболита:

$$\frac{dS_i}{dt} = \sum_{j=1}^r n_{ij} v_j$$

$i = 1, \dots, m$

n_{ij} – стехиометрические коэффициенты метаболита i в реакции j

Данные для верификации метаболической модели

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

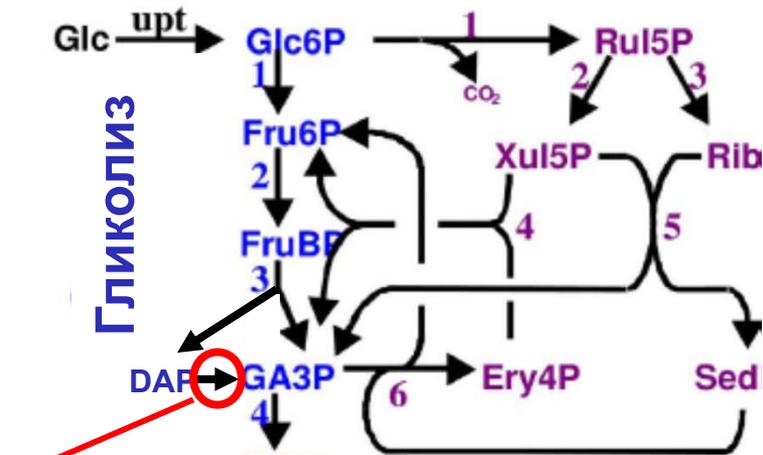
Количественные знания ограничены

1. Существует большая разница между дискретными данными, получаемыми в экспериментах и непрерывными физиологическими процессами.
2. Принципиальное ограничение доступной информации.
3. Данные о некоторых важных клеточных процессах отсутствуют.
4. Данные собираются для разных штаммов разных организмов в разных экспериментальных условиях.

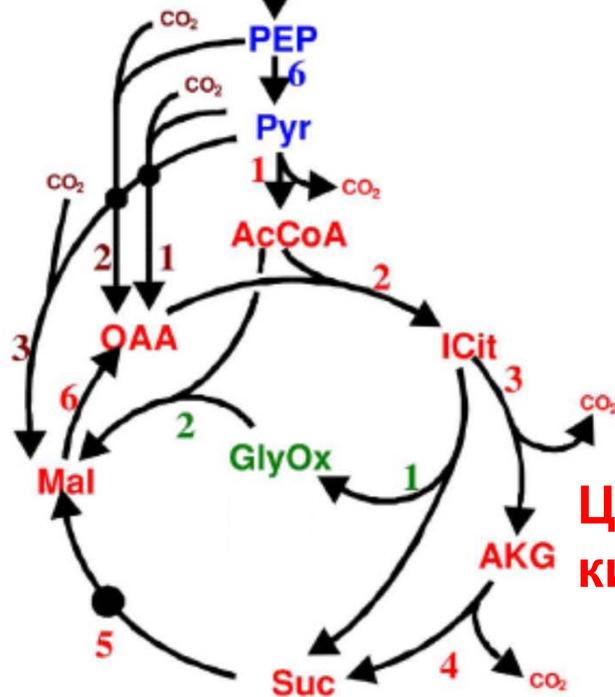
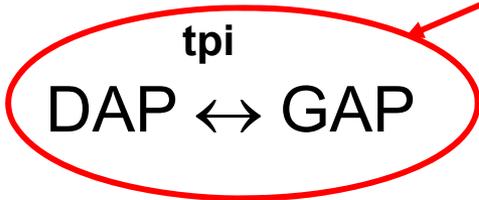
Кинетические модели

- построение схемы метаболического пути
- вывод уравнения скорости для каждой реакции
- объединение в систему дифференциальных уравнений
- подбор параметров
- верификация модели по экспериментальным данным

Центральные метаболические пути

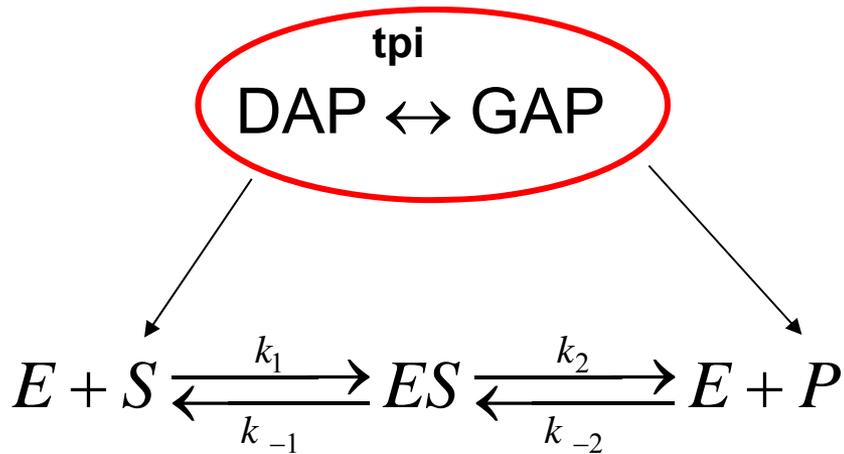


Пентозофосфатный путь



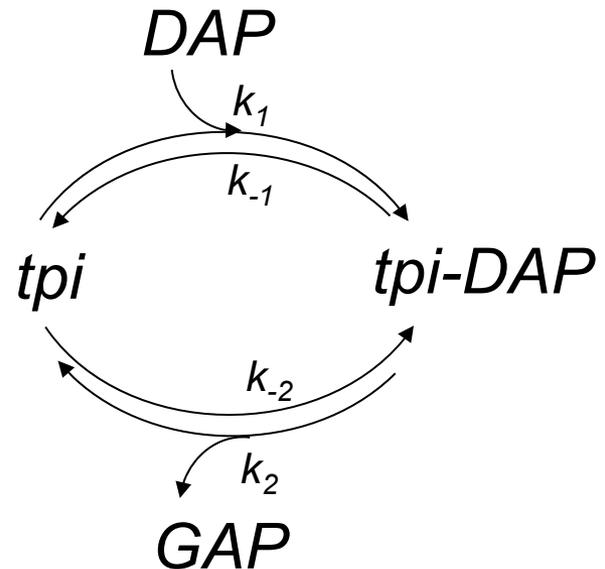
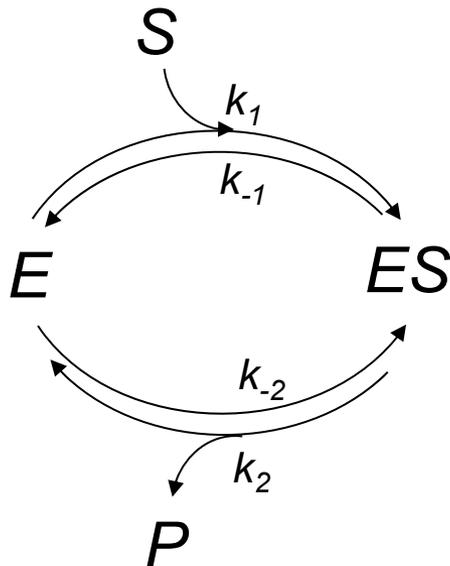
Цикл трикарбоновых кислот

Вывод уравнения скорости



Кинетическая схема взаимодействия субстрата и продукта с ферментом

Каталитический цикл фермента



Вывод уравнения скорости

Метод квази-стационарных концентраций

Кинетическая схема взаимодействия субстрата и продукта с ферментом:



Соответствующая система дифференциальных уравнений:

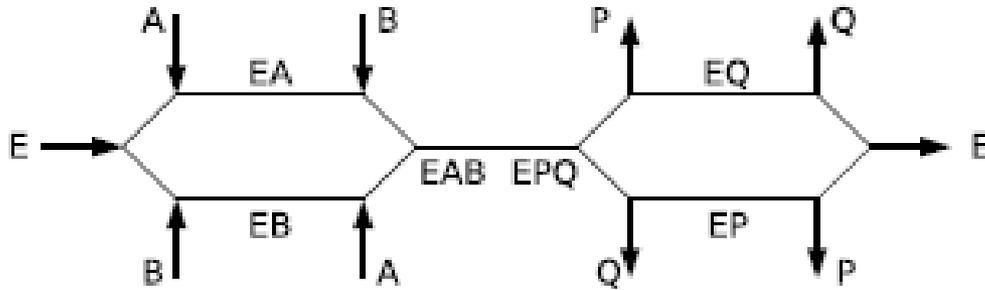
$$\left. \begin{aligned} \frac{dS}{dt} &= -k_1 \cdot S \cdot E + k_{-1} \cdot ES \\ \frac{dP}{dt} &= k_2 \cdot ES - k_{-2} \cdot E \cdot P \end{aligned} \right\} \text{медленные переменные}$$

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

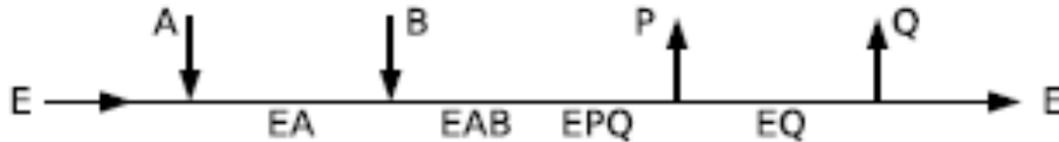
Уравнение скорости:

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

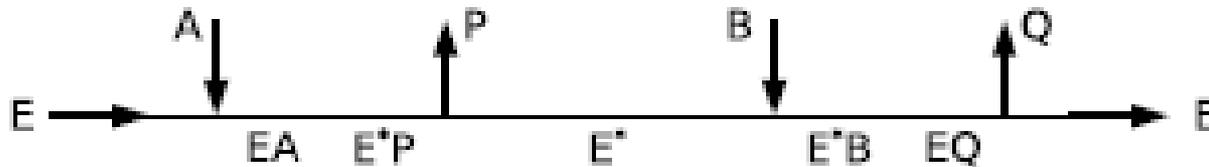
Классификация реакций (Cleland 1963)



Random Bi Bi Mechanism



Sequential Bi Bi Mechanism

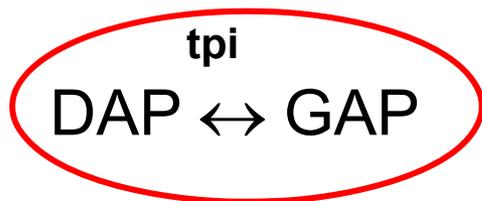


Ping-Pong Mechanism

Как выводится уравнение скорости в случае более, чем одного субстрата и продукта?

Определение констант скорости

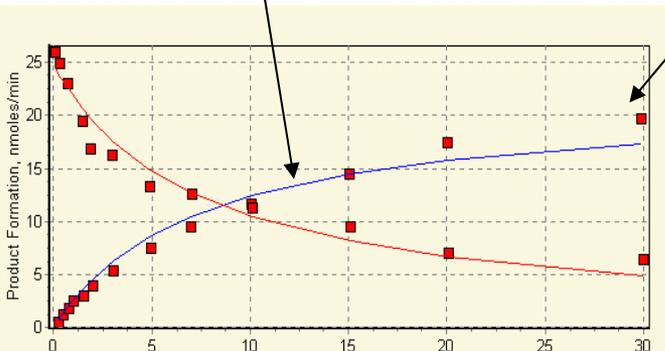
для триозофосфат изомеразы (tpi)



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

фитирование методом
наименьших квадратов

экспериментальные
точки



$$K_m^{DAP} = 2.3 \text{ mM}$$

$$K_m^{GAP} = 1.5 \text{ mM}$$

$$k_2 = 45000 \text{ 1/min,}$$
$$k_{-2} = 520000 \text{ 1/min}$$

константы Михаэлиса для
субстрата и продукта

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

базы данных

MetaСус База данных по метаболическим путям

Enzymatic reaction of: phosphoglucose isomerase

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

[β-D-glucose-6-phosphate <=> D-fructose-6-phosphate](#)

The reaction direction shown, that is, $A + B \rightleftharpoons C + D$ versus $C + D \rightleftharpoons A + B$, 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 β-D-glucose-6-phosphate: 1018 μM [[Ogawa07](#)]

$\text{pH}_{(\text{opt})}$: 8 [[Schreyer80](#)]

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

BRENDA База данных по белкам

	KM VALUE [mM]	KM VALUE [mM] Maximum	SUBSTRATE	ORGANISM	COMMENTARY	LITERATURE	IMAGE
Functional Parameters	0.031	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant S278L	702456	2D-image
KM Value	0.034	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant I525T	702456	2D-image
Turnover Number	0.037	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant wild-type enzyme	702456	2D-image
kcat/KM Value	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
Ki Value	0.039	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant L487F	702456	2D-image
IC50 Value	0.04	-	D-fructose 6-phosphate	Methanocaldococcus jannaschii	50°C, pH 6.3	649517	2D-image
Specific Activity	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
pH Optimum	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
pH Range	0.05	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant E495K	702456	2D-image
Temperature Optimum	0.06	-	D-fructose 6-phosphate	Pyrobaculum aerophilum	pH 7.4, 80°C	661679	2D-image
Temperature Range	0.061	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant R83W	702456	2D-image
pl Value	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
Organism related Information	0.068	-	D-fructose 6-phosphate	Homo sapiens	pH 7.5, 30°C, recombinant mutant R472H	702456	2D-image
Source Tissue	0.147	-	D-fructose 6-phosphate	Escherichia coli	22°C, pH 7.4	661902	2D-image
Localization	0.2	-	D-fructose 6-phosphate	Thermoplasma acidophilum	80°C, pH 7.4	662220	2D-image
Organism	0.21	-	D-fructose 6-phosphate	Aeropyrum pernix	50°C, pH 7.4	662220	2D-image
General Information	0.27	-	D-fructose 6-phosphate	Mycobacterium tuberculosis	pH 7.6, 25°C	682664	2D-image
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							

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 deficiency [Biophys Chem. 1997]

Expression and enzymatic characterization of human glucose phosphate isomerase deficiency [Blood Cells Mol Dis. 1998]

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

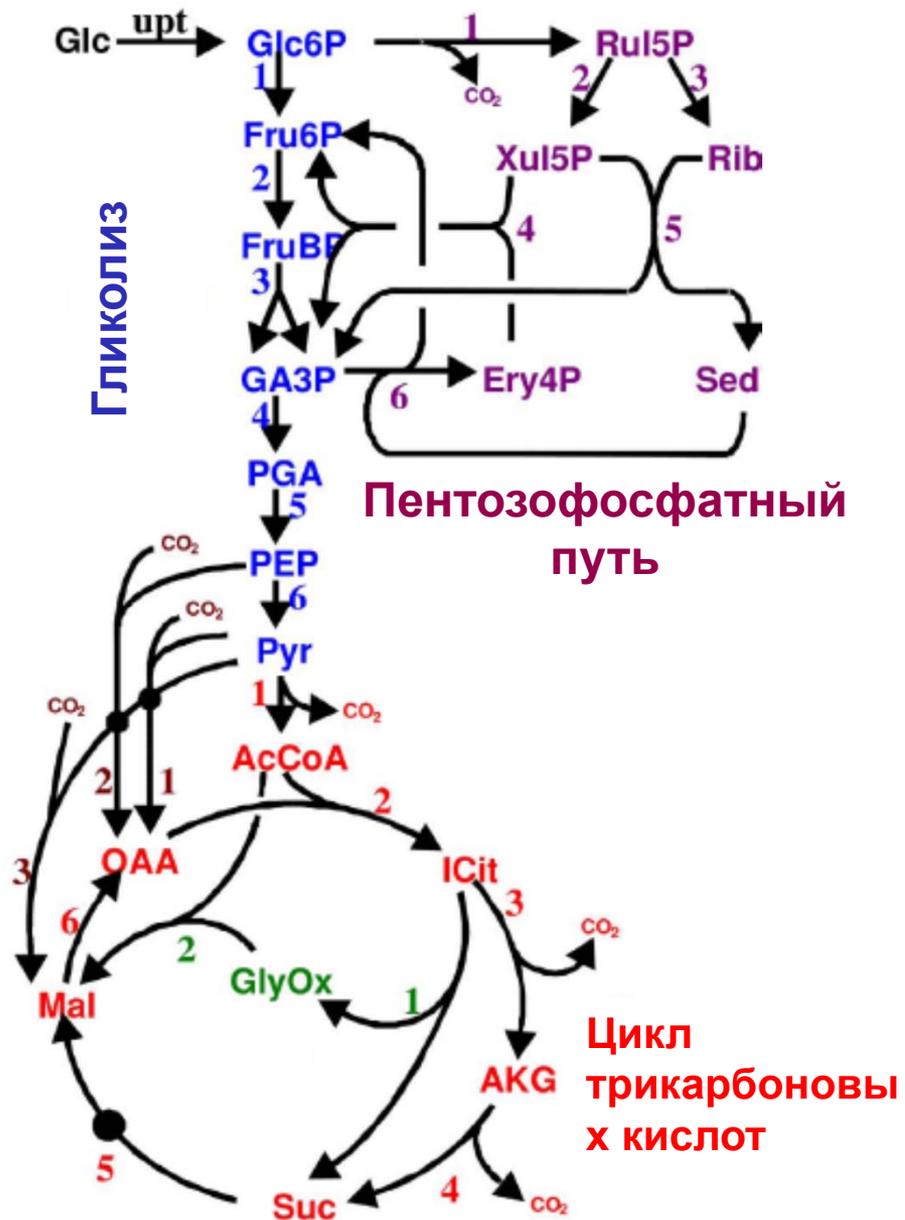
Review Glucose-6-phosphate isomerase deficiency [Baillieres Best Pract Res Clin Haematol. 200...]

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

ссылки на сходные публикации

Модель центрального метаболизма *E. coli*

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



1. Вывели уравнения скорости для каждого фермента.

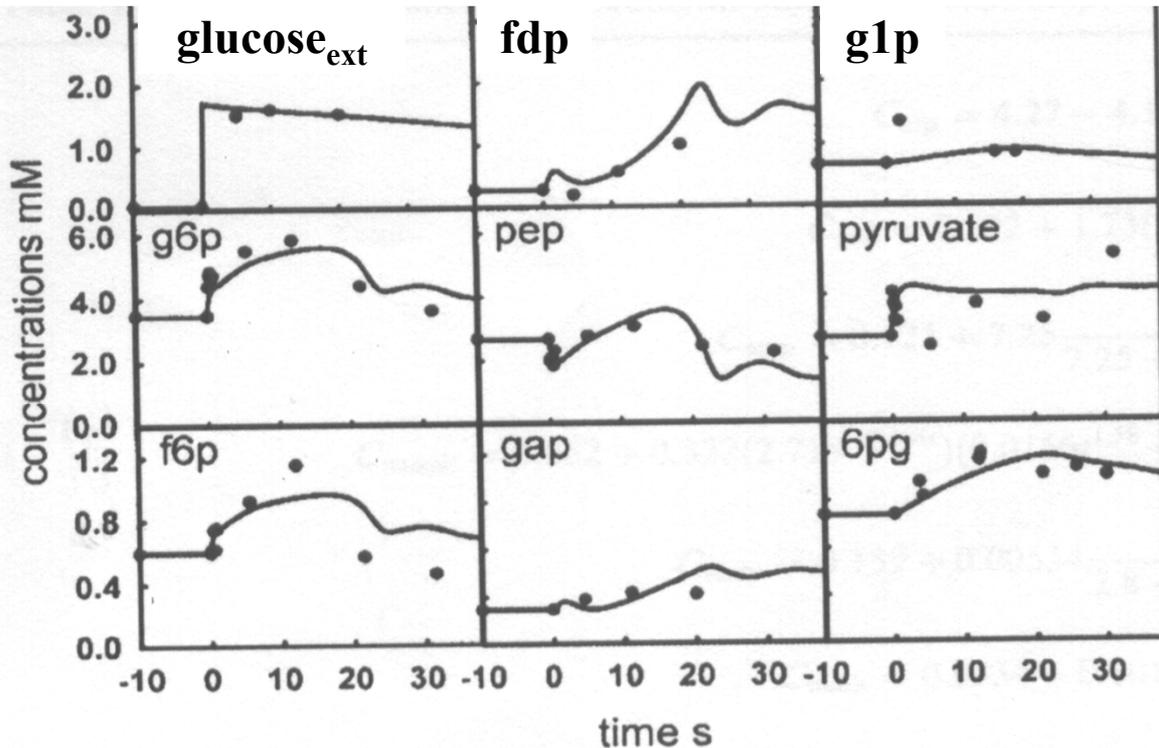
2. Объединили в систему уравнений для всего пути.

3. Оценили параметры модели (константы скоростей)

4. Верифицировали по экспериментальным данным

Результаты моделирования

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



Кинетика метаболитов.

Точки – экспериментальные
данные

Линии – результаты
численного счета

- Описана экспериментально наблюдаемая динамика (в том числе и колебательный процесс).
- Показано, что поглощение глюкозы в основном контролируется двумя системами: транспортной (PTS) и ее ингибиторами.