

# Modellierung und Simulation in der Biochemie

Ursula Kummer

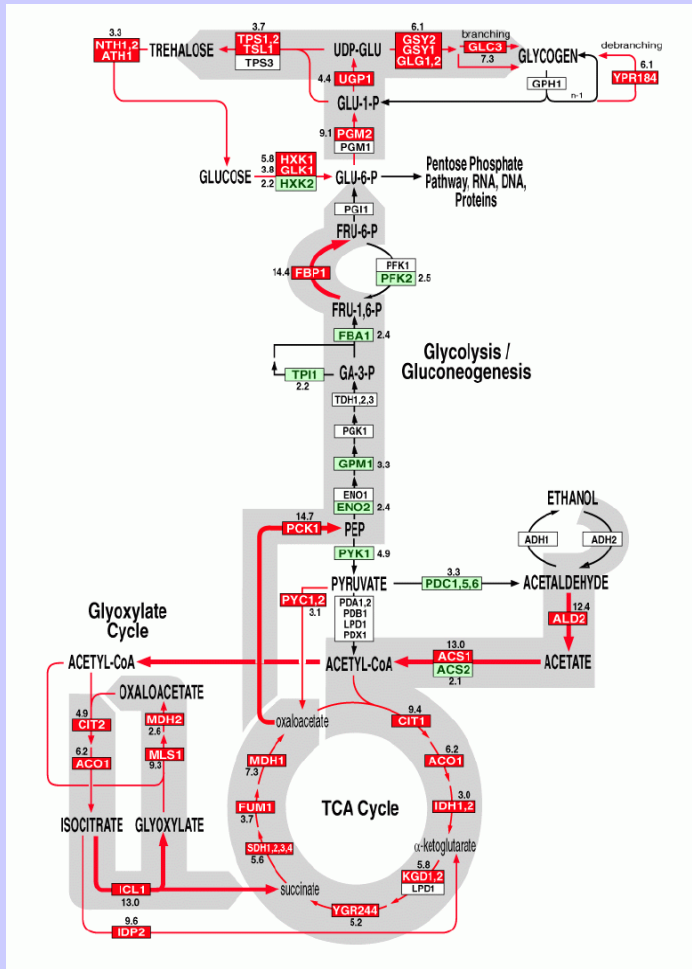
Vorlesung 1

Einzelne Reaktionen, Kinetik,  
Enzymkinetik, Komplexe Kinetik

# Übersicht

- Einführung
- Reaktionskinetik allgemein
- Einfache Enzymkinetik
- Komplexe Enzymkinetik
- Fallbeispiele
- Datenbanken

# Biochemische Netzwerke



- Bestehen aus metabolischen und informationsprozessierenden Pfaden, die miteinander verlinkt sind
- Interaktion zwischen Reaktionen/Pfaden durch Effektoren, die enzymatische Aktivitäten beeinflussen
- Verschiedenste experimentelle Daten als Grundlage der Modellierung

# Aufgaben und Ansatz der Modellierung

Aufgaben:

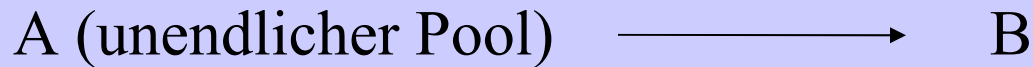
- Modelle zu falsifizieren/validieren
- “Counterintuitive” Hypothesen finden
- Schnelle und effektive Aufklärung von Mechanismen

Ansatz:

- Problemorientierter Ansatz (z.B. Detailierungsgrad)
- Pragmatismus -> “Every model is a lie!”

# Reaktionsordnung

Reaktion 0. Ordnung: z.B. konst. Zerfall



Reaktion 1. Ordnung: z.B. radioaktiver Zerfall



Reaktion 2. Ordnung: z.B. zwei Reaktanten reagieren miteinander



# Einfache Reaktionskinetik I

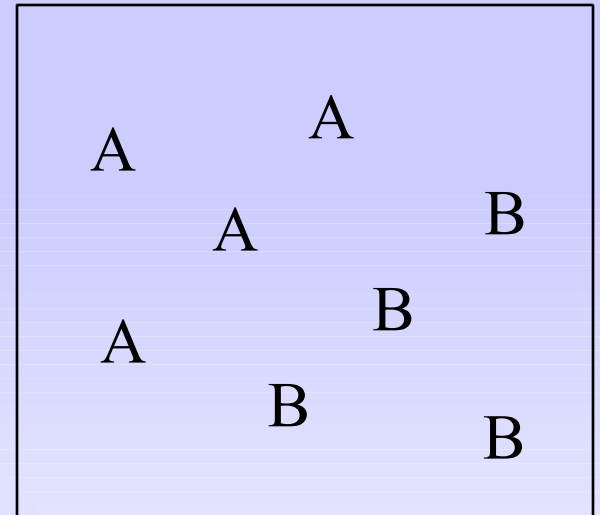
Einfachster Fall:



Reaktionsgeschwindigkeit:

$$d[A]/dt = dA/dt = A' = -k*[A] = -k*A$$

$$d[B]/dt = dB/dt = B' = k*[A] = k*A$$



# Einfache Reaktionskinetik II

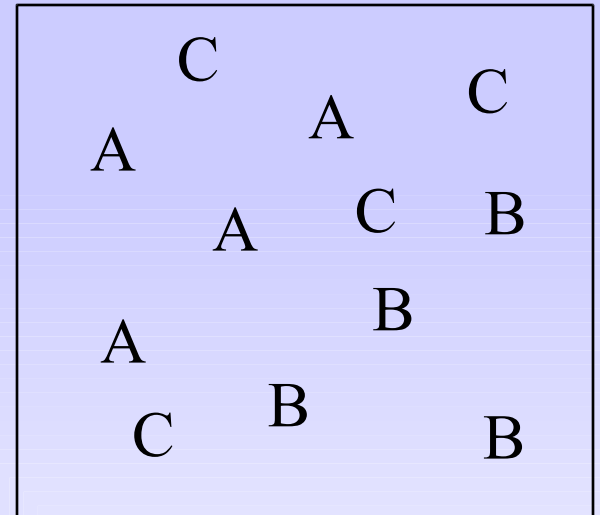
Zwei Reaktanten:



Reaktionsgeschwindigkeit:

$$d[A]/dt = dA/dt = A' = -k*[A]*[B] = -k*A*B$$

$$d[B]/dt = dB/dt = B' = -k*[A]*[B] = -k*A*B$$



# Einfache Reaktionskinetik III

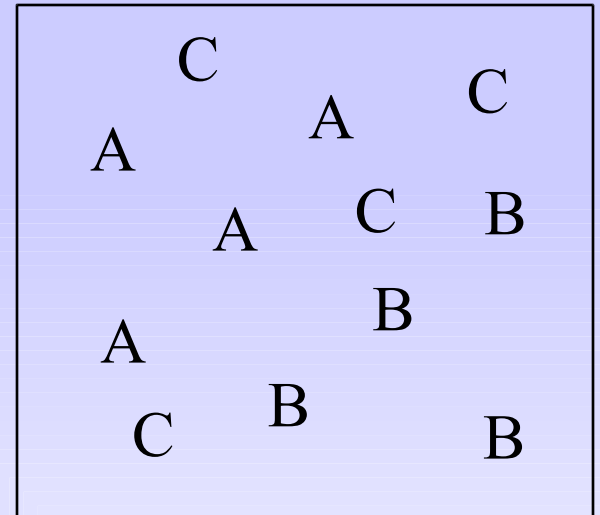
Drei Reaktanten:



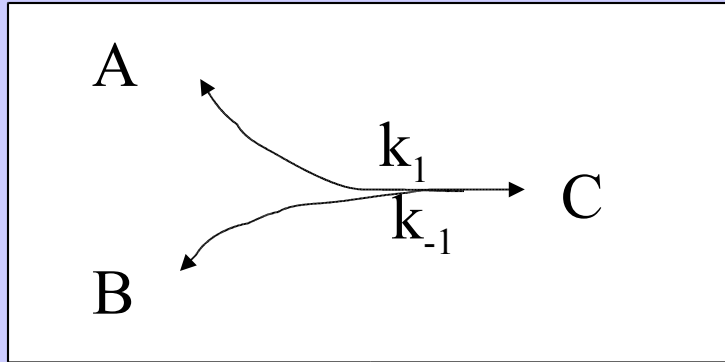
Reaktionsgeschwindigkeit:

$$d[A]/dt = dA/dt = A' = -k*[A]*[B]^2 = -k*A*B^2$$

$$d[B]/dt = dB/dt = B' = -k*[A]*[B]^2 = -k*A*B^2$$



# Reaktionskinetik - Reversibilität



Reversible Reaktion

$$K = \frac{[C]}{[A] * [B]}$$

Gleichgewichtskonstante

$$d[A]/dt = -k_1 * [A] * [B] + k_{-1} * [C]$$

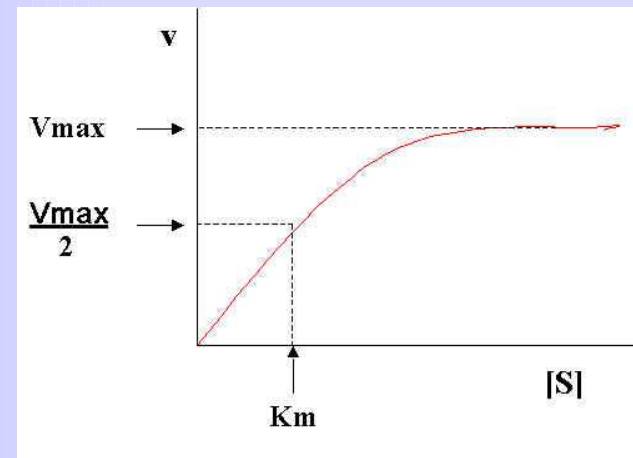
$$d[B]/dt = -k_1 * [A] * [B] + k_{-1} * [C]$$

$$d[C]/dt = k_1 * [A] * [B] - k_{-1} * [C]$$

Systemgleichungen

# Enzyme, die Biokatalysatoren

- Die Geschwindigkeit biochemischer Reaktionen folgt meist einer Sättigungskurve.
- Wenn alle Enzyme belegt sind, kann die Geschwindigkeit nicht mehr zunehmen, auch wenn mehr Substrat dazukommt.
- Die Substratkonzentration bei halbmaximaler Geschwindigkeit entspricht  $K_m$ .



# Reaktionssysteme mit enzymatischer Katalyse

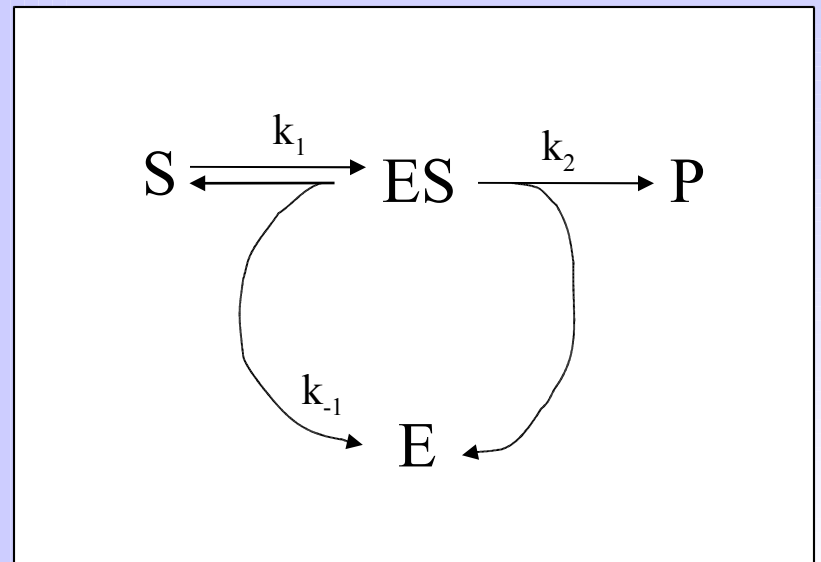
Einfacher Fall:

Als Systemgleichungen ergeben sich mit der Näherung, daß ES sich im partiellen steady state befindet:

$$d \text{ ES}/dt = 0$$

und der Definition  $K_M = (k_{-1} + k_2)/k_1$

$$\frac{dS}{dt} = -k_2 * E_0 * \frac{S}{(K_M + S)}$$



# Herleitung Michaelis-Menten



Systemgleichungen:

$$S' = -k_1 * E * S + k_{-1} * ES$$

$$E' = -k_1 * E * S + k_{-1} * ES + k_2 * ES$$

$$ES' = k_1 * E * S - k_{-1} * ES - k_2 * ES$$

$$P' = k_2 * ES$$

Annahme des “quasi-steady-state”:

$$ES' = 0 \rightarrow k_1 * E * S = (k_{-1} + k_2) * ES$$

$$\rightarrow k_1 * (E_{tot} - ES) * S = (k_{-1} + k_2) * ES$$

$$\rightarrow ES = E_{tot} * S / (S + (k_{-1} + k_2) / k_1)$$

$$\Rightarrow P' = k_2 * E_{tot} * S / (S + K_m)$$

# Einschub: Schnelle und langsame Variablen

## Langsame Variablen:

S,P sind echte Reaktanten, die im Normalfall in großen Konzentrationen auftreten. Herausnehmen eines Teilchens hat keinen Einfluß auf die Konzentration.

Charakteristikum: Große Relaxationszeiten

## Schnelle Variablen:

E, ES etc. sind Katalysatoren und Zwischenprodukte in kleinen Konzentrationen.

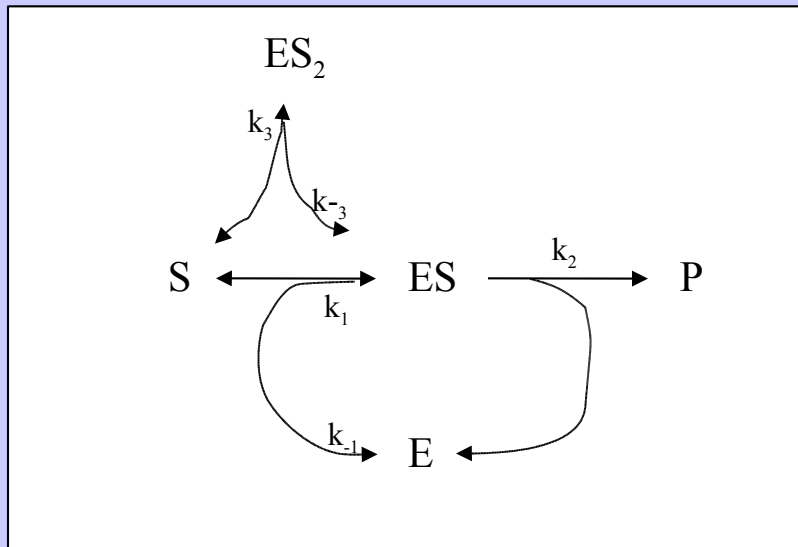
Charakteristikum: Kleine Relaxationszeiten

Dgl. Der schnellen Variablen (sogenannte steife Dgl.) werden gleich null gesetzt. Schnelle Variablen können als quasistationär relativ zu den langsamen Variablen betrachtet werden, da sie sich sofort auf die langsamen einstellen.

Vorsicht: Immer sehr sorgfältig überprüfen!!

# Reaktionssysteme mit enzymatischer Katalyse

Katalyse mit Substratinhibition:



Analoge Vorgehensweise liefert:

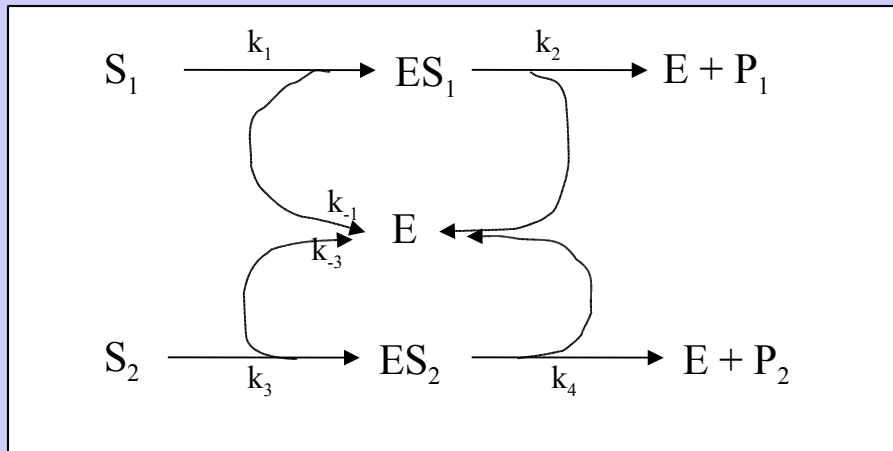
$$\frac{dS}{dt} = -k_2 * E_0 * \frac{S}{(K_m + S + K_i * S^2)}$$

mit

$$K_i = \frac{(k_{-1} + k_2) * k_3}{k_1 * k_{-3}}$$

# Reaktionssysteme mit enzymatischer Katalyse

Zwei konkurrierende Substrate:



Partieller steady state:

$$d ES_1/dt = k_1 * E * S_1 - (k_{-1} + k_2) * ES_1 = 0$$

$$d ES_2/dt = k_3 * E * S_2 - (k_{-3} + k_4) * ES_2 = 0$$

$$\text{Gesamtgeschwindigkeit } v = k_2 * ES_1 + k_4 * ES_2$$

$$E_0 = E + ES_1 + ES_2$$

Bsp: Teilgeschwindigkeit:

$$\frac{dP_1}{dt} = k_2 * E_0 * \frac{S_1 * K_{m2}}{(S_1 * K_{m2} + S_2 * K_{m1} + K_{m1} * K_{m2})}$$

# Reaktionssysteme mit zwei Substraten - BiBi

Das erste Substrat S1 bindet an das Enzym, um den Enzymsubstratkomplex ES1 zu bilden. Dann bindet das zweite Substrat ES1S2. Die Reaktion produziert EP1P2 und Produkt P1 wird vor Produkt P2 freigesetzt.



Davon abgeleitet ergibt sich:

$$V = V_1 * \frac{S1 * S2}{(K_i S1 * K_m S2 + K_m S2 * S1 + K_m S1 * S2 + S1 * S2)}$$

# Reaktionssysteme mit zwei Substraten - Ping-Pong

Das erste Substrat S1 vereinigt sich wiederum mit E zu ES1. Dann wird jedoch schon das erste Produkt P1 freigesetzt. Das zweite Substrat S2 bindet nun und Produkt P2 wird freigesetzt.



Hier ergibt sich folgende Geschwindigkeit:

$$V = V_1 * \frac{S1 * S2}{(K_m S2 * S1 + K_m S1 * S2 + S1 * S2)}$$

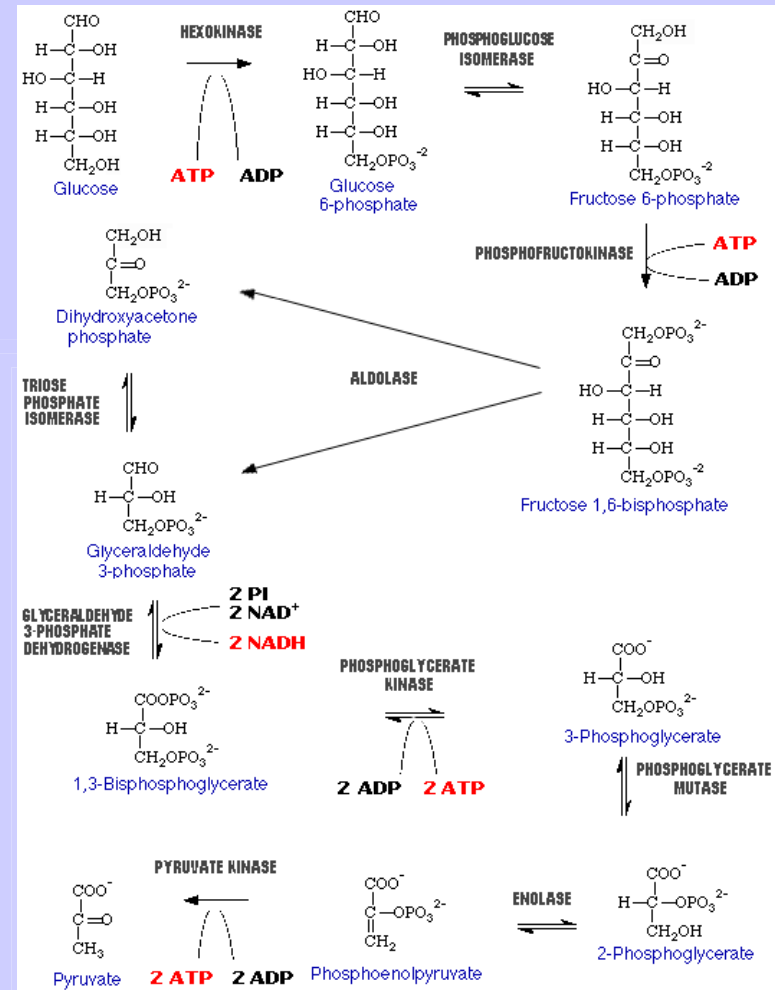
# Fallbeispiel 1 - Pyruvatkinase

Pyruvatkinase:

Katalysiert die Reaktion



Reaktion verläuft schnell



# Fallbeispiel 1 - Pyruvatkinase

$$v_{\rightarrow} = \frac{V_{10\text{max}} [\text{ADP}] [\text{PEP}]}{(K_{10\text{PEP}} + [\text{PEP}])(K_{10\text{ADP}} + [\text{ADP}])}$$

Beide Substrate beeinflussen sich bei der Bindung nicht

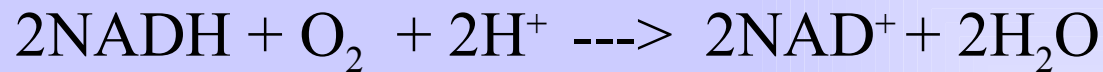
-> Spezialfall der BiBi-Reaktion

$$V = V_1 * \frac{S_1 * S_2}{(K_i S_1 * K_m S_2 + K_m S_2 * S_1 + K_m S_1 * S_2 + S_1 * S_2)}$$

# Fallbeispiel 2 - Peroxidase

## Die Peroxidase-Oxidase-Reaktion

Gesamtgleichung:

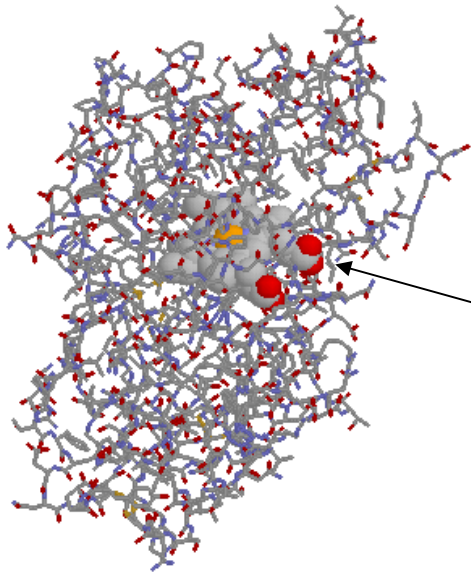


Enzym:

Peroxidase aus Pflanzen und Tieren

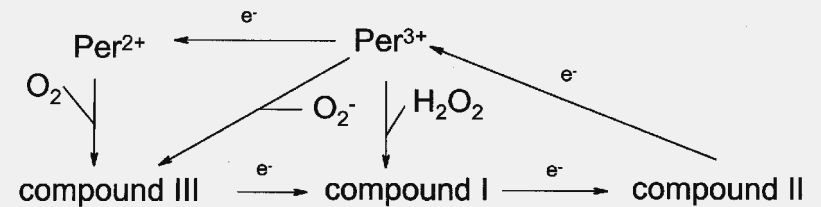
# Fallbeispiel 2 - Peroxidase

## Struktur

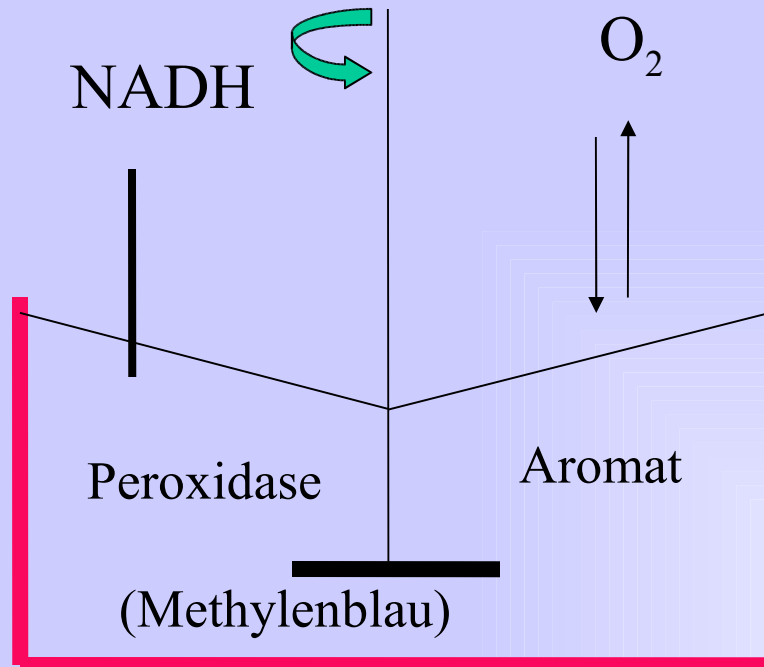


Häm-  
gruppe

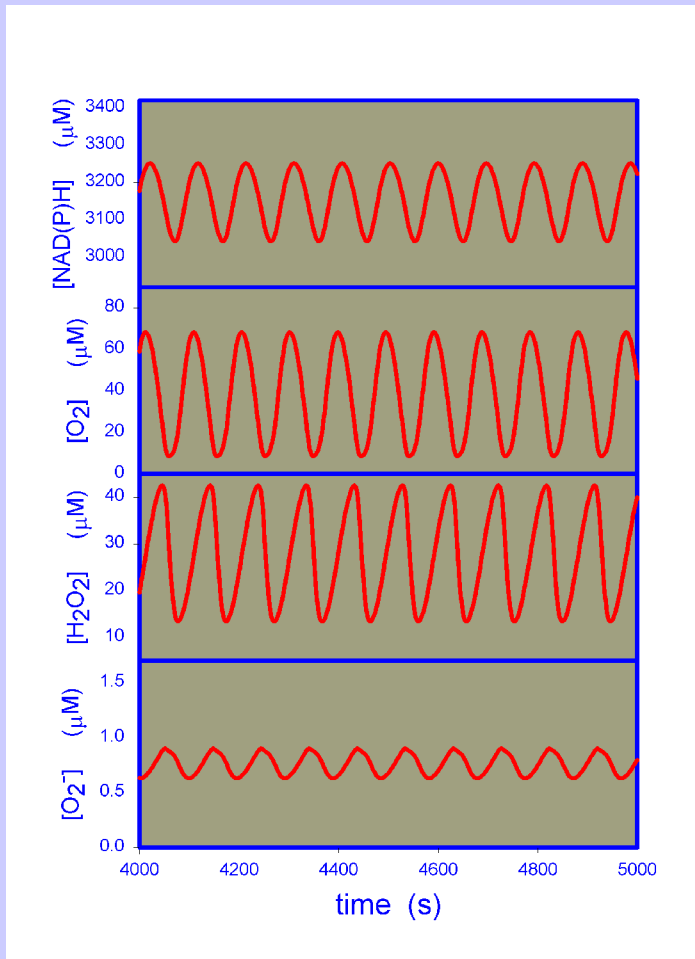
## Enzymintermediate



# Fallbeispiel 2 - Peroxidase *in vitro*



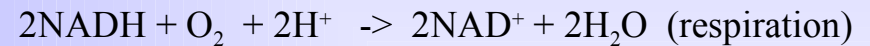
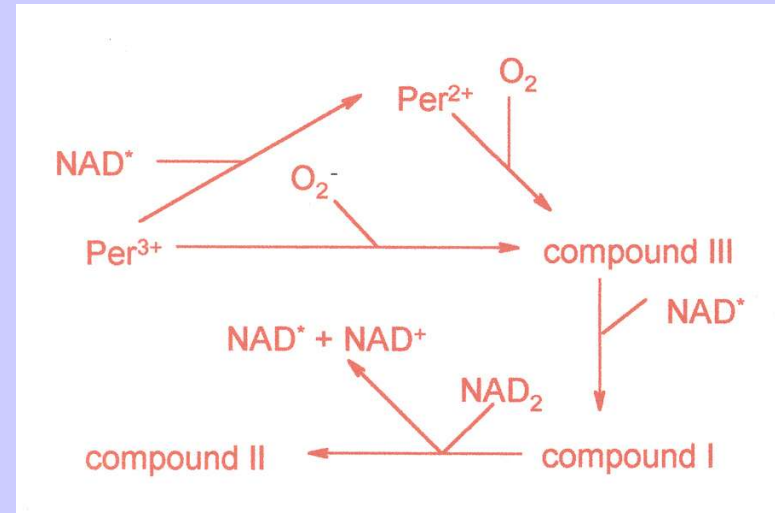
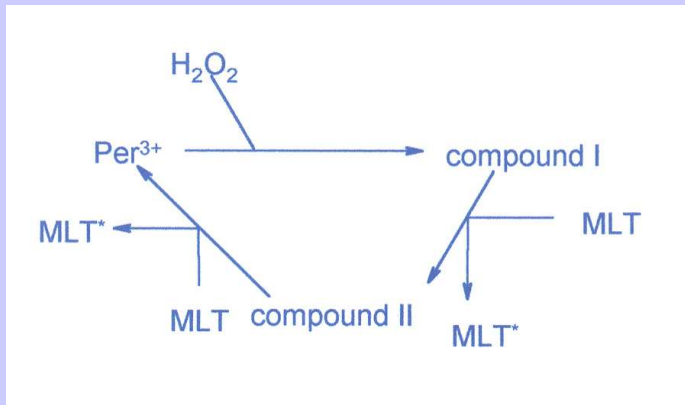
# Fallbeispiel 2 - Peroxidase Kinetik



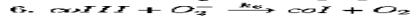
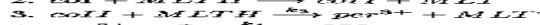
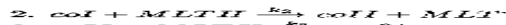
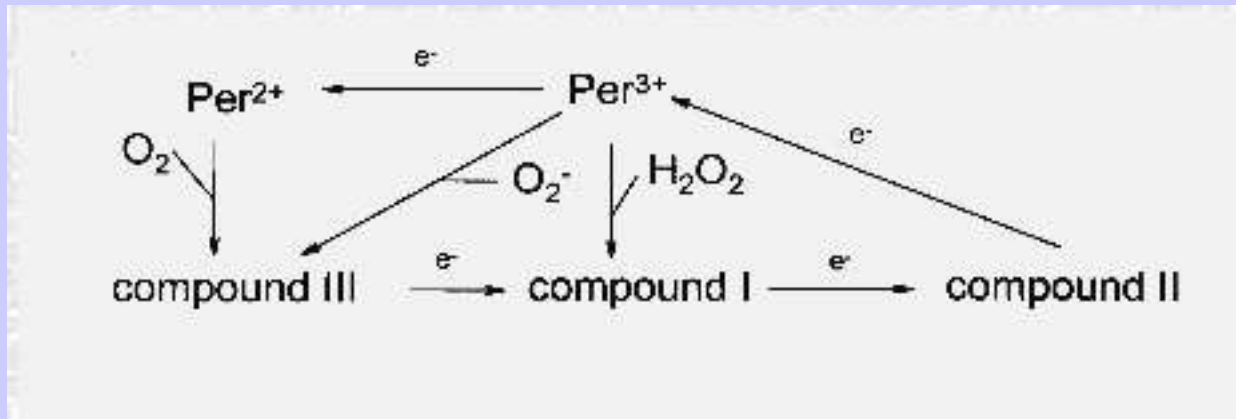
- Die Reaktion oszilliert unter verschiedenen Bedingungen
- Die Oszillationen können viele Stunden andauern

# Fallbeispiel 2 - Peroxidase

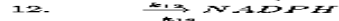
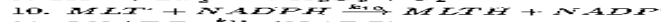
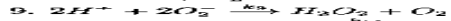
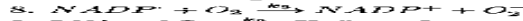
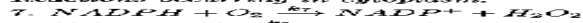
## Elementarreaktionen



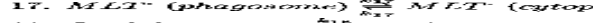
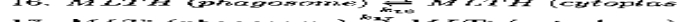
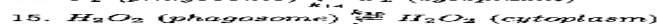
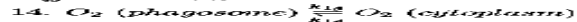
# Fallbeispiel 2 - Peroxidase



Reactions occurring in cytoplasm:



Diffusion terms:



NADPH oxidase:

$$k_1[H_2O_2]_p[Per^{2+}]_p - k_{-1}[coi]_p$$

$$k_2[coi]_p[MLTH]_p$$

$$k_3[coiII]_p[MLTH]_p$$

$$k_4[per^{3+}]_p[O_2^-]_p$$

$$k_5[O_2^-]_p^2$$

$$k_6[coiII]_p[O_2^-]_p$$

$$k_7[NADPH]_c[O_2]_c$$

$$k_8[NADP^+]_c[O_2]_c$$

$$k_9[O_2^-]_c^2$$

$$k_{10}[MLT^+]_c[NADPH]_c$$

$$k_{11}[NADP^+]_c^2$$

$$k_{12} - k_{-12}[O_2]_c$$

$$k_{13} - k_{-13}[O_2]_c$$

$$k_{14}([O_2]_p - [O_2]_c)$$

$$k_{15}([H_2O_2]_p - [H_2O_2]_c)$$

$$k_{16}([MLTH]_p - [MLTH]_c)$$

$$k_{17}([MLT^+]_p - [MLT^+]_c)$$

$$k_{18}([O_2^-]_p - [O_2^-]_c)$$

$$k_1 = 5.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{-1} = 58 \text{ s}^{-1}$$

$$k_2 = 1.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_3 = 4.0 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_4 = 1.1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_5 = 1.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_6 = 1.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_7 = 1 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_8 = 5.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_9 = 5.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{10} = 1.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{11} = 6.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{12} = 22-35 \mu\text{M s}^{-1}$$

$$k_{13} = 12.5 \mu\text{M s}^{-1}$$

$$k_{-12} = 4.5 \times 10^{-2} \text{ s}^{-1}$$

$$k_{14} = 30 \text{ s}^{-1}$$

$$k_{15} = 30 \text{ s}^{-1}$$

$$k_{16} = 10 \text{ s}^{-1}$$

$$k_{17} = 10 \text{ s}^{-1}$$

$$k_{18} = < 0.01 \text{ s}^{-1}$$

Beispiel für Systemgleichung:

$$coII' = k_2 * coi * MLTH - k_3 * coiII * MLTH$$

# Datenbanken 1

- Wenig Quellen für kinetische Parameter außerhalb der Literatur!  
Als Literaturdatenbank empfehlenswert: PubMed

About Entrez

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1: [Deibert M, Grazulis S, Sasnauskas G, Siksnys V, Huber R.](#) [Related Articles](#)  
Structure of the tetrameric restriction endonuclease NgoMIV in complex with cleaved DNA.  
Nat Struct Biol. 2000 Sep;7(9):792–799.  
[Record as supplied by publisher]  
PMID: 10966652

2: [Jez JM, Bowman ME, Dixon RA, Noel JP.](#) [Related Articles](#)  
Structure and mechanism of the evolutionarily unique plant enzyme chalcone isomerase.  
Nat Struct Biol. 2000 Sep;7(9):786–791.  
[Record as supplied by publisher]  
PMID: 10966651

3: [Waugh SM, Harris JL, Fletterick R, Craik CS.](#) [Related Articles](#)  
The structure of the pro-apoptotic protease granzyme B reveals the molecular determinants of its specificity.  
Nat Struct Biol. 2000 Sep;7(9):762–765.  
[Record as supplied by publisher]  
PMID: 10966646

4: [Liao DJ, Qian J, Chisholm DA, Jordan DB, Diner BA.](#) [Related Articles](#)  
Crystal structures of the photosystem II D1 C-terminal processing protease.  
Nat Struct Biol. 2000 Sep;7(9):749–753.  
[Record as supplied by publisher]  
PMID: 10966643

5: [Ishima R, Torchia DA.](#) [Related Articles](#)  
Protein dynamics from NMR.  
Nat Struct Biol. 2000 Sep;7(9):740–743.  
[Record as supplied by publisher]  
PMID: 10966641

6: [Glazewski S, Giese KP, Silva A, Fox K.](#) [Related Articles](#)  
The role of alpha-CaMKII autophosphorylation in neocortical experience-dependent plasticity.  
Nat Neurosci. 2000 Sep;3(9):911–918.  
[Record as supplied by publisher]  
PMID: 10966622

# Datenbanken 2

Zur Identifikation der Funktion von Enzymen, gibt es einige DB:

- Metabolische Pfade

- KEGG: Kyoto Encyclopedia of Genes and Genomes

<http://www.genome.ad.jp/kegg/metabolism.html>

- Auschnitte aus der Boehringer Map

<http://www.expasy.ch/cgi-bin/search-biochem-index>

# Datenbanken 3

## NiceProt View of SWISS-PROT: [P21730](#)

[\[General\]](#) [\[Name and origin\]](#) [\[References\]](#) [\[Comments\]](#) [\[Cross-references\]](#) [\[Keywords\]](#) [\[Features\]](#) [\[Sequence\]](#) [\[Tools\]](#)

### General information about the entry

Entry name	C5AR_HUMAN
Primary accession number	<b>P21730</b>
Secondary accession number(s)	None
Entered in SWISS-PROT in	Release 18, May 1991
Sequence was last modified in	Release 18, May 1991
Annotations were last modified in	Release 36, July 1998

### Name and origin of the protein

Protein name	C5A ANAPHYLATOXIN CHEMOTACTIC RECEPTOR
Synonym(s)	C5A-R CD88 ANTIGEN
Gene name(s)	CSR1 OR C5AR
From	<a href="#">Homo sapiens (Human)</a>
Taxonomy	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

### References

[1]  
SEQUENCE FROM N.A.  
MEDLINE=91156029; PubMed=1847994. [[NCBI](#), [ExpASY](#), [Israel](#), [Japan](#)]  
[Gerard N.P.](#), [Gerard C.](#);  
"The chemotactic receptor for human C5a anaphylatoxin.";  
Nature 349:614-617(1991).

[2]  
SEQUENCE FROM N.A.  
MEDLINE=91175748; PubMed=2007135. [[NCBI](#), [ExpASY](#), [Israel](#), [Japan](#)]  
[Boulay F.](#), [Mery L.](#), [Tardif M.](#), [Brouchon L.](#), [Vignais P.](#);  
"Expression cloning of a receptor for C5a anaphylatoxin on differentiated HL-60 cells.";  
Biochemistry 30:2993-2999(1991).

### Comments

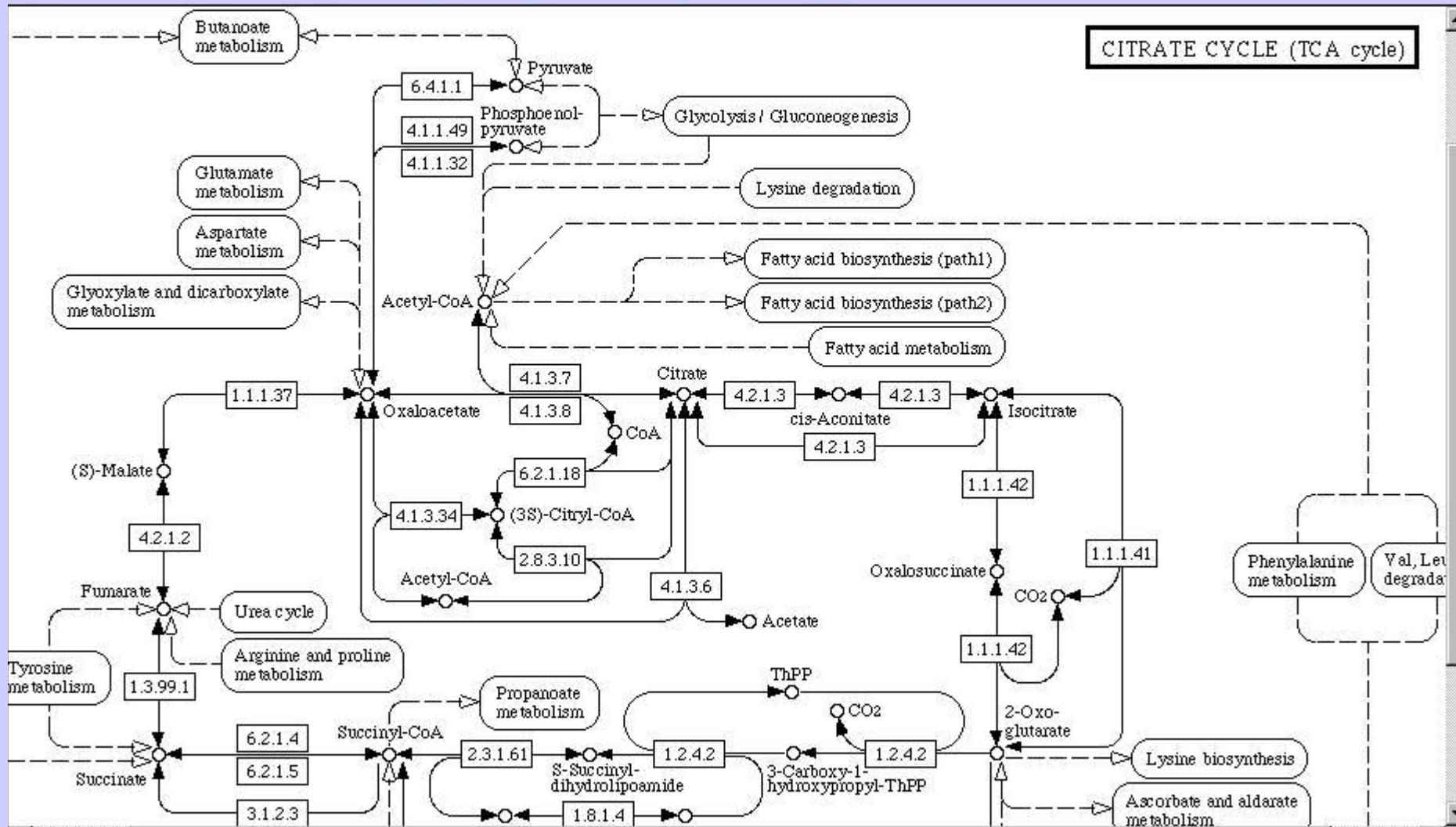
- **FUNCTION:** RECEPTOR FOR THE CHEMOTACTIC AND INFLAMMATORY PEPTIDE ANAPHYLATOXIN C5A. THIS RECEPTOR STIMULATES CHEMOTAXIS, GRANULE ENZYME RELEASE AND SUPEROXIDE ANION PRODUCTION.
- **SUBCELLULAR LOCATION:** INTEGRAL MEMBRANE PROTEIN.
- **SIMILARITY:** BELONGS TO FAMILY 1 OF [G-PROTEIN COUPLED RECEPTORS](#).
- **DATABASE:** NAME=PROW; NOTE=CD guide CD88 entry; WWW="<http://www.ncbi.nlm.nih.gov/prow/cd/cd88.htm>".

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# Datenbanken 4

KEGG:



EMP:

# Datenbanken 5

The screenshot shows a Mozilla browser window displaying the EMP Project website. The browser's address bar shows the URL <http://www.empproject.com/about/>. The website has a navigation menu on the left with links for About, Software, Query EMP, Links, Query Pathways, Metabolic Outlines, and Nomenclature. The main content area features the EMP Project logo and an 'About us' section. The 'About us' section describes the EMP database as a comprehensive electronic source of biochemical data, covering all aspects of enzymology and metabolism. It lists 17 categories of data encoded in the database format, including entry identification, bibliographic description, biological source, host, biochemical genetics, cell cultivation conditions, metabolism, enzyme and reaction, enzyme assay and purification, enzyme kinetics, enzyme regulation, enzyme modification, enzyme structure, equilibrium and thermodynamics, physical chemistry and spectral properties, immunochemistry, and common fields. The text also mentions that the database contains about 30,000 records and is updated with over 8,000 records annually. A separate database, EMP Pathways (MPW), is also mentioned, containing over 3,000 metabolic diagrams. The website footer includes contact information: email: [info@empproject.com](mailto:info@empproject.com) and © EMP Project, Inc. 1999. The browser's status bar at the bottom shows 'Connecting to www.empproject.com...' and a taskbar with a presentation window titled 'Datenbanken 5 / Datenbanken 6 /' at 84% zoom, slide 30 of 31.

Emp Project: About - Mozilla

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http://www.empproject.com/about/ Search

Home Bookmarks The Mozilla Or... Latest Builds

## EMP Project

### About us

Enzymes and Metabolic Pathways database, EMP, is a unique and most comprehensive electronic source of biochemical data. It covers all aspects of enzymology and metabolism and represents the whole factual content of original journal publications. The database format has about 300 subject fields to encode the following categories:

1. Entry identification
2. Bibliographic description
3. Biological source
4. Host
5. Biochemical genetics
6. Cell cultivation conditions
7. Metabolism
8. Enzyme and reaction
9. Enzyme assay and purification
10. Enzyme kinetics
11. Enzyme regulation
12. Enzyme modification
13. Enzyme structure
14. Equilibrium and thermodynamics
15. Physical chemistry and spectral properties
16. Immunochemistry
17. Common fields

The format allows different types of tables and stoichiometric matrices to unambiguously encode metabolic pathways, reaction mechanisms, rate laws and a very wide spectrum of numeric data. EMP contains about 30,000 records compiled from about 15,000 original experimental journal publications. EMP is being updated with over 8,000 records a year to cope with the essentials published in the literature each year. Each EMP record is a translation of the whole factual content of an original journal publication into a structured, indexed, and easy searchable form. The database is being created in Pushchino (Moscow Region, Russia) by a team of 50 scientists, bibliographers and programmers (20 of them have Ph.D. or D.Sc. degree).

A metabolic part of EMP constitutes a separate database, EMP Pathways (earlier known as MPW). It has over 3,000 metabolic diagrams created by Evgeni Selkov and his coworkers. The Pushchino team is updating this collection with some 1000 new pathways a year.

The information stored in EMP is indispensable for analysis and mathematical simulation of metabolic networks, metabolic design, drug development and bioengineering. EMP can easily be integrated into any academic or industrial bioinformatics environment to play a critical role in the metabolic reconstruction technology. WIT2 Pro system of Integrated Genomics, Inc. (<http://igweb.integratedgenomics.com/WIT2/>) is an example of a successful use of EMP for metabolic reconstruction and annotation of over 250 sequenced genomes.

The EMP Project, Inc. was incorporated in New York in 1999 to provide organizational, legal, and financial support for the EMP group projects.

[Terms of use](#)  
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About Software Query EMP Query Pathways Nomenclature Links Metabolic Outlines

email: [info@empproject.com](mailto:info@empproject.com) © EMP Project, Inc. 1999

Connecting to www.empproject.com...

Datenbanken 5 / Datenbanken 6 /

There are no new messages on the server.

5,26 / 10,33 1:00 x 0,00 84% \* Slide 30 / 31 Default

# Datenbanken 6

- Kinetische Daten im Wesentlichen bei BRENDA erhältlich
- BRENDA ist manuell hergestellt! -> fehlerbehaftet
- Oft unvollständig
- [www.brenda.uni-koeln.de](http://www.brenda.uni-koeln.de)

Enzyme Database - BRENDA - Mozilla

http://www.brenda.uni-koeln.de/

BRENDA  
The Comprehensive Enzyme Information System

Release 4.1

EC-Number | Enzyme Name | Organism | Advanced Search | Full text

Search | Display | 10 | entries

New: New features in ontologies  
You have no full access! Please [register BRENDA](#) or [login](#) with your username and password.

Nomenclature	Reaction & Specificity	Functional Parameters
Enzyme Names EC Number Common/ Recommended Name Systematic Name Synonyms CAS Registry Number	Pathway Catalysed Reaction Reaction Type Natural Substrates and Products Substrates and Products Substrates Natural Substrate Products Natural Product	Km Value Ki Value Turnover Number Specific Activity pH Optimum pH Range Temperature Optimum Temperature Range
Isolation & Preparation	Inhibitors Cofactors Metals/Ions Activating Compounds Ligands	Organism-related information
Purification Cloned Renatured Crystallization	Enzyme Structure	Organism Source Tissue Localization
Stability	Sequence/ SwissProt link 3D-Structure/ PDB link Molecular Weight Subunits Posttranslational Modification	Disease & References
pH Stability Temperature Stability General Stability Organic Solvent Stability Oxidation Stability Storage Stability	Disease & References	Disease References
	Application & Engineering	Engineering Application

Webmaster: [Christian Ebeling](#)

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