ВВЕДЕНИЕ В БИОИНФОРМАТИКУ

Лекция №22

Хемоинформатика
и
виртуальный скрининг

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Сайт курса http://intbio.org/bioinf2019-2020

Предсказание биологической активности

Methods

Multilevel Neighborhoods of Atoms (MNA) structure descriptors of a molecule are generated on the basis of connection table and table of atoms types presented the compound...

» read more

Applications

PASS predicts simulta-neously 3678 kinds of activity with mean accuracy of prediction about 95% (leave-one-out cross validation) on the basis of the compound's structural formula. ...

» read more

Publications

Current and past publications, including statistical reports, surveys, press releases, circulars and legislation, are available in electronic format from this section.

» read more

Downloads

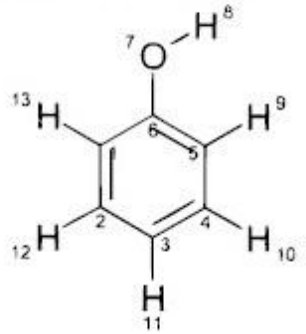
You can download and use locally PASS demo version, which predicts 50 biological activities, and test it on your computer. It possible make a batch with several compounds at the same time.

» click for it

http://www.pharmaexpert.ru/PassOnline/

Предсказание биологической активности

Table 2. Representation of Phenol by MNA Descriptors of Zero, First, and Second Levels (MNA/0, MNA/1, MNA/2)[a]



atom	MNA/0	MNA/1	MNA/2
1	C	C(CC-H)	C(C(CC-H)C(CC-O)-H(C))
2	C	C(CC-H)	C(C(CC-H)C(CC-H)-H(C))
3	C	C(CC-H)	C(C(CC-H)C(CC-H)-H(C))
4	C	C(CC-H)	C(C(CC-H)C(CC-H)-H(C))
5	C	C(CC-H)	C(C(CC-H)C(CC-O)-H(C))
6	C	C(CC-O)	C(C(CC-H)C(CC-H)-O(C-H))
7	-O	-O(C-H)	-O(C(CC-O)-H(-O))
8	-H	-H(-O)	-H(-O(C-H))
9	-H	-H(C)	-H(C(CC-H))
10	-H	-H(C)	-H(C(CC-H))
11	-H	-H(C)	-H(C(CC-H))
12	-H	-H(C)	-H(C(CC-H))
13	-H	-H(C)	-H(C(CC-H))

[a] Hyphen (-) is the chain marker for the atoms in the chains.

MNA – multilevel neighborhoods of atoms

(Filimonov, Poroikov et al., 1999)

PASS

Предсказание биологической активности

Мера сходства – модифицированный **коэффициент Танимото:**

Calculation of Similarity. We have modified the Tanimoto coefficient to take into account the different frequencies of descriptors. The similarity between two molecules, A and B, is given by

$$\mathrm{sim}(A, B) = \frac{\sum_{i=1}^{M} \min[A(i), B(i)]}{\sum_{i=1}^{M} A(i) + \sum_{i=1}^{M} B(i) - \sum_{i=1}^{M} \min[A(i), B(i)]} \quad (1)$$

where $A(i)$ and $B(i)$ are the counts of descriptor i in the molecules A and B, respectively; M is the total number of various descriptors in the dictionary.

PASS

Предсказание биологической активности

Ограничения предсказательной способности

PASS cannot predict the activity spectrum for essentially new compound if all its descriptors are new and so they don't occur in the training set. If a compound has more then 2 new descriptors it is rather new and prediction results may be considered as pilot.

In some cases PASS predicts both agonist's and antagonist's (blocker and stimulator) **actions simultaneously**. Thus, only experiments can clarify the biological activity of a compound, but it has an affinity to appropriate receptor (enzyme).

PASS does not predict if the compound will become a drug, but helps to select the most prospective leads.

Предсказание биологической активности

Swiss Institute of Bioinformatics

SwissTargetPrediction

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This website allows you to predict the targets of a small molecule. Using a combination of 2D and 3D similarity measures, it compares the query molecule to a library of 280'000 compounds active on more than 2000 targets of 5 different organisms.

The webserver is described in detail in our article: SwissTargetPrediction: a webserver for target prediction of bioactive small molecules, *Nucl. Acids Res.* (2014). For technical information about the prediction algorithm, you can refer to this article: Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

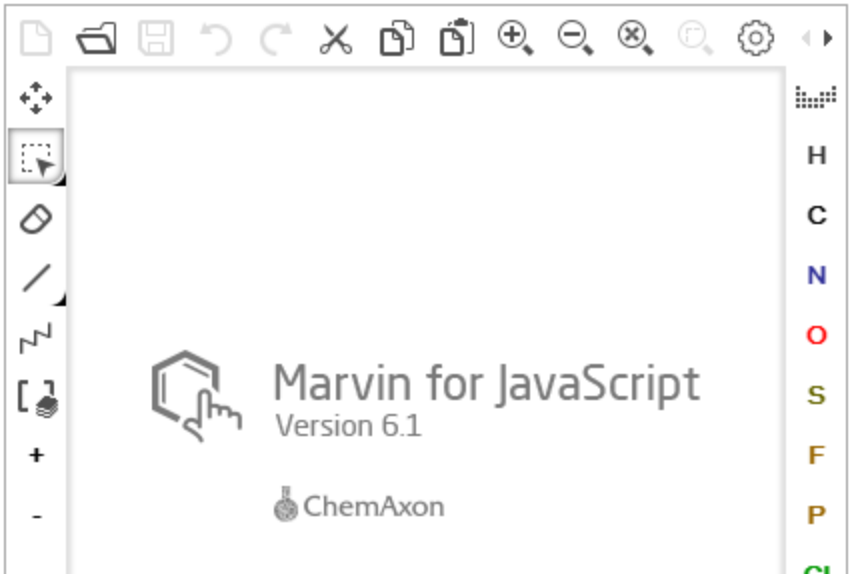
Choose an organism

- (•) Homo sapiens
- ( ) Mus musculus
- ( ) Rattus norvegicus
- ( ) Bos taurus
- ( ) Equus caballus

Paste a SMILES in this box, or draw a molecule

Examples: ▾ Clear

=



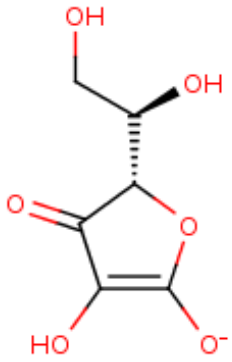
Предсказание биологической активности

List of predicted targets

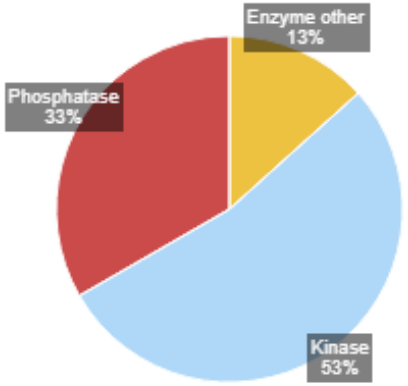
These targets have been predicted using the method described in:

Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



General Target Classes



Retrieve data:

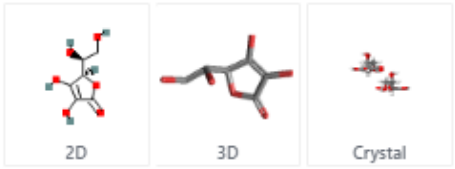
Target	Common name	Uniprot ID	ChEMBL ID	Probability*	# sim. cmpds (3D / 2D)	Target Class
Tyrosyl-DNA phosphodiesterase 1	TDP1	Q9NUW8	CHEMBL1075138		0 / 2	Enzyme
Tubulin--tyrosine ligase	TTL	Q8NG68	CHEMBL5549		0 / 12	Enzyme
Protein kinase C alpha type	PRKCA	P17252	CHEMBL299		0 / 141	Ser_Thr Kinase
Protein kinase C delta type regulatory subunit *(by homology)*	PRKCD	Q05655	CHEMBL2996		0 / 143	Ser_Thr Kinase
Protein kinase C theta type *(by homology)*	PRKCQ	Q04759	CHEMBL3920		0 / 143	Ser_Thr Kinase

Базы данных химических соединений

Compounds: 95,276,293
Substances: 249,470,154
BioAssays: 1,252,883
Tested Compounds: 2,570,179
Tested Substances: 4,157,676
RNAi BioAssays: 170
BioActivities: 235,470,936
Protein Targets: 10,857
Gene Targets: 22,106

Базы данных химических соединений

Ascorbic acid

PubChem CID:	54670067
Structure:	 2D 3D Crystal
Chemical Safety:	DATASHEET AVAILABLE: Laboratory Chemical Safety Summary (LCSS)
InChI Key:	CIWBSHSKHKDKBQ-JLAZNSOCSA-N
Molecular Formula:	$C_6H_8O_6$ or $HC_6H_7O_6$
UNII:	PQ6CK8PD0R
Depositor-Supplied Synonyms:	l-ascorbic acid ascorbic acid vitamin C 50-81-7 L(+)-Ascorbic acid More...
Molecular Weight:	176.124 g/mol
Dates:	Modify: 2019-03-30 Create: 2011-12-26

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CONTENTS

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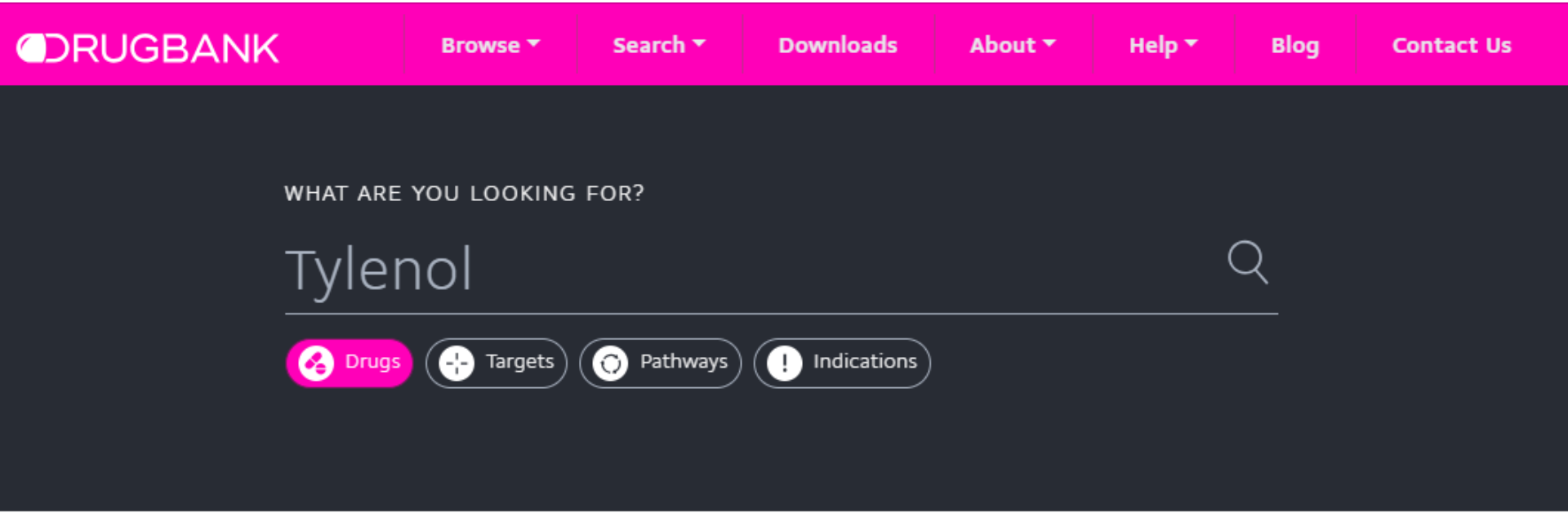
- 12 Identification
- 13 Safety and Hazards
- 14 Toxicity
- 15 Literature
- 16 Patents
- 17 Biomolecular Interactions and Pathways

Базы данных химических соединений



DRUGBANK

The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information.

Базы данных химических соединений

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Shoichet Laboratory docking.org

ZINC 12

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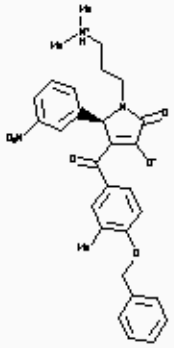
Welcome to ZINC, a free database of commercially-available compounds for virtual screening. ZINC contains over 35 million purchasable compounds in ready-to-dock, 3D formats. ZINC is provided by the Irwin and Shoichet Laboratories in the Department of Pharmaceutical Chemistry at the University of California, San Francisco (UCSF). To cite ZINC, please reference: Irwin, Sterling, Mysinger, Bolstad and Coleman, *J. Chem. Inf. Model. 2012* DOI: 10.1021/ci3001277. The original publication is Irwin and Shoichet, *J. Chem. Inf. Model. 2005;45(1):177-82* PDF, DOI. We thank NIGMS for financial support (GM71896).

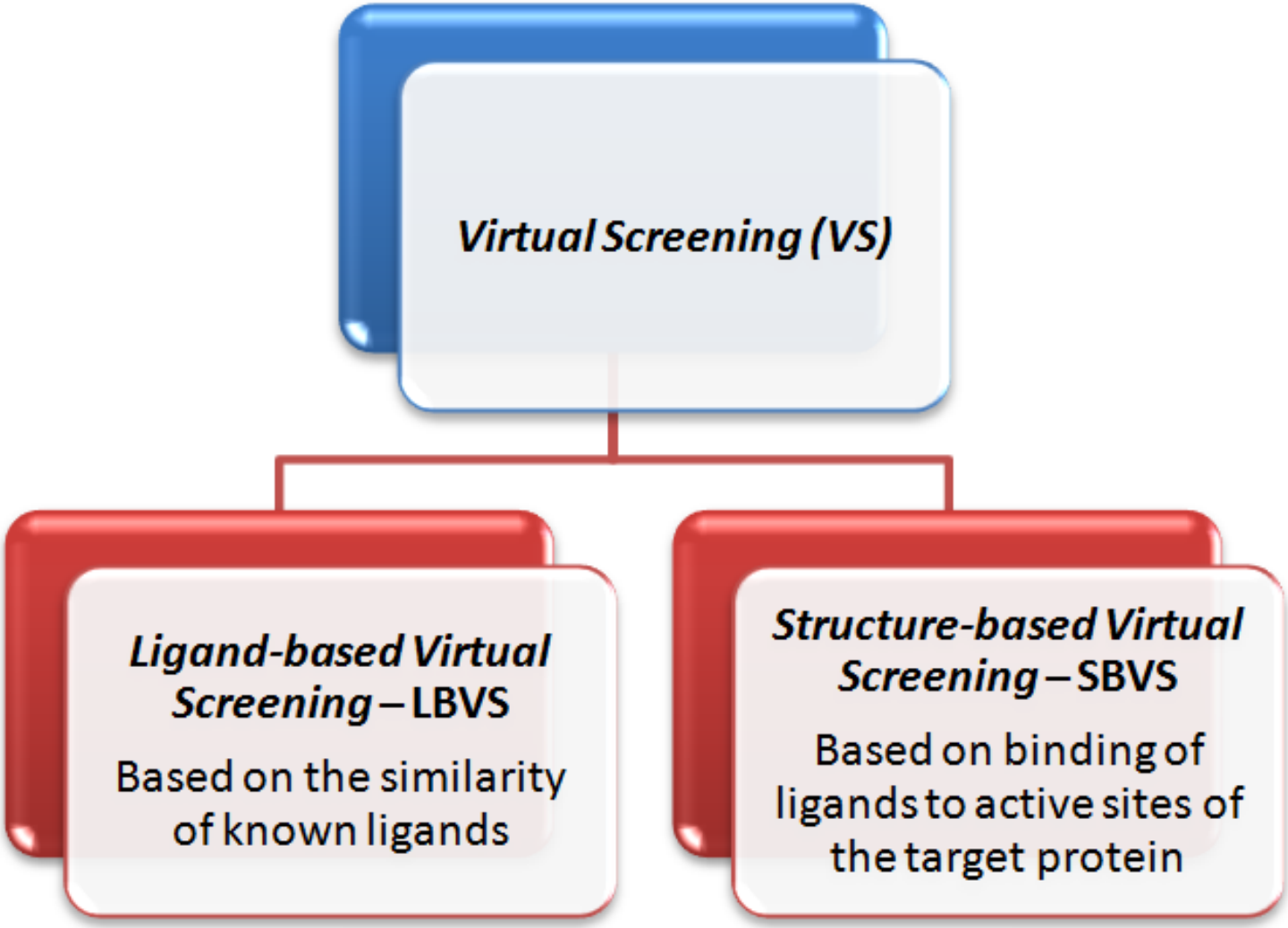
Molecule of the Minute 8817205



ZINC ID, Drug Name, SMILES, Catalog, Vendor Code, Target & r Go

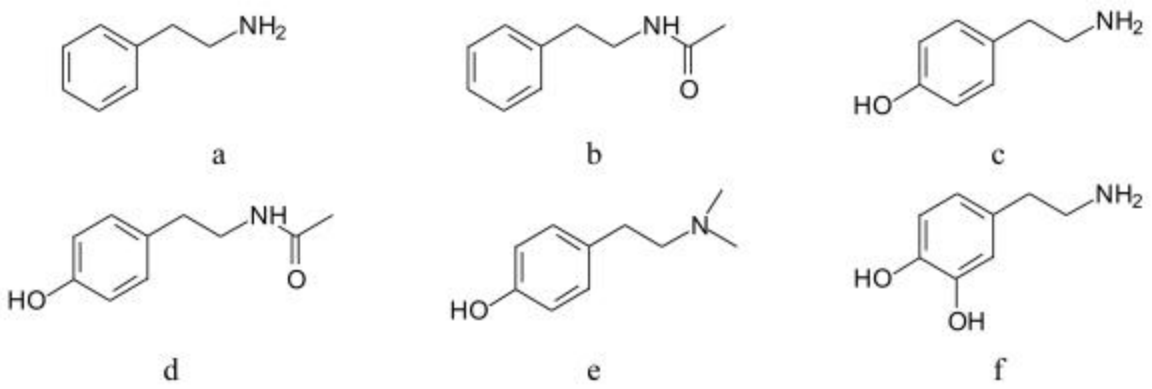
Structure/Draw Physical Properties Catalogs & Vendors ZINC IDS Targets Rings Combination

Виртуальный скрининг

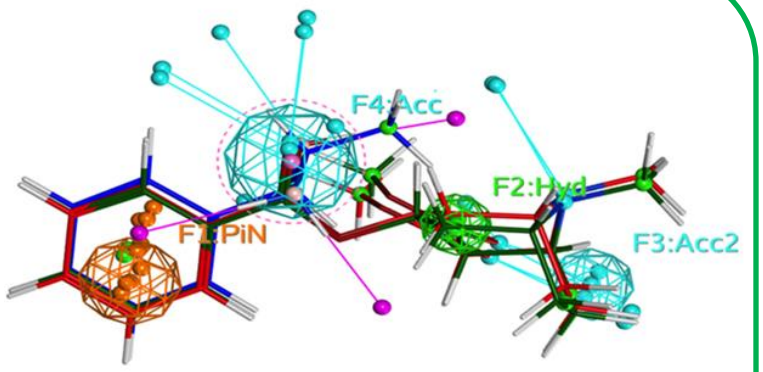


Виртуальный скрининг

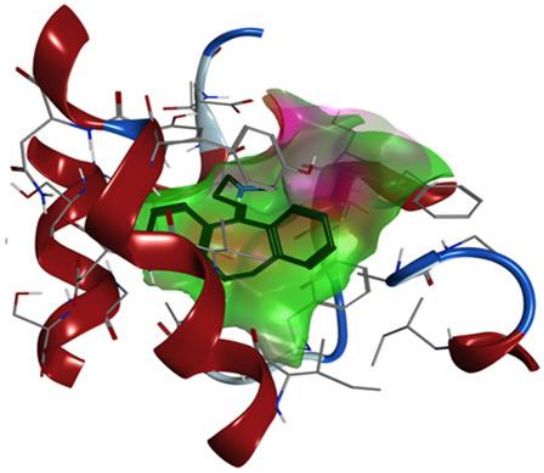
LBVS



Отбор по формальным признакам



Фармакофорный поиск



Молекулярный докинг

SBVS

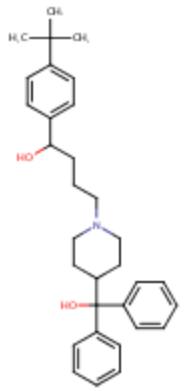
Отбор по формальным признакам. SwissSimilarity

Run parameters

Library screened	ZincDrugLike
Screening method	Combined
Date	Fri Nov 10 11:13:52 2017

If you publish these results, please, cite the following paper: Zoete, V., Daina, A., Bovigny, C., & Michielin, O. SwissSimilarity: A Web Tool for Low to Ultra High Throughput Ligand-Based Virtual Screening., *J. Chem. Inf. Model.*, **2016**, *56(8)*, 1399-1404.

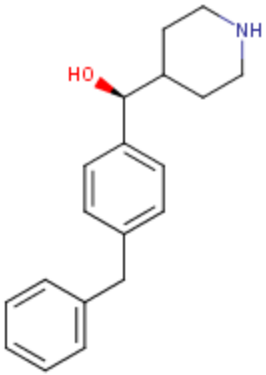
Query Molecule



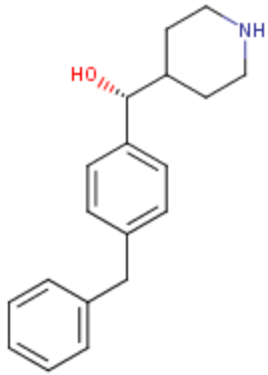
Results

Retrieve data:

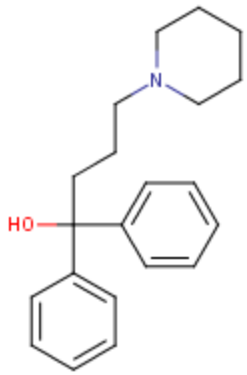
ZINC80181216
Score : 0.983



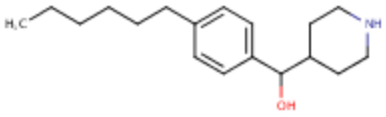
ZINC80181212
Score : 0.983



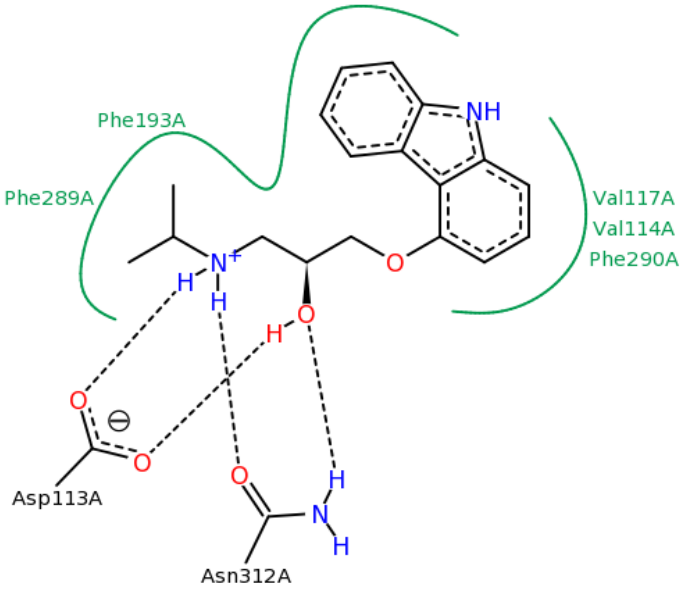
ZINC00968266
Score : 0.972

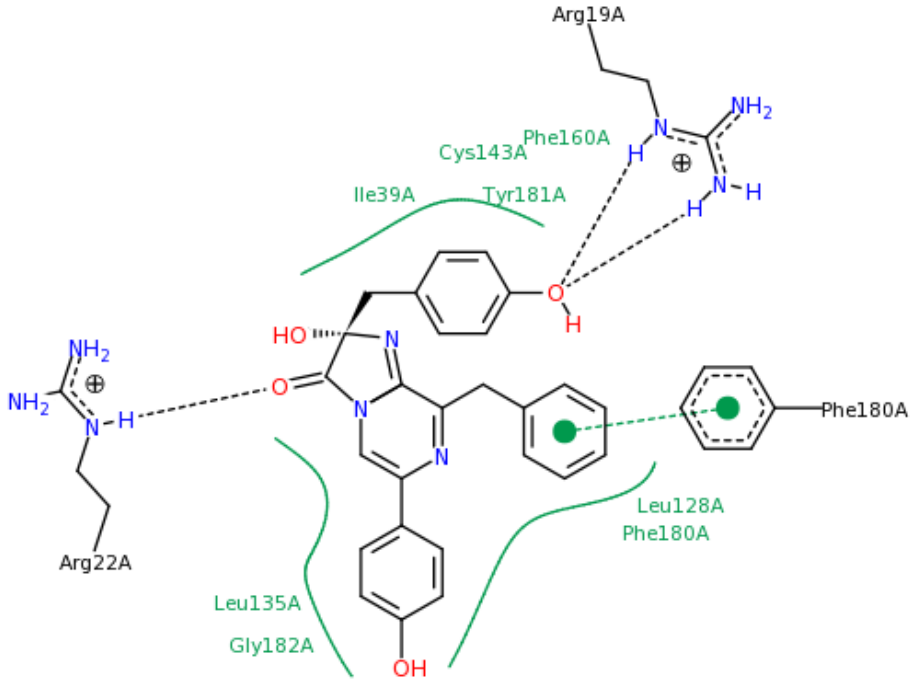


ZINC74369400
Score : 0.969



Межмолекулярные взаимодействия

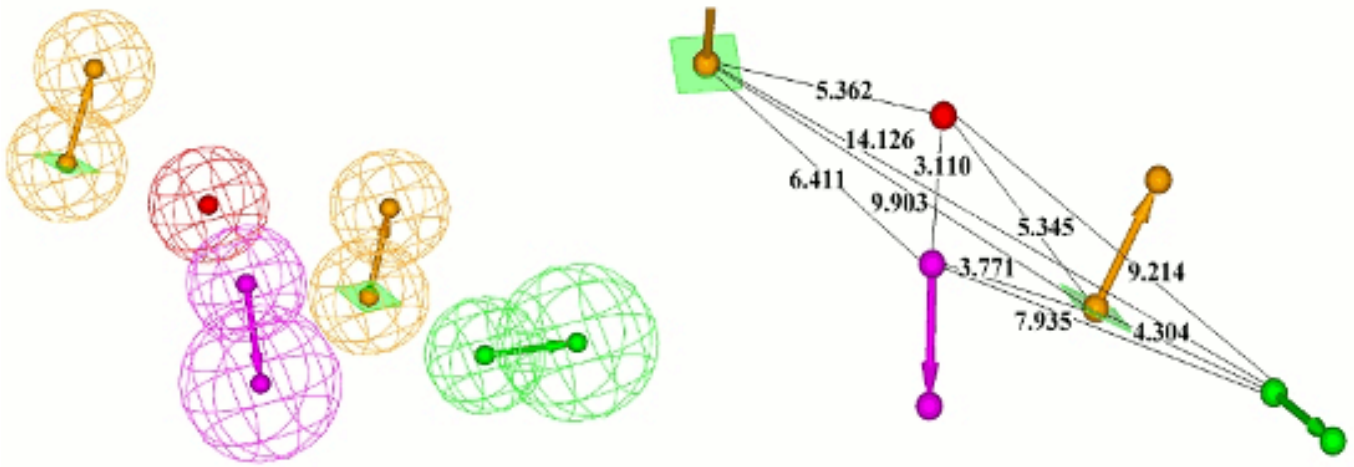




Фармакофорный поиск

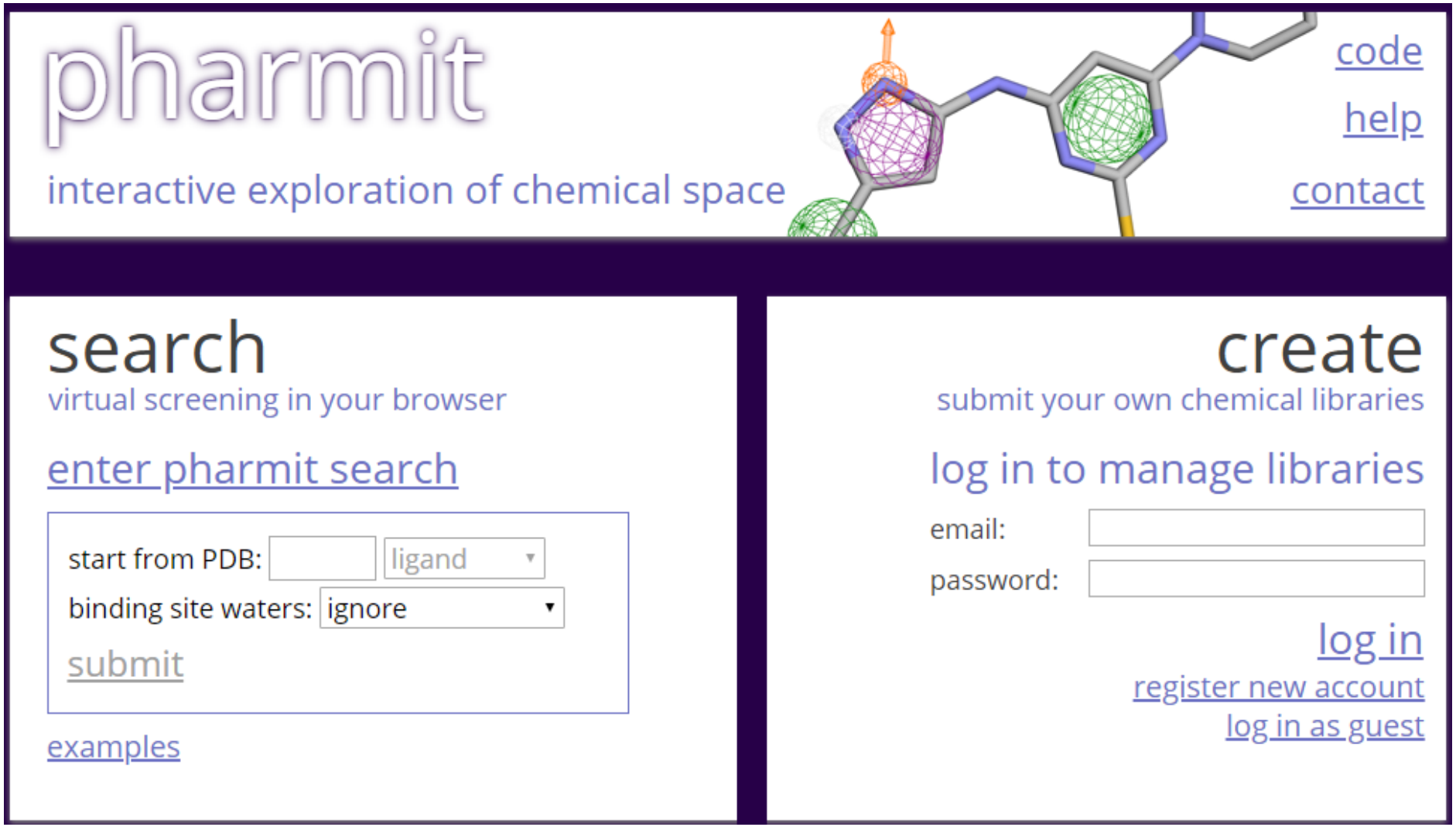
Pharmacophore – “proposed receptor pattern” (Kier, 1971)

Фармакофор — набор пространственных и электронных признаков, необходимых для обеспечения оптимальных супрамолекулярных взаимодействий со специфической биологической мишенью, которые могут вызывать (или блокировать) ее биологический ответ (ИЮПАК).

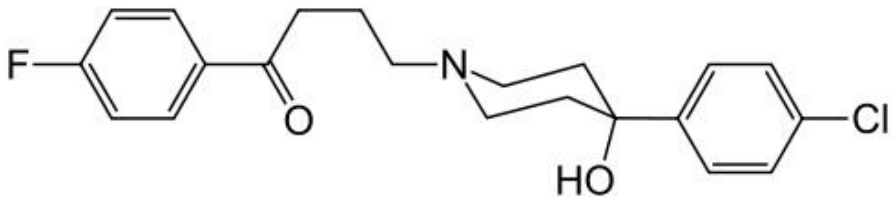


Pharmacophore model for β2-adrenoreceptor agonists generated by HipHop. Features are portrayed as mashed spheres, color-coded as follows: green, hydrogen-bond acceptor, magenta, hydrogen-bond donor, orange, aromatic ring, red, positive ionizable feature.

Фармакофорный поиск. PharmIt



Фармакофорный поиск. PharmIt



Галоперидол

Search PubChem

Pharmacophore Search -> Shape Filter

Load Receptor... Load Features...

Pharmacophore

- ON **Aromatic** (6.08,0.16,-0.02) Radius 1.1
- ON **Aromatic** (-6.31,0.28,-0.05) Radius 1.1
- ON **HydrogenDonor** (2.94,1.31,-1.29) Radius 0.5
- ON **HydrogenAcceptor** (0.47,-0.38,0.73) Radius 0.5
- OFF **HydrogenAcceptor** (2.94,1.31,-1.29) Radius 0.5
- OFF **HydrogenAcceptor** (-3.19,-0.63,-1.63) Radius 0.5
- ON **Hydrophobic** (6.08,0.16,-0.02) Radius 1.0
- ON **Hydrophobic** (-6.31,0.28,-0.05) Radius 1.0
- ON **Hydrophobic** (9.18,-0.06,0.22) Radius 1.0
- ON **Hydrophobic** (-8.77,1.37,0.43) Radius 1.0
- ON **Hydrophobic** (-1.89,-1.26,0.6) Radius 1.0

Load Session... Save Session...

Pharmacophore Results

Name	RMSD	Mass	RBnds
PubChem-118753530	0.390	377	6
PubChem-8957387	0.486	396	9
PubChem-7773328	0.492	379	9
PubChem-7773305	0.519	397	9
PubChem-122716498	0.556	381	9
PubChem-119265	0.581	378	6
PubChem-8957383	0.606	373	10
PubChem-10200496	0.624	392	6
PubChem-11257780	0.645	390	6
PubChem-2795977	0.779	389	10

Showing 1 to 10 of 10 hits

Previous 1 Next

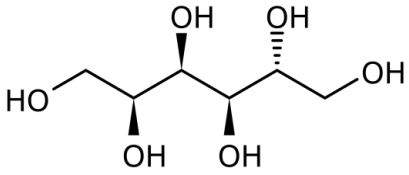
Minimize Save...

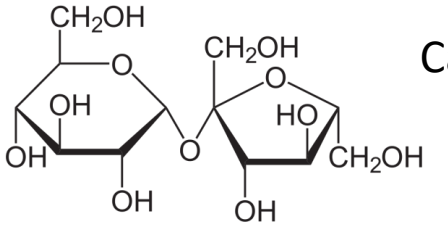
Восприятие вкуса

Сапофор – структурный мотив, обуславливающий вкус вещества (Cohn, 1914)

В частности, несколько гидроксильных групп обуславливают сладкий вкус.

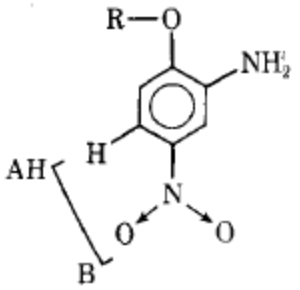
Сорбит (0,6)



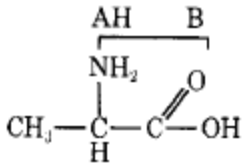


Сахароза (1,0)

AH-B theory of sweetness proposed that to be sweet, a compound must contain a hydrogen bond donor (AH) and a Lewis base (B) separated by about 3 Å (1963)

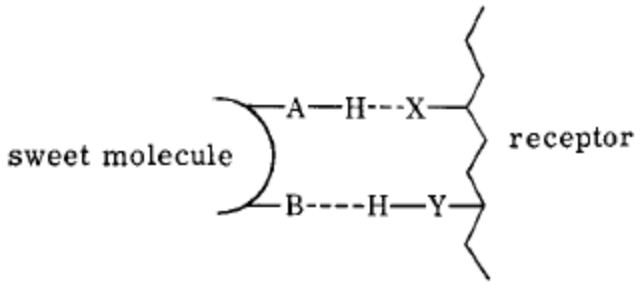


2-amino-4-nitrobenzenes



alanine

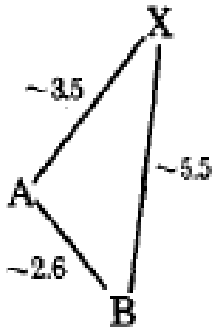
Scheme I—Various sweet molecules showing the A—H and B structural features involved cited by Shallenberger and Acree (5)



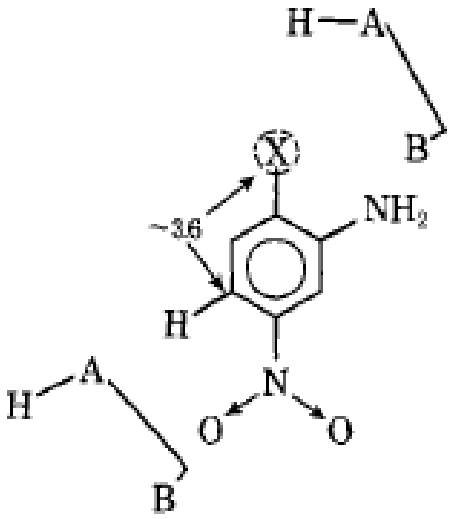
Scheme II—Postulated interaction of molecular sweet feature and receptor, according to Shallenberger and Acree (5)

Восприятие вкуса

B-X theory: существует третий сайт (X), образующий гидрофобный контакт с рецептором (Kier, 1972)



Scheme V—Pattern of atoms imparting a sweet taste (glucophore), postulated from this study



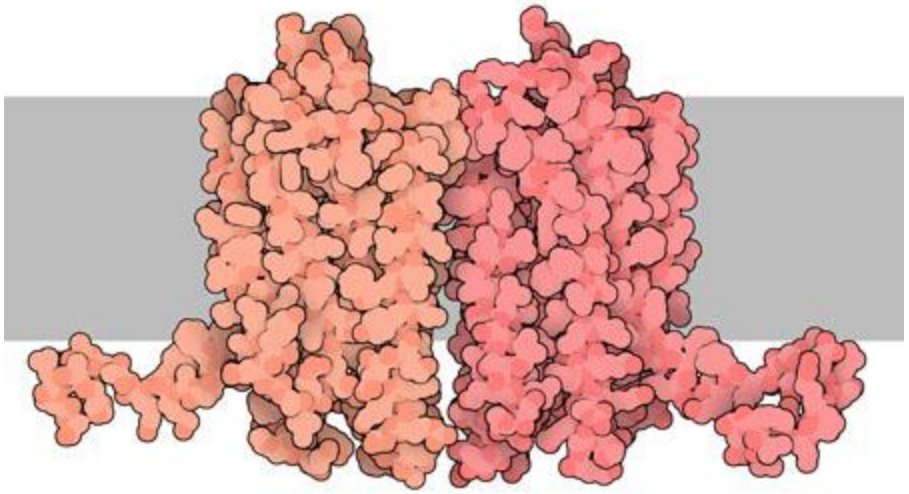
nitroanilines

Scheme VI—Identity of third structural feature comprising the postulated glucophore (Scheme V) in several sweet molecules

Multipoint attachment theory (MPA): существует 8 сайтов взаимодействия между «сладкими молекулами» и рецепторами сладкого, хотя не все они должны быть задействованы (1991).

Восприятие вкуса

Сладкий вкус, горький вкус и вкус умами воспринимаются рецепторами GPCR.

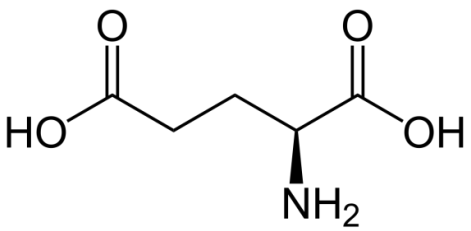


Димер GPCR: two receptors are better than one

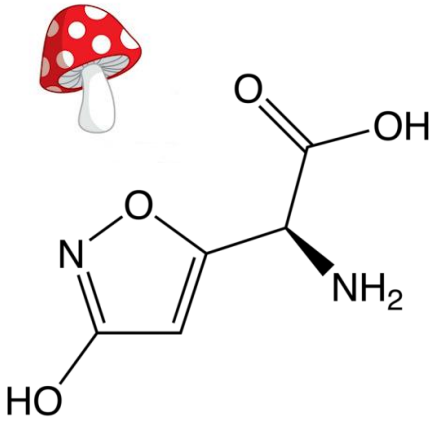
The breakthrough for the present understanding of sweetness occurred in 2001, when experiments with laboratory mice showed that mice possessing different versions of the gene T1R3 prefer sweet foods to different extents. Subsequent research has shown that the **T1R3** protein forms a complex with a related protein, called **T1R2**, to form a G-protein coupled receptor that is the sweetness receptor in mammals.[25]

Восприятие вкуса

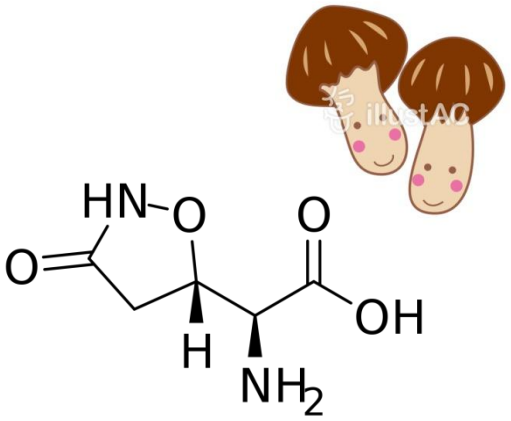
Сладкий вкус, горький вкус и **вкус умами** воспринимаются рецепторами GPCR.



L-глутамат



Иботеновая кислота

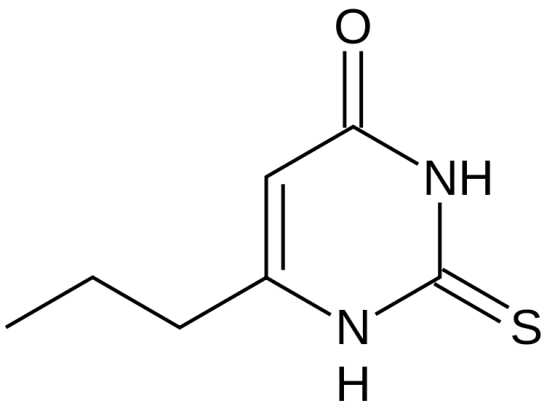


Tricholomic acid

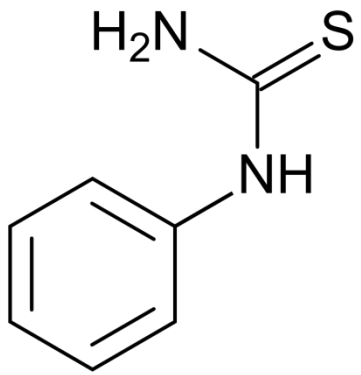
Recent molecular biological studies have now identified strong candidates for umami receptors, including the heterodimer **T1R1/T1R3**, and truncated type 1 and 4 metabotropic glutamate receptors missing most of the N-terminal extracellular domain (taste-mGluR4 and truncated-mGluR1) and brain-mGluR4."[15] Receptors **mGluR1** and **mGluR4** are specific to glutamate whereas T1R1 + T1R3 are responsible for the synergism... However, the specific role of each type of receptor in taste bud cells remains unclear.

Восприятие вкуса

Сладкий вкус, **горький вкус** и вкус умами воспринимаются рецепторами GPCR.



пропилтиоурацил



фенилтиокарбамид

Research has shown that **TAS2Rs** (taste receptors, type 2, also known as T2Rs) such as TAS2R38 coupled to the G protein gustducin are responsible for the human ability to taste bitter substances.[38] The TAS2R family in humans is thought to comprise about 25 different taste receptors, some of which can recognize a wide variety of bitter-tasting compounds.[39]

BitterDB

BitterDB

Institute of Biochemistry, Food Science and Nutrition, Faculty of Agriculture,
The Hebrew University of Jerusalem האוניברסיטה העברית ירושלים

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Welcome to BitterDB!

Bitter taste is one of the basic taste modalities. It is innately aversive for various species, and can be elicited by numerous, chemically different compounds. The aim of this database is to gather information about bitter-tasting natural and synthetic compounds, and their cognate bitter taste receptors (T2Rs or TAS2Rs).

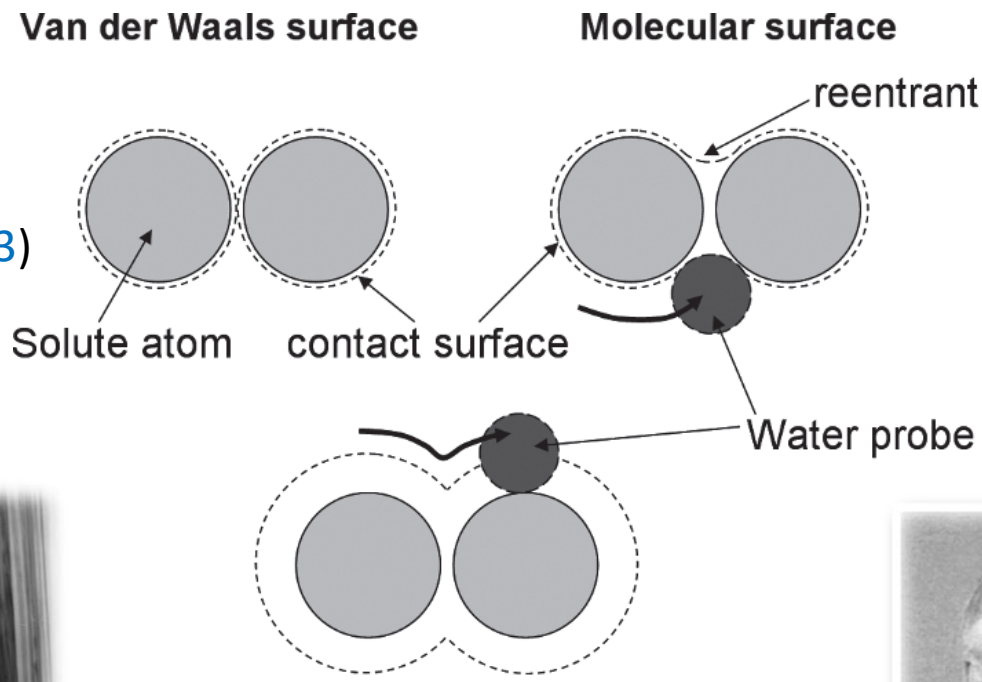
How to Cite BitterDB:

Ayana Dagan Wiener, Antonella Di Pizio, Ido Nissim, Malkeet Singh Bahia; Nitzan Dubovski, Eitan Margulis, Masha Y. Niv. BitterDB: Taste ligands and receptors database in 2019. ***Nucleic Acids Res 2019: gky974.***
Click here to view the paper: BitterDB 2019 paper

Ayana Wiener; Marina Shudler; Anat Levit; Masha Y. Niv. BitterDB: a database of bitter compounds. ***Nucleic Acids Res 2012, 40(Database issue):D413-419.***
Click here to view the paper: BitterDB paper

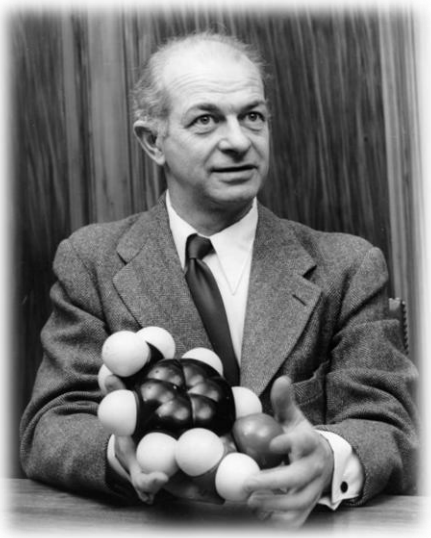
Молекулярные поверхности

(Corey & Pauling, 1953)



(Connolly, 1983)

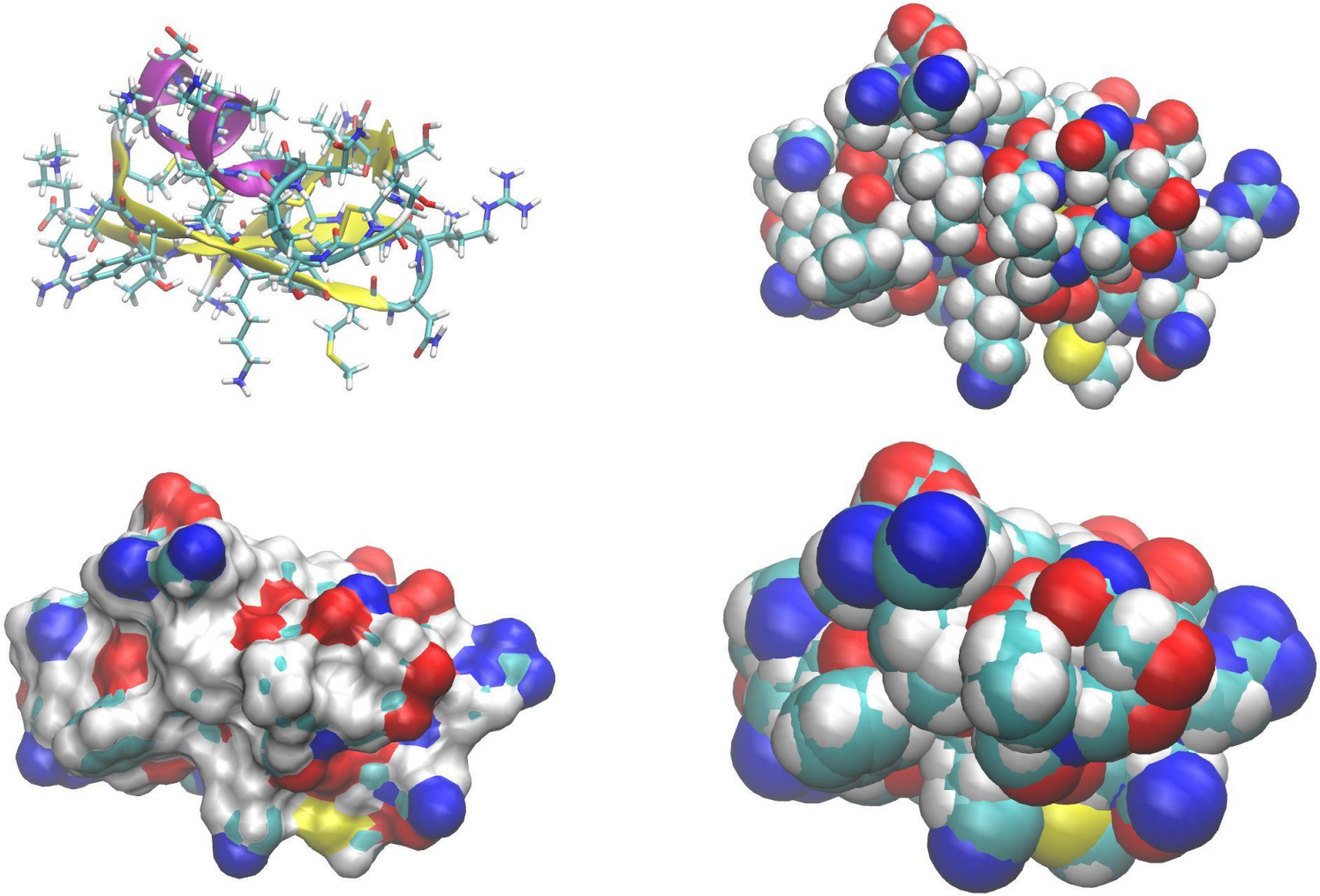
(Richards, 1977)



Linus Pauling
(1901 - 1994)

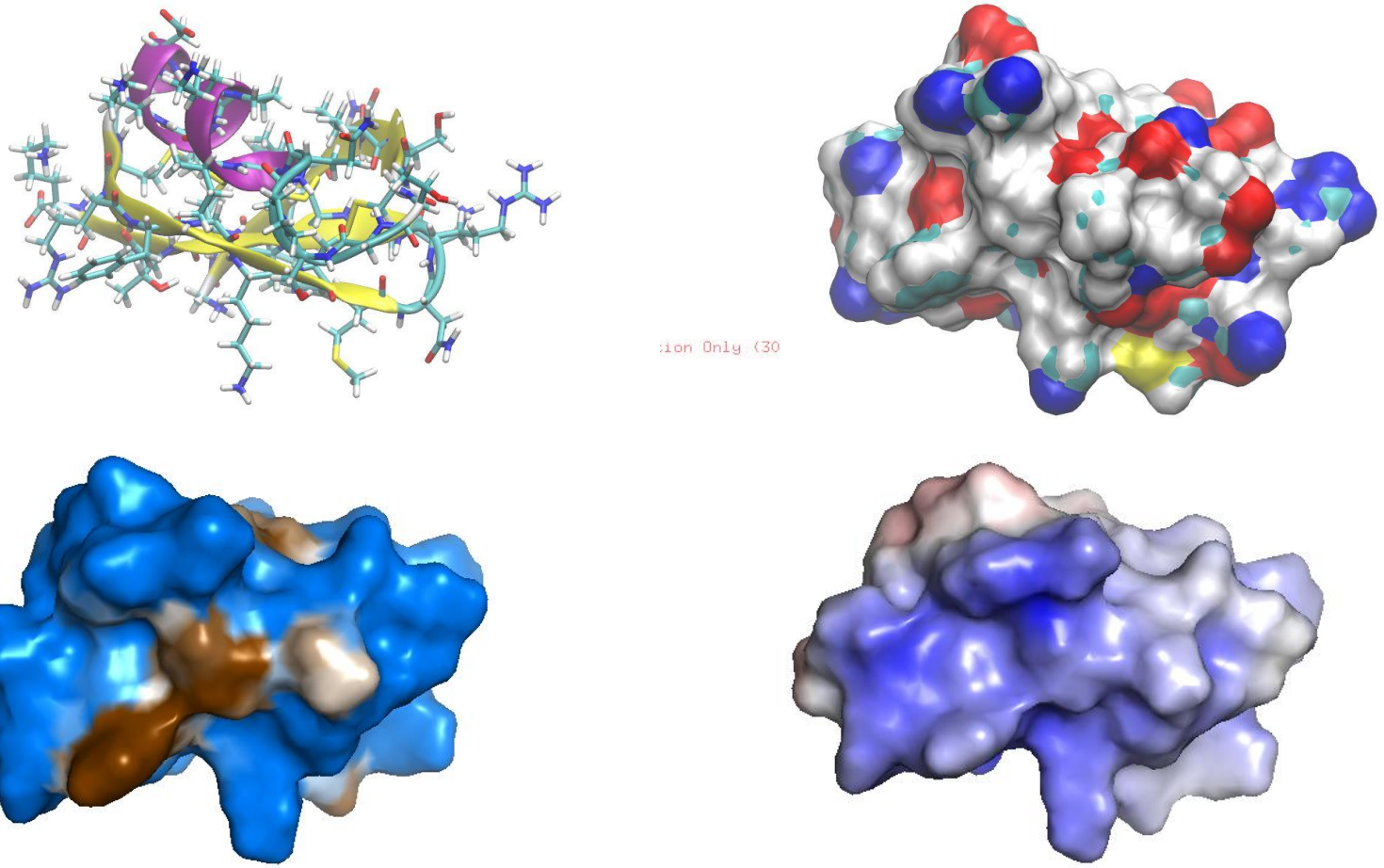
Frederic Richards
(1925 - 2009)

Молекулярные поверхности



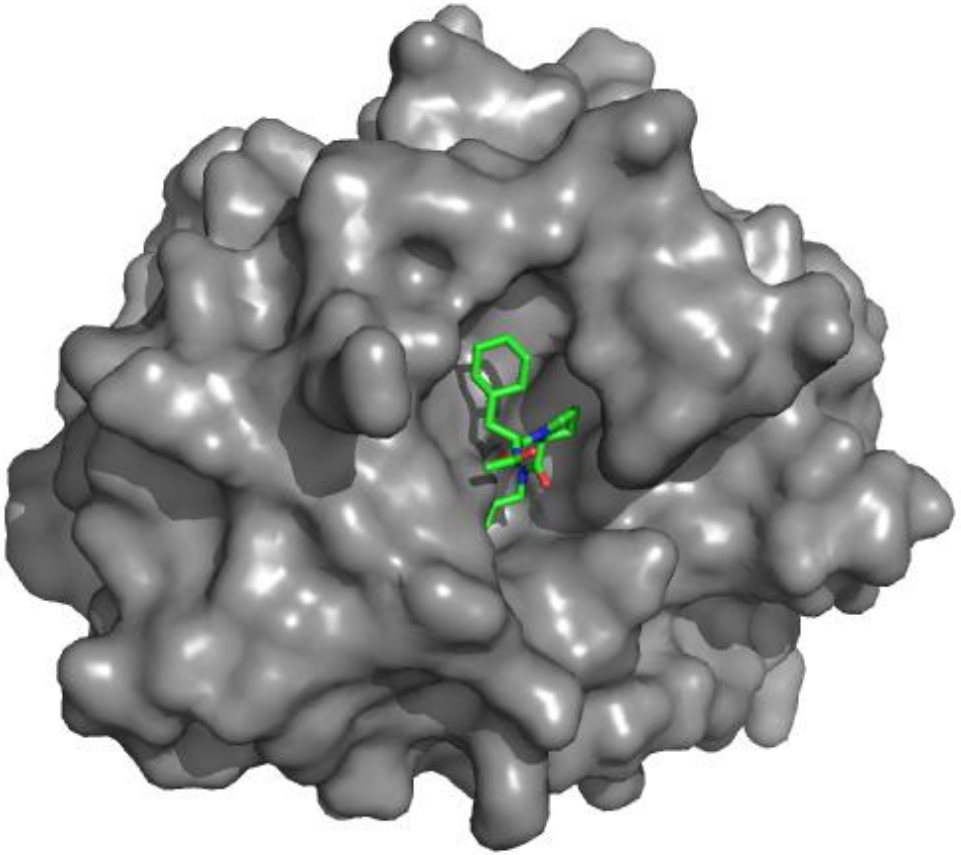
Структура аджитоксина-2 (pdb 1agt) в ленточном и стержневом представлении, в виде сфер ван-дер-Ваальса, а также ее молекулярная поверхность и поверхность, доступная растворителю (SAS)

Молекулярные поверхности

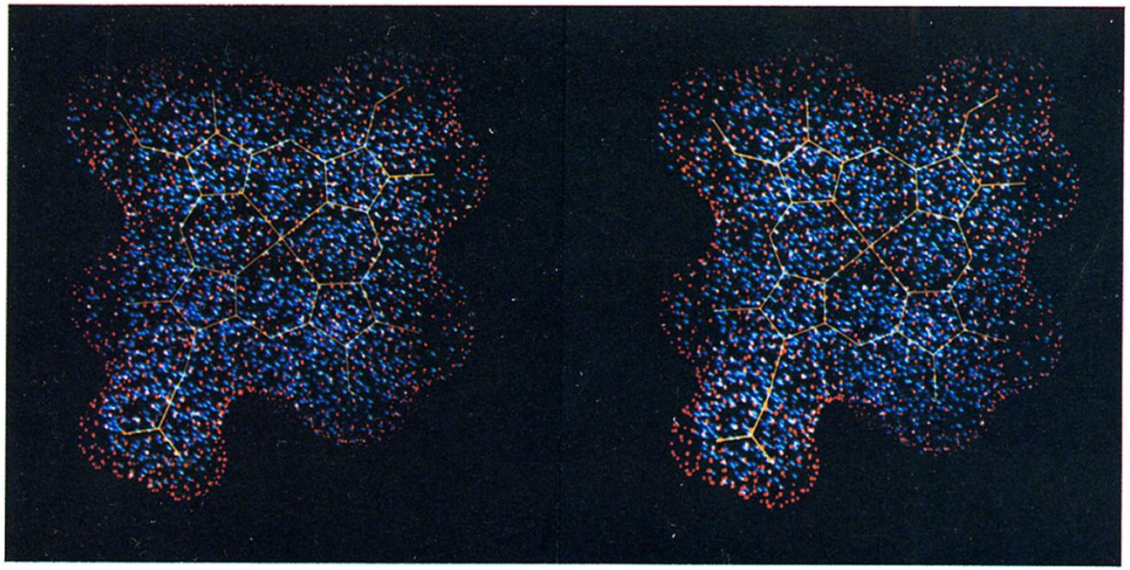


Структура аджитоксина-2 и её молекулярная поверхность, раскрашенная по химическому элементу, гидрофобности и электростатическому потенциалу (синий цвет соответствует положительным значениям, красный отрицательным)

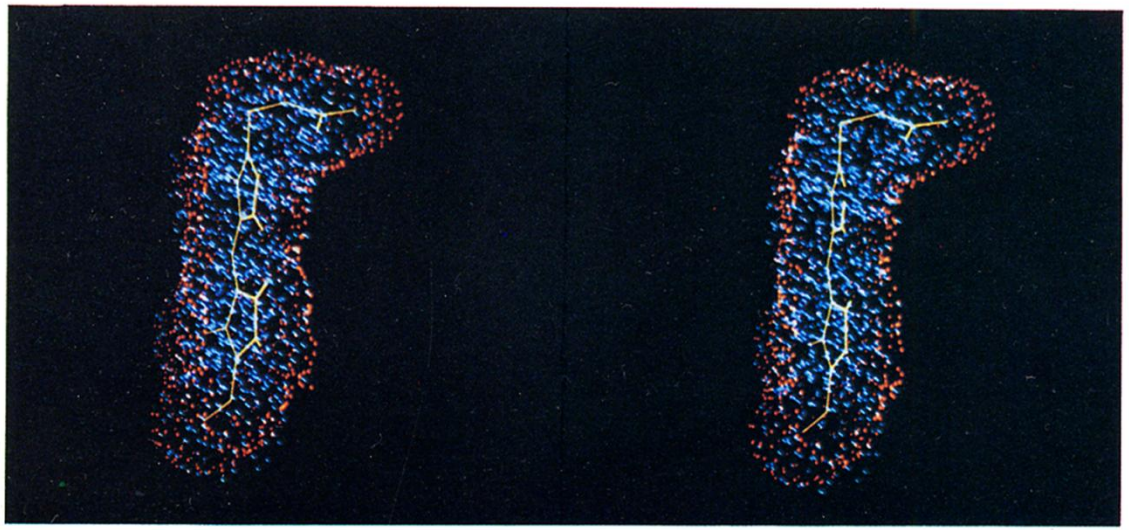
Молекулярный докинг



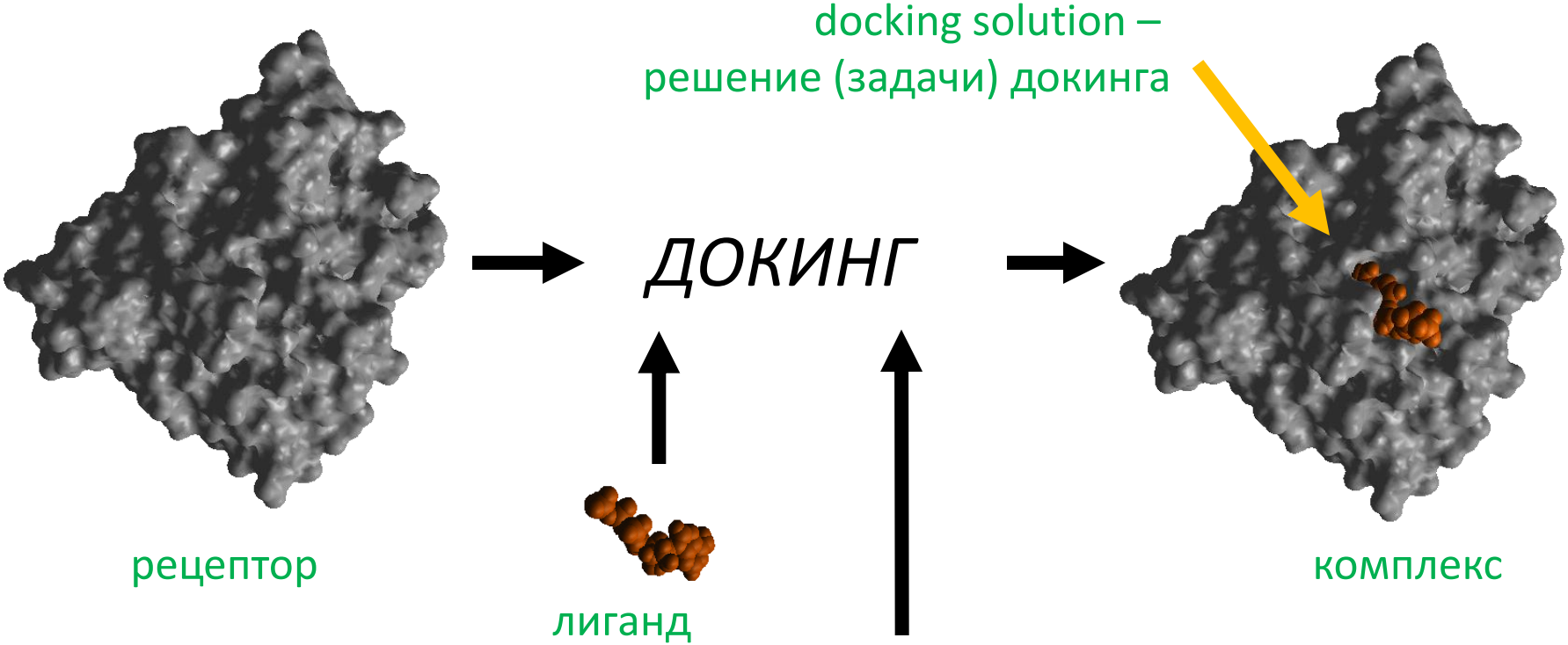
A Geometric Approach to Macromolecule-Ligand Interactions (1982)



(a)



Молекулярный докинг. Общая постановка задачи



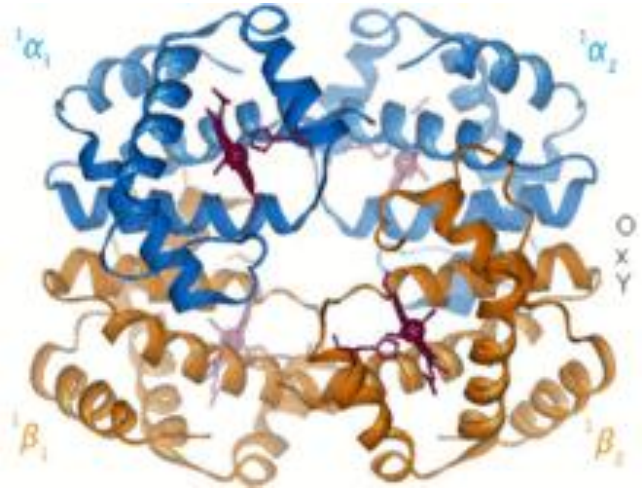
оценочная функция:

водородные связи, гидрофобные контакты, стэкинг-взаимодействия, …

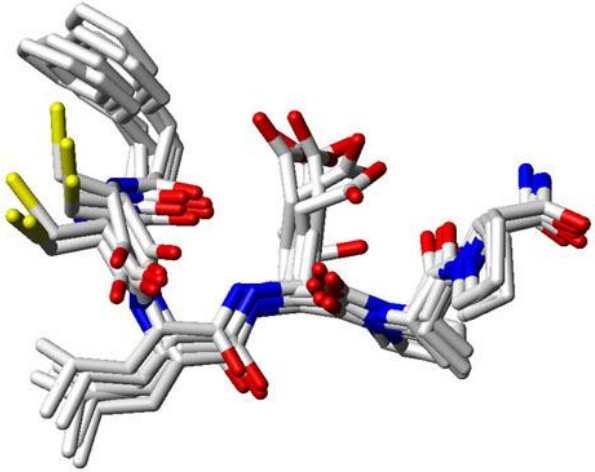
Представление белков и лигандов

Гибкость белка:

- быстрые движения малого масштаба – движение боковых цепей и петель
- медленные движения крупного масштаба – движение доменов
- ренатурация частично развернутых белков



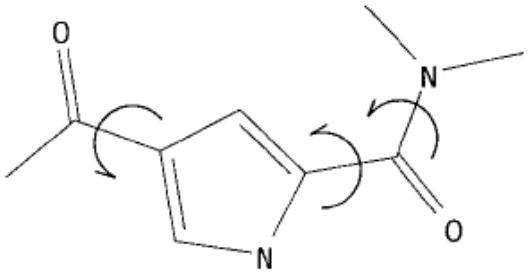
Гибкость лиганда



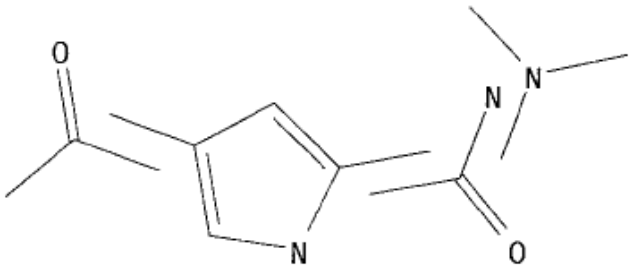
Молекулярный докинг.

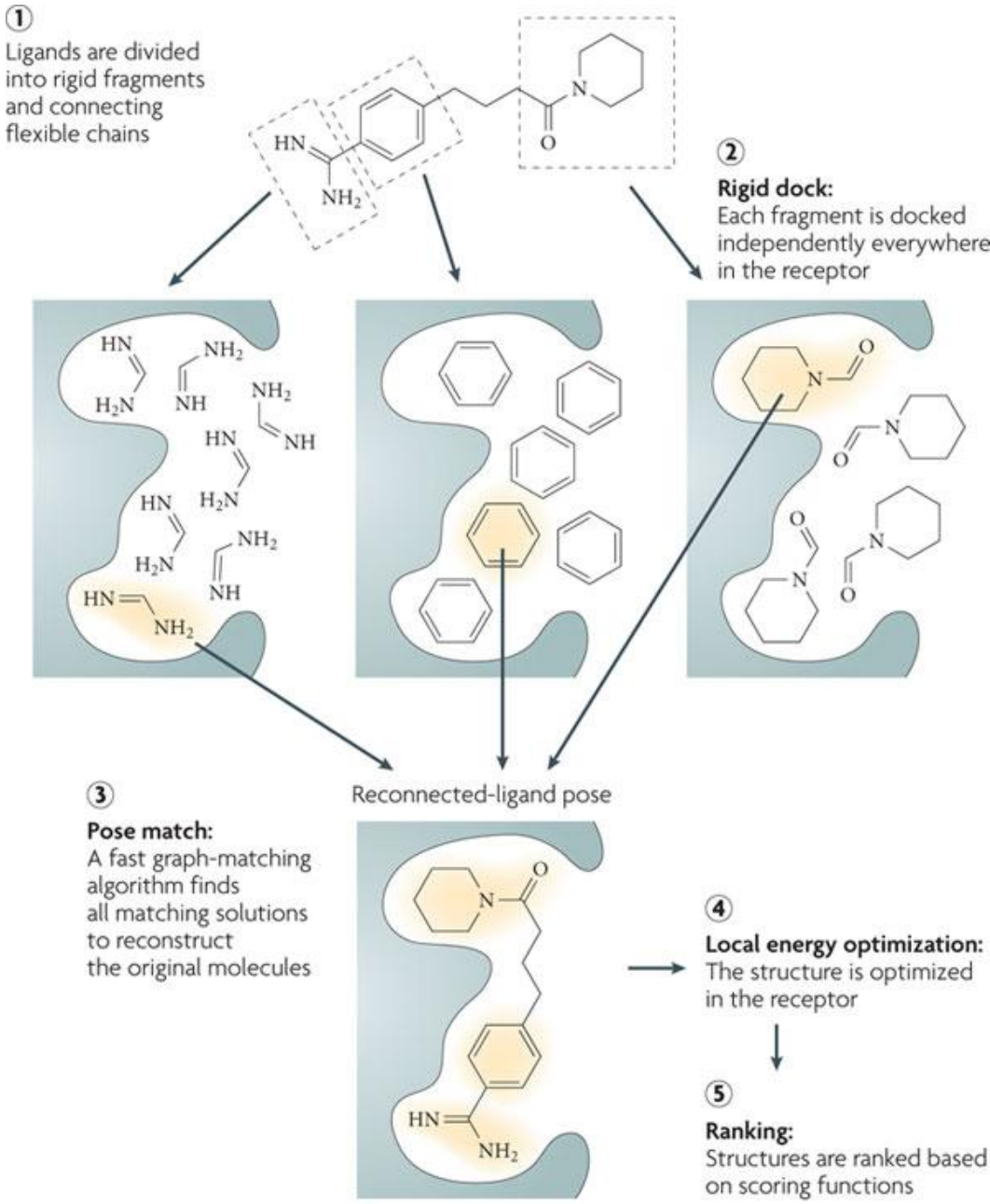
Последовательная сборка и сборка из фрагментов

А



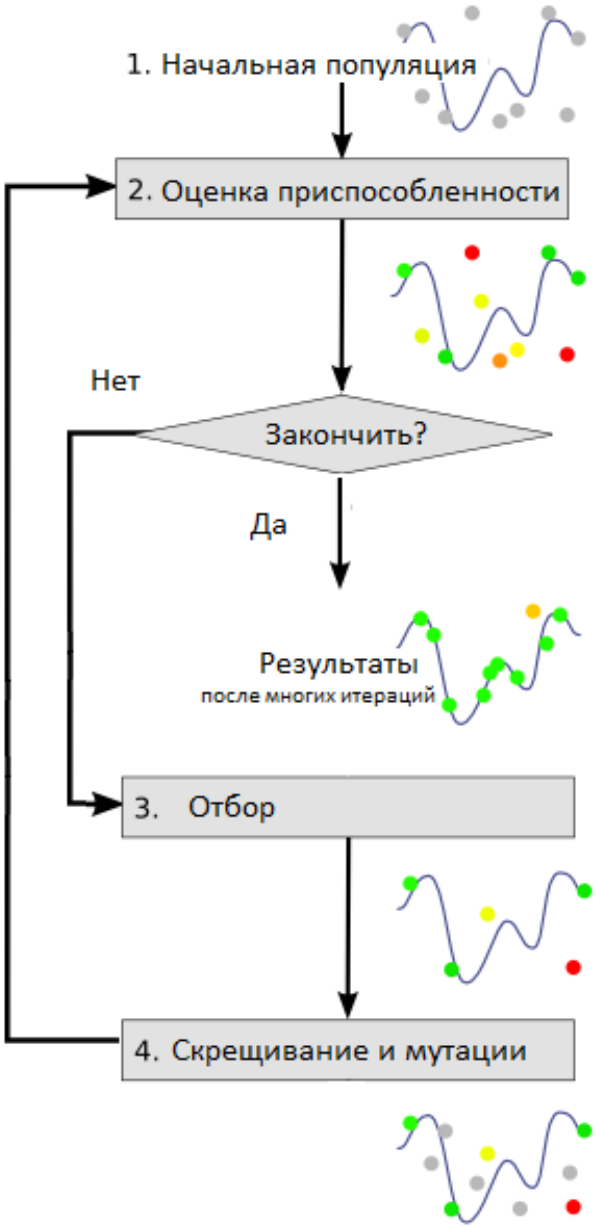
Б





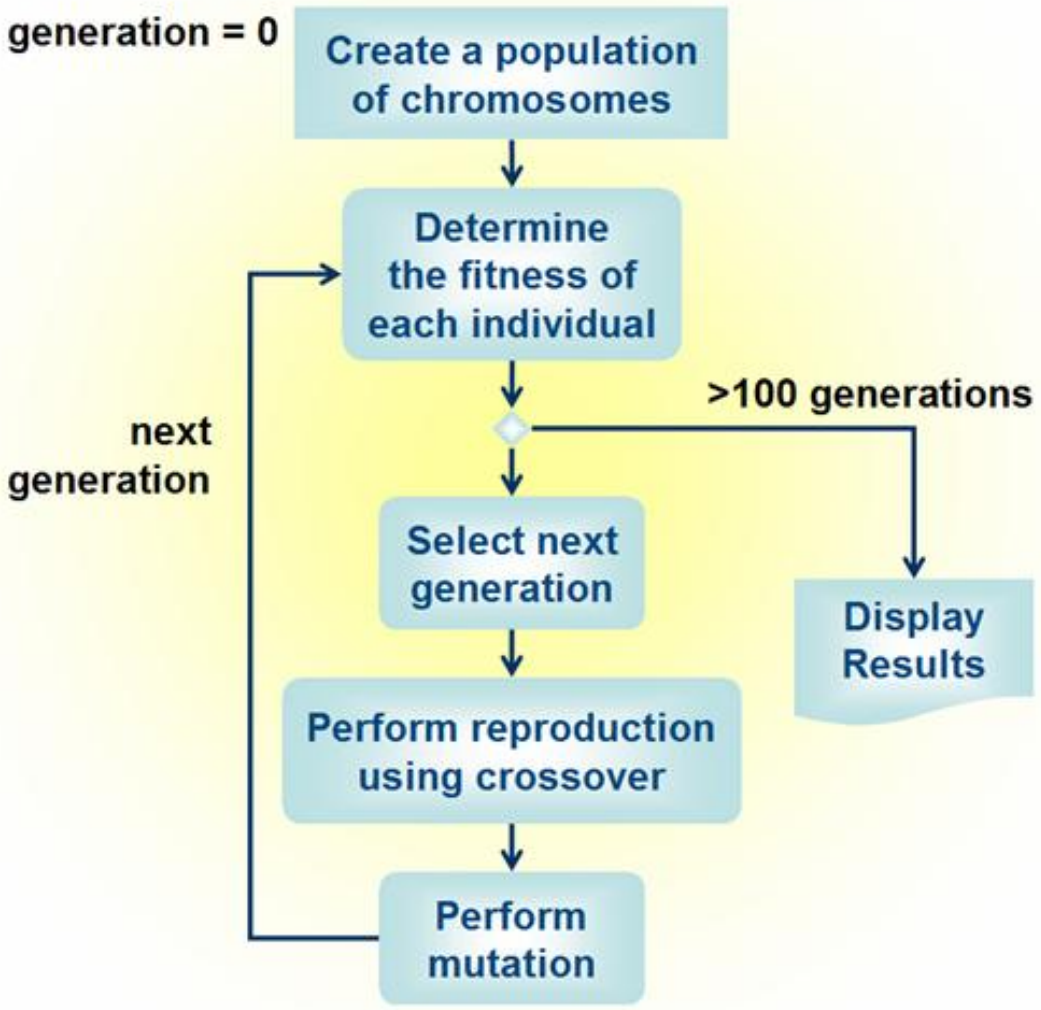
Nature Reviews | Microbiology

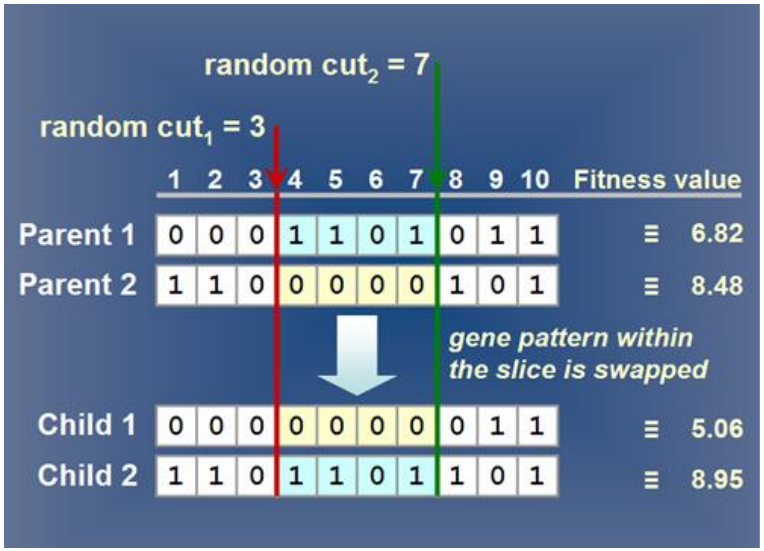
Молекулярный докинг. Генетический алгоритм

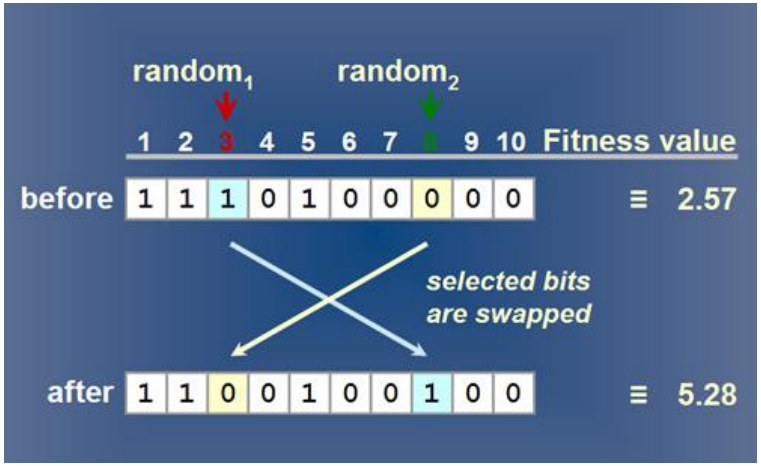


The 2006 NASA ST5 spacecraft antenna. This complicated shape was found by an evolutionary computer design program to create the best radiation pattern.

Молекулярный докинг. Генетический алгоритм

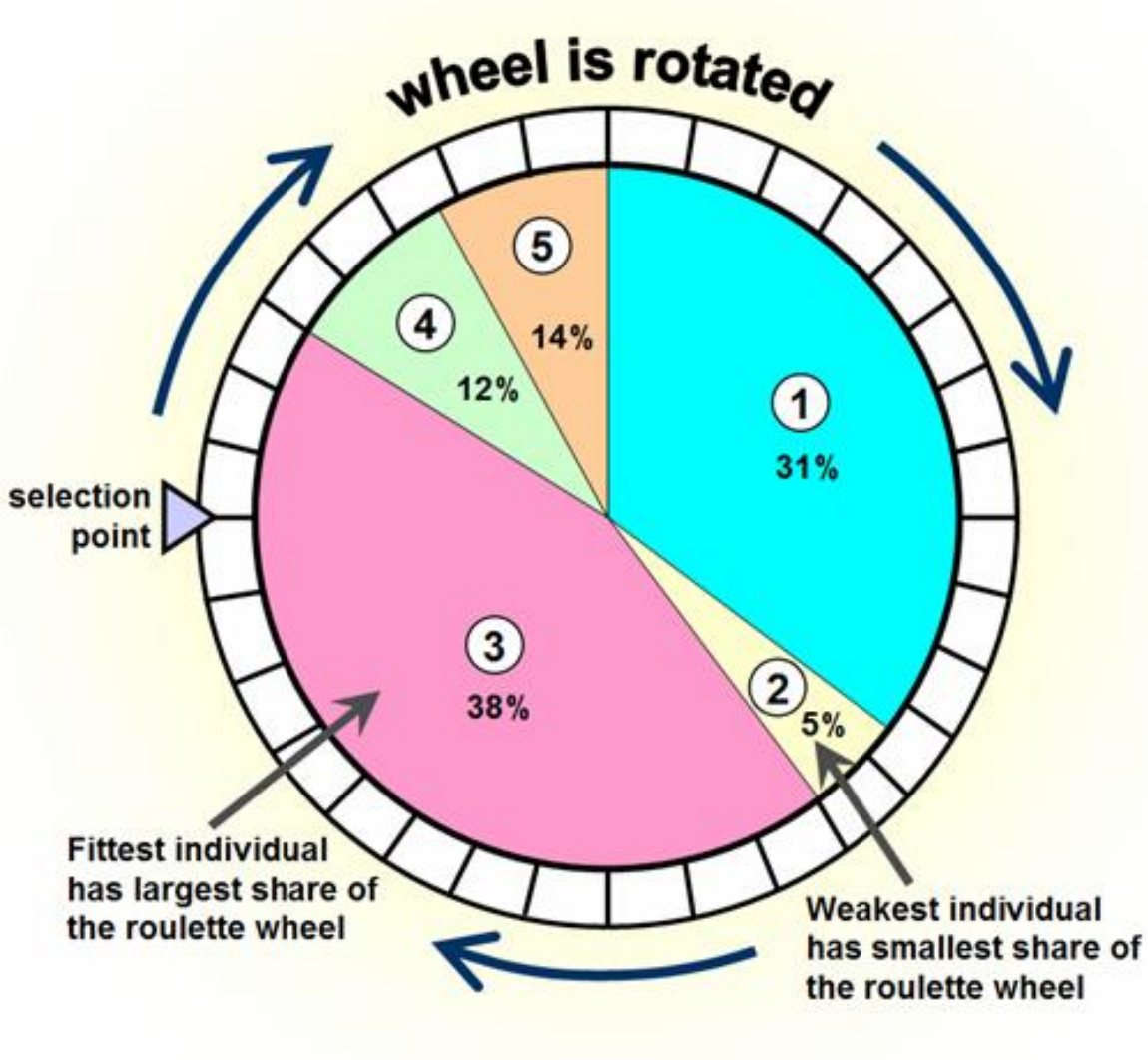






http://www.edc.ncl.ac.uk/highlight/rhjanuary2007.php

Молекулярный докинг. Генетический алгоритм

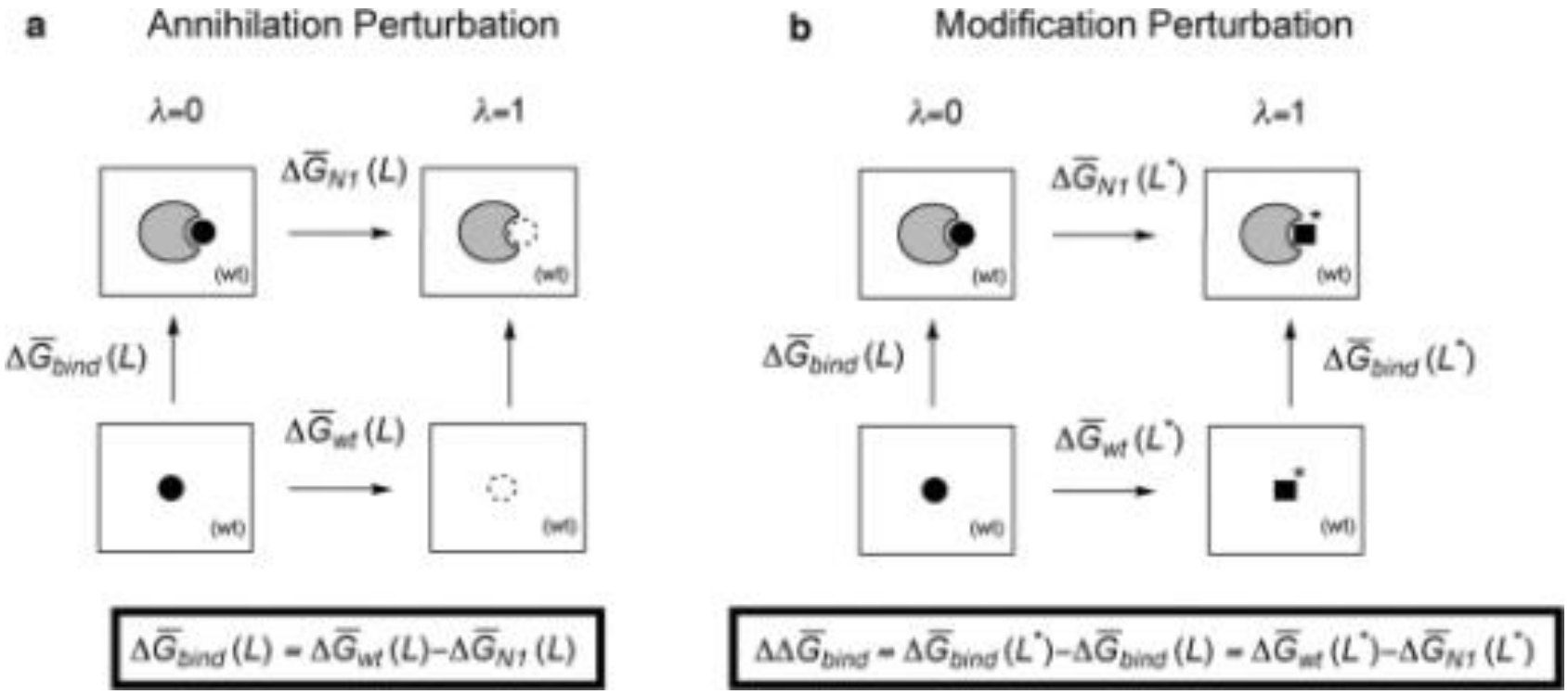


http://www.edc.ncl.ac.uk/highlight/rhjanuary2007.php

Расчет энергии связывания

Термодинамическое интегрирование

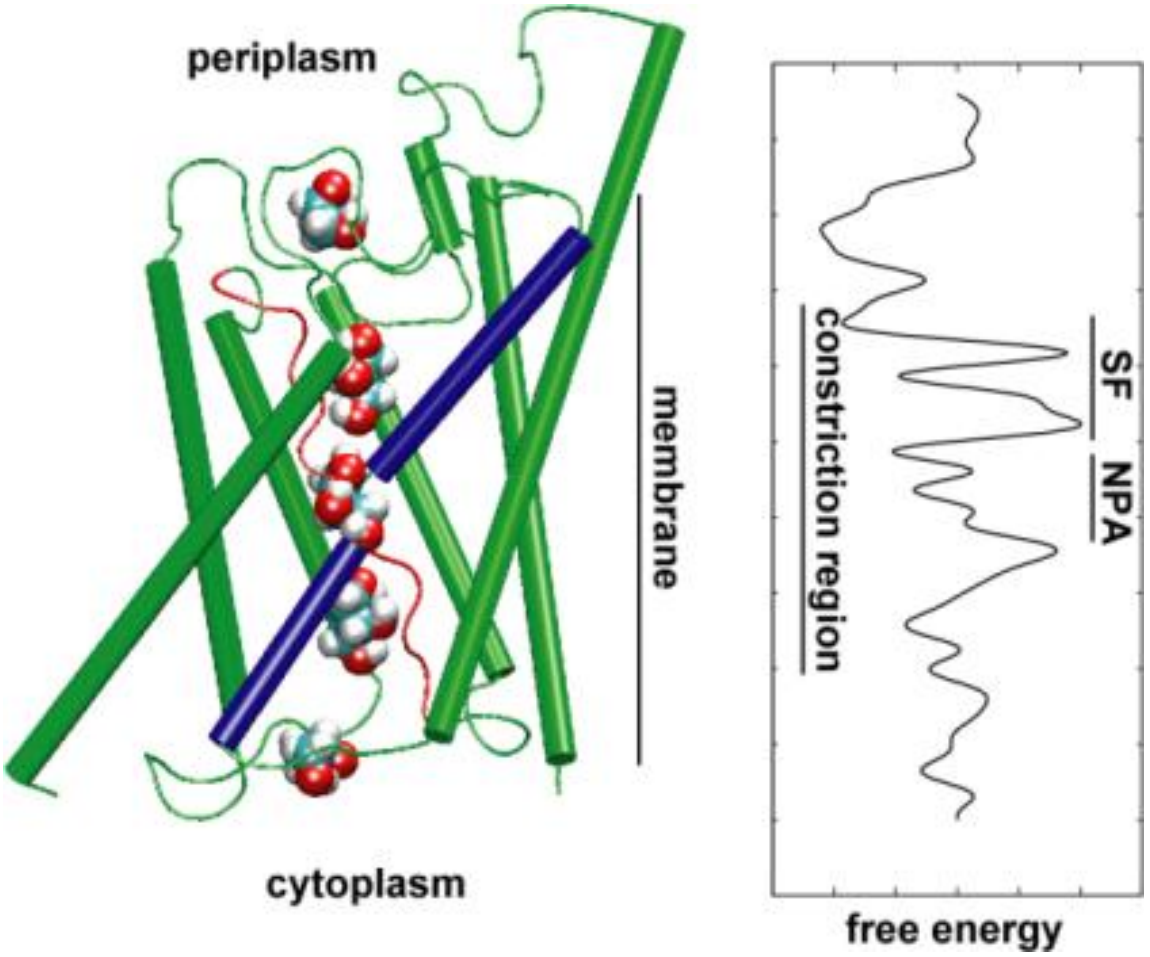
$$\Delta G^{0}_{TI} = \int_{0}^{1} \left\langle \frac{\partial V(\lambda)}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$



Не используется в методах молекулярного докинга

Расчет энергии связывания

Потенциал средней силы



Не используется в методах молекулярного докинга

Молекулярный докинг. Оценочные функции

- Forcefield-based
  - Based on terms from molecular mechanics forcefields
  - GoldScore, DOCK, AutoDock
- Empirical
  - Parameterised against experimental binding affinities
  - ChemScore, PLP, Glide SP/XP
- Knowledge-based potentials
  - Based on statistical analysis of observed pairwise distributions
  - PMF, DrugScore, ASP

Молекулярный докинг. Обучающие наборы

Положение лигандов и константы связывания уже известны

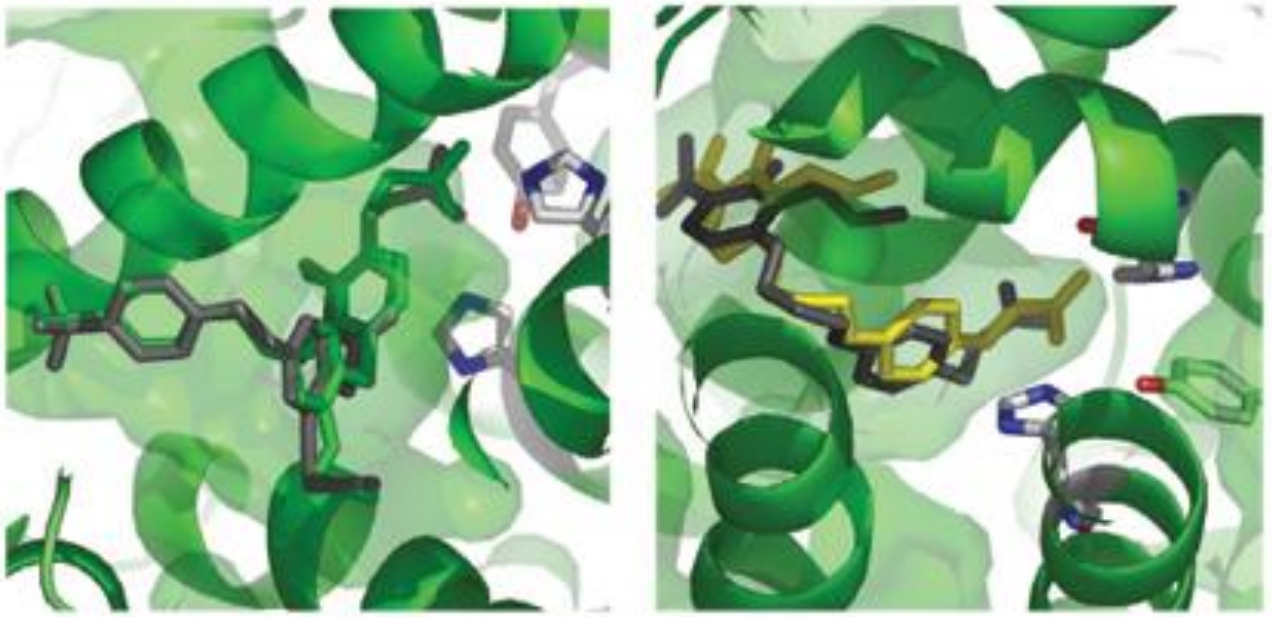
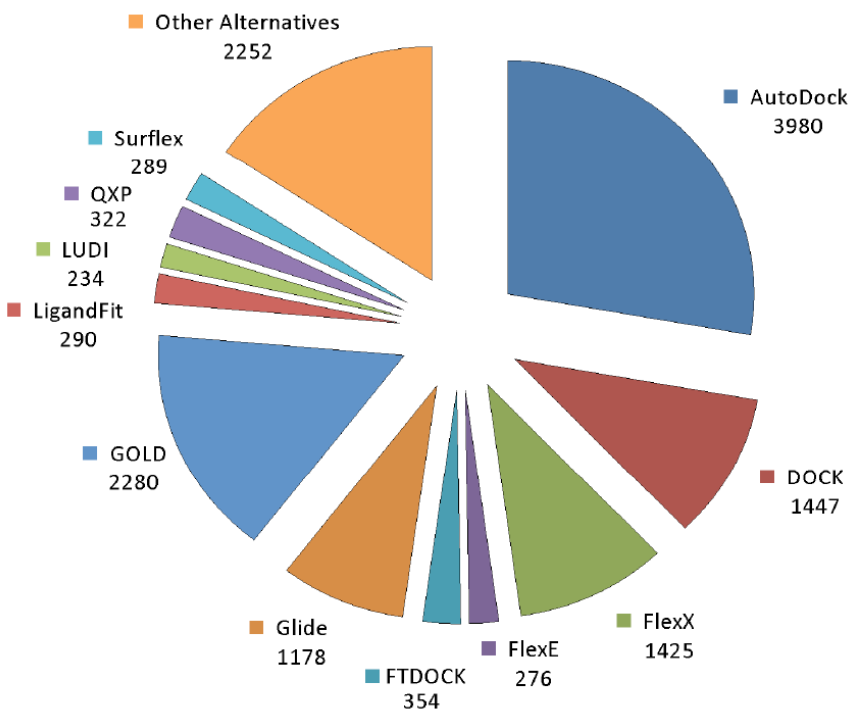
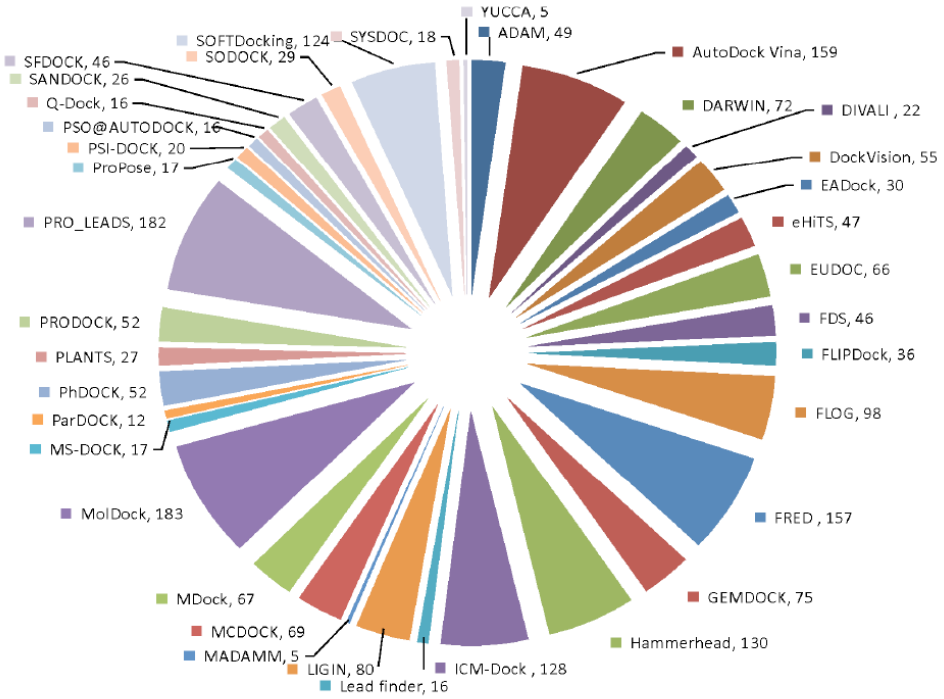


Figure 4. (A) Redocking and (B) crossdocking results. Both crystallographic ligands are shown in gray and the docked ligands are in green (D32) and yellow (L41), respectively. See online for color image.

Молекулярный докинг. Программы

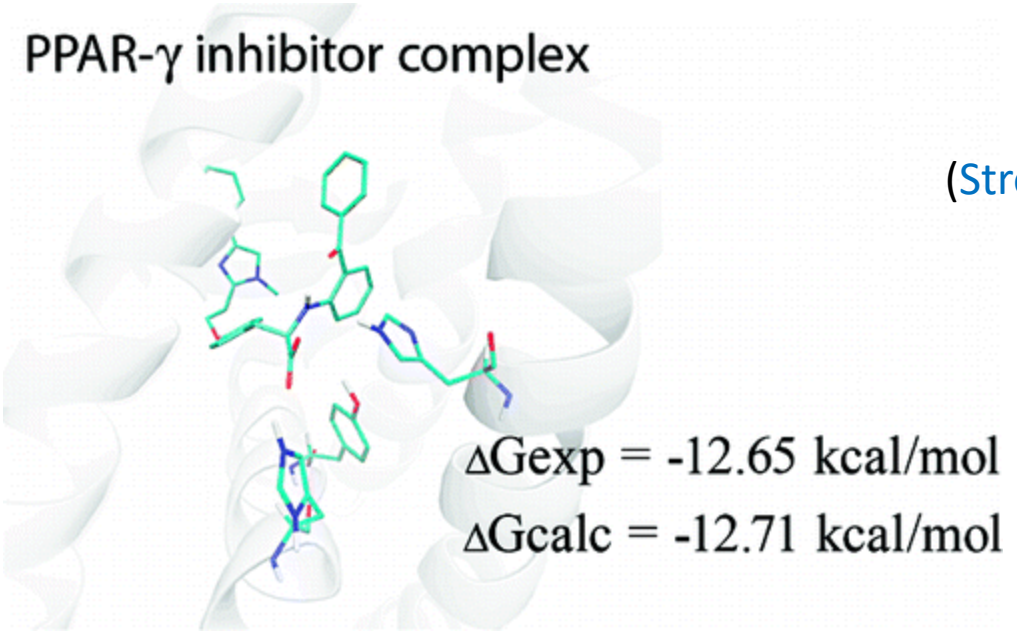


Global



Other Alternatives in detail

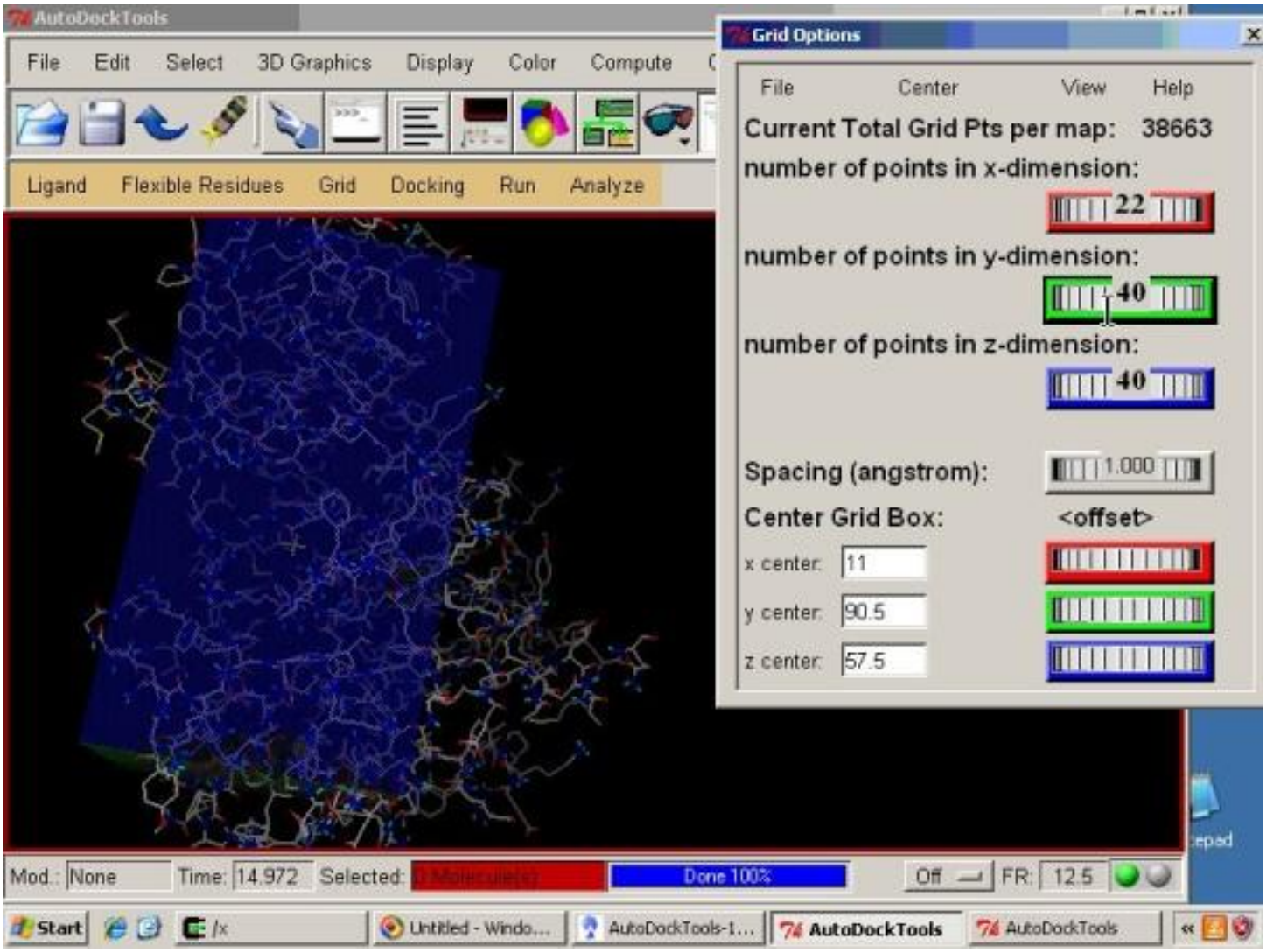
Молекулярный докинг. LeadFinder



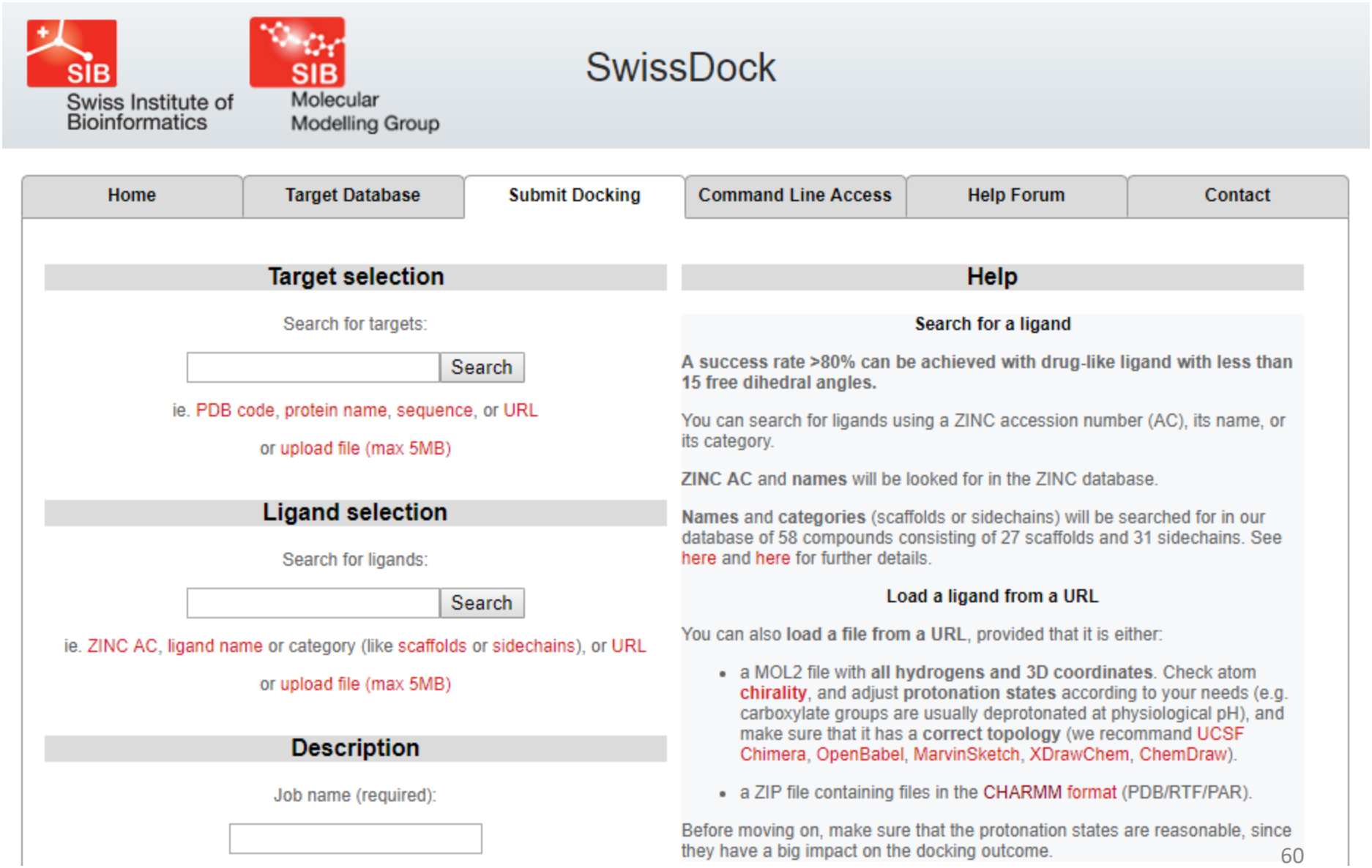
(Stroganov, Chilov et al., 2008)

Молекулярный докинг. AutoDock (->AutoDock Vina)

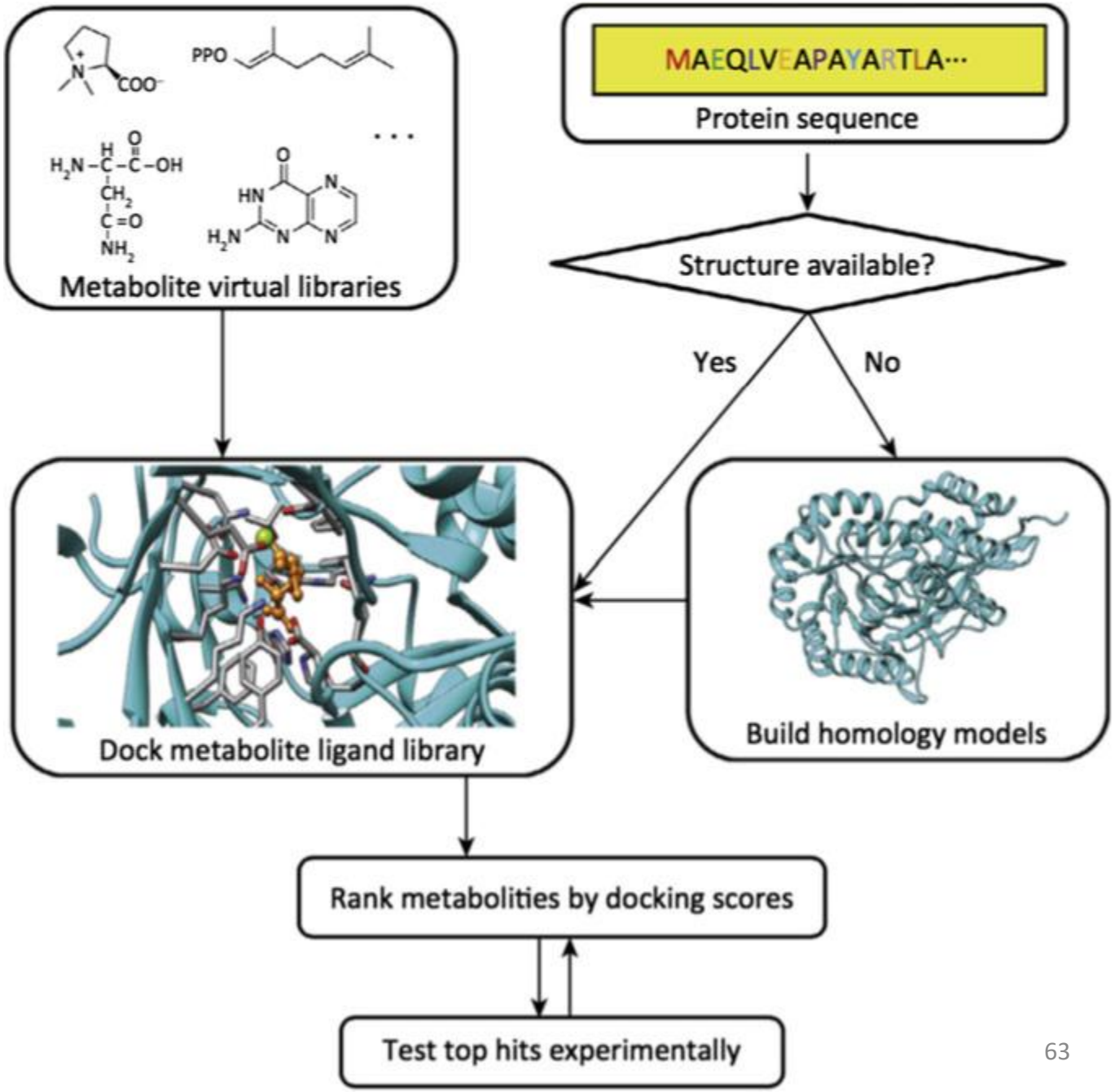
(Goodsell & Olson, 1990; Trott & Olson, 2010)



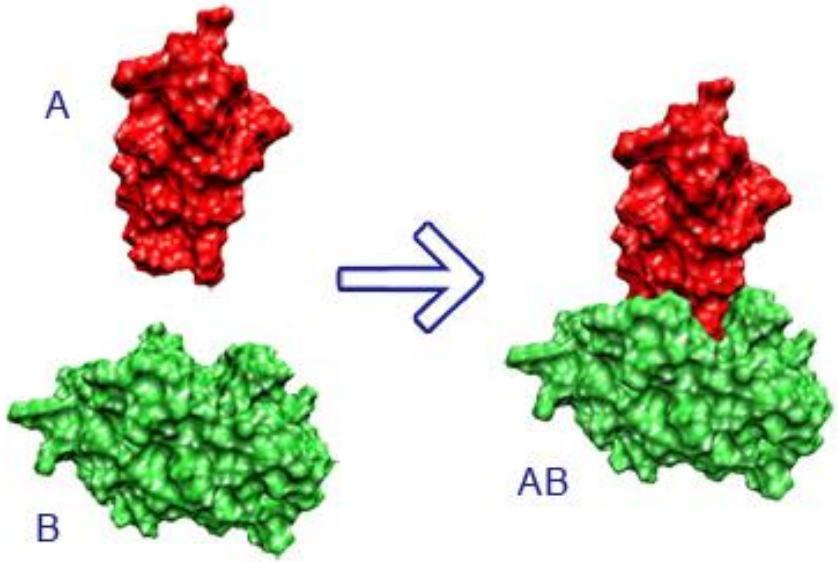
Молекулярный докинг. SwissDock

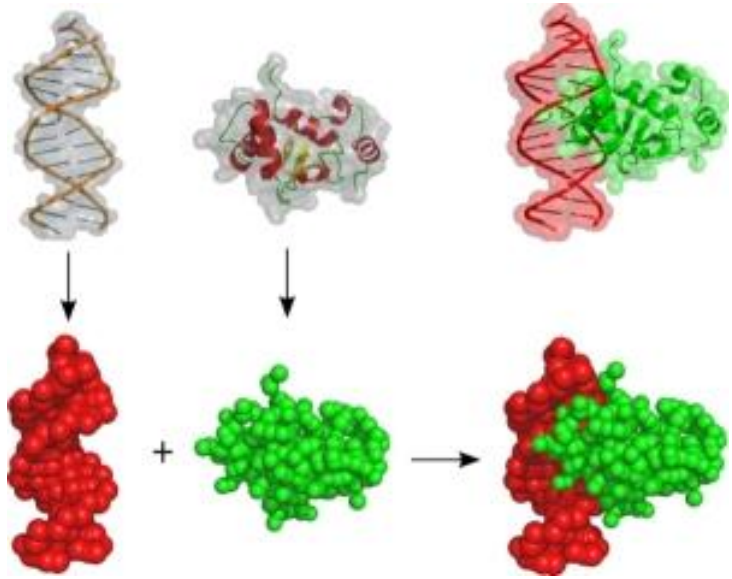


Аннотация функции

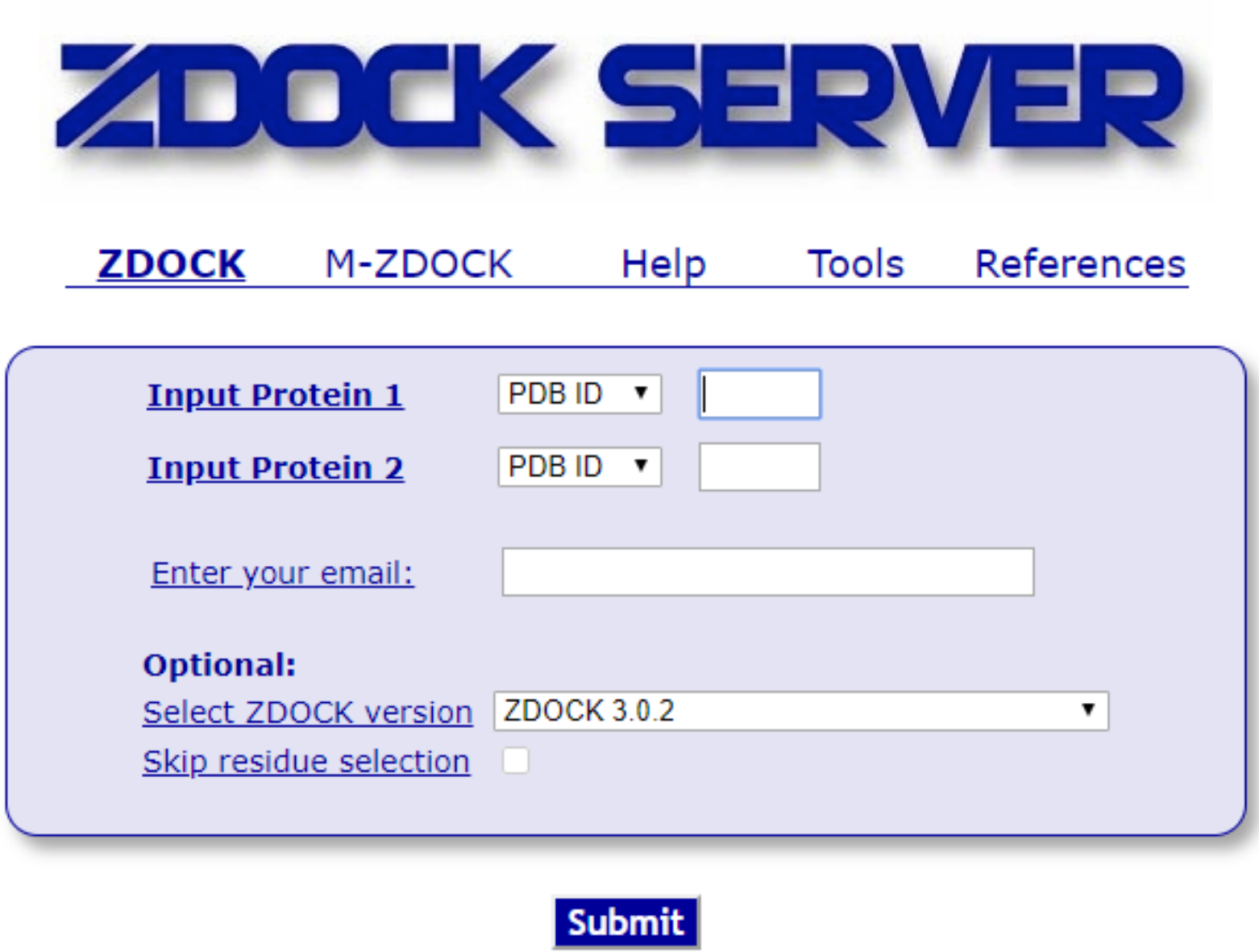


Докинг макромолекул





Докинг макромолекул



XXVI Симпозиум «Биоинформатика и компьютерное конструирование лекарств» в рамках XXVII Российского национального конгресса «Человек и лекарство»

Проводится онлайн с 6 по 25 апреля 2020 года.

ИБМХ