

FAMNITovi izleti v matematično vesolje

Od matematike do razvoja zdravil

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Velika predavalnica UP FAMNIT

Koper, 18. januar 2012

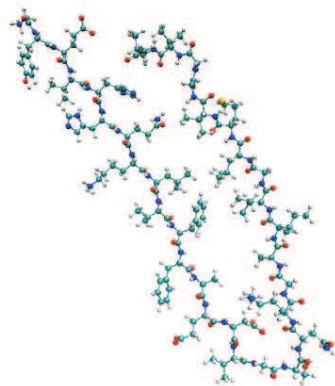
Povzetek

- Pri razvoju novih zdravil se farmacevtska industrija vedno bolj obrača k molekularnemu modeliranju, vedi, ki preučuje lastnosti molekul tako, da jih poustvari kot modele s pomočjo računalnika in jih obravnava z uporabo različnih matematičnih pristopov.
- Razvoj novih zdravil je dolgotrajen in drag proces, ki od ideje do končnega izdelka običajno zahteva 10 ali več let naporenega dela in okroglo milijardo dolarjev.
- Z uporabo novih matematičnih pristopov in modernih računalnikov ga skušamo skrajšati in poceniti, pri čemer nas zanimajo predvsem molekule, vpletene v razvoj različnih bolezni.
- Na predavanju bomo predstavili novo razvita matematična orodja, ki se uporabljajo na področju razvoja novih zdravil.

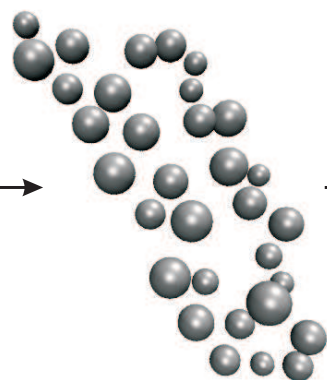
Kaj je molekularno modeliranje?

Molekularno modeliranje je algoritmični zapis matematičnih relacij, ki jih izluščimo iz obravnavanega realnega sistema.

Realni sistem



Model sistema

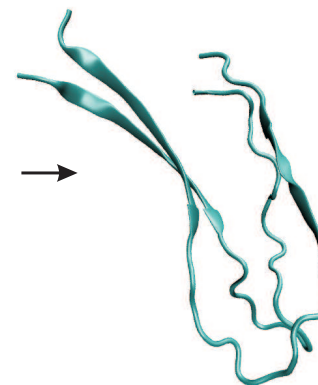


Račun

$$\mathbf{F} = \frac{d(m\mathbf{v})}{dt} = m \frac{d\mathbf{v}}{dt}$$

$$\hat{H}\psi = E \cdot \psi$$

Rezultat računa



Molekularno modeliranje

Molekularno modeliranje je nepogrešljivo pri teoretskih raziskavah v naravoslovnih in tehničnih znanostih, kot so:

- kemija
- molekularna fizika
- strukturna biologija
- farmacija

Uporaba molekularnega modeliranja

Molekularno modeliranje se uporablja za reševanje problemov:

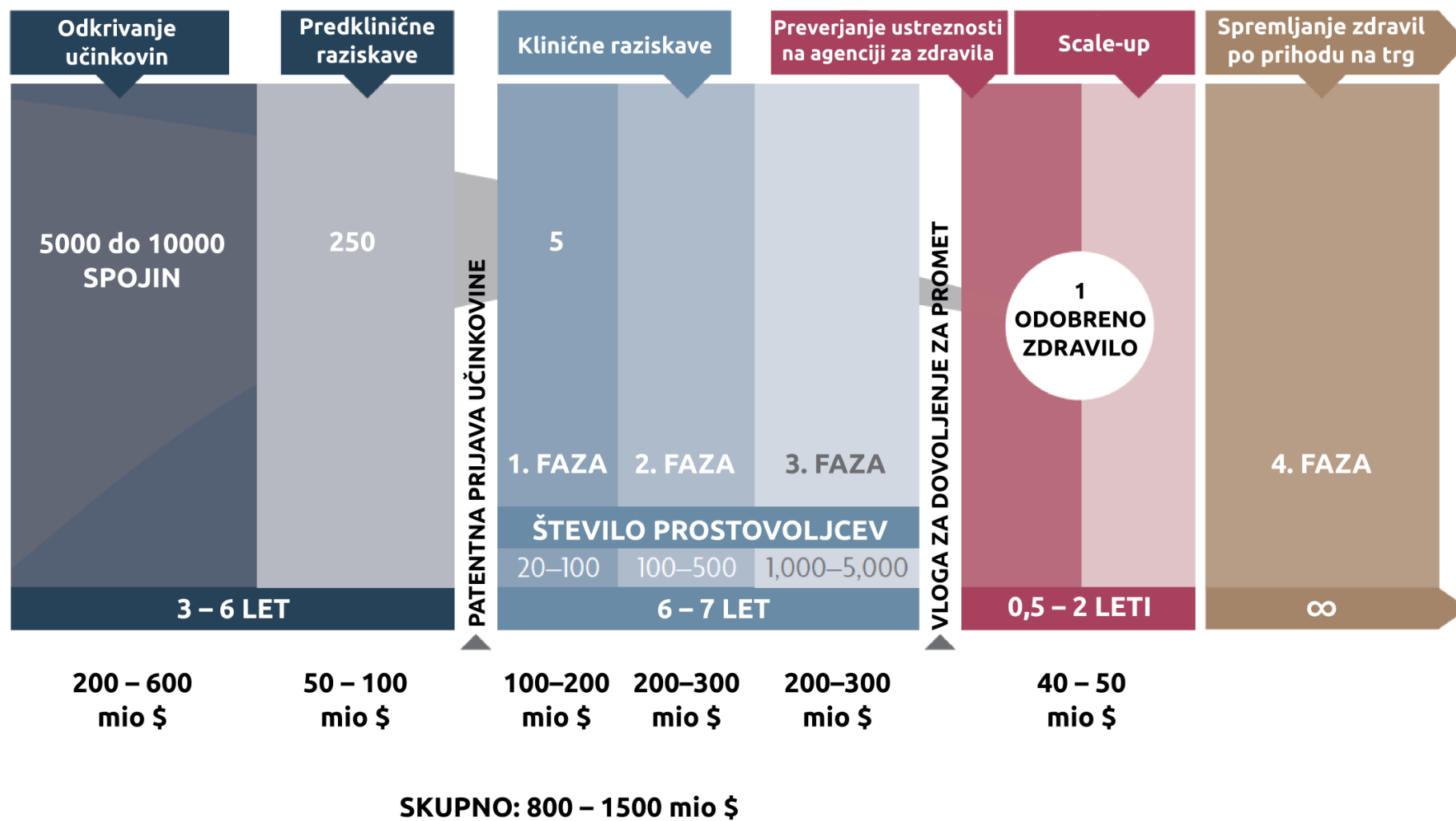
- strukture in dinamike molekul
- snovi v gmoti
- kemijskih in biokemijskih reakcij
- **razvoja novih zdravil**

Razvoj metod molekularnega modeliranja je tesno povezan z razvojem najmodernejših računalnikov.

Molekularno modeliranje v Sloveniji

- Uvajanje računalništva v kemijo v Sloveniji začne akad. prof. dr. Dušan Hadži
- Leta 1993 MZT ustanovi Center za molekularno modeliranje na KI (Vodja: prof.dr. Dušanka Janežič)
- Namen centra je:
 1. Vzdrževati in izpopolnjevati vse skupine metod molekularnega modeliranja
 2. Pomagati raziskovalcem pri uvajanju teh metod v razna področja raziskovalnega dela
 3. Nabaviti, vzdrževati in razvijati potrebno programsko in strojno opremo za molekularno modeliranje
 4. Svetovati uporabnikom pri izbiri programske in strojne opreme potrebne za molekularno modeliranje in izobraževanje kadra
 5. Sodelovanje pri reševanju konkretnih problemov uporabnikov
 6. Sodelovanje pri projektih MVZT oz. ARRS
 7. Sodelovanje z univerzami in inštituti
 8. Sodelovanje z industrijo, predvsem kemijsko in farmacevtsko (LEK, KRKA)
- Leta 2009 KI ustanovi Laboratorij za molekularno modeliranje (Vodja: prof.dr. Dušanka Janežič)

Razvoj novih zdravil



Razvoj novih zdravil

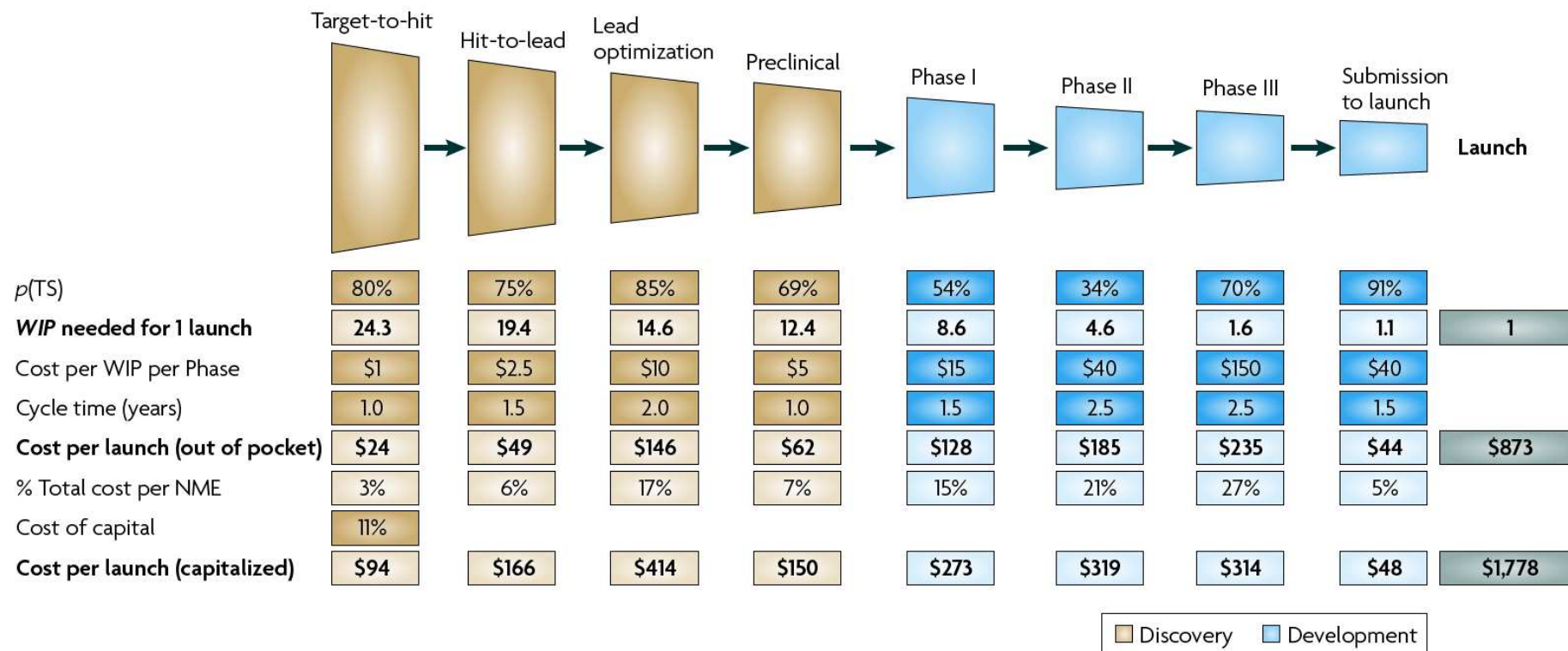
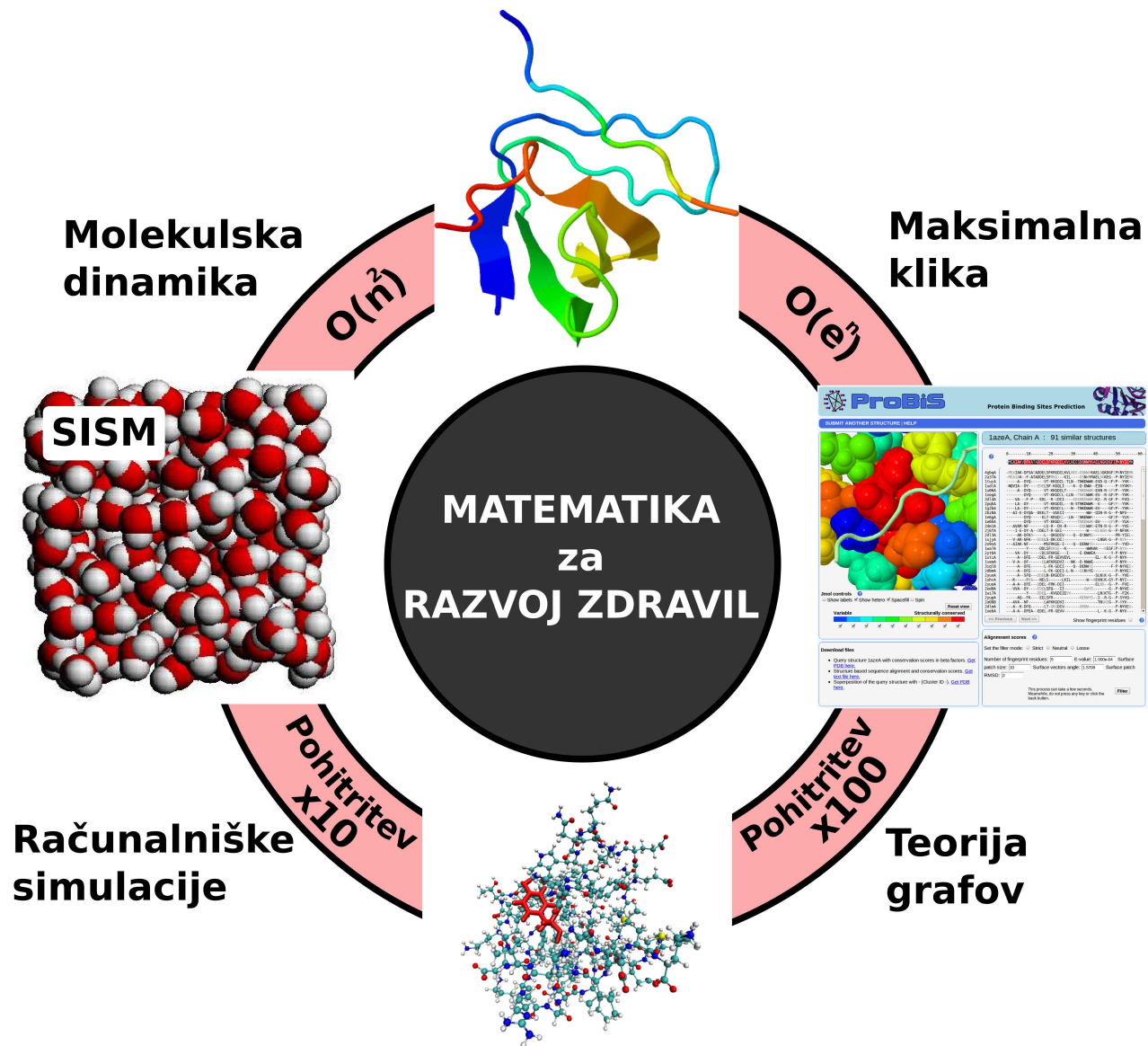


Figure 2 | **R&D model yielding costs to successfully discover and develop a single new molecular entity.** The model defines the distinct phases of drug discovery and development from the initial stage of target-to-hit to the final stage, launch.

Vir: Paul et al. Nature Reviews Drug Discovery 9, 203-214 (2010)

CILJ

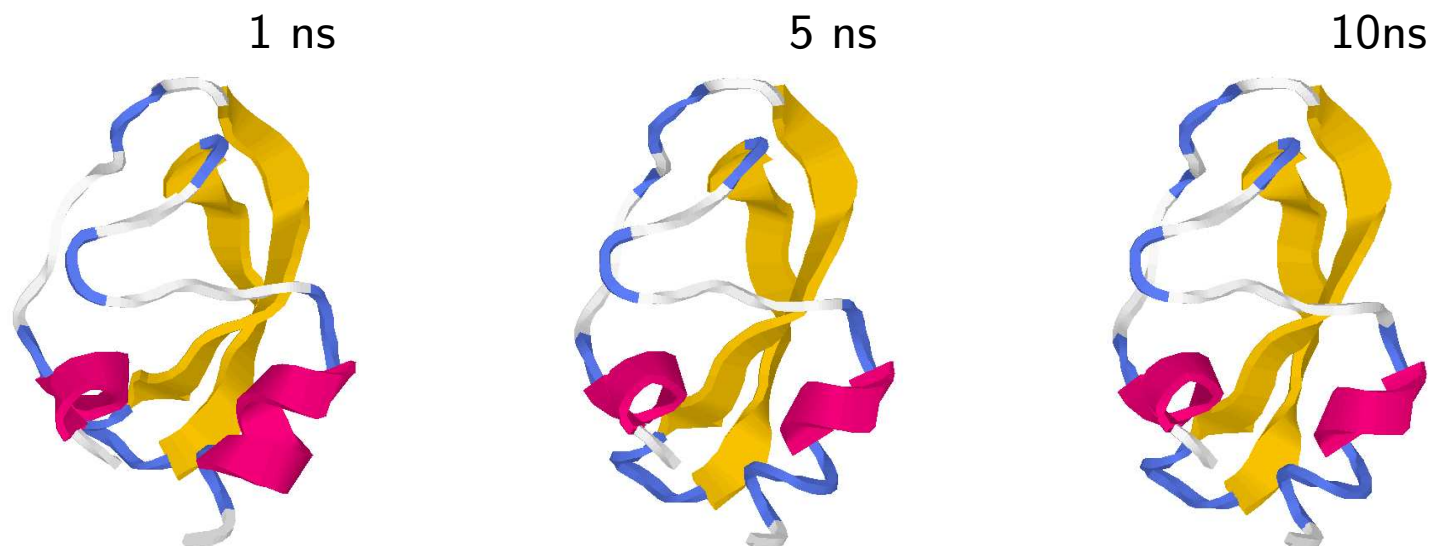


Oris - I. Del

Predstavitev razvoja naših novih metod za molekularno modeliranje bioloških makromolekul. Predvsem:

- Metode za določitev vibracijskih frekvenc in normalnih načinov gibanja velikih sistemov
- Split Integration Symplectic Method, metoda za numerično reševanje enačb za simulacijo molekulske dinamike
- Distributed-Diagonal Force Decomposition Method, vzporedna metoda za simulacijo molekulske dinamike
- Force Decomposition Machine za hitro vzporedno računanje sil na osnovi novo razvite DDFD metode
- VRANA, vzporedene računalniške arhitekture

Harmonska analiza velikih sistemov



1. Bernard R. Brooks, Dušanka Janežič, Martin Karplus, "Harmonic Analysis of Large Systems. I. Methodology," *J. Comp. Chem.* 16, 1522–1542, **1995**.
2. Dušanka Janežič, Bernard R. Brooks, "Harmonic Analysis of Large Systems. II. Comparison of Different Protein Models," *J. Comp. Chem.* 16, 1543–1553, **1995**.
3. Dušanka Janežič, Richard M. Venable, Bernard R. Brooks, "Harmonic Analysis of Large Systems. III. Comparison with Molecular Dynamics," *J. Comp. Chem.* 16, 1554–1566, **1995**.

Metoda SISM

Hamiltonsko funkcijo razcepimo kot

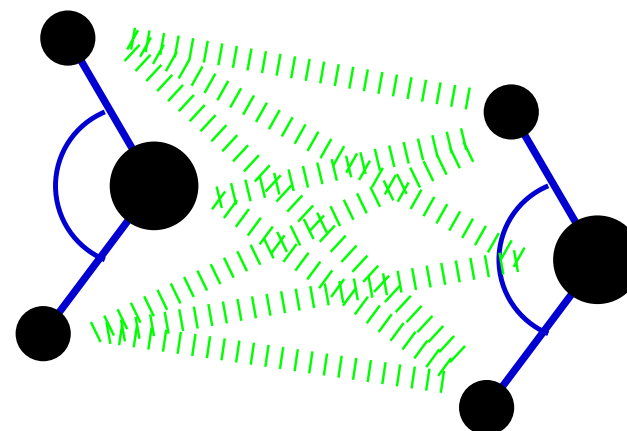
$$H = H_0 + H_r$$

in uporabimo približek

$$\boldsymbol{\eta}|_{t+\Delta t} = \exp\left(\frac{\Delta t}{2}\hat{L}_{H_0}\right) \exp(\Delta t\hat{L}_{H_r}) \exp\left(\frac{\Delta t}{2}\hat{L}_{H_0}\right) \boldsymbol{\eta}|_t + \mathcal{O}(\Delta t^3)$$

Δt je integracijski časovni korak

1. Dušanka Janežič, Matej Praprotnik, Franci Merzel, "Molecular Dynamics Integration and Molecular Vibrational Theory. I. New Symplectic Integrators" *J. Chem. Phys.* 122, 174101, **2005**.
2. Matej Praprotnik, Dušanka Janežič, "Molecular Dynamics Integration and Molecular Vibrational Theory. II. Simulation of Non-Linear Molecules" *J. Chem. Phys.* 122, 174102, **2005**.
3. Matej Praprotnik, Dušanka Janežič, "Molecular Dynamics Integration and Molecular Vibrational Theory. III. The IR Spectrum of Water", *J. Chem. Phys.* 122, 174103, **2005**.



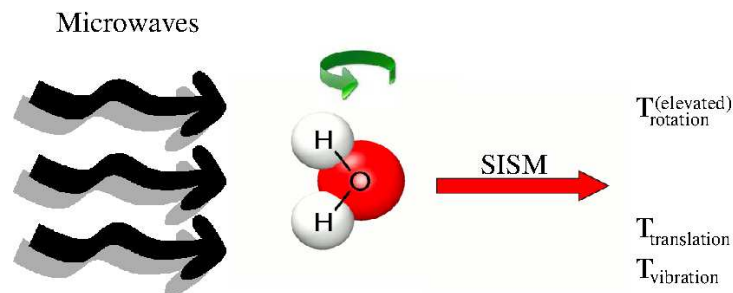
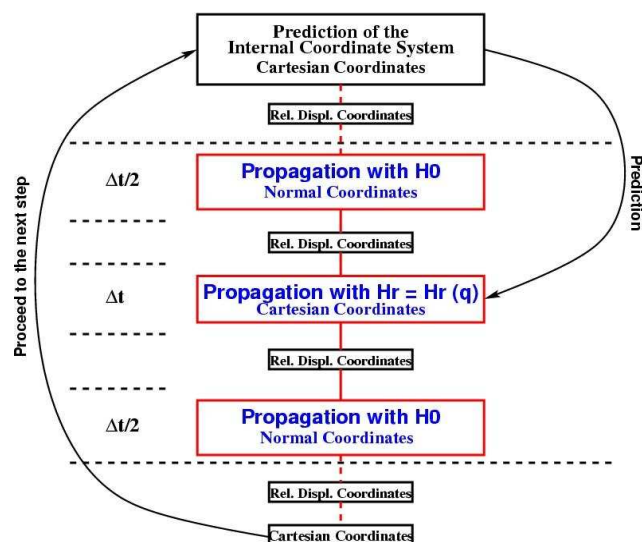
Vzporedna metoda SISM

Nadaljne izboljšave novo razvite metode SISM smo dosegli z njeno implementacijo na vzporednih računalnikih.

Vzporedna metoda SISM se v vzporednem načinu obnaša enako kot vzporedna leap-frog Verlet metoda: pohitritev dosežemo zaradi povečanja integracijskega koraka.

1. Urban Borštnik, Milan Hodošček, Dušanka Janežič, "Improving the performance of molecular dynamics simulations on parallel clusters", *J. Chem. Inf. Comput. Sci.*, 44, 359–364, **2004**.
2. Urban Borštnik, Milan Hodošček, Dušanka Janežič, "Fast Parallel Molecular Simulations", *Croat. Chem. Acta*, 78, 211–216, **2005**.

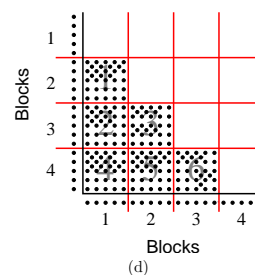
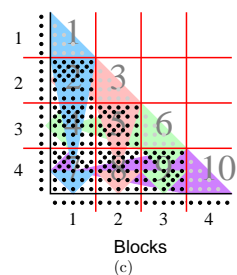
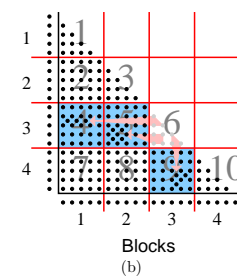
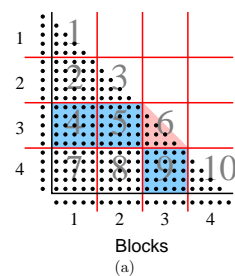
SISM za mikrovalovno katalizo



Urban Bren, Matej Praprotnik and Dušana Janežič, Rotational Motion and the Solvation Properties of Water - Implications for the use of Microwave Irradiation *JCP*, Submitted, 2012

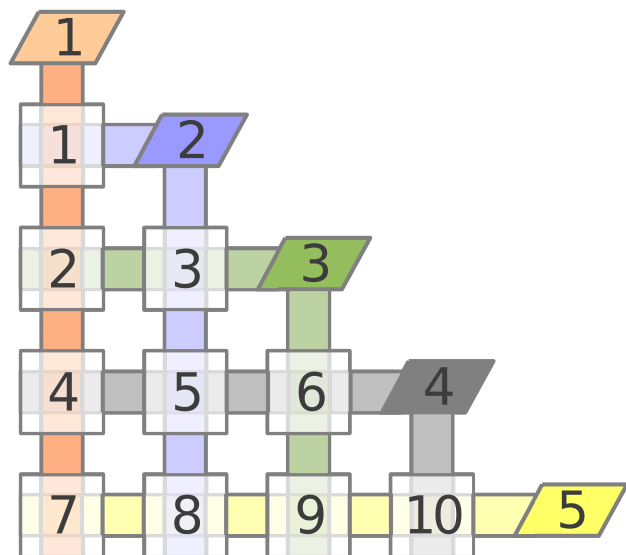
Distributed Diagonal Force Decomposition Metoda

- Izboljšana metoda porazdelitve sil za vzporedno računanje atomskih interakcij
- Uporablja manj procesorjev v danem bloku
- Ima manjše komunikacijske zahteve
- Ima dinamični load balancing



Force Decomposition Machine

- Zgradili smo specialno “force decomposition machine” za hitro vzporedno računanje sil na osnovi novo razvite Distributed Diagonal Force Decomposition metode



Urban Borštnik, Tim B. Miller, Bernard R. Brooks, Dušanka Janežič: Implementation of the Force Decomposition Machine for Molecular Dynamics Simulations, *Submitted, 2012.*

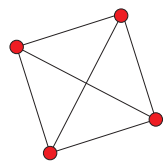
VRANA

VRANA (Vzporedni Računalnik za Akceleracijo Numeričnih Algoritmov)

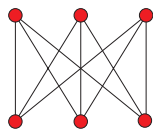


- * VRANA 1 (1998): 4×2 Intel Pentium II 400 MHz; Ring
- * VRANA 2 (1999): 16 Intel Pentium II 450 MHz; Torus
- * VRANA 3 (1999): 32 Intel Celeron 466 MHz; Torus
- * VRANA 4 (2000): 32 Athlon 700 MHz; Hypercube
- * VRANA 5 (2001): 16×2 AMD Athlon MP-1600+; Hierarchical Hypercube
- * VRANA 6 (2002): 8×2 AMD Athlon MP-1900+; Hierarchical Hypercube
- * VRANA 7 (2002): 2 MD-GRAPE II Computers; Gigabit Link
- * VRANA 8 (2003): 64×2 AMD Athlon MP-2200; Hierarchical Hypercube
- * VRANA 9 (2005): 64×2 AMD Opteron 242; Gigabit Switches
- VRANA 10 (2006): 37×2 AMD Dual-core Opteron 265; Gigabit Switches
- VRANA 11 (2007): 46×8 Intel XEON 1.9 GHz; Gigabit Switches
- VRANA 12 (2010): 77×8 Intel XEON 2.3 GHz; Gigabit Switches
- VRANA 13 (2011): $14 \times 16 + 12 \times 32$ AMD 2.0 GHz; Gigabit Switches

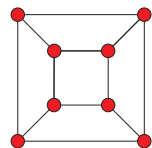
Vzporedne simulacije na hamiltonskih kubičnih grafih



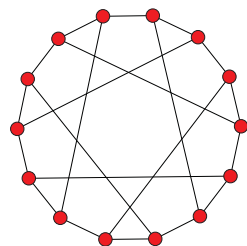
F4



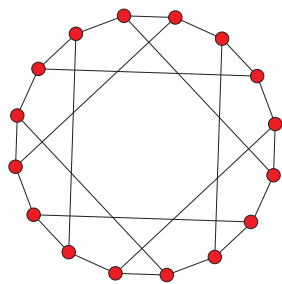
F6



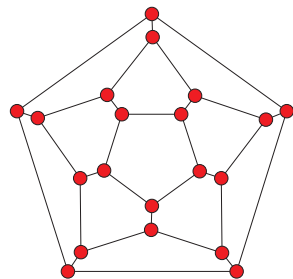
F8



F14



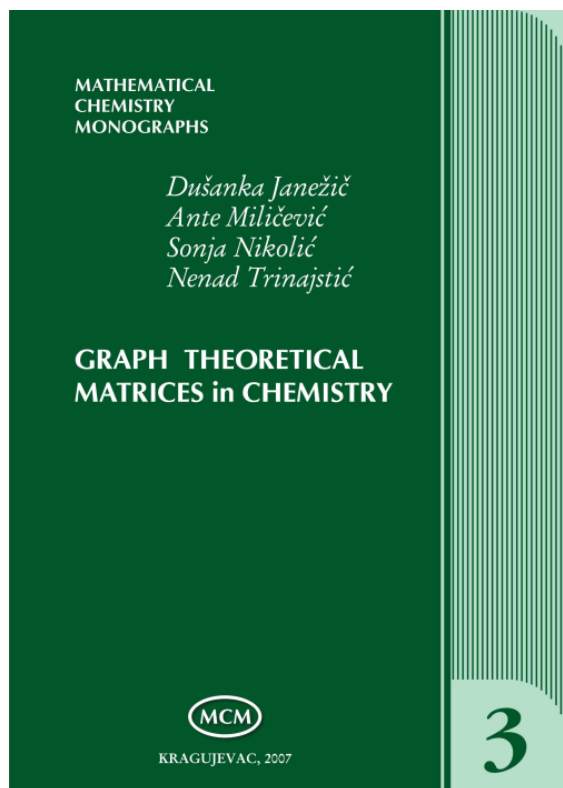
F16



F20A

Predstavili smo razred medsebojno povezanih računalniških mrež za vzporedno računanje simulacije MD na hamiltonskih kubičnih grafih. Analiza komunikacijskih poti pokaže, da so hamiltonski kubični grafi primerni kandidati za vzporedne računalniške topologije, ki omogočajo hitro komunikacijo in s tem hitrejšo vzporedno računanje simulacije MD.

Graf teoretične matrike v kemiji



Mathematical Chemistry Monographs, No. 3

Graph Theoretical Matrices in Chemistry

D. Janežič

A. Miličević

S. Nikolić

N. Trinajstić

Publisher: University of Kragujevac and
Faculty of Science Kragujevac, ki izdaja tudi revijo
MATCH (IF(2007) = 2.5)

2007, VI +195 pp. Hardcover

ISBN: 86-7828-071-9

Oris - II. Del

Predstavitev razvoja naših novih metod za molekularno modeliranje bioloških makromolekul. Predvsem:

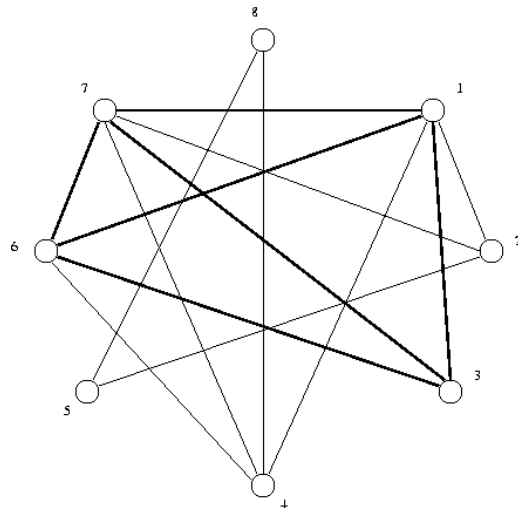
- LSA (Local Structural Alignment) - algoritem za napovedovanje proteinskih vezavnih mest s pomočjo lokalnih strukturnih podobnosti
- ProBiS (Protein Binding Sites) - algoritem za iskanje strukturno podobnih proteinskih vezavnih mest na osnovi lokalnih strukturnih podobnosti
- ProBiS (Protein Binding Sites) - spletni strežnik za iskanje strukturno podobnih proteinskih vezavnih mest

Problem maksimalne klike grafa

Razvili smo algoritem za iskanje maksimalne klike v neusmerjenem grafu, ki je do 10-krat hitrejši od primerljivih algoritmov.

Neusmerjeni graf $G=(V,E)$; V je množica vozlišč in je E množica povezav. Maksimalna klika je popolnoma povezan podgraf danega grafa z maksimalnim številom vozlišč.

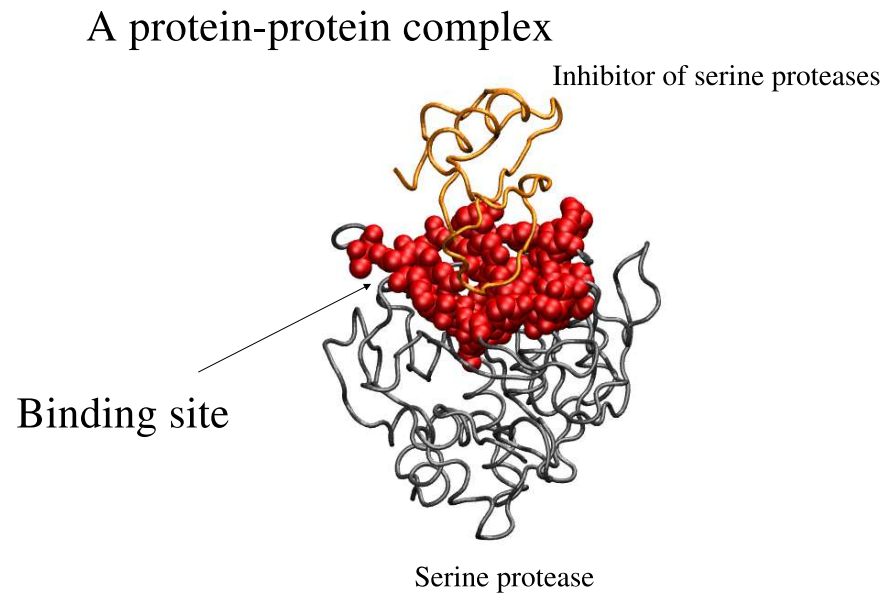
Uporabili smo ga za napovedovanje vezavnih mest na proteinih.



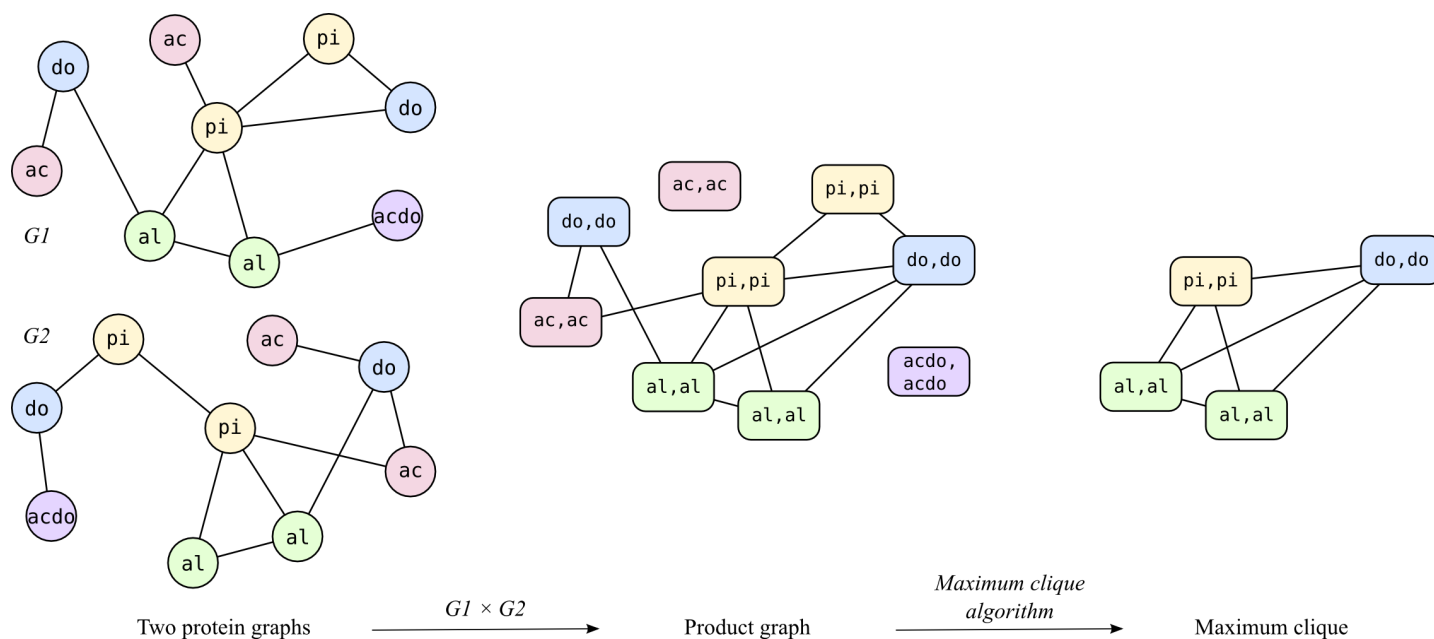
1. Janez Konc, Dušanka Janežič, "An Improved Branch and Bound Algorithm for the Maximum Clique Problem," *MATCH*, **58**, 569–590, **2007**.
2. Janez Konc, Dušanka Janežič, "A Branch and Bound Algorithm for Matching Protein Structures", *Lecture Notes in Computer Science*, **4432**, 399–406 **2007**.

Napovedovanje vezavnih mest na proteinih

Primer dveh proteinov, ki tvorita proteinski kompleks. Serin proteaza je obarvana sivo, inhibitor serin proteaze je obarvan oranžno. Vezavno mesto na sivem proteinu je obarvano rdeče.



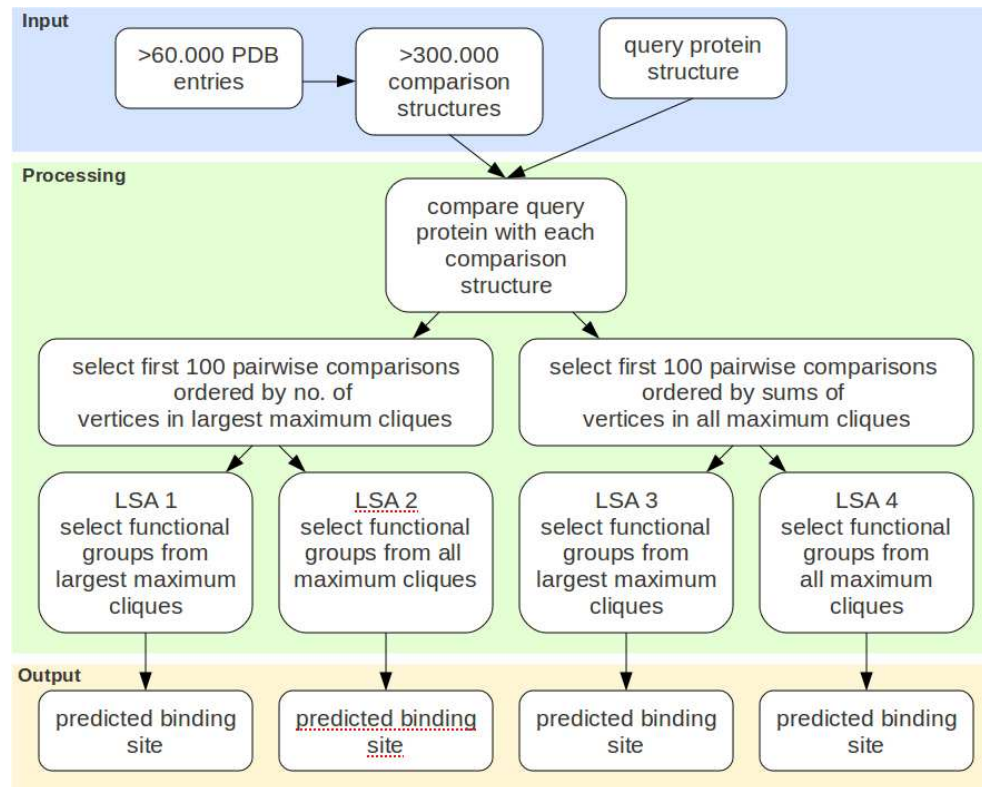
Maksimalna klika



Proces iskanja maksimalne klike v produktnem proteinskem grafu, dobljenem iz dveh proteinskih grafov $G1$ in $G2$. Funkcionalne skupine so označene z DO, AC, ACDO, PI in AL ter predstavljajo donor vodikove vezi, akceptor vodikove vezi, mešan tip, to je akceptor in donor vodikove vezi, aromatsko skupino in alifatsko skupino. Poiščemo maksimalno kliko v produktnem grafu, ki predstavlja največjo skupno podstrukturo v obeh proteinskih grafih.

Nejc Carl, Janez Konc, Blaž Vehar, Dušanka Janežič, "Protein binding site prediction by local structure alignment," *J. Chem. Inf. Model.*, 50, 1906–1913, **2010**.

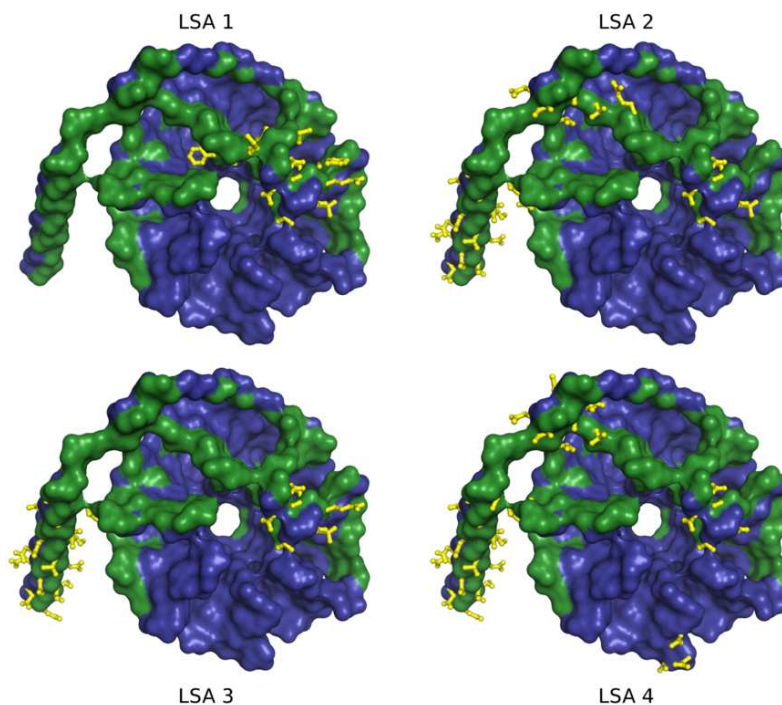
LSA Algoritem



Napovedovanje vezavnega mesta na testnem proteinu. Predstavljene so štiri variante LSA algoritma. Optimalna varianta, podčrtana rdeče, je LSA 2.

Nejc Carl, Janez Konc, Blaž Vehar, Dušanka Janežič, "Protein binding site prediction by local structure alignment," *J. Chem. Inf. Model.*, 50, 1906–1913, 2010.

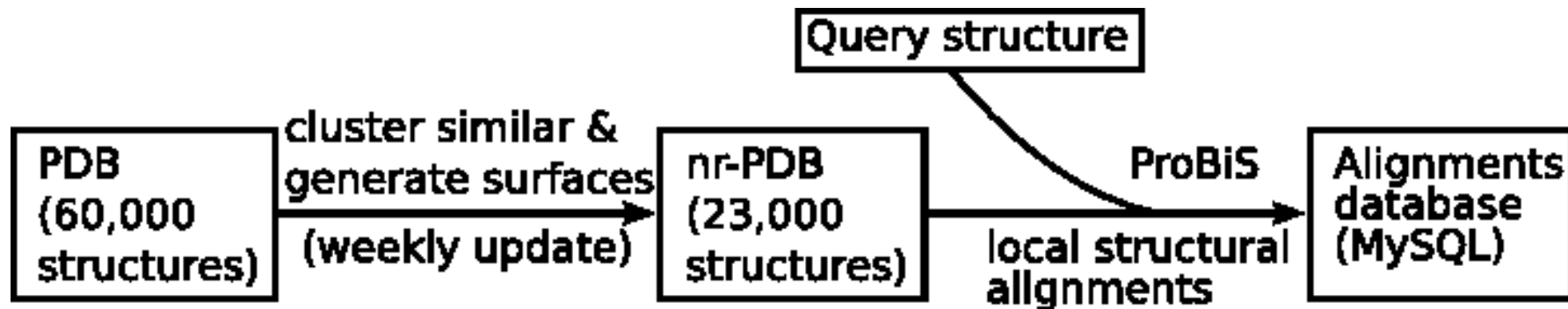
LSA Algoritem



Prikaz vezavnih mest napovedanih z vsako od štirih metod kombiniranja lokalnih strukturnih podobnosti - LSA 1-4 - na β podenoti heterotrimeru proteina G (PDB koda: 1got). Površina proteina je obarvana modro, kristalografsko določeno vezavno mesto, zeleno. Stranske verige aminokislin, ki so bile del napovedanega vezavnega mesta, rumeno.

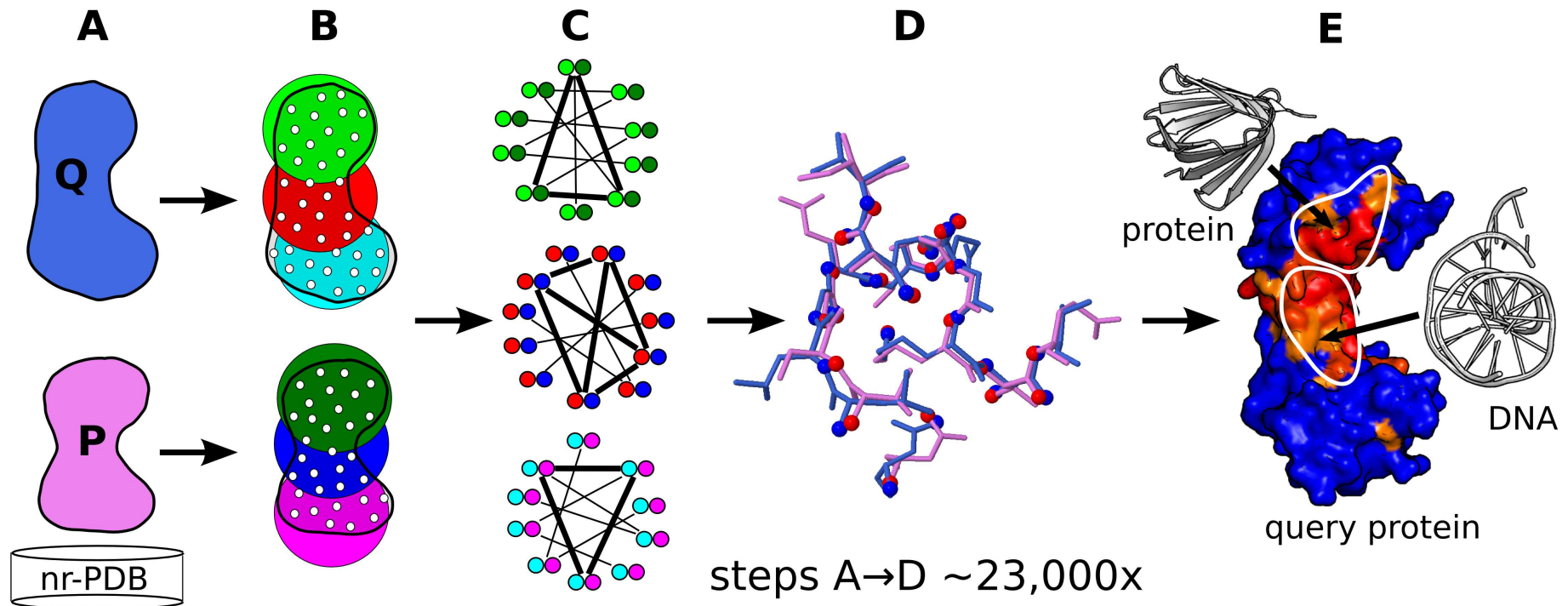
Nejc Carl, Janez Konc, Blaž Vehar, Dušanka Janežič, "Protein binding site prediction by local structure alignment," *J. Chem. Inf. Model.*, 50, 1906–1913, **2010**.

ProBiS - Protein Binding Sites



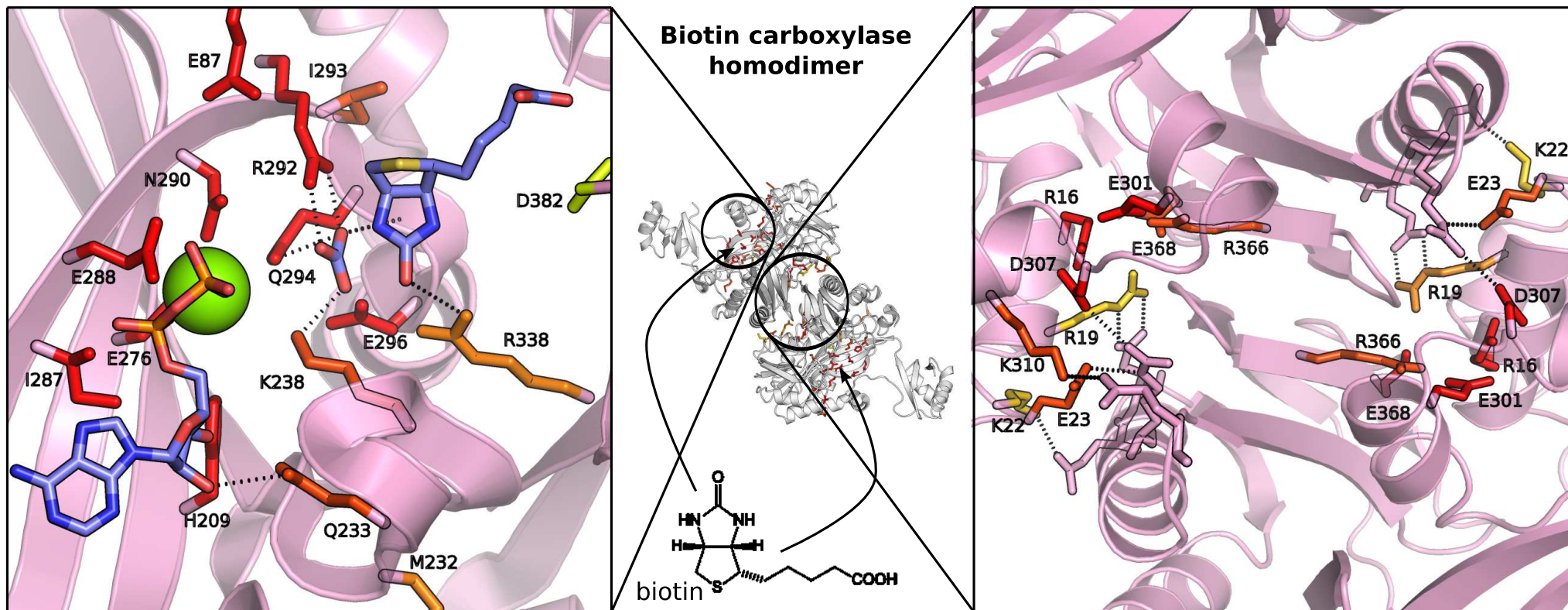
Shematska predstavitev priprave nr-PDB baze, konverzija proteinov v površinsko reprezentacijo in predstavitev ProBiS rezultatov v bazi (MySQL).

ProBiS Algoritem

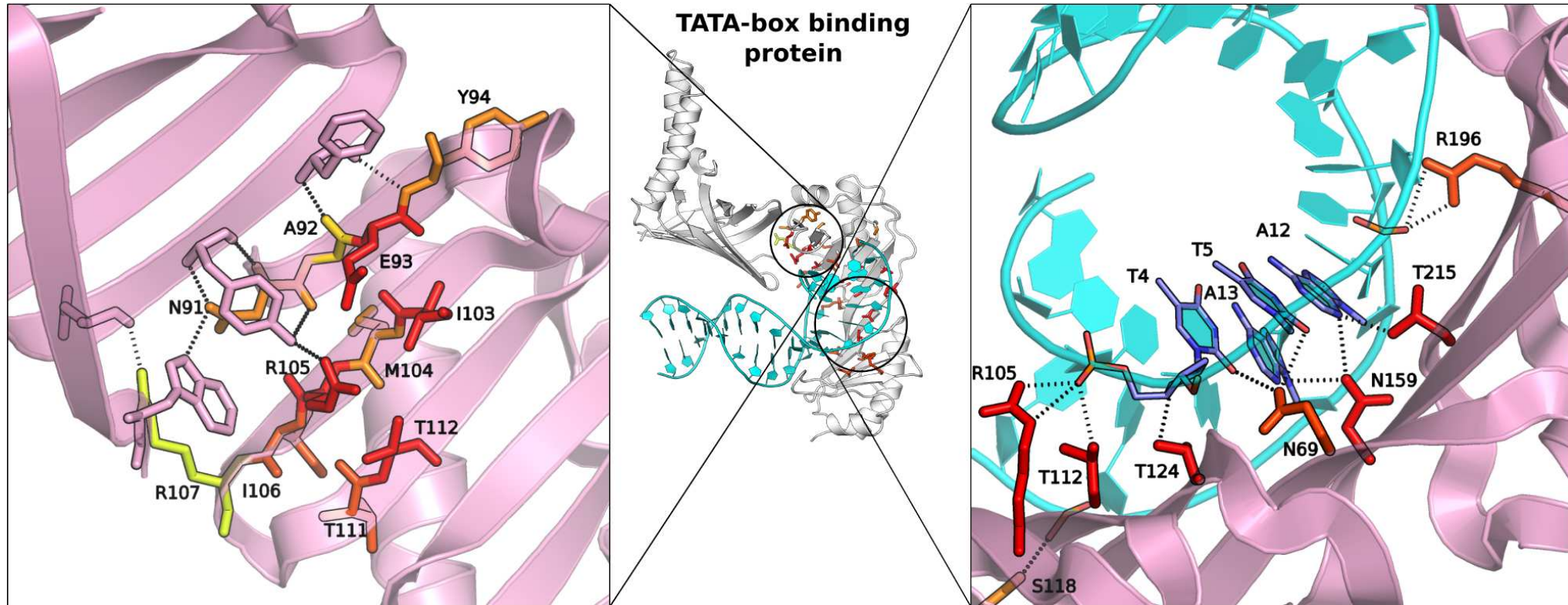


ProBiS algoritem se od drugih pristopov razlikuje po tem, da je povsem neodvisen od aminokislinskega zaporedja proteina in zvitja glavne verige.

ProBiS - Biotin Carboxylase Homodimer



ProBiS - TATA-box binding protein



ProBiS - Web Server : <http://probis.cmm.ki.si>

Input

The screenshot shows the ProBiS web server interface. At the top, the logo 'ProBiS' is displayed next to the title 'Protein Binding Sites Detection'. Below the title, a navigation bar contains links for 'BINDING SITES', 'PAIRWISE ALIGNMENT', 'EXAMPLES', 'GROUP HOME', and 'HELP'. The main content area is divided into several sections:

- New Features:** A section on the left with a blue header, containing a list of updates such as 'Structural alignments now have links to the UniProt database for easier functional annotation.'
- Frequently Asked Questions:** A section on the left with a blue header, containing a list of questions like 'Can I upload a protein structure?'
- Please Cite the Following Articles:** A section on the left with a blue header, containing a list of references.
- Define the query structure ...:** A central form with input fields for 'PDB ID' (containing '1all') and 'Chain ID(s)' (containing 'A'). A callout bubble points to this section with the text 'Define the query structure ...'. Below these fields is a checkbox for 'Alternatively, upload your own PDB file' which is checked.
- ... or upload one of your own.:** A callout bubble points to the 'Choose File' button in the 'Alternatively, upload your own PDB file' section with the text '... or upload one of your own.'.
- Submit Job:** A button at the bottom of the central form with a callout bubble pointing to it with the text 'Click to search the database of ~25,000 structures'.
- 3D Protein Structure:** A 3D ribbon diagram of a protein structure with a red surface representing the binding site. Labels include 'P-loop', 'GDP', and 'Asp196'. A legend below the structure indicates 'Structurally conserved' residues in red.
- Post a Comment:** A section on the right with a blue header, containing a text input field and a 'Post' button.

At the bottom of the page, the copyright notice reads 'ProBiS © 2009-2010 Janez Konc'.

Janez Konc, Dušana Janežič, ProBiS: a web server for detection of structurally similar protein binding sites. *Nucleic Acids Res.*, 38, W436–W440, 2010.

Run

The screenshot shows the ProBiS web interface. The main header includes the ProBiS logo and the text "Protein Binding Sites Detection" with a sub-note "As of Oct 17, 2010 your protein is compared with 26341 structures". The navigation bar contains links for "BINDING SITES | PAIRWISE ALIGNMENT | EXAMPLES | GROUP HOME | HELP".

The "Status of your ProBiS job" section displays a table with the following data:

JobId	JobType	Computer	Status	Time submitted	Action
Your job> 20101088381538	multiple	kavka.dyn	WORKING	10:37:20 20/10/10	Cancel Job

The "ProBiS in Brief" section shows "1 got, Chain A : 408 similar structures". It features a sequence alignment viewer with a highlighted "Input protein's sequence color-coded by structural conservation scores" and a "Click to see structural alignment" button. A detailed view of "Alignment No. 1" is shown, including PDB ID: 1s2t, Chain ID: A, Aligned Vertices: 40, E-value: 0.2689e-16, and RMSD: 1.2 Å.

The left sidebar contains sections for "New Features", "Frequently Asked Questions", and "Please Cite the Following Articles". The bottom footer reads "ProBiS © 2009-2010 Janez Konc".

Janez Konc, Dušana Janežič, ProBiS: a web server for detection of structurally similar protein binding sites. *Nucleic Acids Res.*, **38**, W436–W440, 2010.

Output

The screenshot displays the ProBiS web interface for protein binding site detection. Key features and callouts include:

- Site 2 : protein-protein**: A 3D ribbon representation of a protein structure with a binding site highlighted in orange and green.
- Site 1 : small-ligand**: A 3D ball-and-stick model of a small molecule ligand bound to a protein site.
- Ligands**: A callout pointing to the small-ligand model.
- Conservation coded query structure**: A callout pointing to the orange and green highlighted regions in the protein structure.
- Fingerprint residues**: A callout pointing to a sequence alignment table showing conserved residues across multiple structures.
- Click to see aligned sites**: A callout pointing to a specific entry in the alignment table.
- Structurally aligned residues**: A callout pointing to a section of the alignment table.
- Alignment scores define the similarity threshold**: A callout pointing to the filter settings at the bottom, including E-value and RMSD.
- Download results as text files**: A callout pointing to the download options at the bottom left.
- Locally Aligned Site 1**: A callout pointing to a detailed view of the small-ligand binding site.
- Locally Aligned Site 2**: A callout pointing to a detailed view of the protein-protein binding site.

Janez Konc, Dušanka Janežič, ProBiS: a web server for detection of structurally similar protein binding sites. *Nucleic Acids Res.*, 38, W436–W440, 2010.

ProBiS Link: RCSB PDB & CCL

ProBiS strežnik (<http://probis.cmm.ki.si>) je bil na povabilo avtorjev PDB baze (Protein Data Bank, <http://www.rcsb.org>) uvrščen na listo orodij za analizo proteinskih struktur na RCSB Protein Data Bank spletni strani:

http://www.rcsb.org/pdb/static.dop?general_information/web_links/structure_classification.html

Tu so na enem mestu zbrani najbolj uspešni programi, ki se uporabljajo za klasifikacijo novih, še neopredeljenih proteinov, predvsem tistih, iz projektov strukturne genomike.


Zaradi izjemne odmevnosti RCSB spletne strani, so na povabilo CCL (Computational Chemistry List) spletne strani, web server ProBiS uvrstili tudi na seznam računalniških orodij za analizo proteinov:

<http://www.ccl.net/chemistry/links/software/index.shtml>.

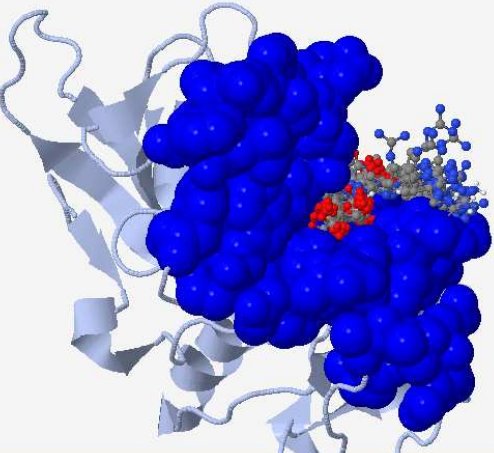
ProBiS - 2012 Web Server

- Hitrejše računanje
- Vnaprej izračunani rezultati
- Izboljšan uporabniški vmesnik
- Web programska orodja
- Metodološke izboljšave

ProBiS - Ligands - Web Server

 **ProBiS** ligands Protein Binding Sites Detection
As of Mar 13, 2011 your protein is compared with 27406 structures

SUBMIT ANOTHER STRUCTURE | HELP ProBiS requires Java...




jmol

Binding Sites ■ Proteins ■ Nucleic acids ■ Small molecules ■ Ions

[Reset View](#) [Download PDB File Containing Viewed Structures](#)

Molecules in the Jmol Viewer (left mouse-click to expand)

	Colored mesh structure (asymmetric unit and biological assemblies)	1	N/A	N/A
---	--	---	-----	-----

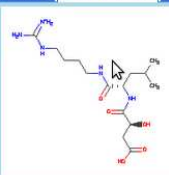
3KSE, chain A : 64 similar structures

Alignments **Binding Sites & Ligands**

Proteins **Nucleic Acids** **Small Molecules** Ions

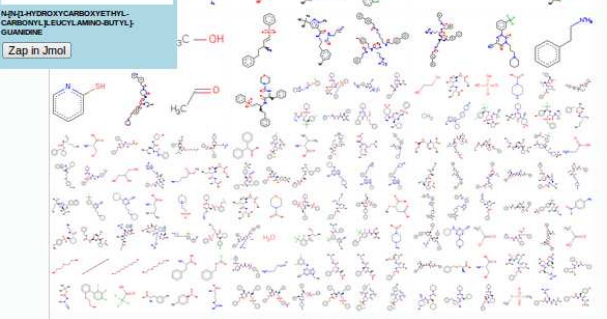
Ligands

[Back to Bind Sites](#)



N-(2-HYDROXYCARBOXYETHYL)-CARBOXYL-L-EUCYLAMINO-BUTYL-L-GUANINE

[Zap in Jmol](#)



Recalculate the Page With a Different Set of Parameters ?

ProBiS - Ligands - Web Server

The screenshot displays the ProBiS Ligands web server interface. At the top left is the ProBiS logo, and at the top right is the text "Protein Binding Sites Detection" with a sub-note "As of Mar 13, 2011 your protein is compared with 27406 structures". A navigation bar contains "SUBMIT ANOTHER STRUCTURE | HELP" and "ProBiS requires Java...".

The main content area is divided into two panels. The left panel shows a 3D molecular model of a protein structure with various components highlighted in blue, yellow, and red. Below the model is a legend: "Binding Sites" (red), "Proteins" (grey), "Nucleic acids" (green), "Small molecules" (blue), and "Ions" (yellow). A "Jmol" viewer label is present. Below the legend are buttons for "Reset View" and "Download PDB File Containing Viewed Structures".

The right panel is titled "3KSE, chain A : 64 similar structures". It features tabs for "Alignments", "Binding Sites & Ligands", "Proteins", "Nucleic Acids", "Small Molecules", and "Ions". Under the "Ligands" section, there is a "Back to Binding Sites" link. A list of ligands is shown, including Cl^- , Zn^{+2} , Cd^{+2} , and Hg^{+2} . A "ZINC ION" entry is highlighted with a "Zap in Jmol" button. At the bottom of the right panel is a link: "Recalculate the Page With a Different Set of Parameters ?".

At the very bottom, a section titled "Molecules in the Jmol Viewer" (left mouse-click to expand) shows a small thumbnail and the text "Colored new structure (asymmetric unit and biological assemblies)" followed by a table with columns for ID, Name, and other details, with "1" in the first column and "N/A" in the others.

ProBiS - Ligands - Web Server

The screenshot displays the ProBiS Ligands web server interface. At the top, the logo "ProBiS ligands" is on the left, and "Protein Binding Sites Detection" is on the right, with a sub-note "As of Mar 09, 2011 your protein is compared with 27406 structures". Below the header, there are navigation links: "SUBMIT ANOTHER STRUCTURE | HELP" and "ProBiS requires Java...".

The main content area is divided into two columns. The left column features a 3D molecular model of a protein structure with red spheres representing binding sites. Below the model, there are controls for "Binding Sites" (Proteins, Nucleic acids, Small molecules) and buttons for "Reset View" and "Download PDB File Containing Viewed Structures".

The right column is titled "1YTF, chain A : 44 similar structures". It has tabs for "Alignments" and "Binding Sites & Ligands". Under "Binding Sites & Ligands", there are sub-tabs for "Proteins", "Nucleic Acids", "Small Molecules", and "Ions". The "Ligands" section includes a "Back to Binding Sites" link and a grid of protein-ligand complexes. One complex is highlighted with a "Zap in Jmol" button.

At the bottom of the right column, there is a section titled "Recalculate the Page With a Different Set of Parameters ?". It includes a "Set the filter mode:" section with radio buttons for "Strict", "Neutral", "Loose", and "Other". Below this are input fields for "Number of fingerprint residues" (set to 2), "E-value" (set to 0.0001), "Surface patch size" (set to 10), "Surface vectors angle" (set to 1.5708), and "Surface patch RMSD" (set to 2). A "Recalculate!" button is at the bottom right of this section.

At the bottom left of the main content area, there is a "Molecules in the Jmol Viewer" section with the instruction "(left mouse-click to expand)". It lists three molecules:

- Colored query structure (asymmetric unit and biological assemblies) with a count of 1 and N/A for other metrics.
- General transcription factor lib with a count of 5 and "Hide all" and "X" icons.
- Protein (transcription factor IIA - toa2 subunit) with a count of 1 and "Hide all" and "X" icons.

ProBiS - Ligands - Web Server

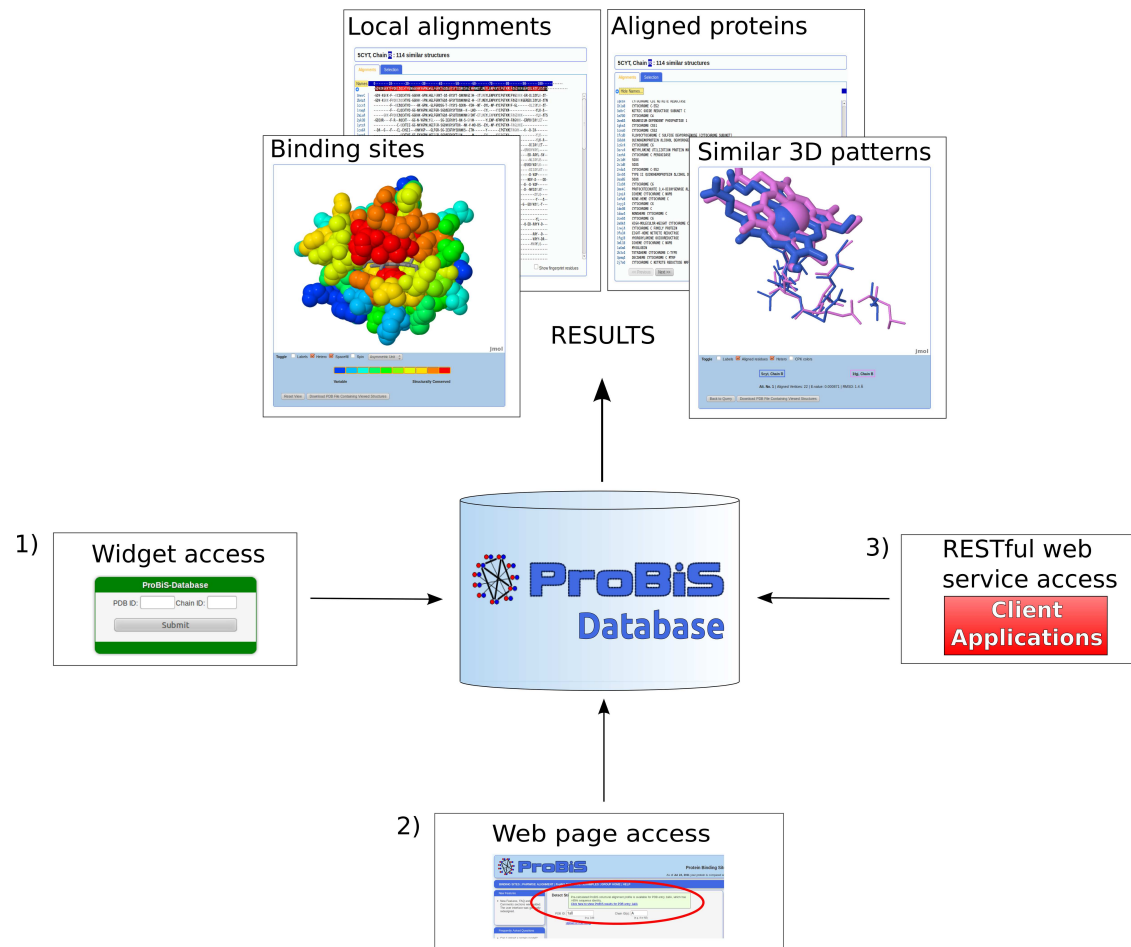
The screenshot displays the ProBiS Ligands web server interface. At the top, the logo "ProBiS ligands" is visible, along with the text "Protein Binding Sites Detection" and "As of Mar 09, 2011 your protein is compared with 27406 structures". Below the header, there are navigation links: "SUBMIT ANOTHER STRUCTURE | HELP" and "ProBiS requires Java...".

The main content area is divided into several sections:

- Left Panel:** A 3D molecular model of the protein structure 1YTF, chain A, with binding sites highlighted in red and green. A legend at the bottom indicates: Binding Sites (red), Proteins (grey), Nucleic acids (green), Small molecules (blue), and Ions (yellow).
- Right Panel:** A sidebar titled "1YTF, chain A : 44 similar structures". It includes tabs for "Alignments", "Binding Sites & Ligands", "Proteins", "Nucleic Acids", "Small Molecules", and "Ions". Under "Binding Sites", there are "Jmol Options" (Subtract nucleic acid..., View all nucleic acid..., Reset View) and "Download" (Binding sites residues). A "Resize By" section allows filtering by the number of ligands or residues. A "Jmol" viewer shows a detailed view of the binding site with a "View in Jmol" and "Ligands" button.
- Bottom Left:** A section titled "Molecules in the Jmol Viewer" with a table listing molecules and their counts.
- Bottom Right:** A section titled "Recalculate the Page With a Different Set of Parameters ?" with a "Set the filter mode:" section (Strict, Neutral, Loose, Other) and input fields for "Number of fingerprint residues", "E-value", "Surface patch size", "Surface vectors angle", and "Surface patch RMSD". A "Recalculate!" button is present.

Molecule	Count	Hide all
Colored query structure (asymmetric unit and biological assemblies)	1	N/A
General transcription factor lib	5	Hide all
Protein (transcription factor IIA - TOA2 subunit)	1	Hide all

ProBiS-Database



ProBiS-Database

ProBiS - Database of Protein Local Structural Similarity Profiles - Chromium

tyr.cmm.ki.si/beta/unstable/newbin/

ProBiS database
Protein Binding Sites Detection
As of Nov 26, 2011 your protein is compared with 29318 structures

e.g., PDB ID Search [HOME](#) | [HELP](#)

Introduction

- If you are new to ProBiS-Database, you can watch the introductory video available here.

Citation

- Konc.J., Cesnik,T., Trykowska Konc.J., Penca.M., Janezic.D. ProBiS-Database: Pre-calculated Binding Site Similarities and Local Pairwise Alignments of PDB Structures. *J. Chem. Inf. Mod.*, **submitted**.

Related Citations

- Konc.J. and Janezic.D. ProBiS algorithm for detection of structurally similar protein binding sites by local structural alignment. *Bioinformatics* 2010, **26**, 1160-1168.
- Konc.J. and Janezic.D. ProBiS: A web server for detection of structurally similar protein binding sites. *Nucleic Acids Res.* 2010, **38**, W436-W440.
- Konc.J. and Janezic.D. Protein-protein binding-sites prediction by protein surface structure conservation. *J. Chem. Inf. Mod.*, 2007, **47**, 940-944.
- Konc.J. and Janezic.D. An improved branch and bound algorithm for the maximum clique problem. *MATCH Commun. Math. Comput. Chem.*, 2007, **58**, 569-590.

ProBiS-Database Access

ProBiS-Database is a repository for structurally similar protein binding sites analysis of the proteins of known structures in the Protein Data Bank (PDB). Structures of each of the non-redundant PDB entries, currently **29318** of them, are locally structurally aligned to all other proteins in this database, using ProBiS local structural alignment algorithm. Non-redundancy to > 95% sequence identical structures ensures that all the structural variability in the PDB is thoroughly covered. The structural similarity scores of each amino acid position in the alignment is calculated.

The ProBiS-Database Widget

The ProBiS-Database Widget provides access to the local structural similarity profile for a protein chain. You can try the fully functioning example below!

Widget:

ProBiS-Database

PDB ID: Chain

ID:

Usage:

To embed in your own website, copy/paste the following line to your HTML code.

```
<script type="text/javascript" src="http://tyr.cmm.ki.si/beta/unstable/newbin/pw/?width=150px&title-color=#f00&body-color=whitesmoke"></script>
```

Options:

The ProBiS-Database Widget is highly customizable to best fit within your site. There are a number of options you specify to customize the widget. You can omit any of these options, and the widget will use default values.

- width** - Specify the width of the widget (ex. 150px). The default width is 280px.
- title-color** - Specify the color of the title and borders in html hex form (ex. #faa). The default is orange.
- body-color** - Specify the color of the body in html hex form (ex. whitesmoke). The default is whitesmoke.

ProBiS-Database in Brief

[click on the slideshow to see static picture]

Mg2+ binding site

Structurally conserved residues (red) correspond with a binding site.

Contact

Your suggestions, questions, comments, or bug reports will help us to improve this site!

Name:

Comment:

The ProBiS-Database RESTful Web Service Interface

The ProBiS-Database features RESTful (REpresentational State Transfer) Web Services to make our data easily accessible from your scripts. ProBiS-Database contains data only for non-redundant PDB chains. This means that you have to use representative non-redundant PDB & Chain IDs as queries (see examples below).

Janez Konc, Tomo Česnik, Joanna Trykowska Konc, Matej Penca and Dušana Janežič, ProBiS-Database: Pre-calculated Binding Site Similarities and Local Pairwise Alignments of PDB Structures *JCIM*, Submitted, 2011.

ProBiS-Database

ProBiS - SCYT.R Local Structural Similarity Profile - Chromium

tyr.cmm.ki.si/beta/unstable/newbin/browse.php?job_id=SCYT.R

5cyt Search HOME | HELP

5CYT, Chain R : 155 similar structures

Rank	Alignments	Chain	Name	Hot	Z-Score
32	View	3mk7.B	Cytochrome c oxidase, ccb3-type, subunit		2.26
33	View	451c.A	Cytochrome c551		2.23
34	View	1w2l.A	Cytochrome oxidase subunit ii		2.20
35	View	2d0w.B	Cytochrome cI		2.19
36	View	1pp9.Q	Cytochrome c1, heme protein, mitochondri	★	2.17
37	View	2zbo.K	Cytochrome c6		2.15
38	View	3oa8.D	Soxx		2.15
39	View	3l70.D	Mitochondrial cytochrome c1, heme protei		2.15
40	View	1c6s.A	Cytochrome c6		2.13
41	View	3dr0.A	Cytochrome c6		2.12
42	View	1zrt.D	Cytochrome c1		2.08
43	View	3dml.A	Cytochrome c6		2.07
44	View	3cp5.A	Cytochrome c		2.03
45	View	1a8c.A	Ferrocycytochrome c-552		2.02
46	View	1h32.A	Diheme cytochrome c		2.01
47	View	2gc7.D	Cytochrome c-I		2.00
48	View	2zxy.A	Cytochrome c552		1.99
49	View	1cor.A	Cytochrome c551		1.97
50	View	1mz4.A	Cytochrome c550		1.96
51	View	1dvv.A	Cytochrome c551		1.95
52	View	3cu4.A	Cytochrome c family protein		1.90
53	View	2xts.B	Cytochrome		1.87
54	View	1gu2.B	Cytochrome c*	★	1.86
55	View	1f1c.A	Cytochrome c549		1.85
56	View	1y1q.A	Quinohemoprotein alcohol dehydrogenase	★	1.85
57	View	1nir.A	Nitrite reductase		1.85
58	View	2c8s.A	Cytochrome c-I		1.84
59	View	1wve.D	4-cresol dehydrogenase [hydroxylating] cyt		1.84
60	View	3b47.A	Methyl-accepting chemotaxis protein		1.84
61	View	3dp5.A	Cytochrome c family protein		1.80
62	View	1c75.A	Cytochrome c-553		1.77
63	View	2qjy.E	Cytochrome c1	★	1.75
64	View	3mk7.M	Cytochrome c oxidase, ccb3-type, subunit		1.74
65	View	1c52.A	Cytochrome-c552		1.73
66	View	3cx5.D	Cytochrome c1, heme protein, mitochondri	★	1.73

Jmol

Toggle Labels Hetero Spacefill Spin Asymmetric Unit

Variable Structurally Conserved

Reset View Download PDB File Containing Viewed Structures

Local structural similarity web page for cytochrome c query protein

ProBiS-Database

ProBiS - 5CYT.R Local Structural Similarity Profile - Chromium

tyr.cmm.ki.si/beta/unstable/newbin/browse.php?job_id=5CYT.R

(a)

Jmol

Toggle Labels Aligned residues Hetero CPK colors

5CYT, Chain R 1c13, Chain M

All. No. 1 | Aligned Vertices: 22 | E-value: 0.0000018 | RMSD: 2.7 Å

Back to Query Download PDB File Containing Viewed Structures

(b)

5CYT, Chain R: 155 similar structures

Similar Proteins Details Selection

Query Protein Aligned Protein

Name: CYTOCHROME C Name: PROTEIN (CYTOCHROME F)
PDB ID: 5CYT PDB ID: 1c13
Chain ID: R Chain ID: M
PFAM: PF00034 PFAM: PF01333

Select Alignment:

- Alignment No. 1

Alignment No. 1

Back to top

Query Protein			Aligned Protein		
Res. Name	Res. ID	Chain ID	Res. Name	Res. ID	Chain ID
CYS	14	R	CYS	21	M
ALA	15	R	ALA	22	M
GLN	16	R	ASN	23	M
CYS	17	R	CYS	24	M
HIS	18	R	HIS	25	M
PHE	19	R	PHE	236	M
VAL	11	R	ARG	18	M
VAL	28	R	ILE	160	M

View in Jmol Download Alignment as XML Download PDB of Superimposition

Z-Score: 1.23
Alignment Score: 4.68
E-value: 1.8E-6
Vertices: 22
RMSD: 2.7
Surf. Vector Angle: 1.14

Legend:

- Structurally equivalent and similar physical-chemical properties.
- Structurally not equivalent, but similar physical-chemical properties.

Superimposition:

To calculate the coordinates superimposition, use the following transformation on aligned protein:

$$X2' = (-0.89) * X2 + (-0.13) * Y2 + (-0.44) * Z2 + (53.09)$$

$$Y2' = (-0.08) * X2 + (-0.9) * Y2 + (0.44) * Z2 + (46.55)$$

$$Z2' = (-0.45) * X2 + (0.43) * Y2 + (0.79) * Z2 + (54.71)$$

Similar binding sites in protein structures of different Pfam families - cytochrome

ProBiS-Database

1TO2, Chain E : 36 similar structures

Similar Proteins | Details | Selection

Previous 29/36 Next

ProBiS found 1 local structural alignment of 1TO2.E with 1AZZ.A.

Query Protein **Aligned Protein**

Name: SUBTILISIN BPN' Name: COLLAGENASE
PDB ID: 1TO2 PDB ID: 1AZZ
Chain ID: E Chain ID: A
Pfam: PF00082 Pfam: PF00089

Select Alignment:

- Alignment No. 1

Alignment No. 1

Back to top

Query Protein				Aligned Protein			
Res. Name	Res. ID	Chain ID		Res. Name	Res. ID	Chain ID	
GLY	166	E	...	GLY	223	A	
TYR	167	E	...	TYR	224	A	
PRO	168	E	...	PRO	225	A	
VAL	203	E	...	VAL	81	A	
SER	204	E	...	THR	82	A	
ILE	205	E	...	ILE	83	A	
GLN	206	E	...	GLN	84	A	
SER	207	E	...	SER	85	A	
THR	208	E	...	THR	86	A	
ASP	32	E	---	ASP	102	A	
HIS	64	E	---	HIS	57	A	
LEU	96	E	---	ILE	99	A	
ALA	152	E	---	THR	213	A	
ASN	155	E	---	CYS	191	A	
SER	221	E	---	SER	195	A	
MET	222	E	---	CYS	42	A	

View in Jmol | Download Alignment as XML | Download PDB of Superimposition

Z-Score: 1.7
Alignment Score: 5.73
E-value: 7.78E-11
Vertices: 20
RMSD: 1.5
Surf. Vector. Angle: 1.35

Toggle Labels Aligned residues Hetero CPK colors

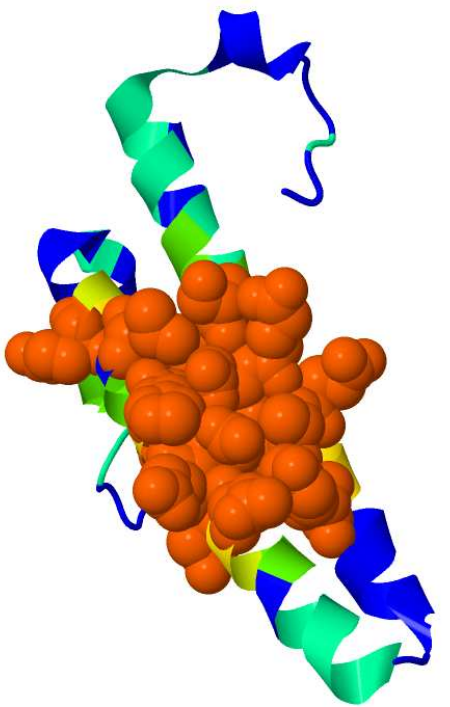
1to2, Chain E | 1azz, Chain A

Ali. No. 1 | Aligned Vertices: 20 | E-value: 7.78e-11 | RMSD: 1.5 Å

Back to Query | Download PDB File Containing Viewed Structures

Detection of Convergent Evolution in PDB structures - subtilisin and trypsin

ProBiS-Database



3K6C, Chain 1 : 75 similar structures

Rank	Alignments	Chain	Name	Hot	Z-Score
1	View	1jm0.C	Protein (four-helix bundle model)		2.75
2	View	1y47.B	Dueferri (df2)		2.69
3	View	2cih.A	Ferritin heavy chain		2.54
4	View	3a68.B	Ferritin-4, chloroplatic		2.39
5	View	2fkz.G	Bacterioferritin		2.29
6	View	3gvy.A	Bacterioferritin		2.26
7	View	1jgc.A	Bacterioferritin		2.25
8	View	1s3q.G	Ferritin		2.10
9	View	2vzb.B	Putative bacterioferritin-related protein		1.99
10	View	2hbj.A	Exosome complex exonuclease rrp6		1.99
11	View	1tjl.J	Dnak suppressor protein		1.96
12	View	2y3q.E	Bacterioferritin		1.96
13	View	3g7c.A	Occludin		1.96
14	View	3p8c.B	Nck-associated protein 1		1.93
15	View	2qqy.A	Sigma b operon		1.92
16	View	2a06.S	Ubiquinol-cytochrome c reductase comple		1.85
17	View	3k29.A	Putative uncharacterized protein		1.84
18	View	2ic6.A	Nucleocapsid protein		1.76
19	View	2huj.A	Lin2004 protein		1.74
20	View	1srr.A	Sporulation response regulatory protein		1.74
21	View	3kit.C	Vimentin		1.73
22	View	1i1q.A	Anthranilate synthase component i		1.72
23	View	3oii.B	Estrogen receptor beta		1.71
24	View	2j69.B	Bacterial dynamin-like protein		1.70
25	View	3ti2.A	Malate dehydrogenase		1.69
26	View	3cpm.A	Peptide deformylase, chloroplast		1.68
27	View	1cii.A	Colicin Ia		1.68
28	View	3lpx.A	Dna gyrase, a subunit		1.66
29	View	2q7t.A	Protein traI		1.65
30	View	1tf5.A	Preprotein translocase seca subunit		1.64
31	View	1v8f.B	Pantoate-beta-alanine ligase		1.64
32	View	115w.B	Maltodextrin phosphorylase		1.63
33	View	2nnw.A	Nop5/nop56 related protein		1.63
34	View	2ysu.B	Colicin-e2		1.58

Toggle Labels Hetero Spacefill Spin Asymmetric Unit

Variable Structurally Conserved

Reset View Download PDB File Containing Viewed Structures

Functional annotation of uncharacterized proteins - putative binding site

ProBiS-Database

3K6c, Chain H : 75 similar structures

Similar Proteins **Details** Selection

Query Protein Aligned Protein

Name: UNCHARACTERIZED PROTEIN NE0167 Name: BACTERIOFERRITIN
PDB ID: 3K6C PDB ID: 2FKZ
Chain ID: H Chain ID: G
Pfam: Pfam: PF00210

Select Alignment:

- Alignment No. 1
- Alignment No. 2
- Alignment No. 3
- Alignment No. 4

Alignment No. 1

Back to top

Query Protein			Aligned Protein			
Res. Name	Res. ID	Chain ID		Res. Name	Res. ID	Chain ID
SER	26	H	—	ILE	14	G
LEU	27	H	—	LEU	15	G
GLU	29	H	—	ASN	17	G
GLU	30	H	—	GLU	18	G
LEU	31	H	—	LEU	19	G
ALA	33	H	—	ALA	21	G
VAL	34	H	—	ILE	22	G
ASP	35	H	—	ASN	23	G
TYR	37	H	—	TYR	25	G
HIS	55	H	—	HIS	46	G
ASN	56	H	—	GLU	47	G
ASP	58	H	—	TYR	45	G
GLU	59	H	—	ASP	50	G
GLU	60	H	—	GLU	51	G
GLU	62	H	—	LYS	53	G
HIS	63	H	—	HIS	54	G
ALA	64	H	—	ALA	55	G
LEU	67	H	—	LEU	58	G
LEU	68	H	—	ILE	59	G

View in Jmol Z-Score: 2.29
Download Alignment as XML Alignment Score: 7.02
Download PDB of Superimposition E-value: 1.04E-9
Vertices: 40
RMSD: 0.7
Surf. Vector. Angle: 1.14

Toggle Labels Aligned residues Hetero CPK colors

3k6c, Chain H 2fkz, Chain G

Ali. No. 1 | Aligned Vertices: 40 | E-value: 1.04e-9 | RMSD: 0.7 Å


Back to Query Download PDB File Containing Viewed Structures

Functional annotation of uncharacterized proteins - superimposition of putative binding site in query protein and known Fe²⁺

Uporaba ProBiS orodij za razvoj novih zdravil


- Hemagglutinin
- ProBiS in proteinske točkovne mutacije
- Sodelovanje s farmacevtsko tovarno LEK

ProBiS - Hemagglutinin primer

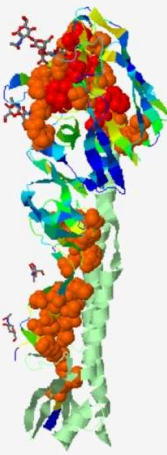


ProBiS

Protein Binding Sites Detection
As of Dec 12, 2010 your protein is compared with 26807 structures



[SUBMIT ANOTHER STRUCTURE](#) | [HELP](#) ProBiS requires Java...



Jmol


Jmol controls

Show labels Show hetero Spacefill Spin

Asymmetric Unit

[Reset view](#)

Variable Structurally conserved



Download files

- Query structure 3HTP_AB with conservation scores in beta factors. [Get PDB here.](#)
- Structure based sequence alignment and conservation scores. [Get text file here.](#)
- Superposition of the query structure with - (Cluster ID -). [Get PDB here.](#)

3HTP_AB, Chain A : 17 similar structures

```
-----70-----80-----90-----100-----110-----120-----
/AGWLGNPEDLLLTANSWSYIETSNSENGTCYRGEFDYEEELREQLSSVSSFERFEIFFK
3htcA /AGWLGNPEDLLLTANANSYIETSNSE-GTGEFDYEEELREQLSSVSSFERFEIFFK
1rv0J /AGWLGNPEDLLLT-SWSYIVETSNSDNGTGDYFDYEEELREQLSSVSNNEKFEIFFK
2wrhH /AGWLGNPEDLLLTANSWSY--EITSNENGTGEF-DYEEELREQLSSVSSFERFEIFFK
1rvxG /AGWLGNPEDCD-LLP--SWSYIVETNNSENGTGDYFDYEEELREQLSSVSSFERFEIFFK
3qbnA /AGWLGNPEDLLLTASW-SY-VEITSNSE--TGDYFDYEEELREQLSSVSNFEK--F--
3l2gA /AGWLGNPEDCE--L--SWSYIVETSNSD-GTGDYFDYEEELREQLSSVSS--RFEIFFK
3ku3A /AGWLGNPEDRLLS--NSYIME--D-LR--F-DYEEELK-----K-----
2wrfg /AGWLGNPEDCD--NSYIME--NGL--F-DYEEELK-----F-DYEEELK-----
1j3mA /AGWLGNP--NSYIME--NGL--F-DYEEELK-----F-DYEEELK-----
3qbnA /AGWLGNP-CD--I-V--NSYIVE--N--GTGDYFDYEEELK-----F-DYEEELK-----
3mlhB /AGWLGNPEDCE--ASWSYIVET--I--GTGDYFDYEEELREQLSSVSS--RFEIFFK
1jedA --G--GNPSCDLL--NSYIVER-DA-NMG--G-----R-QIFF--
1ha0A --LLGDPEPCV--DERS-A--N--D-DY-S-RS-----R-QIFF--
1tr1A -----PQCD-----DERS-A--V--KFWN-----R-QIFF--
3m5jE -----QPQCD-----DERS-A--V--KFWN-----R-QIFF--
3eykA -----ER--R--T--D-DYQS-RS-LSS-----R-QIFF--
2rftA -----G-PKC-----DERS-A--V--KFWN-----R-QIFF--
```

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Filter structures

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Number of fingerprint residues: E-value:

Surface patch size: Surface vectors angle:

Surface patch RMSD:

This process can take a few seconds. Meanwhile, do not press any key or click the back button. [Filter](#)

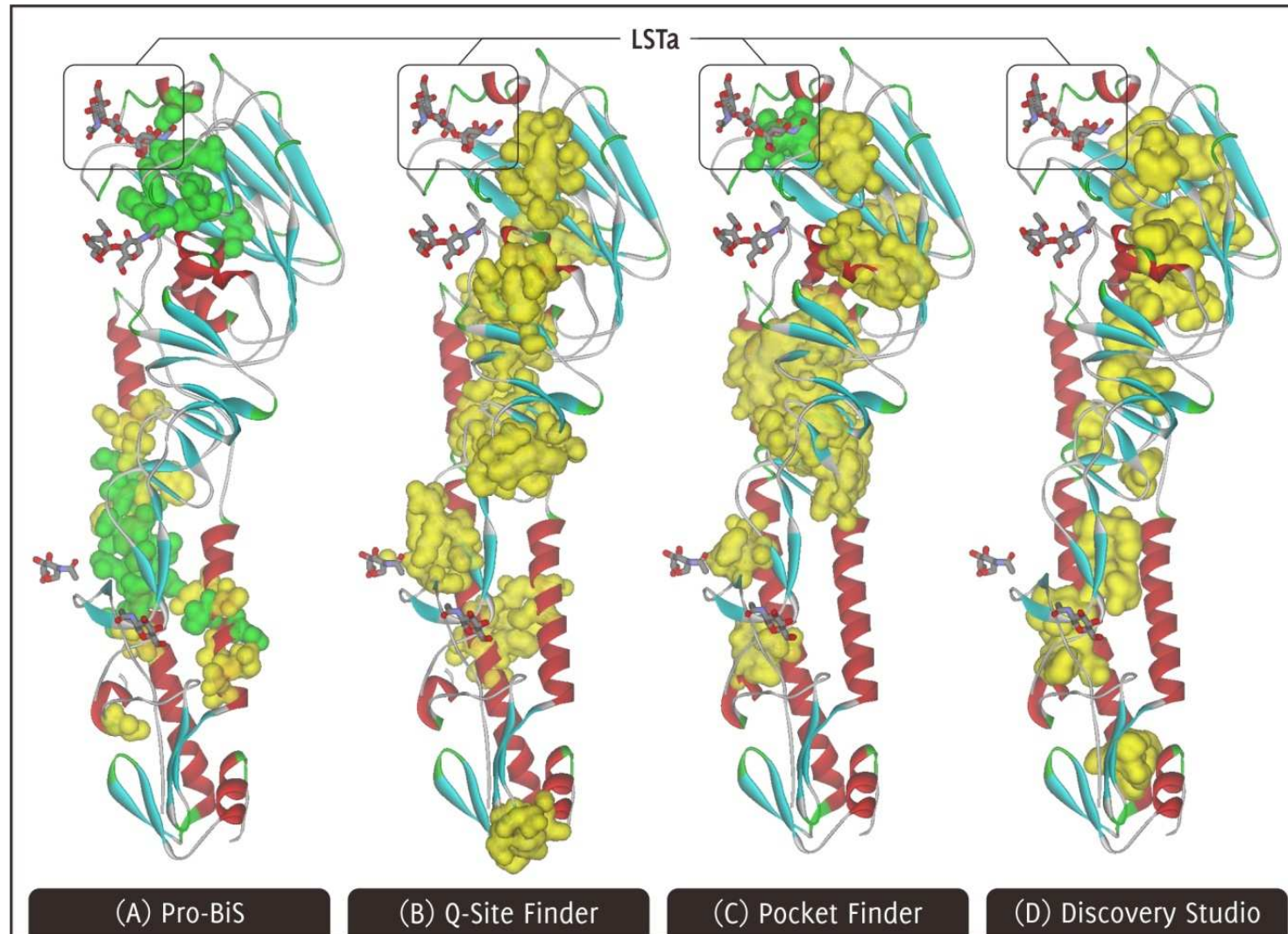
ProBiS © 2009 Janez Konc

ProBiS - Hemagglutinin primer

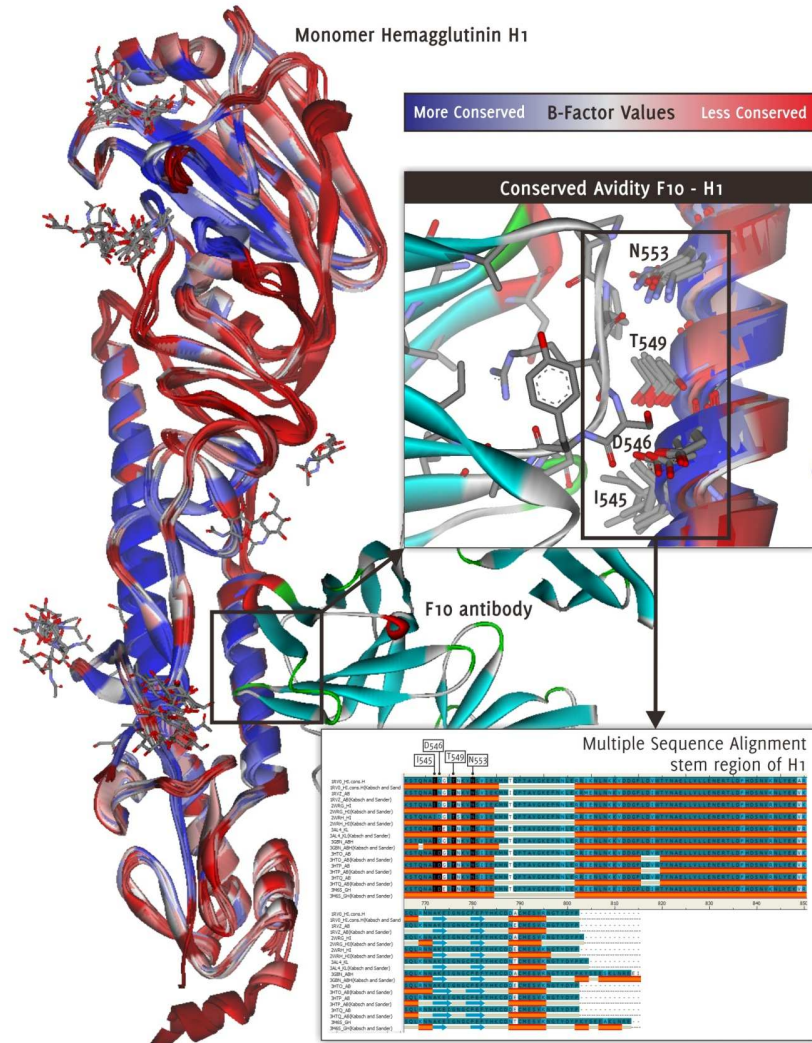
Table 1. PDB structures used in conserved residues prediction using ProBiS.

Subtype	PDB ID_CHAIN	Strain	Complexed with
H1	3AL4_KL	A/CALIFORNIA/04/2009(H1N1)	-
	3M6S_GH	A/DARWIN/2001/2009(H1N1)	-
	2WRG_HI	A/BREVISSION/1/1918(H1N1)	-
	2WRH_HI	A/MALLARD/ALBERTA/35/1976(H1N1)	-
	3HTO_AB	A/WDK/JX/12416/2005(H1N1)	-
	3HTP_AB	A/WDK/JX/12416/2005(H1N1)	LSTa
	3HTQ_AB	A/WDK/JX/12416/2005(H1N1)	LSTc
	3GBN_AB	A/SOUTH CAROLINA/1/1918(H1N1)	Fab CR6261
	1RVZ_AB	A/PUERTORICO/8/34(H1N1)	LSTc
	1RV0_HI	A/SWINE/IOWA/30	LSTa
H2	2WR0_B	UNIDENTIFIED INFLUENZA VIRUS	-
	2WR7_B	A/SINGAPORE/1/1957(H2N2)	-
	2WRF_F	A/CHICKEN/POTSDAM/4705/1984(H2N2)	LSTc
	3KU3_AB	A/JAPAN/305/1957 (Q226, G228)	-
	3KU5_AB	A/JAPAN/305/1957 (L226, S228)	-
H3	1EO8_A	A/AICHI/68 (H3N2)	Fab BH151
	2VIU_A	A/X-31(H3N2)	-
H5	1JSM_A	A/DUCK/SINGAPORE/3/97	-
	2FK0_A	A/VIETNAM/1203/2004(H5N1)	-
	3FKU_A	Not mentioned	Neutralizing antibody F10
	3GBM	A/VIET NAM/1203/2004(H5N1)	Fab CR6261
H7	1TI8_A	A-TURKEY-ITALY-02	-
	3M5H_A	A/ENVIRONMENT/NEW YORK/30732-1/2005(H7N2)	-
H9	1JSD_A	A/SWINE/HONG KONG/9/98	-

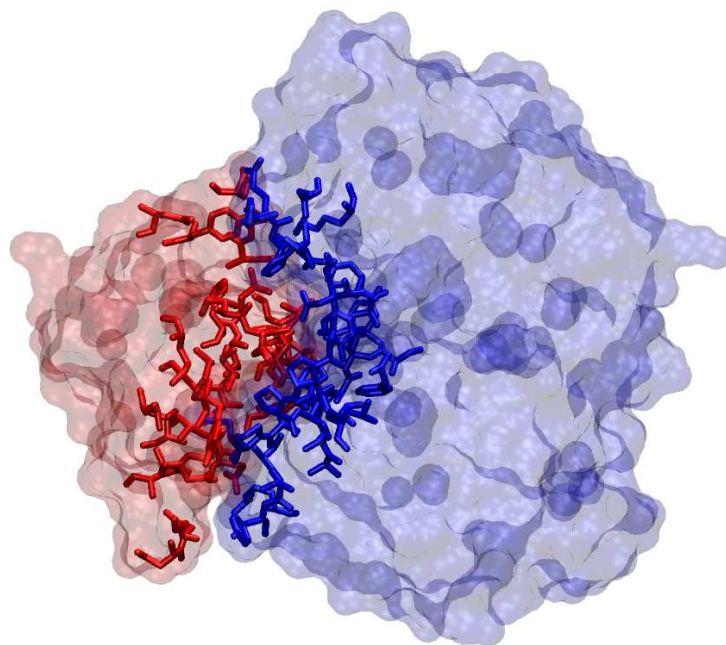
ProBiS - Hemagglutinin primer



ProBiS - Hemagglutinin primer

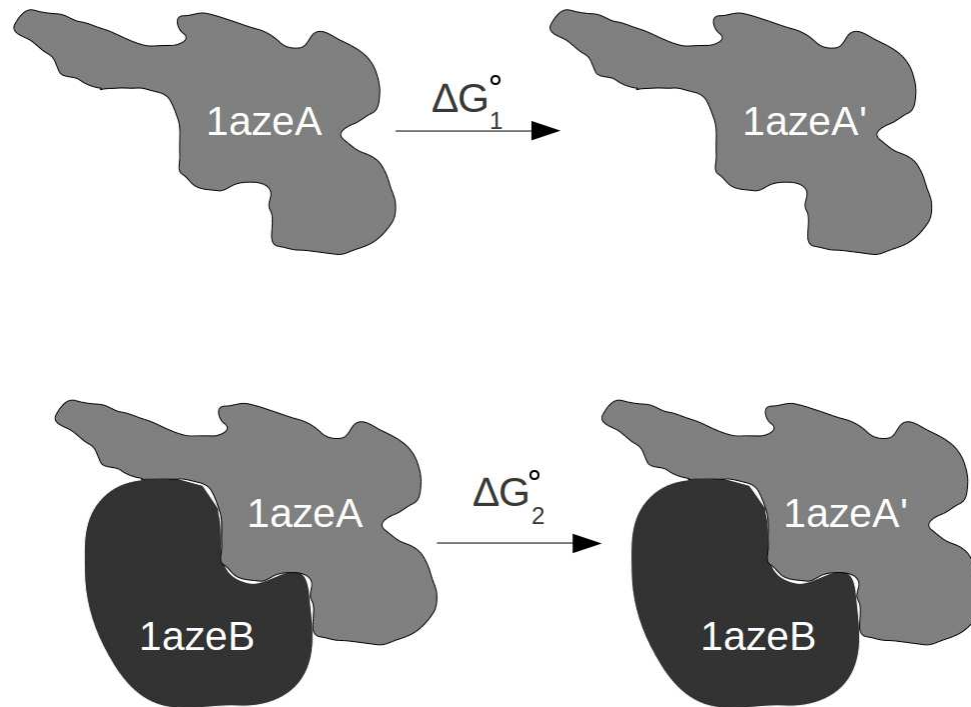


ProBiS in proteinske točkovne mutacije



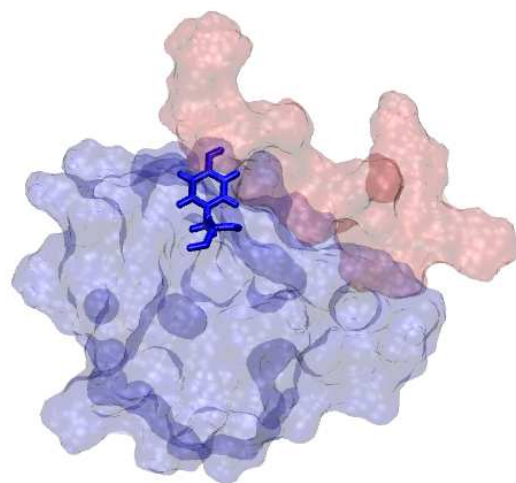
Nejc Carl, Milan Hodošek, Janez Konc, Bernard R. Brooks, and Dušanka Janežič, Interaction Free Energy Calculation of Protein point Mutations, *In preparation*.

ProBiS in proteinske točkovne mutacije



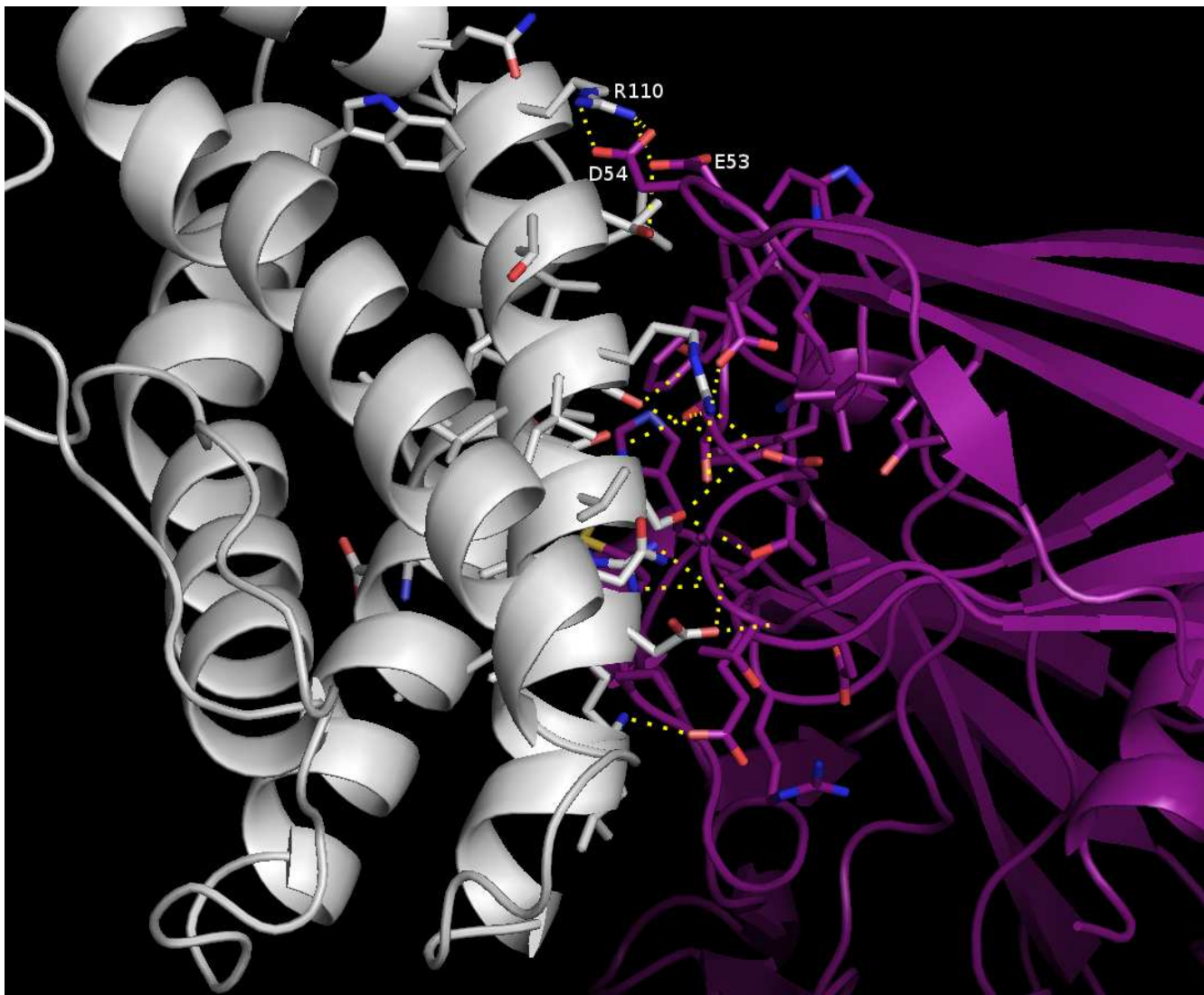
Nejc Carl, Milan Hodošek, Janez Konc, Bernard R. Brooks, and Dušanka Janežič, Interaction Free Energy Calculation of Protein point Mutations, *In preparation*.

ProBiS in proteinske točkovne mutacije



Nejc Carl, Milan Hodošek, Janez Konc, Bernard R. Brooks, and Dušanka Janežič, Interaction Free Energy Calculation of Protein point Mutations, *In preparation*.

Sodelovanje s farmacevtsko tovarno LEK

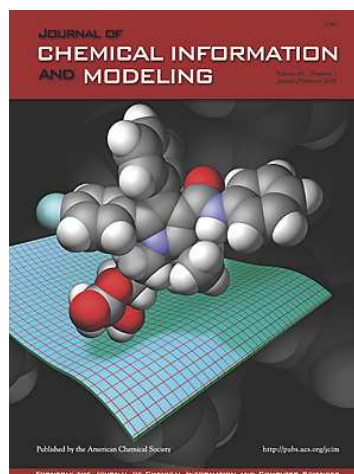


Prihodnost

- Še naprej ostati med vodilnimi strokovnjaki v svetu na področju razvoja molekularnega modeliranja.
- Še naprej prenašati svoje znanje na mlajše generacije preko raziskovalnih in pedagoških aktivnosti - mentorstev.
- Še naprej uspešno poučevati na Univerzi na Primorskem, Fakulteti za matematiko, naravoslovje in informacijske tehnologije.

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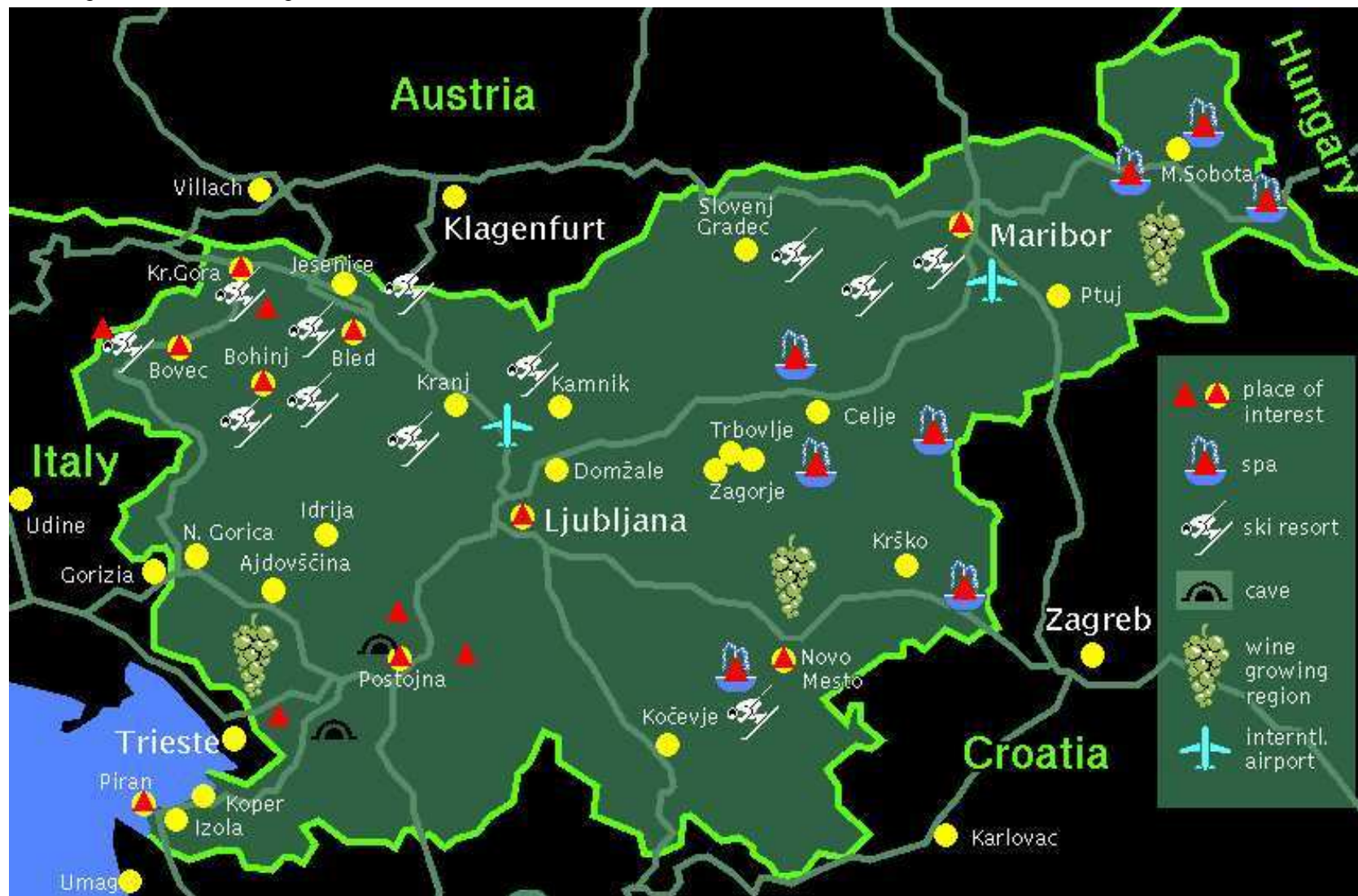
Zahvale

Gredo predvsem

- moji ljubeči družini
- mojim izjemnim sodelavcem
- mojim odličnim prijateljem
- in prijaznim financerjem

ter vsem vam za izkazano pozornost.

Zemljevid Slovenije



ProBiS na You Tube