



KATEDRA FYZIKÁLNÍ CHEMIE
UNIVERZITY PALACKÉHO V OLOMOUCI



INSTITUTE OF MOLECULAR AND
TRANSLATIONAL MEDICINE



7th Advanced in Silico Drug Design workshop 2024

Olomouc

29th January – 1st February 2024



Book of Abstracts

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7ADD workshop (29.1.2024 – 1.2.2024) is focused on using in silico tools and approaches in drug design. We cover both structure-based drug design (molecular docking, molecular dynamics, structural bioinformatics tools) and ligand-based drug design (QSAR, pharmacophores, deep learning) with lectures and on-hand tutorials.

Welcome to Olomouc!

Karel Berka and Pavlo Polishchuk

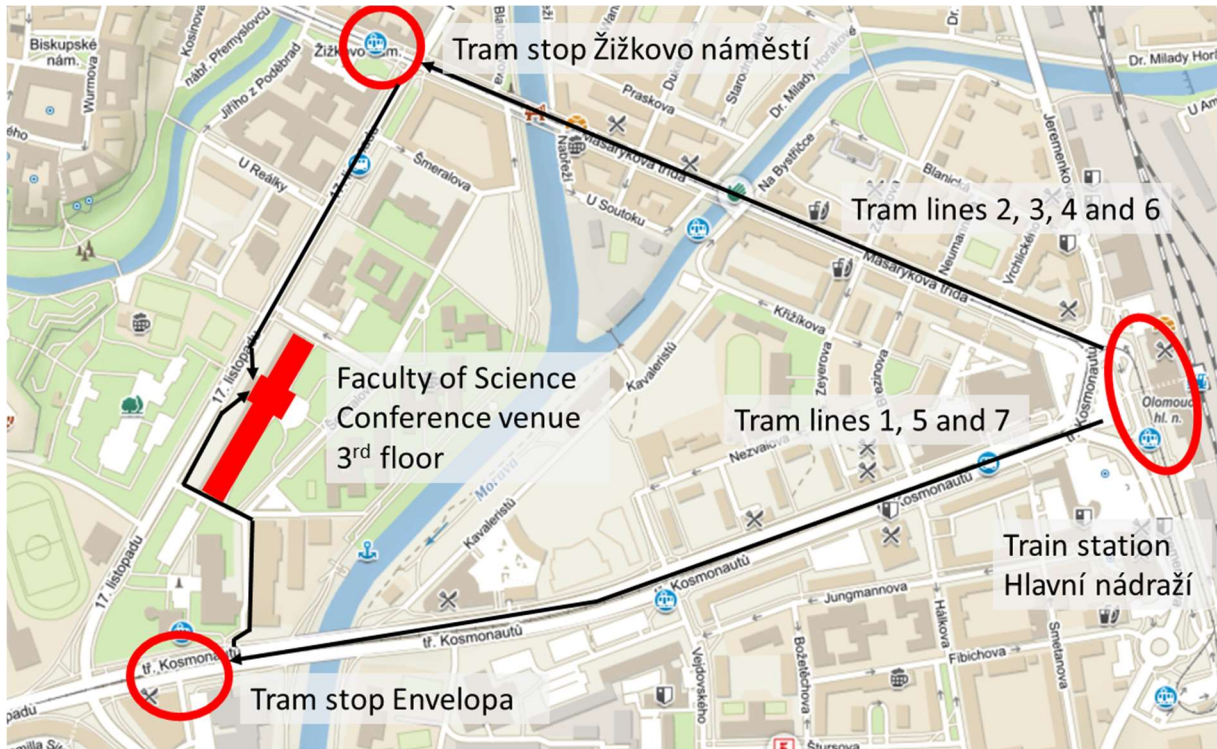
Invited Lecturers

- prof. Thierry Langer (UniVie, Vienna)
- assoc. prof. Johannes Kirchmair (UniVie, Vienna)
- dr. Alžběta Tuerková (CelerisTx, Graz)
- dr. Wim Dehaen (UCT Prague)
- dr.habil. Semen Yesylevskyy (IOCB Prague, IOP Kiev, KFC UPOL, Receptor.AI)
- dr. Martin Lepšík (IOCB Prague)
- dr. Federica Moraca (UNINA, Napoli)
- dr. Paulyna Magana (EMBL-EBI)
- dr. Genevieve Evans (EMBL-EBI)
- dr. Marian Novotný (Charles University, Prague)

Local Organizers

- doc. Karel Berka (KFC UPOL)
- dr. Pavel Polishchuk (IMTM UPOL)
- Guzel Minibaeva (IMTM UPOL)
- Aleksandra Ivanova (IMTM UPOL)
- dr. Václav Bazgier (KFC UPOL)
- Kateřina Storchmannová (KFC UPOL)
- Dominik Martinát (KFC UPOL)
- Anna Špačková (KFC UPOL)
- Nina Kadášová (KFC UPOL)

Venue



Faculty of Science, Palacky University Olomouc, Czech Republic
tř. 17. listopadu 12, Olomouc
GPS: 49.5924922,17.2632337
3rd floor PC room 3.002 + lecture room 3.003



Faculty building in Google Street View

List of On-Site Participants

1. Adam Tywoniak – University of Chemistry and Technology, Prague, CZ
2. Andriy Lubsyy – Palacky University Olomouc, CZ
3. Anna Špačková – Palacky University Olomouc, CZ
4. Ariadna Llop Peiro – University of Rovira i Virgili, IT
5. Asma Haffouz – University of Sfax, TN
6. Atilio Reyes Romero – Palacky University Olomouc, CZ
7. Daniel Lee Číp - Palacky University Olomouc, CZ
8. Darina Barkhatova – Institute of Science and Technology Austria, AT
9. Dominik Martinát – Palacky University Olomouc, CZ
10. Embolo Enyuegue Elisee Libert – Institute of Medical Research and Medicinal Plant Studies, CM
11. Ermin Schadich – Palacky University Olomouc, CZ
12. Eugen Hruška – Charles Universitz, CZ
13. Federica Moraca – University of Naples Federico II, IT
14. Jan Mičan – Masaryk University, CZ
15. Jindřich Lněnička – Palacky University Olomouc, CZ
16. Jiří Žák – IOCB Prague, CZ
17. Jozef Fülöp - University of Chemistry and Technology, Prague, CZ
18. Kaoud Salama – Palacky University Olomouc, CZ
19. Karoll Ferrer - Palacky University Olomouc, CZ
20. Kusuma sai Davuluri – Palacky University Olomouc, CZ
21. Manikandan Mithun – Institute of Physics of the Czech Academy of Sciences, CZ
22. Maryna Krautsova – Palacky University Olomouc, CZ
23. Michał Sobieraj – Adam Mickiewicz University in Poznań, PL
24. Mithun Manikandan - Institute of Physics AS CR, CZ
25. Nina Kadášová – Palacky University Olomouc, CZ
26. Tereza Kubátová – University of Vienna, AT
27. Yevgen Yurenko – IOCB Prague, CZ

Poster Abstracts

Structural Studies of Self-assembling Polymers on Crystal Surface

Mithun Manikandan, Paolo Nicolini, Prokop Hapala

Institute of Physics, Czech Academy of Sciences

In biological systems, molecular motors and machines play crucial roles in various essential processes. Hydrogen bonding, a fundamental molecular interaction, serves as a key element in molecular switches and motors controlled by factors such as light, electrons, pH, and chemical reactions [1]. However, understanding the structural characteristics of molecules and designing them presents an ongoing challenge. In this study, we aim to computationally design photosensitive polymers capable of self-assembling on crystal surfaces, with the potential for integration into surface science and molecular electronics. To achieve this, we explore a vast array of monomers and polymers and employ ab-initio calculations to investigate the atomic details of the optimal structures on different crystal surfaces.

Identification of antileishmanial piperazines

Ermin Schadich¹, **Susanne Nylén**², **Soňa Gurská**^{1,3},
Jana Kotulová¹, **Pavel Polishchuk**¹, **Marián Hajdúch**^{1,3},
Petr Džubák^{1,3}

1, Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry and University Hospital, Palacky University Olomouc, Czech Republic

2, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Solna, Sweden

3, Catrin - Czech Advanced Technology and Research Institute, Palacky University Olomouc, Czech

Republic Using the RDKit software, a series of eleven compounds including eight 1-aryl-4-(phthalimidoalkyl) piperazines and three 1-aryl-4-(naphthalimidoalkyl) piperazines were retrieved from a proprietary library based on their high pharmacophore similarity to haloperidol, an antipsychotic drug with antiparasitic properties, and evaluated in vitro as the potential antileishmanial scaffolds. These compounds were tested for antileishmanial activity against promastigotes of *Leishmania major* and *Leishmania mexicana* in dose-response assays. Two of 1-aryl-4-(naphthalimidoalkyl) piperazines, compounds 10 and 11, were active against promastigotes of both *Leishmania* species without being toxic to human fibroblasts. When structure-activity relations were analyzed, it was found that their activity correlated with the length of their alkyl chains. In assays with the infected mouse J774 macrophages, it was found that compound 11 was also active against intracellular amastigotes of both *Leishmania* species. Subsequent analyses revealed that compound 11 induced collapse of the mitochondrial electrochemical potential and increased the intracellular Ca²⁺ concentration in promastigotes of both species. Thus, it may serve as a promising scaffold for the development of novel antileishmanial drugs.

PDB-CAT: Classification and Analysis Tool for PDBx/mmCIF

Ariadna Llop-Peiró, Gerard Pujadas, Santiago García-Vallvé

University of Rovira i Virgili

Biological databases, such as the PDB (Protein Data Bank), face challenges due to the accumulation of new entries. Consequently, the PDB is undergoing a format change, transitioning to PDBx/mmCIF files. Moreover, the escalating volume of data presents difficulties for some applications, especially virtual screening set up, which requires classification based on ligand-protein complex interactions. Currently, no tool or database option facilitates this classification based on the type of bond between the protein and the ligand. To address this necessity, PDB-CAT classifies PDBx/mmCIF files into ligand-free and covalent and non-covalent complexes, determining the ligand code and whether it is a peptide ligand. Additionally, for datasets involving the same protein, the program enables the identification of sequence mutations by comparing to a reference structure. The program is implemented as a Jupyter Notebook, and it requires pdbcif and biopython libraries and Python 3.10 for optimal performance.

PDB-CAT was tested with SARS-CoV-2 Main Proteases. In this example, the workspace included 50 files downloaded from the PDB. Executing the code with the mutational analysis option, using 5R7Y as the reference structure, outputs a CSV information file within a few minutes. In the local environment, a classification was conducted to distinguish between mutated and non-mutated structures. Non-mutated structures were further categorized as ligand-free structures (in the absence of a ligand), covalent complexes, or non-covalent complexes. This process resulted in 40 non-mutated structures, classified into 10 free enzymes, 15 covalent complexes, and 15 non-covalent complexes. This work was supported by the project PID2022-138327OB-I00 financed by MCIN/AEI/10.13039/501100011033/FEDER, UE.

Quantification of Non-covalent Interactions at Protein-Protein Interface

Y. P. Yurenko, A. Muždalo, M. Černeková, A. Pecina, J. Řezáč, J. Fanfrlík, L. Žáková, J. Jiráček, P. Hobza, M. Lepšík

Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague, Czech Republic

The quantitative characterization of insulin/insulin receptor binding has posed a significant challenge due to the considerable size of the interface, its inherent flexibility, and the absence of suitable computational tools for the reliable assessment of non-covalent interactions. In this study, we present a comprehensive computational protocol employing molecular dynamics (MD), fragmentation, and quantum chemical (QM) as well as molecular mechanical (MM) calculations. These calculations are performed on a cryo-electron microscopy (cryo-EM) structure of the insulin/insulin receptor (IR) complex, aiming to pinpoint interaction "hotspots" within the primary site of the IR.

Through this hierarchical computational approach, we successfully identified interaction hotspots in insulin Site 1, including Ile A2, Glu A4, Tyr A19, Cys B7, Val B12, Glu B13, Tyr B16, Phe B24, and Phe B25. Notably, these findings exhibit excellent agreement with experimental data. The established protocol not only enhances our understanding of insulin binding but also provides a versatile tool for investigating the binding of insulin analogs. Additionally, it can be employed in the design of new insulin analogs with predefined properties, offering promising applications in the field.

Why Did the Compound Cross the Bilayer: Making Sense of Permeability Values

Adam Tywoniak¹; Kateřina Storchmannová²; Martin Balouch¹;
Jakub Juračka²; František Štěpánek¹; Karel Berka²

(1) Department of Chemical Engineering, UCT Prague, CZ

(2) Department of Physical Chemistry, Palacky U, Olomouc, CZ

Passive permeability is a crucial molecular property in drug discovery, as it co-determines pharmacokinetics whenever drug molecules cross phospholipid bilayers, e.g., in the gastrointestinal tract or across the blood-brain barrier. Its quantitative measure is the permeability coefficient P (cm/s), acting as the coefficient of proportionality of molar flux to a difference in concentration gradient: $J = P \cdot \Delta c$. It is often reported as $\log \text{Perm} = -\log[10] P$.

Many methods for determination of permeability have been developed, including cell line assays with colon carcinoma or kidney cells. Cell-free model systems include parallel artificial membrane permeability assays mimicking e.g., gastrointestinal epithelia or the skin, as well as the Black lipid membrane (BLM) and sub-micrometre liposomes. Unlike cell-based methods, these reduced models exclude active or paracellular transport and metabolism. In silico approaches are now established as well, based on molecular dynamics, or e.g., the solubility-diffusion model.

This contribution aims to interpret reported permeability values in proper physical context, as well as to showcase existing discrepancies in existing datasets.

Relevant thresholds are identified and discussed, incl. method-specific lower limits linked to experimental timescales and instrumental quantitation limits, underestimations caused by the presence of a stagnant water layer adjacent to any membrane, as well as upper limits pertaining to unrestrained self-diffusion in solution.

Permeability data sourced from literature (including ChEMBL) was aggregated and curated in MolMeDB (<https://molmedb.upol.cz>), a FAIR database of compound-membrane interaction data. For this contribution, the set was narrowed down to permeabilities measured or predicted for uncharged small molecules at a neutral pH across cellular, intestinal, or artificial membranes. Distributions for values from individual methods and their correlations are identified and discussed.

Docking Cytochrome P450

Eugen Hruška

Charles University, CZ

The metabolism of drugs in the human body is performed mostly by Cytochrome P450. For virtual screening of drug candidates, a rapid and accurate estimation of metabolism by the most common isozymes of Cytochrome P450 is beneficial to avoid compounds with adverse metabolism. The site of metabolism for each drug candidate can be estimated by the proximity to the enzymatically active heme centre. The proximity can be obtained by docking the compound into the active site of Cytochrome P450. A comparison of docking results with different software into Cytochrome P450 isozyme active site was performed.

Structure analysis of Organic cation transporters in the SLC22

Nina Kadášová, Karel Berka

Dpt Physical Chemistry, Palacky University, Olomouc, Czech Republic

Solute carrier transporters (SLC) comprise a diverse group of membrane-bound proteins, with over 500 representatives classified into 65 families based on sequence homology and transport function. SLCs are crucial for transporting a wide range of solutes across biological membranes. Dysfunctions in these transporters contribute to the development of various diseases. Therefore, investigating these proteins is essential for understanding metabolic principles in the human body and disease mechanisms. This study focuses on the SLC22 family, specifically, organic cation transporters (OCTs) subclades. To investigate the ligand binding properties of OCT1 and OCT2, AI-predicted models generated by AlphaFold and SWISS-MODEL were utilized, along with the available cryo-EM structures of OCTs. Molecular docking using AutoDock Vina was performed to identify suitable ligands transported by these proteins. The results aim to determine the efficacy of the prediction methods and the preferred structural models for understanding the ligand binding of OCTs.

ChannelsDB 2.0: A Comprehensive Database of Protein Tunnels and Pores in AlphaFold Era

Anna Špačková¹, Ondřej Vávra^{2,3}, Tomáš Raček^{4,5}, Václav Bazgier¹, David Sehnal^{4,5}, Jiří Damborský^{2,3}, Radka Svobodová^{4,5}, David Bednář^{2,3}, Karel Berka¹

(1) Department of Physical Chemistry, Faculty of Science, Palacký University, Czech Republic

(2) Loschmidt Laboratories, Department of Experimental Biology and RECETOX, Faculty of Science, Masaryk University, Czech Republic

(3) International Clinical Research Center, St. Anne's University Hospital Brno, Czech Republic

(4) CEITEC – Central European Institute of Technology, Masaryk University Brno, Czech Republic

(5) National Centre for Biomolecular Research, Faculty of Science, Masaryk University Brno, Czech Republic

ChannelsDB 2.0 has been upgraded to offer a comprehensive insight into protein channels' structural characteristics, geometry, and physicochemical attributes, encompassing both tunnels and pores. These channels are computed on deposited biomacromolecular structures originating from the PDBe and AlphaFoldDB databases. In the new version of the ChannelsDB database, we have incorporated data generated through the widely used CAVER tool, augmenting the insights previously acquired only through the original MOLE tool. Additionally, we have extended the database's coverage by introducing tunnels originating from cofactors localised within the AlphaFill database or from cognate ligands within PDB structures. This expansion has increased the available channel annotations by almost five times. ChannelsDB 2.0 houses information concerning geometric properties such as length and radius and physicochemical attributes based on the amino acids lining the channels. These stored data are intricately linked with the existing UniProt mutation annotation data, facilitating in-depth investigations into the functional roles of biomacromolecular tunnels and pores.

In summary, ChannelsDB 2.0 represents an invaluable resource for conducting in-depth analyses of the significance of biomacromolecular channels. The database is freely accessible to the public at the address <https://channelsdb2.biodata.ceitec.cz>.

MolMeDB - Molecules on Membranes Database

Jakub Juračka¹, **Kateřina Storchmannová¹**, Dominik Martinát¹,
Václav Bazgier¹, Jakub Galgonek², Karel Berka¹

(1) Dpt Physical Chemistry, Palacky University, Olomouc, Czech Republic

(2)

(3) Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague,
Czech Republic

Biological membranes are natural barriers of cells. The membranes play a key role in cell life and also in the pharmacokinetics of drug-like small molecules. There are several ways how a small molecule can get through the membranes. Passive diffusion, active or passive transport via membrane transporters are the most relevant ways how the small molecules can get through the membranes. There is an available huge amount of data about interactions among the small molecules and the membranes also about interaction among the small molecules and the transporters. MolMeDB (<https://molmedb.upol.cz/detail/intro>) is a comprehensive and interactive database. Data is available from 52 various methods for 40 biological or artificial membranes and for 184 transporters in MolMeDB. The data within the MolMeDB is collected from scientific papers, our in-house calculations (COSMOmic and PerMM) and obtained by data mining from several databases. Data in the MolMeDB are fully searchable and browsable by means of name, SMILES, membrane, method, transporter or dataset and we offer collected data openly for further reuse. Newly are data available in RDF format and can be queried using SPARQL endpoint (<https://idsm.elixir-czech.cz/sparql/endpoint/molmedb>). Federated queries using endpoints of other databases are also possible. Lately this database has been used for analysis of different functional groups influence on molecule-membrane interactions.

Proteome secondary structures generated by AlphaFold

Ivana Hutařová Vařeková¹; Martinat, Dominik¹; Svobodová,
Radka^{2,3}; Berka, Karel¹

1. Department of Physical Chemistry, Faculty of Science, Palacký University Olomouc

2. CEITEC – Central European Institute of Technology, Masaryk University Brno

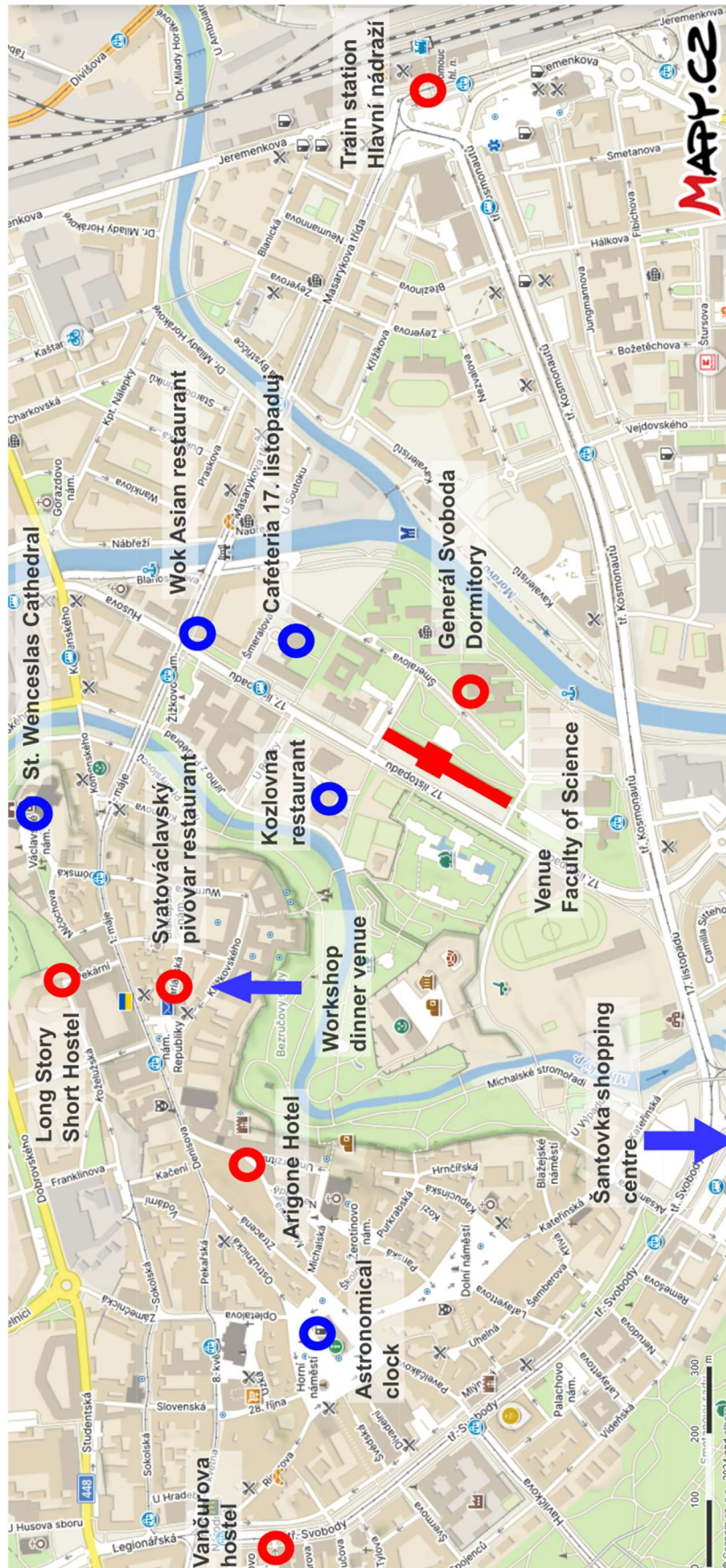
3. National Centre for Biomolecular Research, Faculty of Science, Masaryk University Brno

The AlphaFold[1] algorithm and its associated database[2] provide convenient access to the structural data for entire proteomes across various species, facilitating comprehensive statistical analysis. In our study, we examined the distribution of secondary structures, specifically alpha helices and beta strands, within the proteomes of model organisms and those of relevance to human health. While there seems to be a general distribution of secondary structures within proteins in all analyzed life forms, our findings reveal several noteworthy functional exceptions: 1) abundance of short proteins with small amounts of secondary structures in plant proteomes, 2) spike of structures with 9-12 alpha helix count in some mammals (e.g., mice or rat) from the abundance of olfactory receptors from GPCR family and 3) enhanced presence of long proteins with abundant secondary structures (50+) in the human proteome. These insights contribute to a deeper understanding of the structural diversity within proteomes, shedding light on specific patterns and variations across different species and functional categories of proteins.

1. Jumper J., Evans R., Pritzel A. et al. Highly accurate protein structure prediction with AlphaFold. *Nature* 596, 583–589 (2021). <https://doi.org/10.1038/s41586-021-03819-2>

2. Varadi M., Anyango S., Deshpande M. et al. AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models, *Nucleic Acids Research*, Volume 50, Issue D1, D439–D444 (2022), <https://doi.org/10.1093/nar/gkab1061>

Accommodation, Restaurants and Sights



Notes

Program

Monday, January 29

11:00am		Registration
12:15pm		Start
12:30pm	Karel Berka	Drug design intro (lecture)
1:15pm	Genevieve Evans/ Paulyna Magana	PDBe/PDBe-KB (lecture/tutorial)
3:15pm		Coffee
3:30pm	Marian Novotný	Binding site identification (lecture)
4:15pm	Alžběta Tuerková	Insights from a Biotech Startup: How Computational Chemists Shape the Design of Proximity-Inducing Compounds (lecture)
5:00pm		Poster session

Tuesday, January 30

9:15am	Pavel Polishchuk	Virtual screening (lecture)
10:00am	Martin Lepšík	QM in drug design
11:00am		Coffee
11:15am	Semen Yesylevskyy	AI in drug design
12:00pm		Lunchtime
1:00pm	Johannes Kirchmair	Frequent hitters (lecture)
2:00pm	Wim Dehaen	QSAR (lecture)
3:00pm		Coffee
3:15pm	Wim Dehaen	QSAR (tutorial)
7:00pm		Conference dinner

Wednesday, January 31

9:15am	Karel Berka	Alphafoldology (lecture)
10:00am	Federica Moraca	Molecular Drug design (lecture)
10:45am		Coffee
11:00am	Federica Moraca	Molecular docking (lecture)
12:00pm		Lunchtime
1:00pm	Federica Moraca	Molecular docking (tutorial)
3:00pm		Coffee
3:15pm	Aleksandra Ivanova	MD (tutorial)
6:30pm	Pavel Polishchuk	Excursion to IMTM

Thursday, February 1

9:15am	Pavel Polishchuk	De novo (lecture)
10:15am		Coffee
10:30am	Pavel Polishchuk/ Guzel Minibaeva	De novo (tutorial)
12:00pm		Lunchtime
1:00pm	Pavel Polishchuk	CACHE (lecture)
2:00pm	Thierry Langer	Pharmacophores (lecture)
3:00pm		Coffee
5:15pm	Thierry Langer	Pharmacophores (tutorial)
6:30pm		Farewell party
