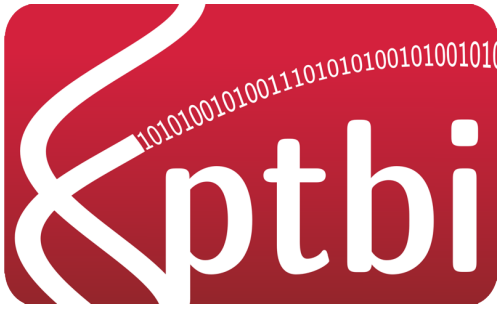
Bioinformatics Fights Viruses
Book of Abstracts

24 June 2021, Toruń, Poland



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Session 1

Application of informatics to decision making in drug discovery

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Getting a drug to market has been described as one of the most complicated processes that face scientists. Typically it takes 10 years or more to get a drug to market and costs can be 2.5 billion dollars or more. Therefore any advantage that can be garnered from the plethora of information that is already available either in the public domain of through proprietary databases, is vitally important to selecting the best targets and planning the best critical path though drug discovery. The role of informatics in designing a critical path and in decision making about drug discovery, will be described through a series of examples.

Crowding affects the activity and dynamics of the NS3/4A protease of the hepatitis C virus

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Living cells are densely crowded with many macromolecules. However, our understanding of biochemical processes mostly relies on experiments performed in dilute solutions. Using spectroscopic methods and molecular dynamics simulations, we investigate how macromolecular crowders affects the activity and dynamics of a protein crucial in the replication of the hepatitis C virus (HCV). This protein, called NS3/4A, is a protease with disordered tails that have to fold to anchor to the human endoplasmic reticulum membrane. We find that PEG crowders decrease the NS3/4A catalytic activity and inhibition as well as decrease diffusion of the enzyme and substrates. PEG crowders also promote folding of one of the NS3/4A tails into a helical structure.

Protein flexibility and glycan dynamics of the SARS-CoV-2 spike: clues on infection mechanism and epitope masking

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein mediates viral entry to the host cells and initiates the infection. As the only exposed surface protein, it is a primary target for vaccine development. We combined cryo-electron tomography, subtomogram averaging, and molecular dynamics simulations to visualise and structurally characterise spike proteins on the surface of intact virions. We discover three hinges in the stalk of spike protein that endow it with surprising flexibility and can be relevant in the process of binding to the surface of the host cell. Prompted by extensive glycosylation visible in the tomograms, we explore glycans' role in protecting the spike protein from interactions with the immune system. We discover highly conserved epitope candidates not shielded by glycans that could be instrumental in the fight against the emerging SARS-CoV-2 variants and pave the road for the next generation of vaccines.

Nanomechanical aspects of nanobodies-protein S SARS-CoV-2 virus complexes – a computational study

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Antibodies against pathogens such as SARS-CoV-2 are promising candidates for effective drugs [1]. However, their direct application is hampered by difficulty in lab production of these complex molecules. Recently much attention is devoted to nanobodies - single-domain antibodies that can be effectively produced using molecular biology techniques. Effective screening of nanobodies gave systems with sub-picomolar affinity SARS type viruses [2]. Here we will present preliminary results of computational study of nanobody-protein S stability using a computational strategy called Virtual Atomic Force Microscopy. Using cryo-EM structures of Nb6 nanobodies bound to closed and open SpikeS2P protein [2], we apply Steered Molecular Dynamics to assess unbinding forces and to determine molecular mechanisms of binding-unbinding processes. Our approach is effective and should allow for efficient ranking of synthetic nanobodies affinities to protein S. Notably, our computations "automatically" indicated a residue exploited by the Nature to create new, more aggressive variants of SARS viruses.

Acknowledgement: This project is funded by IDUB N. Copernicus ANTICO and #MEMOBIT grants. ICNT UMK computer facilities are acknowledged.

[1] X. Saelens and B. Schepens, "Single-domain antibodies make a difference", Science 371, 681-682(2021).
[2] Schoof et al.," An ultrapotent synthetic nanobody neutralizesSARS-CoV-2 by stabilizing inactive Spike", Science 370,1473–1479 (2020).

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Session 2

Accelerating Drug Discovery and Repurposing by Combining Transcriptional Signature Connectivity with Docking

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The development of targeted treatment options for precision medicine is hampered by a slow and costly process of drug screening. While small molecule docking simulations are often applied in conjunction with cheminformatic methods to reduce the number of candidate molecules to be tested experimentally, the current approaches suffer from high false positive rates and are computationally expensive. We present a novel in silico approach for drug discovery and repurposing, dubbed connectivity enhanced Structure Activity Relationship (ceSAR) that improves on current methods by combining docking and virtual screening approaches with pharmacogenomics and transcriptional signature connectivity analysis. ceSAR builds on the landmark LINCS library of transcriptional signatures of over 20,000 drug-like molecules and 5,000 gene knock-downs (KDs) to connect small molecules and their potential targets. For a set of candidate molecules and specific target gene, candidate molecules are first ranked by chemical similarity to their 'concordant' LINCS analogs that share signature similarity with a knock-down of the target gene. An efficient method for chemical similarity search, optimized for sparse binary fingerprints of chemical moieties, is used to enable fast searches for large libraries of small molecules. A small subset of candidate compounds identified in the first step is then re-scored by combining signature connectivity with docking simulations. On a set of 20 DUD-E benchmark targets with LINCS KDs, the consensus approach reduces significantly false positive rates, improving the median precision 3-fold over docking methods at the extreme library reduction. We conclude that signature connectivity and docking provide complementary signals, offering an avenue to improve the accuracy of virtual screening while reducing run times by multiple orders of magnitude.

Joint work with Alexander W. Thorman, James Reigle, Somchai Chutipongtanate, and Behrouz Shamsaei.

Virxicon: a lexicon of viral sequences

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Virusology is a very complex field, the amount of information gathered every day is tremendous. Especially during the pandemic, it is necessary to facilitate access to all the information, so the experts can find everything they need very quickly and easily. Our aim was to present important data from other databases in a clear, ordered fashion. Two source databases are NCBI and GENBANK, both widely used by biologists. Users can customize their search using the set of filters, which helps to limit the results to only those viruses they are interested in. Other features which should be mentioned are: downloading sequences in FASTA format (either of the whole virus or single genes) and filtering the results by keywords. All the information is presented using web interface, which has its mobile and PC version. Virxicon can be accessed via the Internet at `http://virxicon.cs.put.poznan.pl/`

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Modelling COVID-19 pathophysiology through knowledge graphs and its application

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In silico evaluation of SARS-CoV-2 primers performance

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Throughout course of SARS-CoV-2 pandemic, diagnostic laboratories and researchers all around the world had observed that different clades/lineage s may impact COVID-19 diagnosis, leading to false results. Such misdiagnosis allows for further, unnoticed spread of virus. We had placed hypothesis that SNPs can drastically decrease diagnostic power and value of primer sets. With obtained in-vitro results of amplification of SARS-CoV-2 for the purpose of sequencing, hypothesis has been strengthened and we had evaluated in-silico how variability in genomes of novel coronavirus in primer/probe binding sites may potentially affect their interactions, and suggest the best combinations for further consideration. We downloaded nearly 1.5 million of SARS-CoV-2 genomes from GISAID, applied quality filters, and performed an analysis with usage of our own Python library pyprimer for the 15 publicly available primers/probe sets We had found that the five sets are susceptible to the currently most abundant clades/lineages. Mismatches encompassing the binding sites for them are present in current Variants of Concern. On the other hand, best performing five sets of primers can still detect almost all of VOC with high overall accuracy. Nonetheless, secondary structure of some of best performing papers raises concerns regarding similar structure properties from retracted sets, which by dimerization were producing false-positive results.

The influence of SARS-CoV-2 infection on the RAA system

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SARS-CoV-2 infection in patients with essential hypertension in combination with renal complications usually worsens the course of this infection. Hypertensive patients are treated with ACEI or ARB, or both, which may affect SARS-CoV2 entry into the cell. In our study, we focused on the effect of SARS-CoV-2 infection on hypertension. In addition, we have examined the link between this infection and ACEI or ARB administration. For this purpose, we have built a model of the studied phenomenon in the language of Petri nets theory, and we have used knockout analyzes. On this basis, we found that the use of ACEI and ARB did not affect the course of the infection. In addition, we have shown that ACEI in an infected hypertensive patient is effective, so it lowers blood pressure, unlike ARB drugs, which even slightly increase hypertension in such a patient. Until now, it is not possible, due to the relatively short duration of the COVID-19 pandemic, to obtain the results of long-term studies testing the effectiveness of these drugs in patients with hypertension, infected with SARS-COV-2; hence a systemic approach to detect a possible link between this viral infection and commonly used antihypertensive drugs seems to be a good option.

Session 3

Mapping chromatin accessibility and active regulatory elements reveals pathological mechanisms in human gliomas

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Gliomas are brain tumors frequently associated with epigenetics-related gene deregulation. We performed whole-genome analysis of histone modifications, chromatin accessibility and DNA methylation patterns together with transcriptome analysis for multiple samples representing different tumor grades. Based on the results of the integrative analysis of the acquired profiles we constructed an atlas of cis-regulatory elements active in human high- and low-grade gliomas. We also identify enhancer-promoter contacts operating in gliomas and used collected data for identification of chromatin loop which activates FOXM1-ANXA2R regulatory network, relevant for pathogenic processes in glioblastomas.

Ligand dissociation pathway investigation by τ-random acceleration molecular dynamics (τRAMD)

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Early stages of drug design focus on equilibrium binding affinity to the target. Since many drugs have non-equilibrium binding characteristics, there is an increasing need to optimize binding kinetics early in the drug discovery process. The residence time concept takes into account the conformational dynamics of the target molecules that affect the binding and dissociation of the drug. Therefore drug-target residence time (τ) is the reliable determinant of drug efficacy prediction but challenging to predict computationally.

In the present work we were aiming to examine whether τ-random acceleration molecular dynamics (τRAMD) can be useful for obtaining insights into ligand-target dissociation mechanisms. The τRAMD simulations were run for EGFR kinase domain with a quinazoline inhibitor - lapatinib.

Our study suggests that there are many different factors that can alter the transition barrier on the dissociation pathway. In case of EGFR in a complex with lapatinib a relationship between detected ligand release pathways and the initial direction of the RAMD force was observed. The τRAMD method is a computationally inexpensive tool that can be used for analysing the dissociation mechanism and characterising the transition states.

The work was co-financed by the European Union through the European Social Fund (grant POWR.03.02.00-00-I029).

Stop the biting: tracking the insecticide-mediated allosteric changes in muscarinic acetylcholine receptors and design of selective, photoactivated bitopic ligands

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Surprisingly, the most dangerous animals in the world are mosquitoes. They are the primary vectors of many diseasessuch as malaria, encephalitis, yellow fever, dengue fever, West Nile fever or Zika virus disease, transmitted in 89 countries,. The main way to reduce transmission is vector control with chemicals. However, mosquitoes and other insects have developed resistance to repellents and insecticides.

Muscarinic acetylcholine receptors (mAChRs), which are rhodopsin-like GPCRs, play a crucial role in both human and insect neuronal system. Recent studies on D. melanogaster showed that they modulate olfactory responses and food-seeking behavior thus are a potential target for new a generation of repellents.

Currently, in drug design, there is a shift towards the allosteric ligands that bind in spatially distinct and less conserved sites than orthosteric ones. Apart of acting as the subtype-selective agonist or inverse-agonists, they can modulate the efficacy and potency of orthosteric ligands which may allow reducing the dose of active substance in drugs or repellents.

By using molecular dynamics (MD) we investigated the conformational changes of M1 receptor in a series of multiple docking of insect repellents (DEET, IR3535) and allosteric modulators (pirenzepine, BQCA). We fused an orthosteric ligand that exerts repellence activity with the allosteric modulator using azobenzene functional group as a linker. Thus, we obtained M1 selective, potentially photoswitchable insect repellent which could serve as controlled by light protection from mosquitoes biting.

Acknowledgements: The authors acknowledge funding from the National Science Centre, Poland (Grant 2016/23/B/ST4/0177(Support from the project POWR.03.05.00-00-Z302/17 Universitas Copernicana Thoruniensis in Futuro-IDS "Academia Copernicana" is also acknowledged. Calculations have been performed in the Centre of Informatics - Tricity Academic Supercomputer & network (CI TASK).

PATH to prediction of long amyloid and functional amyloid peptides

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Amyloids are protein aggregates most commonly known for their role in the development of severe neurodegenerative diseases such as Alzheimer's or Parkinson's disease. However, the unique features of such structures were utilized by many organisms for a wide range of physiological roles including biofilm formation and hormone storage. Despite the importance of amyloids, our understanding of these proteins is still limited due to costly and time consuming experiments required to investigate the aggregation process. In order to overcome this limitation, several bioinformatics tools were developed, unfortunately, due to historical reasons, the vast majority of them focus on the prediction of the amyloid propensity of hexapeptides. In this work, we aimed to extend our previously developed tool – PATH, for the classification of much longer peptides. Furthermore, we have shown that it is capable of correct classification of functional amyloids, despite their lack of sequence similarity to their much better studied pathological counterparts.

Docking to purinergic P2X7 receptor as a part of the battle against glioblastoma

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The purinergic P2X7 receptors are non-selective channels transporting mainly cations. The channel is activated by high concentration of ATP. After binding of three ATP molecules, trimeric P2X7 forms a transmembrane pore and induces a cytolytic signal. P2X7 receptors are highly expressed on the surface of cancer cells in the central nervous system. This makes them attractive targets in potential anti-cancer therapies, i.a., a treatment of gliomas. A commercially used drug in the fight against glioblastoma is temozolomide (TMZ). TMZ is a prodrug, and when transformed, the active compound is released. The transformation of TMZ occurs on the intracellular side of the membrane. However, recent studies show that this compound may also exhibit extracellular effects, especially through the interaction with P2X7. In order to get insight into a mechanism of TMZ extracellular action we performed extensive molecular docking studies of TMZ and ATP to several P2X7 models using SMINA software. We sought preferred docking sites. Results show that TMZ may compete with ATP in certain physiological conditions. This is an important finding, since such propensity demonstrates the potential for a more efficient combination therapy with ATP and TMZ in the fight against glioblastoma.

Molecular dynamics as a tool to improve thermostability of NHase - biotechnologically important enzyme

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Nitrile hydratase (NHase) is an enzyme that is used in the industry for the production of acrylamide [1]. Experimentally it is difficult to check the dynamical properties of proteins. Molecular dynamics is a powerful tool for analyzing how mutations or changes in temperature and solvent composition influence enzymes [2]. Here we present results of Polish/Chinese cooperation in the semi-rational improvement of NHase which exhibits high thermostability. Using theoretical modeling tools we were able to explain molecular reasons for the high thermal stability of Nhases with artificially inserted linkers. Additional salt bridges, hydrogen bonds, and hydrophobic interactions prove to be substantial in the stabilization of NHase [3].

1. Cheng Z, Xia Y, Zhou Z. Recent Advances and Promises in Nitrile Hydratase: From Mechanism to Industrial Applications. Frontiers of Bioengineering and Biotechnology, 2020, 8, 352. doi:10.3389/fbioe.2020.00352.

2. Cheng, Z, Lan, Y, Guo, J, Ma, D, Jiang, S, Lai, Q, Zhou, Z, Peplowski, L. Computational Design of Nitrile Hydratase from Pseudonocardia thermophila JCM3095 for Improved Thermostability. Molecules 2020, 25, 20, 4806. https://doi.org/10.3390/molecules25204806.

3. Guo J, Cheng Z, Berdychowska J, Zhu X, Wang L, Peplowski Ł, Zhou Z. Effect and mechanism analysis of different linkers on efficient catalysis of subunit-fused nitrile hydratase. International Journal of Biological Macromolecules, 2021, V2021 181, 444-451. https://doi.org/10.1016/j.ijbiomac.2021.03.103.

Hot spots, proteins, and machine learning

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Protein-protein interfaces are very important in cellular metabolic networks but difficult to model computationally. Numerous approaches and servers were proposed to determine residues particularly prone to participate in strong protein-protein coupling, so called hot spots. Here, we present preliminary assessment of hot spots in 15-LOX/PEBP1 complex (human model based on rabbit PDB code: 1BEH (PEBP1) and 1LOX (15LOX-1) using machine learning techniques, such as SVM. Popular servers indeed predict a series of hot spots. Unfortunately, none of servers predicted PRO112 (PEBP1) interacting with $\alpha 2$ helix of LOX found to be crucial in the experimental paper (1). In the future we will use those sets of hot spots to model pharmacophore models for ferroptosis inhibitors.

Acknowledgment: Support of National Science Centre, Poland, No 2019/35/D/ST4/02203 (KMR, TM) is acknowledged.

(1) Wenzel, S. E., Y. Y. Tyurina, J. Zhao, C. M. S. Croix, H. H. Dar, G. Mao, V. A. Tyurin, T. S. Anthonymuthu, A. A. Kapralov, A. A. Amoscato, K. Mikulska-Ruminska, I. H. Shrivastava, E. M. Kenny, Q. Yang, J. C. Rosenbaum, L. J. Sparvero, D. R. Emlet, X. Wen, Y. Minami, F. Qu, S. C. Watkins, T. R. Holman, A. P. VanDemark, J. A. Kellum, I. Bahar, H. Bayır, and V. E. Kagan. 2017. PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals. Cell 171(3):628-641. e626.

Session 4

Predicting the evolution of influenza for vaccine composition design

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Length Dependent Folding Kinetics of Alanine-Based Helical Peptides from Optimal Dimensionality Reduction

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We present a computer simulation study of helix folding in alanine homopeptides (ALA)n of length n=5, 8, 15, and 21 residues. Based on multi-microsecond molecular dynamics simulations at room temperature, we find helix populations and relaxation times increasing from about 6% and 2 ns for ALA5 to about 60and 500 ns for ALA21, and folding free energies decreasing linearly with the increasing number of residues. Helix folding is analyzed with the Optimal Dimensionality Reduction method, yielding coarse-grained kinetic models that provide a detailed representation of the folding process. Shorter peptides, ALA5 and ALA8, tend to convert directly from coil to helix, while ALA15 and ALA21 travel through several intermediates. Coarse-grained aggregate states representing the helix, coil, and intermediates are heterogeneous, encompassing multiple peptide conformations. Folding involves multiple pathways. Interesting intermediate states are present on the folding paths, with partially formed helices, turns, and compact coils. Statistically, helix initiation is favored at both termini, and the helix is most stable in the central region. Importantly, we found the presence of underlying universal local dynamics in helical peptides with correlated transitions for neighboring hydrogen bonds. Overall, the structural and dynamical parameters extracted from the trajectories are in good agreement with experimental observables, providing microscopic insights into the complex helix folding kinetic.

CONFORMATIONAL LANDSCAPING AND MUTATIONAL CARTOGRAPHY OF THE SARS-COV-2 PROTEINS: PROBING ALLOSTERIC MECHANISMS OF SPIKE FUNCTIONS AND ANTIBODY-INDUCED NEUTRALIZATION

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The coronavirus disease 2019 (COVID-19) pandemic associated with the severe acute respiratory syndrome (SARS) has been at the focal point of biomedical research. The structural and biochemical studies of the SARS-CoV-2 spike glycoproteins and complexes with highly potent antibodies have revealed multiple conformation-dependent epitopes highlighting the link between conformational plasticity of spike proteins and capacity for eliciting specific binding and broad neutralization responses. We have developed an integrated computational strategy that includes bioinformatics sequence and coevolutionary analysis, atomistic biophysical simulations and novel perturbation-based hierarchical network modeling of the SARS-CoV-2 spike complexes with antibodies targeting distinct epitopes to explore molecular mechanisms underlying binding-induced modulation of dynamics and allosteric signaling in the SARS-CoV-2 spike proteins. This computational approach was also used to examine molecular mechanisms underlying functional roles and effects of novel circulating mutational variants in the SARS-CoV-2 S protein targeting K417, N439, E484 and N501 residues. The results of our studies showed that antibody-escaping mutations can target allosteric hotspots with sufficient dynamic plasticity and evolutionary adaptability to modulate binding with the host receptor, while reducing efficiency of antibody recognition and compromising the long-range allosteric communications in the SARS-CoV-2 spike proteins. We suggest that SARS-CoV-2 S protein may function as a versatile and functionally adaptable allosteric machine that exploits plasticity of allosteric regulatory centers to generate escape mutants that fine-tune response to antibody binding without compromising activity of the spike protein. I will discuss allosteric regulatory mechanisms of SARS-CoV-2 S proteins and a strategy for therapeutic intervention of the SARS-CoV-2 spike binding with the host receptor by targeting allosteric hotspots of allosteric interactions in the SARS-CoV-2 proteins.