MATHEMATICS OF LIFE

MoL 2021

September 13-16, 2021, Hisarya, Bulgaria & online

Book of Abstracts
&
Short Communications

IICT Institute of Information and Communication Technologies
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BULGARIAN SCIENCE FUND
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EUropean TOPology Interdisciplinary Action CA 17139
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ICT CENTRE OF EXCELLENCE IN INFORMATICS AND INFORMATION AND COMMUNICATION TECHNOLOGIES

MATHEMATICS of LIFE

MoL2021

13-16 September, 2021, Hisarya, Bulgaria & online

The Workshop "Mathematics of Life" (MoL2021, 13-16 September 2021, Hisarya, Bulgaria & online) is devoted to selected topics in mathematical biology research in both its analytical and computational components illustrating the synergy between mathematics, physics, computing and biology. The program is mainly focused on problems related to the modelling and simulations of topologically complex structures and dynamics, including, but not being limited to:

- Protein structure, dynamics and interactions
- Large-scale molecular simulations
- Topology in biomodelling and bioinformatics
- Biologically inspired materials & technology
- Neural networks from/in biological research
- Bio-medical applications

The workshop, originally planned for May 2020, was postponed due to the Covid-19 pandemic but a new research topic has also been added:

- Model studies on SARS-CoV-2 and COVID-19

MoL2021 aims to bring together experts and young researchers in the analytical and computational studies of biomolecules and, among others, will provide a cross-package discussion forum for participants in the COST Action EUTOPIA (EUropean TOPology Interdisciplinary Action, CA 17139) with interests in these particular aspects of the Action's program.

The Workshop MoL2021 is organised by the Institute of Information and Communication Technologies at the Bulgarian Academy of Sciences (Sofia, Bulgaria) and CIC biomaGUNE (Donostia, Spain), in association with the

European Topology Interdisciplinary Action (COST EUTOPIA, CA 17139), the Bulgarian Center of Excellence for Informatics and Information and Communication Technology, Section "Biomathematics and Scientific Computing" of the Union of Bulgarian Mathematicians, and the Bulgarian Section of SIAM, with partial support from EUTOPIA COST Action and the Bulgarian Science Fund (Grant KP-06-COST-9).

The Opening Lecture will be given by David A. Leigh (Royal Society Research Professor & Sir Samuel Hall Professor of Chemistry, from the University of Manchester, UK. The list of keynote speakers includes Adam Liwo (University of Gdansk, Poland), Antti J. Niemi (NORDITA & Uppsala University, Sweden), Franco Ferrari (University of Szczecin, Poland), Marek Cieplak (Institute of Physics, Polish Academy of Science, Warsaw, Poland), Noam Kaplan (TECHNION, Israel), Pietro Faccioli (University of Trento, Italy), Roumen Anguelov (University of Pretoria, South Africa), and Sarah Harris (University of Leeds, UK). In a presentation of BioExcel Centre of Excellence, the European response to the HPC challenges in biomolecular research will be outlined (Rossen Apostolov, KTH).

This booklet contains the programme scheme of MoL2021, (extended) abstracts of conference talks and the participants index.

September 2021

Nevena Ilieva (IICT – BAS, Bulgaria)
Ivan Coluzza (CIC biomaGUNE, Spain)
Luca Tubiana (University of Trento, Italy)

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OPENING LECTURE
&
INVITED TALKS

Making the Tiniest Machines

David A Leigh FRS

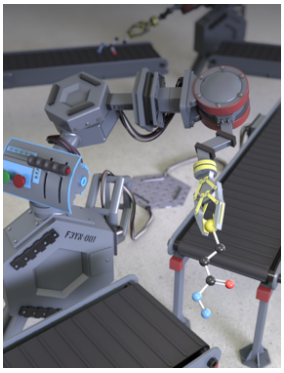
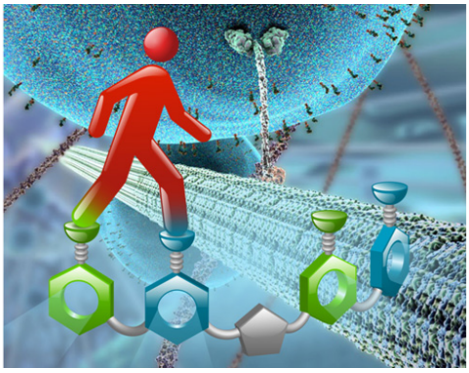
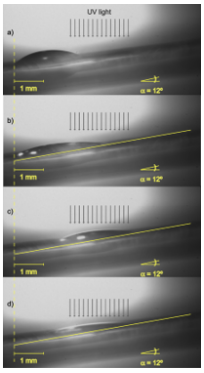
University of Manchester, UK

> *"We are at the dawn of a new industrial revolution of the twenty-first century, and the future will show how molecular machinery can become an integral part of our lives. The advances made have also led to the first steps towards creating truly programmable machines, and it can be envisaged that molecular robotics will be one of the next major scientific areas."*
>
> The 2016 Nobel Prize in Chemistry Committee, October 2016 [1]

Over the past few years some of the first examples of synthetic molecular level machines and motors – all be they primitive by biological standards – have been developed [2] These molecules are often best designed to work through statistical mechanisms, rectifying random thermal motion through ratchet mechanisms [3, 4, 5, 6] in a manner reminiscent of Maxwell's Demon. Recently the first programmable systems have been developed [7, 8], the forerunners of a new technological era of molecular robotics.

Perhaps the best way to appreciate the technological potential of controlled molecular-level motion is to recognise that nanomotors and molecular-level machines lie at the heart of every significant biological process. Over billions of years of evolution Nature has not repeatedly chosen this solution for achieving complex task performance without good reason. In stark

contrast to biology, none of mankind's fantastic myriad of present day technologies exploit controlled molecular-level motion in any way at all: every catalyst, every material, every plastic, every pharmaceutical, every chemical reagent, all function exclusively through their static or equilibrium dynamic properties. When we learn how to build artificial structures that can control and exploit molecular level motion, and interface their effects directly with other molecular-level substructures and the outside world, it will potentially impact on every aspect of functional molecule and materials design. An improved understanding of physics and biology will surely follow.

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Theory and Practice of Coarse Graining

Adam Liwo

University of Gdansk, Poland

Coarse-grained approaches, in which several atoms are merged into extended interaction sites, are widely used in simulating large systems, including biological macromolecules. Such reduction of representation offers a tremendous benefit of extending the accessible time- and size-scales by orders of magnitude. However, designing the pertinent force fields poses problems and simple translation of all-atom energy terms to coarse-grained representation does not give satisfactory result. The fundamental physical principle behind the coarse-grained force field is Boltzmann averaging over the degrees of freedom that are lost when passing from the all-atom to the coarse-grained representation; consequently an effective coarse-grained energy function is a potential of mean force (PMF). Approximation of the PMF is, however, necessary, for tractability and transferability. This can be done by (1) defining the components of the PMF as statistical potentials extracted from structural databases (e.g., the ROSETTA or CABS force fields), (2) fitting neo-classical expression from all-atom force fields to thermodynamic and structural quantities (e.g., the MARTINI force field), (3) iterative Boltzmann inversion, (3) force matching, and (iv) factor expansion of the PMF into Kubo's cluster cumulants (e.g., the UNRES force field). The factor expansion approach enables aggressive coarse graining with retaining the ability to models the structural features without knowledge-based restraints. In this talk, these approaches will be described and examples to illustrate the ability of coarse-grained models to treat large systems at long time scales will be presented.

Time Crystals and Rotary Molecular Motors

Antti J Niemi

NORDITA, Stockholm & Uppsala University, Sweden

I develop a novel theoretical physics based approach to explain how a general class of autonomous rotating molecular motors function: Molecular machines are not rigid bodies, they are deformable bodies, and I propose new paradigms that are appropriate for their description. For this I employ topological and geometrical methods that are already indispensable in numerous theoretical studies elsewhere, including particle physics, condensed matter physics and gravity. I exploit the geometry in the shape space of deformable bodies to explain how a cyclic motion in one set of variables, in my case the vibrations of individual atoms in a molecule, produces other kind of periodic motion in another set variables, that in my case describe the rotational motion of the entire molecule. This self-organization of fast individual atom oscillations into a slow rotational motion of the entire molecule can occur even with no angular momentum. It is due to the geometric concepts of holonomy, and a connection in the shape space. I also reveal an analogy between a rotating molecular machine and the concept of a driven time crystal, a material system that can sustain cyclic motion in response to an external cyclic drive, albeit with a different frequency. I use the analogy to develop an effective theory description that I combine with detailed all-atom molecular dynamics simulations, to investigate various ring-like and knotted molecular rotors. As a proof of concept, I describe how in the case of a single cyclopropane molecule, the individual atom vibrations can transduce into a uniform and sustainable rotational motion of the entire molecule.

Modeling Polymer Systems in the Presence of Non-Trivial Topological Relations: a Combined Analytical-Numerical Approach

Franco Ferrari

University of Szczecin, Poland

This lecture attempts to present a joint analytical-numerical point of view on the properties of knotted and topologically linked polymer rings with a perspective for future applications and experiments. Single knots and links formed by polymers are complex systems. Even in the case of knots consisting of a homopolymer in a bad solvent, a Monte Carlo Wang-Landau study has revealed that their energy landscape exhibits a funnel-like structure similar to that of proteins. Computer simulations show also that several different phases may be observed when a knot is stretched. A more complicated behaviour is obtained by changing the monomer compositions. The possibility of controlling the amplitudes and the temperatures of the reversible expansions of single knots and other properties by tuning topology, monomer composition and polymer length, paves the way for applications of polymers subjected to topological constraints as molecular motors and machines. Despite the fact that for a long time the problem of knotted and linked polymer rings has been considered as mathematically untractable, it is now possible to model links using analytical methods. These methods provide not only important hints about the way in which the monomers interact due to the

presence of topological relations. They allow also to establish new correspondences with other systems in which the topological relations between quasi one-dimensional objects become relevant, such as for instance the lines of the solar magnetic fields. Some calculations in the case of two linked ideal polymer rings can be performed exactly or, in the case in which the excluded volume interactions are present, several approximations are possible. The results are in agreement with the observations on on linked DNA rings made in the ninties of the previous century by Nicholas Cozzarelli and his group. Finally, a way for checking experimentally some of the numerical and analytical findings using calorimetry will be outlined.

Dynamics of Intrinsically Disordered Proteins and their Droplet-like Aggregates

Marek Cieplak

Institute of Physics, Polish Academy of Science, Warsaw, Poland

The intrinsically disordered proteins (IDPs) may aggregate and form multiprotein droplets that act as membraneless organelles. Theoretical understanding of the formation and dynamics of such droplets requires using coarse-grained molecular dynamics models. We describe a novel model (constructed with Lukasz Mioduszewski) that is a generalization of the so-called Go-like model, originally designed for structured proteins, and based on the concept of contact interactions between amino acids. In the case of the IDPs, the contacts are derived primarily from an instantaneous shape of the backbone and not from the geometry of a single reference state (such as the native state). The metastable proteinaceous droplets may arise within the two-fluid coexistence region that is bounded by the binodal and spinodal lines. We present novel theoretical methods to derive these lines. As an illustration, we discuss phase diagrams for systems of elastins and polyglutamines.

Deciphering 3D Genome Organization with Probabilistic Models

Noam Kaplan

TECHNION Israel Institute of Technology, Haifa, Israel

The spatial organization of the genome is closely linked with its function. Recent genomic technologies allow interrogating 3D genome organization by measuring spatial interaction frequencies of all pairs of loci in the genome. Investigation and interpretation of the resulting interaction matrices, which represent an average representation of highly stochastic genomic structures across a cell population, poses a major challenge. In my talk I will show how probabilistic models provide an excellent framework to accomplish this goal. These models allow to capture explicit mechanistic hypotheses, while simultaneously utilizing the large amounts of available data to infer genome-wide biological meaningful parameters. Modelling specific patterns of genomic structure such as topologically associating domains and genomic compartments, I will show how these models can be used to methodically ask biological questions about 3D genome organization.

Pharmacological Protein Inactivation by Targeting Protein Folding Intermediates

Pietro Faccioli

University of Trento, Italy

Enhanced path sampling methods developed by our group over the last decade have made it possible predict the folding process of biologically relevant proteins (consisting of several hundreds of amino acids), using realistic all-atom force fields. Based on this technological advancement, we proposed an entirely new paradigm for rational drug discovery named Pharmacological Protein Inactivation by Folding Intermediate Targeting (PPI-FIT). This scheme is based on the rationale of identifying small molecule that bind to theoretically predicted folding intermediates, thus blocking the protein folding process and targeting protein degradation. Using the PPI-FIT paradigm we have discovered molecules that can selectively and dose-dependently modulate the cellular expression of the human prion protein (PrPc), a protein considered undruggable with conventional method and is involved in many fatal neurodegenerative diseases. An experiment is planned for 2022 in in International Space Station, to exploit microgravity conditions to attempt the crystallization of partially folded PrP proteins in complex with one of the small molecules discovered using PPI-FIT. The PPI-FIT approach is now being exploited industrially and has been applied to a number of different targets.

Mathematical Models and Analysis of the Impact of CTCE9908 and Kynurenine Metabolites on the Proliferation and Survival of Tumour Cells

Roumen Anguelov

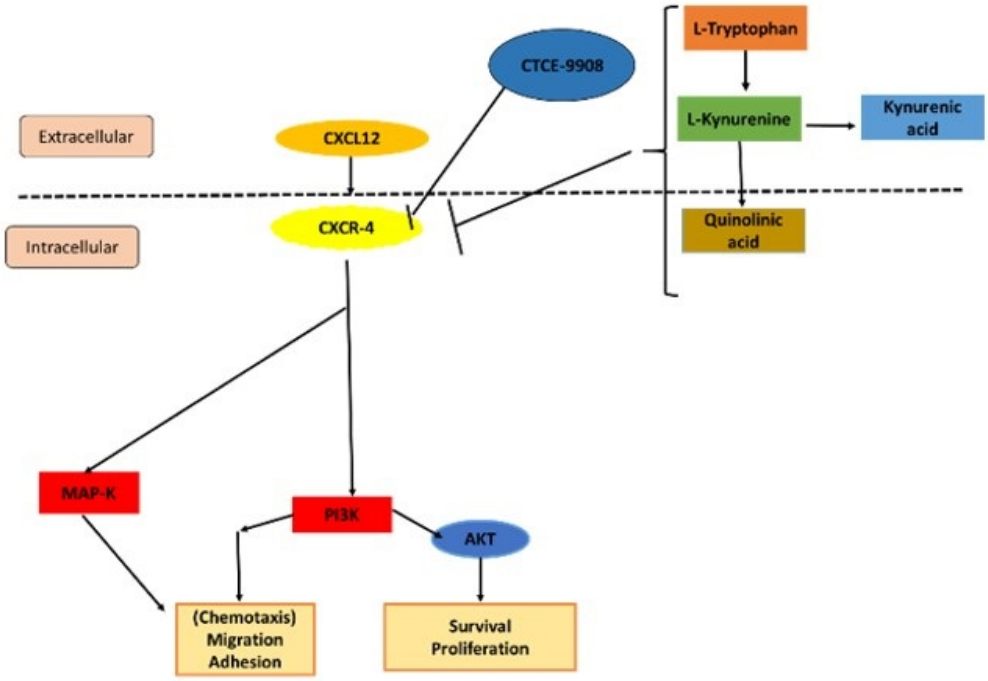
University of Pretoria, South Africa

Melanoma cells express chemokine receptor 4 (CXCR-4). When bound to chemokine ligand 12 (CXCL12) it activates signalling pathways such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) that promote tumour cell proliferation, migration and adhesion.

CTCE9908 binds to the receptor CXCR-4 and prevents CXCL12 to dock on this sensor thus inhibiting adhesion and proliferation ability of the cell. The kynurenine metabolites act in a similar way as indicated on the diagram. Further, sufficient level of blocking the CXCR-4 receptor and inhibition of the respective signalling pathways causes cell death.

A generic mathematical model is constructed using the principle of mass action - reaction kinetics. It is a competitive dynamical system capturing the interplay between the activation process, that is CXCL12 docks on a CXCR-4 sensor, and the inhibition process, that is, an inhibition agent (CTCE9908 or a kynurenine metabolite) attaches to CXCR-4 and blocks it. Theoretically the unique equilibrium is reached via two processes (i) fast: occupying available docking places and (ii) slow: replacement of CXCL12 by the inhibition

agent. Therefore, while the equilibrium itself does not depend on the initial state, the time to get near it does. When the equilibrium is in the domain of sufficient inhibition for cell death, the equilibrium is only theoretical in the sense that it cannot be reached, this being a desirable outcome.



Joint work: Y. Hlophe[1], J. Serem[2], P. Bipath[1], T. Nyakudya[1], A.E. Phiri[3], M. Gandhi[1], and R. Anguelov[3]
[1] Department of Physiology, [2] Department of Anatomy,
[3] Department of Mathematics
University of Pretoria, South Africa

Understanding the Structure and Dynamics of the SARS-CoV2 Helicase (nsp13) from Molecular Dynamics Simulations

Sarah Harris

University of Leeds, UK

The SARS-CoV-2 nsp13 is one of the non-structural proteins of the SARS-CoV-2 coronavirus. It is a helicase protein that has a number of functions in the host cell during viral replication: it is involved in the separation of double stranded nucleic acid helices, it plays a role in single stranded nucleic acid translocation and it has nucleotide triphosphatase activity as part of the RNA capping machinery of the virus.

The SARS-CoV2 helicase consortium is an international team of volunteers using atomistic molecular dynamics simulations to model this protein in the context of the broader replication/transcription and proof-reading machinery. We have collectively generated multiple microseconds of simulation data for analysis. We have observed that binding either RNA or ATP leads to substantial stiffening of the helicase, suggesting that the apo protein is a bad target for rational drug-design compared to the bound helicase complexes. We have also seen that the major mode of flexibility of the apo helicase is consistent with the large-scale structural changes observed in recent cryo-EM studies of the co-transcriptional capping machinery.

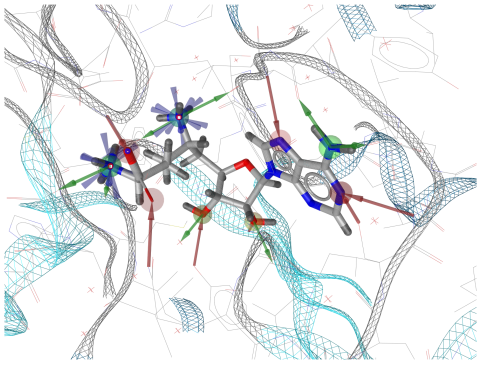
CONTRIBUTED TALKS

Fighting Antimicrobial Resistance – *In Silico* Screening for Novel TrmD Inhibitors

Adam Stasiulewicz[1,2], Mai Lan Nguyen[1,3], Joanna Sułkowska[1]

[1] Centre of New Technologies, University of Warsaw, Poland
[2] Faculty of Pharmacy, Medical University oo Warsaw, Poland
[3] Faculty of Mathematics, Informatics and Mechanics, University of Warsaw, Poland

Because of increasing antimicrobial resistance, there is a constant need for finding novel antimicrobial drugs. Bacterial tRNA methyltransferase TrmD is a vital enzyme for such pathogens as Pseudomonas aeruginosa or Haemophilus influenzae. It is an excellent molecular target for the design of new antibiotics or chemotherapeutics. The major difficulty is the analogous enzyme in the human organism – tRNA methyltransferase Trm5. Existence of this pair significantly hinders the process of finding new inhibitors selective only for the pathogenic protein. Fortunately, there are major structural differences at the cofactor binding sites of these two enzymes. The main one is the occurrence of a deep trefoil knot in TrmD. This knot partially forms the binding site, imposing specific geometry, and therefore, a unique binding mode of cofactors or inhibitors, distinct from those found in unknotted Trm5. These differences create an excellent possibility to design novel, selective, and safe TrmD inhibitors, which is the major aim of this project.



However, this is a complex enterprise. The employment of intricate topological differences in fast and moderately accurate drug design methods is very challenging. Thus, such project should be developed step by step. The first phase is to establish a computational procedure that will be able to identify potent TrmD inhibitors. Only then, there will be merit to include the aspect of inhibitors' selectivity.

Herein, we present a comprehensive, multi-step, computational workflow to find new TrmD inhibitors. We have used various in silico methods, merging both structure- and ligand-based ones. In the first part – pharmacophore screening, we utilized LigandScout. We conducted hybrid structure/ligand-based pharmacophore screening of over 15 mln drug-like compounds from

ENAMINE database. In the figure, pharmacophore based on a TrmD-S-adenosylmethionine complex is shown. Compounds with best values of scoring function were selected by us for the second part – molecular docking. In this phase, we used Schrödinger Glide. We docked chosen molecules to the selected TrmD model that performed best in the prior extensive validation. We conducted a double-step filtration with Glide SP function and molecular mechanics – generalized Born surface area (MM-GBSA) binding energy values. The best 64 scored compounds were then clustered by their structural features.

We selected five main groups of potential hit compounds that may act as TrmD inhibitors for in vitro binding assay.

Formal Representation of the Repertoire of IgM Antibody Specificities

Anastas Pashov[1], Shina Pashova[2], Peter Petrov[3]

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[2] Institute of Biology and Immunology of Reproduction – BAS
[3] Institute of Mathematics and Informatics – BAS

Testing of individual antibody reactivtities as an interrogation of the immune history of an individual is routine practice. Recently it has become increasingly evident that the global view of the repertoire of antibodies may provide information about the internal environment beyond the sum of the individual immune responses and the immune history. As part of the multi-omics endeavor to capture a holistic image of the biological systems, repertoire studies develop in two directions – repertoire sequencing (RepSeq) and functional probing of the repertoire with arrays of diverse structures (e. g. -peptides or glycans, referred to as igome). We used the igome approach based on high throughput probing of the human IgM repertoire by selection of mimotopes from phage display random peptide library followed by next generation sequencing. This technique yields 105 106 different sequences each a target for at least one antibody in the repertoire. These sequences

fit the same binding pocket as a putative nominal epitope for a given antibody without representing exactly the same sequence or structure, hence - mimotopes. To analyze bioinformatically the igome image of the repertoire first a suitable metric reflecting the mimotope properties was selected using ROC curves. Longest common subsequence proved most suitable although it predicted only about 80% of the mimotopes of a given monoclonal antibody. Next the igome was represented as a graph of sequences connected if their longest common subsequence exceeds a conservative threshold of 4 out of 7 residues. In our first analysis this graph helped us define neighborhoods of sequences which contain predominantly mimotopes of the repertoire in healthy donors vs neighborhoods representing mostly mimotopes of the repertoire of patients with anti-phospholipid syndrome. A key feature of the IgM mimotopes proved to be them mirroring sequences from the binding site (paratope) of other antibodies. This is a confirmation of the controversial theory of the antibody networks (idiotypy). A correlation between idiotopes (epitopes within the paratopes of other antibodies) and biological function was found. These initial studies attest to the igome's potential to provide a new class of biomarkers.

Topological Approach for a Global Description of the Antibody Repertoire

Anastas Pashov[1], Peter Petrov[2]

[1] Stefan Angeloff Institute of Microbiology
at the Bulgarian Academy of Sciences, Sofia, Bulgaria
[2] Institute of Mathematics and Informatics – BAS, Sofia, Bulhgaria

We are interested in characterizing the antibody-antigen interactions in a high throughput "omics" context. Epitopes are small domains (10 to 22 residues) of the protein molecules identified as targets of binding by specific antibodies. Our approach is based on the analysis of large libraries of potential epitopes or their simulacra – short peptide mimotopes. We propose to apply persistent homology after formalizing the relations between the epitopes (mimotopes) using the longest common subsequence metric. The concept of

the shape of the data cloud, and how to analyze it rigorously using tools from topology will be discussed. Our aim is to obtain some qualitative description of the data cloud of epitopes with more than 3×10^6 objects, applicable to studies of antibody-antigen recognition, antibody (poly)specificity, and immune networks.

Interscale Simulation: a Novel Combined Methodology to Bridge Between Scales and Methods

Andrey Brukhno

STFC, UK Research and Innovation – Daresbury Laboratory, UK

The talk will present a new state-of-the-art (encapsulated / parallel) Inter-scale approach, as opposed to (disjoint / sequential) multi-scale, for systematically upscaling, but also automated bridging between simulation models, e.g. all-atom (AA) to coarse-grain (CG) models and vice-versa. The well-established methods for coarse-graining, e.g. Inverse Monte Carlo (IMC) and relative entropy minimisation (REM) provide the scope and basis for further development and improvements in the multiscale domain. We combine these with adaptive replica-exchange sampling along the Kirkwood parameter to arrive at hybrid AA/CG accelerated molecular dynamics within the framework of self-consistent interscale model optimisation. The methodology has been implemented in development versions of two leading Daresbury codes: DL_POLY and DL_MESO. Proof-of-concept results from interscale simulations will be presented for water (AA/CG) and simple fluid (LJ/DPD) systems, topped with recently obtained data for more challenging cases of surfactants (SDS) and phospholipids (DOPC and POPC) in aqueous solution.

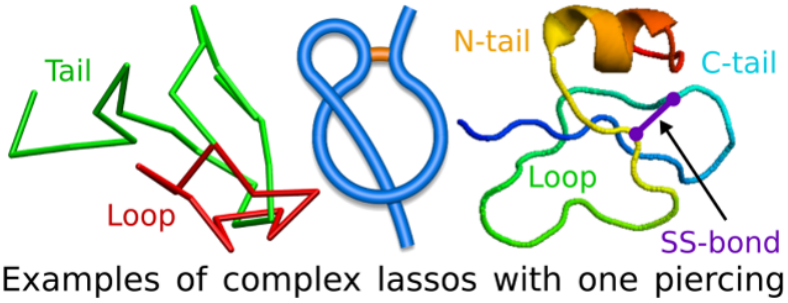
The talk will discuss the capacity of the interscale approach in concurrent exploitation of advanced simulation and coarse-graining methods to tackle challenges in self-assembling soft condensed matter, by switching between and (re-)optimising models on different scales.

Statistical properties of lasso polymers and implications for lasso proteins

Bartosz A. Greń, Paweł Dabrowski-Tumański,
Joanna I. Sułkowska

University of Warsaw, Poland

Lasso is a topology which consists of a loop connected to a tail (or two tails). This topology apears in any proteins with inter-chain covalent bond e.g. disulfide bridge or isopeptide bond. Such additional inter-chain bond affect not only local but also global properties of a molecule. Complex lassos are lassos with lasso-loop pierced by its lasso-tail. Currently we know that 18% of PDB proteins with disulfide bridges have complex lasso topology [1, 2]. There are few protein examples of complex lasso topologies performing important roles in protein function [3, 4, 5], but general role of this topology is unknown.



Examples of complex lassos with one piercing

To understand better properties of lasso topology in proteins we decided to compare lassos from proteins with lassos from computer simulated polymeric model. We have found that there are differences in lasso loop shapes and that threading of lasso loop have different effect on them. Furthermore, in general in proteins there is smaller number of pierced lassos then the polymeric model predicts. However, short-tailed proteins have much higher pierced lasso probability [6].

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Translocation Dynamics of Vesicles Through Narrow Pores

Bogdan Rangelov and Andrey Milchev

Institute of Physical Chemistry "Acad. Rostislav Kaishev"
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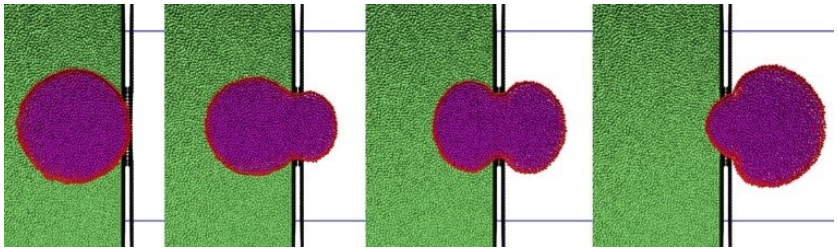
Lipid vesicles and biological membranes as real physical objects attract wide interest towards diverse phenomena like all kinds of cellular biochemistry general processes, including transendothelial migration, controlled (and targeted) drug delivery, nanocarriers releasing substances, filtration, etc. One of the most intriguing problems in this field for which only few theoretical predictions so far exist is the translocation dynamics of a partially filled membrane through a narrow pore, e.g., when driven by pressure difference between the two sides of the pore. This is the main focus of the present work where we carry out comprehensive investigations involving membranes of different size. Using extensive Molecular Dynamics simulations, we demonstrate as a principal result that the mean translocation time $\tau_{trans}(M)$ of a triangulated membrane with M vertices depends on the pore radius R_p according to a general scaling law, $\tau_{trans}(M) \sim 1/\sqrt{(R_p - R_p^{\infty})}$, where R_p^{∞} denotes the least pore orifice for a vesicle of size M. With respect to the driving pressure difference, ΔP, it is found that $\tau_{trans}(M)$ scales as $\Delta P^{-1/3}$. In addition, our computer experiments show that larger vesicles penetrate more easily through pores due to increasing bending flexibility with growing size M. The impact of few key parameters on the membrane properties is also examined and optimal values for faster translocation suggested.



The authors acknowledge the support from EUTOPIA – EUropean TOPology Interdisciplinary Action – COST Action CA17139 and Project CoE National center for mechatronics and clean technologies, BG05M2OP001-1.001-0008.

InterCriteria Analysis Approach to Assess the AMMOS2 Software Platform Performance

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The *in silico* (computer-aided) approaches are among the fastest evolving ones when considering rational drug design and chemical risk assessment. These approaches successfully concur with the time-consuming and costly process of drug design, thus motivating investigators to develop and apply intensively a variety of computer-aided techniques. The structure-based virtual screening (SB-VS) is one of the most promising methods as it helps a lot in the discovery of hit molecules by docking them in proteins' binding sites. The efficiency of SB-VS can be further improved via post-docking optimization of the protein-ligand binding energies, and thus, the software platform AMMOS (Automatic Molecular Mechanics Optimization for *in silico* Screening) is in the focus of this investigation. AMMOS has been developed as a multi-step structure-based procedure for efficient computational refinement of the interactions in the protein-ligand complexes. Currently, AMMOS is also available as an interactive web server AMMOS2 (http://drugmod.rpbs.univ-paris-diderot.fr/ammosHome.php) and provides an automatic procedure for energy minimization of a large number of experimental or modelled protein-small organic molecules complexes including water molecules and metal atoms. AMMOS2 allows optimization of protein-ligand interactions at five levels of protein flexibility, while the ligand is always flexible: (*i*) entirely flexible protein; (*ii*) flexible sidechains of the protein; (*iii*) flexible protein atoms within a user-defined radius around the ligands; (*iv*) flexible atoms of protein sidechains within a user-defined radius around the ligands; and (*v*) entirely rigid protein.

Recently we proposed a procedure to assist the decision-making process in the structure-based docking protocols by using the InterCriteria Analysis (ICrA) approach. ICrA is based on the mathematical formalisms of index matrices and intuitionistic fuzzy sets and has been elaborated as an approach to distinguish possible relations in the behavior of pairs of criteria when multiple objects are considered.

In this study, the effectiveness of applying different levels of protein flexibility in the post-docking optimization via AMMOS2 is assessed using ICrA

to advice about their interchangeability. The outcomes from ICrA implementation confirm the effectiveness of AMMOS2 and further demonstrate the need of protein-ligand interaction optimization at different levels of protein flexibility.

Acknowledgement: This investigation is supported by the Bulgarian National Science Fund, grant DN-17/6.

Applied Mathematics for Forensic Medicine

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Facial approximation is a method for rebuilding a deceased person's face based on the skull morphology and data for facial soft tissue thicknesses (FSTT). Facial approximation is used to support the identification of unknown bone remains when conventional methods for identification such as DNA have failed. The FSTT investigation methods have changed over the years from needle puncturing on cadavers' heads to application of current imaging technologies, which enables in vivo measurements. Among the used technologies are radiography, ultrasound, magnetic resonance imaging, and computed tomography (CT).

Traditional facial approximation techniques are based on FSTTs measured at particular anatomical landmarks, which requires the areas between these points to be subjectively interpolated. However, current imaging modalities provide alternative approaches for acquisition of dense FSTT data which ensures abundant information for studying the skull/skin relationship and supports building of more accurate facial approximations. Methods for simultaneous calculation of numerous FSTT distances over the whole face have been currently introduced [Shui et al., 2016, Simmons-Ehrhardt et al., 2018]. Moreover, Gietzen et al. [2019] proposed an automated method for

forensic facial approximation based on dense statistics of FSTTs. The previous studies have used different approaches for calculation of the FSTTs. Simmons-Ehrhardt et al. [2018] and Gietzen et al. [2019] have used Hausdorff metric, i.e. the shortest Euclidean distances between points from two surfaces, while Shui et al. [2016] have measured the Euclidean distance from each vertex of the skull to the corresponding intersecting point on the skin with the same z-coordinate.

The present study aims to propose an original dense approach for computation of FSTTs. For this purpose, three-dimensional surface models of the skull and skin were generated from CT image data and the skull-to-skin distances were calculated using ray tracing in the normal direction. Our goal is to eliminate wrong pairing of skull and skin points, which is typical for the Hausdorff metric in regions, where the two surfaces possess different geometric properties such as convexity / concavity.

For the implementation, both 3D surfaces are a priori triangulated and encoded in corresponding STL files, which serve as input data for our algorithm. As output, we document signed distances from the mass centers of each outer skull surface triangle to their corresponding intersection point with the skin surface. Our first model was pure theoretical and there we considered the offsets solely with respect to the normal direction, prescribed by the STL input (in this format, the triangulated surface is represented as groups of 4×3 real matrices that correspond to the coordinates of the three vertices of a given triangulated patch, followed by the coordinates of its unit normal vector). This approach is not very computationally effective as it involves ray tracing in two directions (positive and negative normal directions) and with respect to two surfaces. Indeed, the normal directions in the STL files are not outer oriented in general, plus some of the triangles of the skull surface correspond to inner skull parts, which do not have a skin counterpart and in order to characterize them - we need to check if in both directions the normals intersect the skull surface before the skin one. The ray tracing is implemented via a brute force algorithm, where we successively check if the normal ray of the given skull triangle patch intersects the interior of a selected skin triangle patch until a positive answer. For the second model, we consider semi-infinite cylinders with a fixed radius r instead of pure rays and apply a software for determining the "first" intersection point of them with the skin surface. Varying the parameter r serves as a tradeoff between Hausdorff and Euclidean metrics which provides an extra degree of freedom.

Acknowledgement: This study was partially supported by the Bulgarian National Science Fund under Grant DN11/9-15.12.2017.

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Enhanced Sampling Molecular Modeling of Peptide-Membrane Interactions: a Case Study

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Membrane active peptides are promising biological molecules with possible applications in the treatment of various infection diseases. There are two classes of membrane active peptides that attract great scientific interest in the last two decades – cell penetrating peptides, which act as cargo carriers across cellular membranes and could be employed as drug-delivery systems and antimicrobial peptides (AMPs). AMPs have broad-spectrum activity against a wide variety of pathogens, including gram-positive and gram-negative bacteria, fungi, parasites, and even some viruses. In the age of multi-drug resistant bacterial strains, AMPs emerge as especially interesting research objects as generally bacteria develop little to none resistance to their action.

Membrane active peptides, and AMPs in particular, exert their action by interacting with target cellular membranes, whereas they either insert into or penetrate the lipid bilayer. It is widely accepted that the mechanism of action of AMPs is based on their cationic and amphiphilic nature, which enables them to interact with negatively charged bacterial surfaces and membranes, thus causing membrane disruption or altering metabolic processes. Therefore, understanding of the AMP's mechanism of action requires experimental studies and computational modelling of the peptide-membrane interaction. However, this interaction presents some challenges to standard atomistic simulations, due to slow relaxation times of the lipid bilayer, conformational changes in the peptides upon interaction with the membrane, peptide self-assembly and pore formation, requiring prohibitively long simulation times.

Here, we report the computational study of the interaction of a particular AMP with a model bacterial membrane. The studied AMP was isolated from the mucus of garden snails *Helix aspersa*. The model membrane is constructed to resemble the *E. Coli* membrane: asymmetric, with POPE (neutral) and POPG (negatively charged) phospholipids in ratios 85/15 and 70/30 in the external, resp. internal layer. To enhance the conformation space sampling of the AMP–membrane complex we employed well-tempered metadynamics, which allowed for exploration of multidimensional free energy surfaces in terms of appropriate collective variables.

Acknowledgement This work was supported in part by the Bulgarian Science Fund (Grant KP-06-OPR 03-10/2018) and Bulgarian Ministry of Education and Science (Grant D01-358/17.12.2020) under the National Research Programme "Innovative Low-Toxic Bioactive Systems for Precision Medicine (BioActiveMed)" approved by DCM # 658/14.09.2018. Computational resources were provided by the BioSim HPC Cluster at the Faculty of Physics at Sofia University "St. Kl. Ohridski", Sofia (Bulgaria) and by CI TASK (Centre of Informatics – Tricity Academic Supercomputer & networK), Gdansk (Poland).

Heteropolymer Design: Learning Protein Evolution by Reverse Engineering

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CIC biomaGUNE, San Sebastian, Spain

Proteins are the workhorse of life. They are the building infrastructure of living systems; they are the most efficient molecular machines known, and their enzymatic activity is still unmatched in versatility by any artificial system. Perhaps proteins' most remarkable feature is their modularity. The large amount of information required to specify each protein's function is analogically encoded with an alphabet of just 20 letters. The protein folding problem is how to encode all such information in a sequence of 20 letters. In this talk, we go through the last 30 years of research to summarize the state of the art and highlight some applications related to fundamental problems of protein evolution.

AllerScreener: a Tool for Allergenicity and Cross-Reactivity Prediction of Proteins

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Allergy is a hypersensitive reaction of the immune system to typically innocuous substances in the environment, developing in two stages: the sensitization stage and the effector (elicitation) stage. In the sensitization stage, an allergen is recognized as an antigen by human T cells. As a result, the allergen-specific T cells drive B cells to become allergen-specific, and produce immunoglobulin E (IgE). The specific IgE binds to the surface of mast cells, basophils, and activated eosinophils. In the effector stage, the subsequent re-exposure to the same allergen triggers IgE to cross-link the allergen, activate the mast cells, basophils, and eosinophils and induce inflammatory reactions. A protein is considered as an allergen if it triggers the immune system

to release IgE antibodies. Only a small peptide fragment from the allergen, called epitope, binds to IgE. Some allergens share common IgE epitopes – a phenomenon known as IgE cross-reactivity. Because of the cross-reactivity, some people sensitized to a specific allergen (peanut) react to the exposure to other allergen (hazelnut). IgE epitopes are linear – composed of sequential amino acids, or conformational – composed of residues patched on the allergen surface. The existing methods for allergenicity prediction are based on similarity search to known allergens and/or IgE epitopes. They are not able to predict the sensitization and rely only on the release of IgEs. Here, we describe a tool for allergenicity prediction, named AllerScreener, which is based on the molecular mechanisms of sensitization. The sensitization includes several processes: allergen intake by antigen-presenting cells, proteolysis in the lysosome, peptide binding to MHC class II protein, presentation of the peptide-MHC class II protein complex on the cell surface, recognition by naive T cells, T-cell differentiation to Th2 cells, activation, proliferation and differentiation of B cells by Th2 cells. Peptide binding to MHC proteins is a crucial step in the process of sensitization. It takes place in antigen recognition by T cells and activation, proliferation and differentiation of B cells. Not all peptides binding to MHC are T-cell epitopes, but all T-cell epitopes are MHC binders. In humans, the MHC class II protein complex is encoded by the human leukocyte antigen gene complex (HLA). There are 3 major MHC class II loci encoded by HLA: HLA-DP, HLA-DQ, and HLA-DR. Human MHC genes are highly polymorphic, i.e. each locus has many alleles. Due to their polymorphism, HLA proteins bind to a large variety of antigen peptides. The peptide binding core consists of nine residues, i.e. in order to be recognized as allergen, the protein should contain at least one nonamer (9 amino acid long peptide) binding to a HLA class II protein. AllerScreener utilizes the predictions by two other tools for HLA binding: EpiTOP and EpiDOCK. EpiTOP predicts peptide binding to 24 most common HLA alleles. The EpiTOP models have been derived by proteochemometrics – a ligand-based method for quantitative analysis. The model in EpiDOCK are docking-based quantitative matrices for peptide binding prediction to 23 HLA alleles. AllerScreener uses an extensive database of allergenic proteins with different origin. The HLA binders in each protein were predicted by EpiTOP and EpiDOCK and compiled into a database. A second database containing known T-cell and B-cell epitopes was implemented. AllerScreener uses the databases for HLA binders and epitopes search in a tested protein. Additionally, AllerScreener is able to find common HLA binders in different proteins and to predict cross-reactivity between them. AllerScreener is freely accessible at: https://www.ddg-pharmfac.net/AllerScreener.

Topological Aspects to How Life Uses Liquid Crystals

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Liquid crystals are a state of matter which has properties between those of conventional liquids and those of solid crystals. Biological liquid crystals are of particular importance, as they form the basis of organization of molecules, and with this, organization of biologically fabricated soft and hard tissue. Liquid crystals unite order and mobility, the most important requirements for self-organization and structure formation in living systems. As molecular chains are stiff, liquid crystalline materials can self-assemble into larger structures and produce films and fibers without requiring containment or molding. In the animal and plant kingdoms, the liquid crystal structure is a recurrent design, suggesting cases of convergent evolution. Examples include the organization of DNA, chromatin, chitin, cellulose, collagen, viruses, silk, and cholesterol esters in atherosclerosis. Liquid crystalline structures can be found in bacteriophages, archaea, eukaryotes, bacterial nucleoids, unicellular algae chromosomes, sperm nuclei of many vertebrates, crustacean and insect cuticles, mollusc shell microstructures and the pearls they produce, bone, tendon, cornea, fish scales and scutes, squid pens and cuttlebone, plant cell walls, virus suspensions, silk produced by silkworms and spiders, and arterial wall lesions. The roles and functions of these biological liquid crystals include maximization of packaging efficiency, morphogenesis, mechanical stability, optical information, and protection against radiation. The liquid crystal structure that is ubiquitously present in living matter, and whose chirality is one of the most important characteristics, is a cholesteric structure found in almost all types of animals and plants. The unifying structure of biological cholesteric liquid crystals is attributed to the helical organization of basic modules such as molecules, macromolecules and microfibrils (chitin, collagen and cellulose), without a positional order for these basic entities, which is the structure of the cholesteric liquid crystal phase. However, even though of main importance and despite many decades of chemical, biochemical, cell-biological and structural research, we have only a crude idea about how liquid crystalline macromolecule organization is tuned in vivo and in vitro for the generation of the large variety of structures that we find in nature today. In this talk I shall highlight topological issues inherent in how life uses liquid crystals.

Quantum Analog Computational Device in Life Sciences

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The present work introduces the new concept of *quantum analog computing*, developed by infinityQ Technology, to efficiently and effectively carry out computations. Our new approach takes advantage of analogies with atomic quantum systems to build an artificial atom as a basic computational structure, without the need to use actual atoms or molecules (which are extremely sensitive to the external environment) to carry out quantum computations. The quantum analog device, in turn, is able to tackle a variety of optimization problems, and due to its circuitry and the use of collective analog computing to efficiently explore the space of possible solutions. We touch upon implementations of the quantum analog device in the area of protein-protein docking, FFT analysis and more.

Ring-o-rings: Joining the Ends of Poly[n]-Catenanes to Capture Supramolecular Torsion

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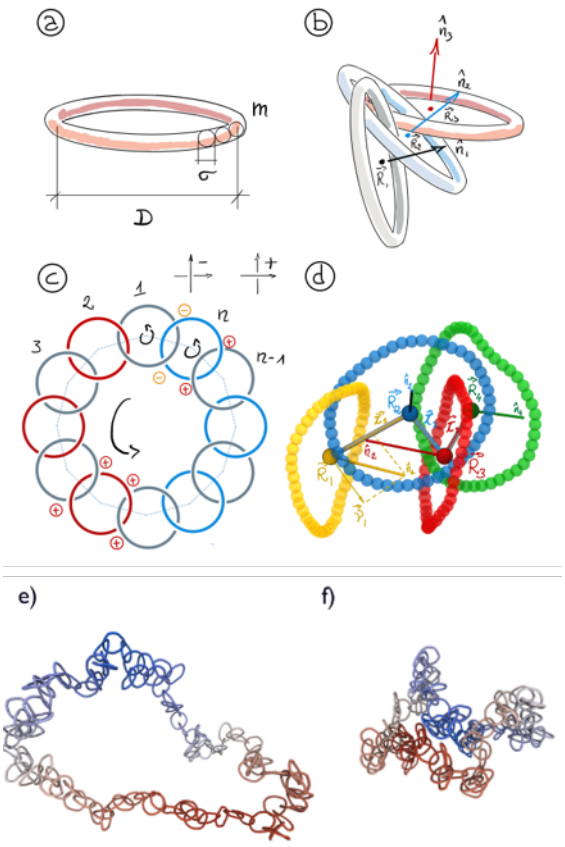
Recent advancements in chemical synthesis and self-assembly as well as modelling and simulations have offered a framework to design systems of interlocked rings with controllable properties. These systems can be produced

at scales varying from a few nanometers to several micrometers, and have been proposed for applications ranging from smart materials, to catalyzers and nano-machines. Of particular interest are poly[n]-catenanes, linear sequences of n mechanically interlocked circular molecules, which can be synthesised through self assembly.



Most of the work so far has been focussed on the variety of features that the molecular mobility of the mechanical bond may confer to poly[n]-catenanes compared to standard polymers. Here we show that, by joining the two ends of a poly[n]-catenane to form a supramolecular ring, it is possible to capture different amount of torsion and hence alter significantly the average extension of the structure as well as local properties such as the relative orientation of the elementary rings along the backbone.

Finally, by extending the notion of twist and writhe of ribbon-like structures to circular poly[n]-catenananes we show that their sum is, on average, conserved and follows a scaling relation with the length n of the catenane. Our results indicate that versatile supramolecular structures can be designed in such a way to store a controlled amount of torsional stress, opening several potential applications for novel smart materials.

In the figure, the systems studied are shown. The simulated catenanes are composed of n rigid rings of thickness sigma and diameter D (a), topologically linked with each other to form a circular catenane (b), (c). The amount of stored torsion contained in the catenane can be controlled in the simulation by changing the twist inserted through linking (d). Different amounts of stored torsion radically change the system behaviour, as shown by the snapshots in panels (e) – zero torsion, and (f) – maximum torsion.

Keywords: catenanes, topology, rings, simulations, supramolecular chemistry, polymers

Nascent Folding of Proteins Across the Three Domains of Life

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We study the nascent behavior of three model coarse-grained proteins in six rigid all-atom structures representing ribosomes that come from three domains of life. The synthesis of the proteins is implemented as a growth process. The geometry of the exit tunnel is quantified and shown to differ between the domains of life: both in volume and the size of constriction sites. This results in different characteristic times of capture within the tunnel and various probabilities of the escape. One of the proteins studied is the bacterial YibK which is knotted in its native state. A fraction of the trajectories results in knotting and the probability of doing so is largest for the bacterial ribosomes. Relaxing the condition of the rigidness of the ribosomes should result in a better avoidance of trapping and better proper folding.

Understanding the role of YARS2-tRNA complex in MLASA disease

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Last year an 8 week old infant passed away from MLASA disease. Usually people with this disorder live much longer, even 31 years. This severe case of the genetic mitochondrial disease was studied in depth. Scientists found two novel mutations in YARS2 protein that cause symptoms.YARS2 is Tyrosyl-tRNA synthetase working inside mitochondrion. The goal of the study is to explain how substitution in the first chain and deletion in the second chain

of YARS2 affect the catalyzed reaction and the protein itself. Analyzed variants are interesting due to the fact that mutations are far from active and docking sites. The system was studied mainly using molecular dynamics and dynamical network analysis. Calculated signal paths demonstrated that mutations cause changes in some of them. It was found that, despite YARS2 being a homodimer, two chains act differently to some extent which is shown by dynamical network analysis.

The Reaction Network Approach in Mathematics of Life

Part I – Translation to ODE System

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The mathematics of life (biological mathematics, biomathematics, mathematical modelling in biology) is an well-established scientific area with numerous university lecture courses, popular books and student textbooks, see e.g. [1], [2], [3], [4].

The reaction network (RN) approach in the mathematics of life is a rapidly developing tool for the construction of mathematical models in life sciences [5], [6], [7].

This work presents the main principles, terminology and notation of RN theory. We show how diverse types of interactions (chemical, biological or social) can be formalised as reaction networks. We further demonstrate how these networks give rise to systems of ODEs that describe the evolution of various populations or mixtures.

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Part II – Examples and Numerical Simulations

There exists a rich array of applications of the RN-method in diverse subfields of biomathematics, such as population dynamics [1], enzyme kinetics [2], epidemiological modelling [3], metabolic and signalling pathways [4], etc. In this work we apply the tools of RN theory to present several examples of RN models that are widely applicable in biomathematics. We formulate these models, state some of their mathematical properties and illustrate them by means of numerical simulations.

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Numerical simulations and analytical studies of TASEP – a model of biological transport

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In the equilibrium statistical mechanics, the study of simple models has proven a very effective tool. In the non-equilibrium case the study of simple models like TASEP and its different variants is expected to be similarly of great help. In the last years an intensive research is mounting with a focus on the study of different variants of TASEP and TASEP-like models, taking into account more realistic features of the real non-equilibrium systems. The one-dimensional Asymmetric Simple Exclusion process (ASEP) is a paradigmatic model for understanding a variety of systems in the rich world of nonequilibrium phenomena, since it is one of the rare examples of exactly solvable models far from equilibrium. It is one of the simplest models of self-driven many-particle systems with particle conserving stochastic dynamics which describes phase transitions between three non-equilibrium stationary phases in one dimension. The process was first introduced to model kinetics of protein synthesis [1, 2], but later found a number of other applications, e.g., in vehicular traffic flow [3], in biological transport [4] forced motion of colloids in narrow channels [5] etc. We focus here on our results in the study of TASEP – the extremely asymmetric version of ASEP, when particles are allowed to move in one direction only. The model is defined on an open network, in one dimension, in terms of discrete-time discrete-space stochastic dynamics of hard-core particles. Its properties are determined by the choice of boundary conditions. In the thermodynamic limit, the open system exhibits three distinct phases in the plane of particle input-output rates (α, β). We study two interesting cases of TASEP, which have their respective value in studying more realistic systems of biological transport: a model of aggregation and fragmentation of clusters of particles [6, 7] and TASEP on open networks with a nontrivial topology [8], in particular, networks containing bifurcation and merging points that simulate the motion of molecular motors along microtubules with varying number of protofilaments.

Acknowledgements Partial financial supports by the Bulgarian MES through Grant No. D01-221/03.12.2018 for NCDSC—part of the Bulgarian National Roadmap on RIs, and by the Plenipotentiary Representative of the Bulgarian Government at the Joint Institute for Nuclear Research, Dubna, through grant No. 01-3-1137-2019/2023 (and also by BNR of MES) are thankfully acknowledged.

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In silico Study of the Molecular Mechanism of LMWH Antiinflammatory Action Within the COVID-19 Context

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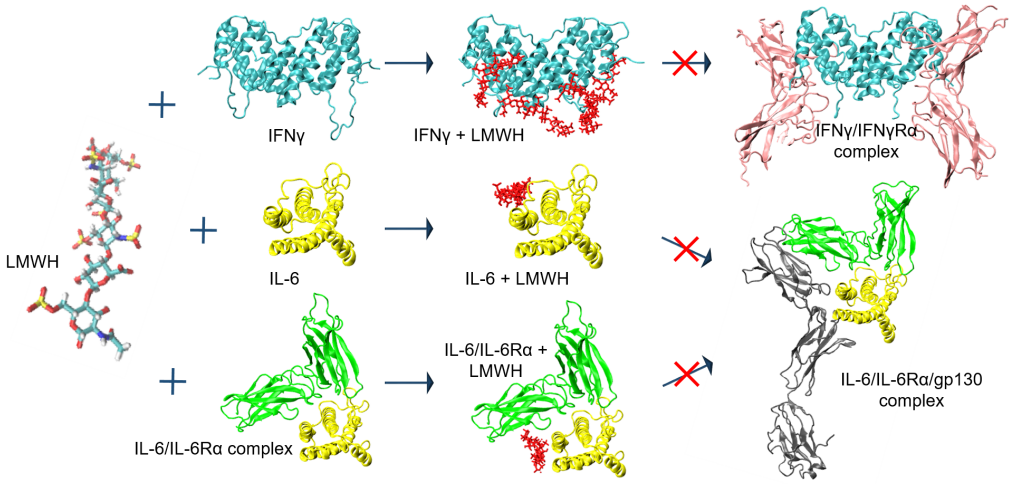
We perform *in silico* study of the ability of low-molecular-weight heparin (LMWH) to inhibit both IFNγ and IL-6 signalling pathways. While heparin's binding affinity to these cytokines is well-known, the molecular mechanism of its impact on their biological activity has not been studied in detail. Our results show (see the figure) that LMWH is able to fully inhibit the interaction



of IFNγ with its cellular receptor, thus blocking the IFNγ signalling pathway. It also influences the biological activity of IL-6 by preventing the formation of the IL-6/IL-6Rα/gp130 signalling complex.

These findings shed light on the molecular mechanism of the antiinflammatory action of LMWH, relating it to the impairment of the biological activity of these cytokines, and underpin heparin's ability to influence favourably conditions characterised by overexpression of the latter. Such conditions are associated with autoimmune diseases, but also with inflammatory processes, in particular with COVID-19. Our results put forward heparin as a promising means for prevention and suppression of the development of severe CRS in acute COVID-19 patients and encourage further investigations on its applicability as an anti-inflammatory agent.

Acknowledgements This work was supported in part by the Bulgarian National Science Fund under Grants DN-11-20/2017 and KP-06-DK1/5/2021. Computational resources were provided by the Centre for Advanced Computing and Data Processing, supported under Grant BG05M2OP001-1.001-0003 by the Science and Education for Smart Growth Operational Program (2014-2020) and co-financed by the European Union through the European structural and investment funds.

Statistical properties of handcuffs in ideal polymers

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Theoretical and experimental research conducted in the last years shows that the presence of disulfide bridges in peptides leads to curious topological structures along their chains called lassos. Lasso peptides have been shown to be functional e.g. antimicrobial cytokines. But why we should limit ourselves only to a structure composed by a one bridge? Systems containing more of them may be mathematically modeled as spatial graphs. The set of spatial graphs with two vertices is divided into two distinct classes the first one consists of theta curves graphs. Their appearance in biological structures has already been analysed [1]. The second is handcuff graphs (Figure a) that are made of two separate loops connected by a linker. When the drawing of such a graph contains crossings i.e. loops intersects themselves or the linker goes through surfaces spanned by them, non-trivial topologies of a handcuff graph may appear (Figure b and c [2]).

(a) handcuff graph (b) non-trivial handcuff graph 2_1 (c) non-trivial handcuff graph 6_1

Our research aims to explore the statistics and its properties of non-trivial topologies in randomly generated handcuff structures in an ideal polymer. That knowledge will allow us to determine which topologies may appear in biological structures and which are well preserved when the system enlarges. As the complexity of the problem increase exponentially within the length of the polymer, the strict mathematical approach is hard to apply. Therefore we generate handcuff structures and study their topologies by the spatial graphs' invariant- Yamada polynomial [3]. The linker is generated by a random walk and loops by Cantarella's algorithm [4]. Yamada polynomials for handcuff graphs with up to seven crossings have been already calculated by Moriuchi in [2] and that allow us to distinguish generated graphs and thus create the statistics. Although the calculations of Yamada polynomial have been made before e.g. by Moriuchi, there always have been used its relations to other invariants like a bracket polynomial, derived for a particular type of a

spatial graph and there is no freeware software available online that calculates Yamada polynomial for any kind of graph fast enough to be useful for our purpose. There is only a Python implementation in an actual Topoly [5] package which is too slow to hold the needed calculations. That is why we developed a C++ program to calculate its values for any graph, it will be available in Topoly soon.

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Spike Timing Neural Network Model of Conscious Visual Perception

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Since the earliest days of psychophysiology, there has been a debate about the link between sensation, perception, attention, and consciousness. The main question is: what happens to a sensory signal in the brain when it reaches a conscious stage of processing as opposed to being processed outside of awareness? In search of an answer to this question the concept of "Neural correlates of consciousness" is introduced that represents the set of neuronal events and mechanisms generating a specific conscious perception. Based on

it in [3, 4] consciousness is viewed as a state-dependent property of some complex, adaptive, and highly interconnected biological structures in the brain. A model of consciousness is a theoretical description that relates brain phenomena such as fast irregular electrical activity and widespread brain activation to expressions of consciousness such as qualia [16].

Recent studies on neural correlates of consciousness are a continuation of the research initiated at the end of the 19th century [11]. The contemporary trend in this intensively developing nowadays area of research was initiated in the 1990s by the development of an empirical approach focusing on visual awareness because the visual system was already intensively investigated [2, 3, 4, 9]. Since then, consciousness research becomes more diverse but its link to visual perception continued [14, 15]. Irrespective of the intense interest and research efforts in studying consciousness, there is still no consensus about the neural correlates of consciousness, i.e. what are the minimal neural mechanisms that are jointly sufficient for any one conscious perception, thought or memory, under constant background conditions [3]. It is still unclear which brain regions are essential for conscious experience.

Recently, a dominant trend is to view consciousness as emerging from interactions between distributed networks of neurons and especially to the global activity patterns of corticocortical and thalamocortical loops [5, 6, 7, 12, 18, 19, 20]. In [13] a hypothesis was proposed that the thalamus is the primary candidate for the location of consciousness since it has been referred to as the gateway of nearly all sensory inputs to the corresponding cortical areas. This theory was supported by numerous works. Lately, a view of thalamocortical processing is proposed in [17] where two types of thalamic relays are defined: first-order relays receiving subcortical driver input, e.g. retinal input to the lateral geniculate nucleus, and higher-order relays, receiving driver input from layer 5 of the cortex, that participate in corticothalamo-cortical circuits. Recent findings [8] support the important role of the lateral geniculate nucleus in the emergence of consciousness and provide a more complex view of its connections to the other parts of the thalamus and the visual cortex. In [1] it was suggested that the hallmark of conscious processing is the flexible integration of bottom-up and top-down thalamocortical streams and a novel neurobiological theory of consciousness called Dendritic Information Theory, was proposed.

We have already developed a hierarchical spike timing model of visual information perception and decision making including detailed structure of thalamic relay and laretal geniculate nucleus [10]. The model was implemented on NEST Simulator on the supercomputer Avitohol.

The aim of presented here study is to investigate the influence of thalamocortical connectivity on the conscious perception of visual stimuli. We con-

ducted simulation experiments changing the key parameters of our model that are supposed to be related to conscious perception, namely bottom-up and top-down connections between thalamic relay (TRN) and lateral geniculate nucleus (LGN) and primary visual cortex (V1). The model output that is perceptual based decision for left or right saccade generation was observed. Conclusions about the influence of altered key parameters on the ability of our model to take proper decision were commented in respect to the presence or absence of conscious visual perception of the visual stimuli presented to the model input.

Acknowledgement: The reported work is supported by the project "Supercomputer simulation investigation of a neural model of brain structures involved in conscious visual perception" by a co-funding scheme of the Bulgarian Science Fund, COST action CA18106 (Neural architectures of consciousness).

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Biomolecules and Random Matrices

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I will discuss how simplified models of biomolecules are related to sophisticated mathematical structures (such as fatgraphs, chord diagrams, genus characteristics, topological recursion, moduli spaces of Riemann surfaces, etc.) that arise in random matrix theory and inspire research in this area.

Mathematical Modeling of the Estrogen Paradox in the Treatment of Breast Cancer

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In this work, we propose a novel ODE-based mathematical model that investigates the mechanisms behind the estrogen paradox, whereby estrogen is a risk factor for the development of breast cancer, while it can also cure it. The model incorporates the protein p53, which plays a key role in breast cancer suppression.

By means of a global stability analysis and bifurcation, along with numerical simulations, we determined some interplays, characterised by bifurcation curves, between estrogen and p53 that can explain the estrogen paradox.

Driving European HPC for Biomolecular Research: Advanced Software Applications and Support Structures from BioExcel Centre of Excellence

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Europe continues its decades long investments in HPC infrastructures for scientific and applied computational research. The rapid development of novel hardware technologies is pressuring software developers to ensure that their applications are making best use of the available compute capabilities. As the applications become more powerful and complex, there is a growing need to provide adequate training, expertise, and support to end-users. "Black-swan" events such as the ongoing Covid pandemic exemplify the need for concerted efforts by the wider communities (incl. funding agencies, resource providers, application developers, end-users) to put in place systems for adequate response. In this talk I will discuss the work by BioExcel Centre of Excellence (www.bioexcel.eu) in the development of advanced HPC software, training and supporting its end-users, as well as strengthening the computational biomolecular research communities."

Optimal Reduced Representations and Multiple Resolution Models of Biomolecules

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One of the outstanding challenges of computational biophysics is represented by the intrinsic multi-scale nature of several processes and phenomena, ranging from large conformational changes induced by ligand binding to the epigenetic regulation of gene expression and beyond. A unique framework

for the in silico investigation of such phenomena is impossible and inappropriate, as different properties take place at distinct characteristic length- and time-scales; consequently, models and representations at various resolutions have been developed, which address each property specifically. A critical issue, however, is how to integrate these models to account for the interplay of processes occurring at different scales.

In this talk I will present methods and techniques that have been recently developed and applied to fill this gap. Particular attention will be posed on those strategies aimed at identifying functionally relevant regions of proteins, based on the amount of information that a reduced representation can preserve from the underlying high-resolution model. Subsequently, I will discuss the general properties of these reduced representations and the kind of information they can provide about the system under examination. Finally, I will tackle the issue of integrating models at different levels of detail in the same setup, and how these models can be optimised to balance computational efficiency and chemical accuracy.

Iterative Solution of Large-Scale Biomedical Problems and Rational Approximation of Fractional Laplacians

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The considered mathematical models of living tissue are described by systems of partial differential equations. We discuss a class of multiscale and multiphysics problems, the components of which can be defined in domains of different dimensionality. Such systems are coupled trough interface conditions. For instance, they model drug delivery, thermo ablation of unwanted tissues, waste clearance of the brain, capillarity networks, tissue perfusion, excitation of cardiac cells, to name a few.

When applied to real-life problems, this type of models leads to very large-scale systems of linear algebraic equations. In the case of 3 dimensional space domains, the number of degrees of freedom (unknowns) can be of order $O(10^9)$.

Developing efficient preconditioned iterative solution methods is the only way to implement such computer models. Our goal is to construct robust preconditioners of optimal computational complexity.

Example 1: The exchange between a Stokes flow inside a blood vessel and a Darcy flow in the surrounding tissue is modeled (see, e.g. [5]) by the system of equations in the form:

$$\begin{array}{rcll} -\mu\Delta\mathbf{u}_S + \nabla p_S &=& \mathbf{f}_S & \text{in } \Omega_S, \\ \nabla\cdot\mathbf{u}_S &=& 0, & \text{in } \Omega_S, \\ K^{-1}\mathbf{u}_D + \nabla p_D &=& 0 & \text{in } \Omega_D, \\ \nabla\cdot\mathbf{u}_D &=& \mathbf{f}_D & \text{in } \Omega_D, \\ \mathbf{u}_D\cdot\mathbf{n} - \mathbf{u}_S\cdot\mathbf{n} &=& 0 & \text{on } \Gamma, \\ -\mu\frac{\partial\mathbf{u}_S}{\partial\mathbf{n}}\cdot\mathbf{n} + p_S &=& p_D & \text{on } \Gamma, \\ -\mu\frac{\partial\mathbf{u}_S}{\partial\mathbf{n}}\cdot\tau - D\mathbf{u}_S\cdot\tau &=& 0 & \text{on } \Gamma. \end{array} \tag{1}$$

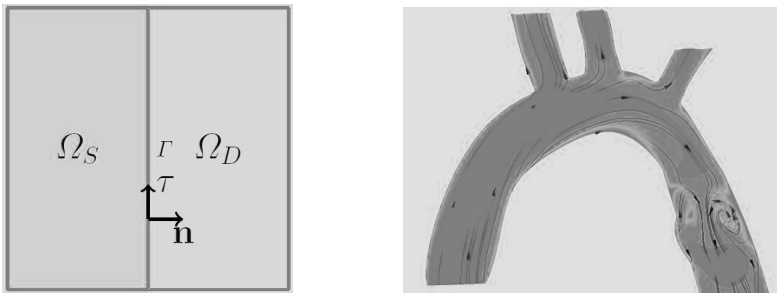

Figure 1: Darcy-Stokes system: model problem with simple geometry (left); realistic problem with more complicated geometry of the interface

Under certain assumptions, the block-diagonal preconditioner

$$C = (-\Delta + DT_S^T T_D,\ K^{-1}(I - \nabla\nabla\cdot),\ I,\ KI,\ (-\Delta + I)^{1/2})) \tag{2}$$

provides optimal condition number estimate for the Darcy-Stokes problem (1).

Example 2: Let Ω be a bounded domain in 3D, while Γ represents a 1D structure inside Ω. The preconditioning of the following trace coupled

problem is studied in [4]:

$$\begin{array}{rcll} -\Delta u + u + p\delta_\Gamma & = & f & \text{in } \Omega, \\ -\Delta v + v - p & = & g & \text{on } \Gamma, \\ Tu - v & = & h & \text{on } \Gamma. \end{array} \tag{3}$$

Applications of such 3D-1D models include, for example, transport of oxygen to brain or fluid exchange between the microcirculation and the surrounding tissue. For 3D-1D problem (3), the following block-diagonal preconditioner is studied in [4]:

$$C = (-\Delta + I, \ -\Delta + I, \ -\Delta^{-0.14}). \tag{4}$$

The key issue in implementing the preconditioners (2) and (4) concerns the solution of systems with the last blocs. The spectral decomposition of the Laplacian on the interface Γ is directly applicable in very limited simplified cases, see e.g. Fig. 1, left. For this purpose, specialized multigrid methods for discrete fractional Sobolev spaces are developed in [1]. The abstract additive multilevel framework is adapted there. The constructed smoother involves small blocks in the form $A_{k,\nu}^{-s}$ of a size ν equal to the graph-degree of the corresponding mesh node.

Here we discuss an alternative approach based on the best uniform rational approximation (BURA) method for A^{-s}, $s \in (0,1)$. The aim is to improve the overall robustness and computational complexity of the preconditioning algorithm. As correctly noted in [1], a disadvantage of the method we introduced in 2018 is that its accuracy depended on the condition number of the matrix A. This drawback is overcome in the improved BURA approximation developed in [3]. It reads as $A^{-s} \approx \lambda_{1,h}^{-s} r_{s,k}(\lambda_{1,h} A^{-1})$, $r_{s,k}$ is the best uniform rational approximation of degree k of z^s on $[0,1]$. Further improvement of the computational efficiency of the BURA methods is presented in [3], where problem-specific model reduction techniques are utilized. The proposed approach is robust with respect to the size of discrete problem (the condition number of the related Laplacian), to the shape and dimensions of Ω and Γ, being directly applicable to the case of intersecting interfaces.

Acknowledgement: The partial support through the Bulgarian NSF Grant No DFNI-DN12/1 is highly appreciated.

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Slipknotted and Unknotted Proteins Might Share a Common Ancestor

Vasilina Zayats, Agata P. Perlinska, Aleksandra I. Jarmolinska, Borys Jastrzębski, Stanisław Dunin-Horkawicz, Joanna I. Sułkowska

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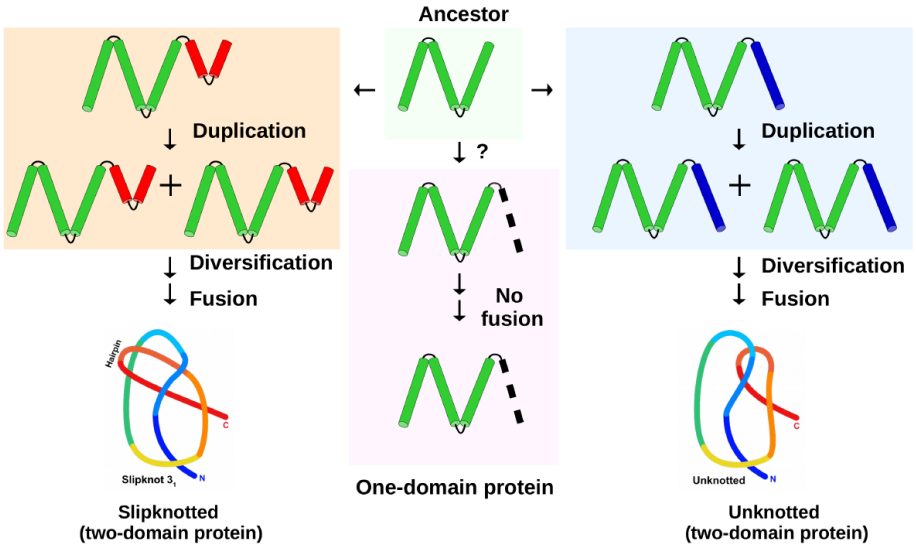
The slipknot topology in proteins has been known for over a decade, although their evolutionary origin is still a mystery. We have identified a previously overlooked family of two-domain membrane transporters as having a slipknot. Moreover, we found that these proteins are homologous to several families of unknotted membrane proteins. This allows us to directly investigate the evolution of the slipknot motif. Based on our comprehensive analysis of 17 distantly related protein families we have found that slipknotted and unknotted proteins share a common structural motif. Moreover, this motif is conserved on the sequence level as well.

In the figure, conserved helical region (core) found in the monovalent cation-proton antiporter superfamily are shown. Conservation of this region



suggests that three different fold types, including one possessing a non-trivial topology (a slipknot), evolved from a common, single-domain ancestor. The putative ancestor is shown in light green box in the middle. Three arrows from the ancestor navigate to the three proteins with different folds: 1) left – two-domain slipknotted protein; 2) middle - one-domain unknotted protein; 3) right – two-domain unknotted protein. Slipknotted protein, left (PDBID: 5a1s) is colored according to slipknot topology (slipknot loop – red, knotted core – blue, unknotted part – gray. Unknotted protein (PDBID: 4bwz) is shown in gray.

Our results suggest that, regardless of topology, the proteins we studied evolved from a common unknotted ancestor protein made up of a single domain. Additionally, our phylogenetic analysis suggests the presence of at least seven parallel evolutionary scenarios that led to the current diversity of proteins in question. The tools we have developed in the process can now be used to investigate the evolution of other repeated-domain proteins.

Phase Behaviour of Coarse-Grained Fluids

Vlad Sokhan, Michael Seaton, Ilian Todorov

STFC, UK Research and Innovation – Daresbury Laboratoru, UK

Coarse-grained (CG) modelling is an important topic in condensed matter theory providing simple but powerful tools to interrogate complex condensed matter phenomena. Developing of efficient CG models is the backbone of its successful accomplishment, and a great stride has been made with the advent of Dissipative Particle Dynamics (DPD). Using soft, short range potentials provides enormous speedup in phase space exploration of soft matter, but necessary alters its phase diagram. Interrelation between the CG and atomistic levels is further complicated by inability of standard DPD potential to form interfaces due to lack of cohesive forces.

Here, we present a development of a new class of simple soft force field with attractive terms, and demonstrate how the coarse-graining of simple atomic fluids can lead to an enrichment of CG phase diagram including some thermodynamic 'anomalies' of certain associated liquids.

Lasso Proteins – Is this Topology Functional?

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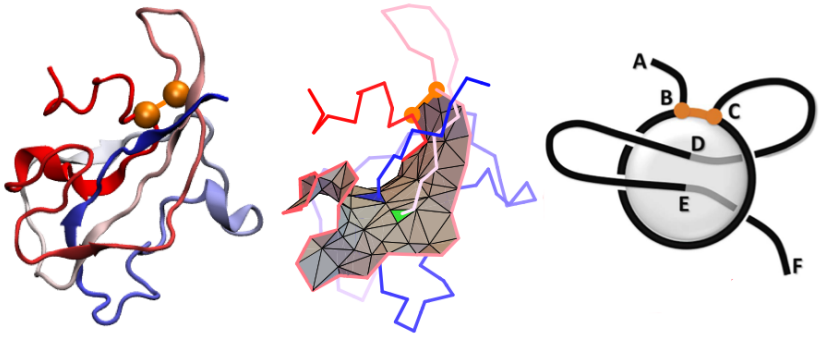
The complex lasso proteins are a recently identified class of biological compounds, present in a considerable fraction of proteins with disulfide bridges (see the figure below) [1]. In this talk I will present the results of an extensive survey of complex lasso proteins based on the data available in the LassoProt server [2]. I will analyze the motif conservation, evolution, and based on the

rigidity of the structure, introduce the way to identify structures with potentially functional motif. In particular, two groups of complex lasso protein with the motif important for the function can be selected – the antimicrobial proteins and cytokines. Finally I will present the database and the LassoProt server to the audience, showing a simple example of its use.



Left panel: cartoon representation of an oxidoreductase protein (PDB code 2oiz), forming complex lasso of L2 type. Middle panel: the triangulated minimal surface ("soap bubble"), spanned on the covalent loop, is crossed twice by a tail, through triangles in blue and green. Two cysteines and a cysteine bond are shown in orange. Right panel: scheme of lasso configuration of L2 type. Two cysteines form a disulfide bridge (orange) that closes (B,C) part of the backbone chain into a covalent loop. (A–B,C–F) Parts of the backbone chain are called tails. A minimal surface (in gray) spanned on the (B,C) loop is pierced twice by the (C–F) tail, at positions (D,E).

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Grafting a Parkinson Inhibitor Peptide on a Cyclotide: a Geometry and Dynamics Study

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Cyclotides are special knotted peptides stabilized by three pairs of disulfide bonds. With such a molecule as the scaffold, small peptides can be grafted onto it, thus engineering some specific conformations and functions. It has been shown that MCoCP4, formed by the peptide CP4 (CLATWAVG) grafted on loop 6 of the cyclotide MCoTI-I, can reduce the cytotoxicity of α-synuclein and, hence, has potential to inhibit the Parkinson Disease. In this study, we analyze the dynamical and geometrical properties of this specific grafted molecule based on molecular dynamics (MD) simulations. By visualizing the local geometry in a discrete Frenet frame (DFF) along the trajectory, we locate several stable segments in MCoCP4. We find that the grafted peptide CP4 is the longest and most stable segment, which prefers a helical structure throughout the simulation. Furthermore, we also analyze the backbone twisting and the side-chain orientation in MCoCP4 by calculating the folding index and the orientation of the Cβ atoms in DFF. Finally, several other grafting schemes between CP4 and loop 1-5 in MCoTI-I are proposed and analyzed in a similar way.

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PROGRAMME SCHEME

Monday, 13.09		Tuesday, 14.09	
9:00 - 9:30	Registration	9:00 - 9:45	Antti Niemi
9:30 - 9:50	OPENING		
9:50 - 10:50	David Leigh	9:45 - 10:30	Franco Ferrari
10:50 - 11:10	*COFFEE BREAK*	10:30 - 10:50	*COFFEE BREAK*
11:10 - 11:45	Rossen Apostolov	10:50 - 11:25	Ivan Coluzza
11:45 - 12:20	Luca Tubiana	11:25 - 12:00	Raffaello Potestio
12:20 - 14:00	*LUNCH*	12:00 - 14:00	*LUNCH*
14:00 - 14:45	Noam Kaplan	14:00 - 14:45	Adam Liwo
14:45 - 15:20	Svetozar Margenov	14:45 - 15:15	Vlad Sokhan
15:20 - 15:50	Andrey Brukhno	15:15 - 15:45	Julyan Cartwrigh
15:50 - 16:10	*COFFEE BREAK*	15:45 - 16:15	Bogdan Rangelov
16:10 - 16:40	Ivan Dimitrov	16:15 - 16:35	*COFFEE BREAK*
16:40 - 17:10	Meglena Lazarova	16:35 - 17:05	Mateusz Chwastyk
17:10 - 17:40	Markov, Vassilev	17:05 - 17:35	Kristina Kapanova
17:40 - 18:10	Nadezhda Bunzarova	17:35 - 18:35	ROUND TABLE
18:10 - 18:40	Stanislav Harizanov		
19:30	*WELCOME*		

Wednesday, 15.09		Thursday, 16.09	
9:00 - 9:45	Pietro Faccioli	9:00 - 9:45	Roumen Anguelov
9:45 - 10:30	Sarah Harris	9:45 - 10:15	Rachid Ouifki
		10:15 - 10:45	Anastas Pashov
10:30 - 10:50	*COFFEE BREAK*	10:45 - 11:10	Peter Petrov
10:50 - 11:20	Nevena Ilieva	11:10 - 11:20	Short Talks - Part III
11:20 - 11:50	Joanna Sulkowska	11:20 - 11:30	CLOSING
11:50 - 12:20	Short Talks - Part I		
12:20 - 14:00	*LUNCH*	12:00 - 14:00	*LUNCH*
14:00 - 14:45	Marek Cieplak		*Departure*
14:45 - 15:15	Piotr Sulkowski		
15:15 - 15:45	Petia Koprinkova		
15:45 - 16:15	Short Talks - Part II		
	Cultural programme		
19:30	*SOCIAL DINNER*		

ONLINE ONLY

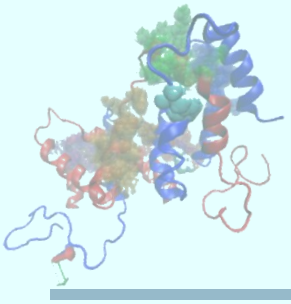
Identification of Protein Topology Using Topoly and the KnotProt Database API

Paweł Rubach

University of Warsaw, Poland

The non-trivial topology may significantly influence the characteristics of proteins and their function. This presentation will focus on the practical methods of finding knots and slipknots on proteins or other biopolymers. The first part will contain a short hands on demonstration of using the Topoly Python package to compute and identify entangled structures. The second part will demonstrate how to efficiently use the KnotProt Database's API to search for already identified knots and slipknots on protein chains.

NOTES



MATHEMATICS OF LIFE
MoL 2021

Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better.
Joel Cohen (2004)

September 13-16, 2021, Hisarya, Bulgaria & online

The Workshop is devoted to selected topics in mathematical biology research in both its analytical and computational components, thus illustrating the synergy between mathematics, physics, chemistry, computing and biology. The program is mainly focused on problems related to the modelling and simulations of topologically complex structure and dynamics, including, but not being limited to:

- Protein structure, dynamics and interactions
- Large-scale molecular simulations
- Topology in biomodeling and bioinformatics
- Neural networks from/in biological research
- Bio-medical applications
- Model studies on SARS-CoV-2 and COVID-19

The Workshop aims to bring together experts and young researchers in the analytical and computational studies of biopolymers and, among others, will provide a cross-package discussion forum for participants in the COST Action EUTOPIA (CA 17139) with interests in this particular aspect of the Action's program.

Opening Lecture: David A. Leigh *(Royal Society Research Professor & Sir Samuel Hall Professor of Chemistry (University of Manchester, UK)*

Keynote speakers (confirmed): Adam Liwo *(University of Gdansk, Poland)*, Antti J. Niemi *(NORDITA & Uppsala University, Sweden)*, Franco Ferrari *(University of Szczecin, Poland)*, Marek Cieplak *(Institute of Physics, Polish Academy of Science, Warsaw, Poland)*, Noam Kaplan *(TECHNION, Israel)*, Pietro Faccioli *(University of Trento, Italy)*, Roumen Anguelov *(University of Pretoria, South Africa)*, Sarah Harris *(University of Leeds, UK)*

Organisers:

Institute of Information and Communication Technologies, Bulgarian Academy of Sciences, (Sofia, Bulgaria) and CIC biomaGUNE (Donostia, Spain), in association with the European Topology Interdisciplinary Action (COST EUTOPIA, CA 17139), the Bulgarian Center of Excellence for Informatics and Information and Communication Technology, Section "Biomathematics and Scientific Computing" of the Union of Bulgarian Mathematicians, and the Bulgarian Section of SIAM, with partial support from EUTOPIA Cost Action and the Bulgarian Science Fund (Grant KP-06-COST-9).

Scientific Committee:

Nevena Ilieva (IICT – BAS, Bulgaria), Ivan Coluzza (CIC biomaGUNE, Spain)
Luca Tubiana (University of Trento, Italy & EUTOPIA Chair)

Location:

The Workshop will take place in the picturesque resort Hissarya, in the Plovdiv Province of Bulgaria. The area was inhabited since prehistoric times (before V millennium BC), with amazing archeological findings from this period. Under Romans, this was one of the main cities in Thrace (known as Diocletianopolis or Augusta). Hisarya is notable for the impressive remains from the Roman period and for its numerous hot springs.

For further details and registration, please visit
http://parallel.bas.bg/Conferences/MoL2021/

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