

A CONFERENCE DEDICATED TO THE 65-TH ANNIVERSARY OF PROFESSOR MAIA ANGELOVA



INSTITUTE OF BIOPHYSICS AND BIOMEDICAL ENGINEERING • SOFIA • BULGARIA • 8-9 JUNE 2023

BOOK OF ABSTRACTS



Institute of Biophysics and Biomedical Engineering,
Bulgarian Academy of Sciences



Data Analytics Research Lab, Deakin University



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INVITED SPEAKERS

Bridging Topological Data Analysis and Machine Learning

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Clustering is a powerful technique for discovering patterns and hidden structures in data. However, many real-world datasets contain clusters with varied densities and irregular shapes, which pose challenges for traditional clustering algorithms. Kernel-based clustering is a technique designed to identify non-linearly separable clusters with irregular shapes, but they have high computational costs. In this talk, I will present some recent advances in kernel-based clustering that use an adaptive distributional kernel to overcome the limitations of existing clustering algorithms. These methods can achieve better clustering quality with lower computational cost than existing kernel-based algorithms and can handle large datasets efficiently. Their applications can range from image and speech processing to gene pattern extraction, community detection and market segmentation.

INVITED SPEAKERS

Distributional Kernels: An Under-Utilized Resource

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This seminar presents recent works on distributional kernels based on kernel mean embedding (KME). KME has a strong theoretical underpinning, and guarantees that the resultant kernel mean map is injective, i.e., the kernel mean maps of two distributions have their difference equals to zero if and only if the distributions are the same. Yet, KME's applications have been less successfully so far. One key breakthrough is the identification of the root cause of KME's (seemingly) failures, i.e., the use of Gaussian kernel. The seminar presents works, following this identification, that release the power of this under-utilized resource. The works demonstrate that the distributional kernels can solve long-standing problems, some of which have evaded decades of effort, in terms of efficiency and task-specific accuracy issues. These include point and group anomaly detections, clustering, and anomaly detections in trajectories, periodic time series and graphs/networks.

INVITED SPEAKERS

Discovering Meaningful Clusters from Massive Datasets Using Distributional Kernel

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Topological data analysis (TDA) extracts the topological features that are complementary to statistical quantities, which has been found in many applications in computer vision. In TDA, Persistence diagram (PD) has been considered as a compact descriptor for topological data analysis (TDA). Unfortunately, PD cannot be directly used in machine learning methods since it is a multiset of points. Recent efforts have been devoted to transforming PDs into vectors to accommodate machine learning methods. However, existing methods share one common shortcoming: the mapping of PDs to a feature representation depends on a pre-defined polynomial. This presentation will introduce two recent advances: polynomial representation and Hilbert representation for PD, with the aim of extracting the discriminative topological features. Finally, potential applications in the field of computer vision, and biomedical science will be discussed.

INVITED SPEAKERS

Random Generation of Fuzzy Measures for Simulations in Decision Making

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Non-additivity of fuzzy measures offers a formal mathematical treatment of interdependencies of various inputs. In the context of multiple criteria decision making they model redundancies and synergies among the decision criteria. The weights are assigned to the individual criteria and all their possible subsets, at the cost of exponential number of parameters. Even with some simplification strategies the number of importance weights are often too high. Simulation studies allow one to select the most frequent decision outcomes based on a large number of suitable fuzzy measures. For this we need a reliable technique of random generation of fuzzy measures, which translates into uniform generation of random points in high-dimensional polytope. This talk presents various approaches to that challenging problem.

INVITED SPEAKERS

Coulomb Blockade and Selectivity in Biological Ion Channels

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Biological ion channels are essential to life in all its forms. By enabling the selective transfer of ions across lipid bilayers, they facilitate the establishment of intracellular media able to support the biochemical reactions involved in metabolism and replication. Their selectivity for particular kinds of ions is known to be associated with a fixed negative charge Q_f in a narrow part of the channel known as the selectivity filter. Remarkably, many properties of ion channels can now be understood [1] by analogy with the physics of quantum dots: e.g. Coulomb blockade oscillations in quantum dots correspond to the alternating conduction bands and stop bands seen for ions in channels as Q_f is varied – emergent phenomena that could not have been anticipated based on the known channel structure. The Coulomb blockade model will be summarised and some systematic experimental and numerical tests [2] will be discussed, together with more recent work developing a fundamental statistical theory [3] of the conduction process.

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INVITED SPEAKERS

Can Non-autonomous Dynamics in Mathematics Adequately Describe Open Systems in Physics? Lessons from Data Analysis in Cellular, Cardiovascular and Brain Dynamics



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Physics distinguishes between isolated systems (no exchange of energy or matter with the environment), and non-isolated systems. The latter can either be closed, only able to exchange only energy with the environment, or open in which case they can exchange both energy and matter with the environment. Already by 1943 during his lectures delivered under the auspices of the Dublin Institute for Advanced Studies where he was Director of Theoretical Physics, at Trinity College, Dublin, Erwin Schrödinger pointed out that

...living matter, while not eluding the “laws of physics” as established up to date, is likely to involve “other laws of physics” hitherto unknown, which however, once they have been revealed, will form just as integral a part of science as the former.

Schrödinger furthermore clarified [1] that living matter evades the decay to thermodynamic equilibrium by homeostatically maintaining negative entropy in an open system.

However, even today, we do not have the new laws of physics needed to describe living systems. Open systems are usually treated within the framework of statistical physics and stochastic dynamics, and the data measured from such systems are increasingly analysed using artificial intelligence.

In this talk we will propose oscillatory non-autonomous dynamical systems ([2] as potential candidates to describe open systems. The talk will consist of four parts. First, we will consider several examples on a variety of timescales and size scales – including cellular systems up to the cardiovascular and brain dynamics, as well as diurnal oscillations and population levels [3-6], to illustrate the motivation for our proposal. Secondly, we will introduce chronotaxic (chronos – time,

INVITED SPEAKERS

taxis – order) systems [7], proposed to provide a framework for non-autonomous systems that can endure continuous external perturbation, focusing on the properties of frequency-modulated dynamical systems and networks. We will illustrate that oscillators subject to driving with a slowly varying frequency, counterintuitively, have enlarged Arnold tongue in the parameter space [8]. Thirdly, we will present an experimental model of electrons on the surface of liquid helium subject to an electromagnetic field and microwaves that exhibit chronotaxic dynamics [9]. So far, chronotaxic dynamics has been observed mainly in living systems allowing only very limited possibilities for studying experimentally the effect of changing relevant parameter values. In contrast to these biological observational studies, the superfluid helium experiments offer us an opportunity to gain an understanding of chronotaxic behavior based on well-controlled laboratory investigations that promise to reveal fully the relationship between the physical world and the fundamental nature of chronotaxic dynamics. Lastly, we will introduce the idea of describing living systems as networks of networks of chronotaxic systems. We will propose that the conservation of phase difference could be the new law of physics that underlines living systems.

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INVITED SPEAKERS

Differential Delay Models in Biology

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Differential delay equations are frequently used as mathematical models of diverse real-world phenomena where the time delays are intrinsic features of their functioning. In the past half a century they were particularly useful in adequate modeling of various biological processes, especially in population dynamics and physiology.

Two particular differential delay equations of interest are a model of hematopoiesis (blood cell production) [4] and a model of megakaryopoiesis (platelet production) [1]. Both models are described mathematically by simple form scalar differential delay equations, which are closely related by several properties. Dynamics of solutions in these equations are comprehensively studied. Sufficient conditions are derived when the unique positive equilibrium is globally asymptotically stable [2]. The stability conditions are given in terms of induced interval maps, one set being delay independent criteria and another one involving the size of delay.

The existence of periodic solutions slowly oscillating about the equilibrium is also established [3]. The periodic oscillations in the models always exist when the positive equilibrium is linearly unstable. The proof of existence follows the established ejective fixed point techniques with necessary modifications due to the specific form of the equations.

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INVITED SPEAKERS

The Conductome – A New Paradigm for Understanding Human Behaviour

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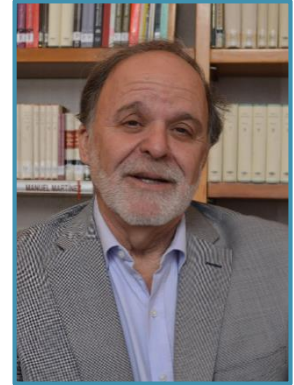
As almost every major problem that humankind faces are a consequence of human behaviour, predicting behaviour and behaviour change is fundamental. Given the multitude of factors that affect our decision making, a transdisciplinary understanding of behaviour is impossible without the integration of data that cross disciplinary boundaries. The concept of Conduct-“ome” is an analog of those holistic –“omic”-approaches found in the biological sciences which take a “totality of factors” approach, and provides a framework for studying human behaviour in a multifactorial, multidisciplinary context, accounting for a wealth of potential causes of behaviour, from the genetic and epigenetic to psychological, neurological, social, physiological, clinical, socio-economic, socio-demographic, socio-political and ethical factors. Conductome, as opposed to behaviour-ome, is used, as it directly addresses the “whys” (causes) of the considered behaviour. We argue that behaviour can only be understood probabilistically, through a process of statistical inference that constructs $P(A|X)$, the probability for a conduct A conditioned on the large set of factors, X , that predict it. This inference process can be based on an “external” ensemble of objective, countable events, using a frequentist interpretation of probabilities, or on an “internal” ensemble, implicit in our mental models and based on a Bayesian interpretation. Including both these approaches allows one to compare objective, observable reality with the subjective perception of reality constructed within a mental model, allowing for the identification of discrepancies between the two in the form of cognitive biases. A key component for constructing the Conductome is the obtention of data that transcends disciplines, and which can be used to link a range of relevant behaviours, as effects, to their causes, both internal and external. A second component is the use of advanced modelling tools, such as machine learning, for the analysis of such multi-scale data and the construction of explicit prediction models for a given conduct. In this article, the feasibility of the Conductome approach is illustrated by considering obesity-related behaviours; as obesity has become one of the key social problems that affects a growing segment of the population worldwide. In summary: The objective is to understand, interpret and provide an interdisciplinary, computational and data-based framework for generating prediction models for addressing problems that originate in human behaviour.

INVITED SPEAKERS

Symmetry and Criticality in Biological Systems: A New Approach to Multisignal Analysis

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In biology, criticality refers to the phenomenon where a system or network of components is poised at a point between order and disorder, with the potential for rapid transitions or changes in behavior. This critical state is thought to be a key feature of many biological systems, from the functioning of the brain to the behavior of ecosystems. In this talk I present a multisignal time series analysis based on scale invariance of the correlation matrices and discuss some applications.

INVITED SPEAKERS

Decision-Making in Complex Competitive Environments: From Wars to Soccer

Sergiy Shelyag, Maia Angelova, Ishara Bandara, Abhiram Thiruthummal, Mathew Zuparic, Alex Kalloniatis, Dan Dwyer, Shitanshu Kusmakar, Chandan Karmakar, Sutharshan Rajasegarar, Ye Zhu



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How do people make and implement decisions? Decisions are based on time-dependent interactions with the environment, which is invariably complex, volatile, and uncertain. This is applicable to any kind of decision-making, including competitive sports, co-operational and competitive organisational structures, military conflicts. Characterising and modelling decision-making processes and designing model-informed strategies for organisational structures with the aim to achieve favourable results, therefore, would be of interest. In my presentation, I will show a mathematical model of decision-making, which is based on interactions between agents of different kinds. The interactions are modelled to be adversarial, supportive and contributing. The model is studied both analytically and numerically, and I will discuss applicability of the model to a variety of real-life scenarios.

INVITED SPEAKERS

Frailty Syndrome as a Transition from Compensation to Decompensation: Application to the Biomechanical Regulation of Gait



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Most gait parameters decrease with age and are even more importantly reduced with frailty. However, other gait parameters exhibit different or even opposite trends for aging and frailty, and the underlying reason is unclear. Literature focuses either on aging, or on frailty, and a comprehensive understanding of how biomechanical gait regulation evolves with aging and with frailty seems to be lacking. We monitored gait dynamics in young adults (19–29 years, $n = 27$, 59% women), middle-aged adults (30–59 years, $n = 16$, 62% women), and non-frail (>60 years, $n = 15$, 33% women) and frail older adults (>60 years, $n = 31$, 71% women) during a 160 m walking test using the triaxial accelerometer of the Zephyr Bioharness 3.0 device. Frailty was evaluated using the Frail Scale (FS) and the Clinical Frailty Scale (CFS). We found that in non-frail older adults, certain gait parameters, such as cadence, were increased, whereas other parameters, such as step length, were decreased, and gait speed is maintained. Conversely, in frail older adults, all gait parameters, including gait speed, were decreased. Our interpretation is that non-frail older adults compensate for a decreased step length with an increased cadence to maintain a functional gait speed, whereas frail older adults decompensate and consequently walk with a characteristic decreased gait speed. We quantified compensation and decompensation on a continuous scale using ratios of the compensated parameter with respect to the corresponding compensating parameter. Compensation and decompensation are general medical concepts that can be applied and quantified for many, if not all, biomechanical and physiological regulatory mechanisms of the human body. This may allow for a new research strategy to quantify both aging and frailty in a systemic and dynamic way.

INVITED SPEAKERS

Impact of Knowledge-based Filtering on Clinical Decision-Making System — Arrhythmia Detection Case Study

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The Electrocardiogram (ECG) is a vital signal used to monitor heart conditions, but it is prone to contamination by various types of noise. Traditional approaches for filtering ECG noise rely on predefined filters, which often lead to the unintentional removal of noise-free signals. To overcome this challenge, we present a novel framework that automatically detects and classifies ECG signals based on the presence and types of noise, enabling the application of tailored filtering techniques.

We demonstrate the advantages of employing noise-aware and noise-type-based filtering approaches compared to noise-unaware filtering by quantifying the distortions in ECG biomarkers, specifically the QT and QRS intervals, caused by the filtering process. Our experimental results showcase the effectiveness of our hierarchical model, utilizing Adaboost, in achieving exceptional performance. The model achieved a 100% accuracy rate for noise detection and an impressive 97.19% accuracy rate for noise classification. These results further validate the efficacy of our approach in accurately identifying and categorizing different types of noise present in ECG signals.

The reported results were obtained using the inter-dataset splitting approach, employing six diverse datasets called CINC-2011, CINC-2014, ECG-ID, MIT-Bih arrhythmia, BIDMC, and teleECG. Our investigation focused on comparing the performance of noise-aware, noise-unaware, and noise-type-based filtering techniques. Notably, the noise-type-based filtering approach exhibited the smallest mean difference (2.50ms) in the QT interval, surpassing both noise-aware (-16.37ms) and noise-unaware (-38.23ms) filtering methods. Moreover, for the QRS interval, noise-unaware filtering produced the highest mean difference (-10.33ms), whereas this was significantly reduced to -2.43ms and 4.28ms with noise-aware and noise-type-based filtering, respectively. These outcomes convincingly demonstrate the superiority of noise-aware and noise-type-based filtering approaches in preserving the integrity of clinical biomarkers in ECG signals.

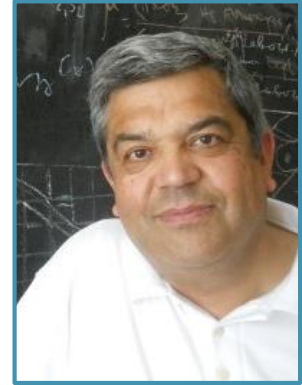
We also used our knowledge-based filter framework for arrhythmia detection and compare the result with noise-unaware and noise-aware filter to show the significance of knowledge-based filtering system.

INVITED SPEAKERS

On Self-Organization of Generalized Nets

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Generalized Nets (GNs) are the most powerful extension of the Petri nets and the rest of their extensions and modifications. The GN tokens enter the net with initial characteristics and obtain next ones during the time of their transfer through the net, collecting their own history. Moreover, the GN transitions can have special matrices with predicates that determine whether a token from some input place can transfer to an output place or not. Following R. Valk's idea for self-modifying Petri nets that can change their structure (at some moments some arcs of the net can disappear, at others – they can appear), in the end of the 1980s, self-modifying GNs were constructed. They had the capability to change both their structure and their behaviour (change affecting the functions that give next token characteristics, the predicates associated with the GN transitions, and others). These modifications of the GN-structure and self-organization of its behaviour are based on the operators, defined over GNs.

In the present paper, we discuss another approach to the implementation of self-modification (in Valk's sense) and self-organization of the behaviour of a given GN. It is based only on the possibilities of the transition predicates and of the tokens characteristic functions to have as arguments values of other token characteristics and situations, that have occurred in the net by the present time-moment. This GN has three contours: first one – that represents a concrete real process; second one, that estimates the values of the token characteristics of all or at least a part of the tokens from the first contour and of the evaluations of the transition predicates obtained by the current time-moment; and third one – that determines possibilities for the change of some characteristic functions or transition predicates with the aim of correcting the current parameters of the first contour. In this third contour, a decision for stopping of the process in the first contour can be generated, if some parameters of the first contour are irreversibly changed.

INVITED SPEAKERS

A Tale of Symmetry: From Viruses to Protein Nanoparticles

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Viruses are examples of symmetry in biology. The majority of viruses package, and thus protect, their genomes in protein cages, called capsids, that are organised according to icosahedral symmetry. Protein nanoparticles, either derived from viruses or de novo designed, play pivotal roles in a host of applications, including drug delivery, vaccination and diagnostics. Mathematical Virology has provided unprecedented insights into the structure, self-assembly and evolution of viral capsids. Exploiting synergies between virology and protein nanotechnology, I will demonstrate how this work informs the rational design of protein nanoparticles for diverse applications.

INVITED SPEAKERS

Data-driven Models for Precision Healthcare

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Precision healthcare is an emerging approach for personal healthcare and disease prevention that considers the individual's variability in health, genes, lifestyle, and environment. For example, sleep and nutrition are essential and repeating processes which are vital for the quality of life and wellbeing of every individual. These processes involve complex dynamics, interactions between organs and environment, and regulation at multiscale that reflect the developmental changes in mental and physical health, along with the day-to-day fluctuations. In this talk, I will consider the potential of hybrid data-driven models and artificial intelligence in multiscale modelling for patient-centered digital healthcare of the future.



Heart Rate Variability-Based Disease Screening System

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Disease screening is the application of medical procedures or tests among non-symptomatic people for a particular disease to determine their likelihood of having the disease. Detecting diseases in their earliest stage could benefit from treatment. For a disease screening tool to be used, it should be demonstrably simple, valid, reliable, quick to administer, cost-effective, easy to use, and accessible to all income groups. Heart Rate Variability (HRV) is the time variation between each heartbeat and indicates health problems. In this talk, I will present the potential of HRV captured from commercial wearables in screening for chronic diseases.

Is There a Relationship Between Sleep Quality and Sedentary Behaviour in Adults with Chronic Insomnia?

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Sleep and sedentary behaviour are associated with several negative health consequences, including obesity, cardiovascular disease and all-cause mortality. The mechanisms underlying the association between sedentary behaviour and sleep are not fully understood, but may be related to disruptions in circadian rhythms, increased stress, and changes in hormone levels. The association between sedentary behaviour and sleep highlights the importance of addressing both of these for overall health and well-being. In my presentation, I will explore the relationship between night activities and the following daytime sedentary behaviour in adults with chronic insomnia and their corresponding bed partners. This study investigates the sleep parameters for the night and total sedentary time, various lengths of sedentary bouts (6 minutes-30 minutes, 30 minutes-60 minutes and >60 minutes) during the day, with the aim of uncovering potential correlations. Surprisingly, the analysis reveals a weak association between night activities and subsequent day sedentary activities in both individuals with chronic insomnia and their bed partners. These findings underscore the need for further investigation of the multifaceted factors that influence daytime sedentary behaviour in people with chronic insomnia, providing information for the development of more comprehensive interventions and treatment strategies for this population.

A Single Variate Multiple Time Series Framework with Neural Hierarchical Interpolation for Real Estate Forecasting

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Machine learning (ML) has been widely applied in various fields to improve performance and efficiency. One area where ML has shown significant promise is in time series predictions. Time series predictions refer to forecasting future values of a variable based on historical data. This has been used in a wide range of applications, including financial forecasting, weather forecasting, and demand forecasting. In this paper, we aim to improve the accuracy of the real estate prices prediction when the original data has three typical crucial issues, namely missing data, non-stationary, and not big. In particular, we propose an effective framework that contains various ML techniques to predict real estate prices, including three main components: data imputation (by interpolation, k-nearest neighbors, random forest), clustering (by Euclidean, dynamic time warping, dynamic time warping with Barycentre averaging, soft dynamic time warping, weighted dynamic time warping) and forecasting (by recurrent neural network, long short-term memory, gated recurrent unit, neural hierarchical interpolation for time series), which is called as ICF. After running 120 sub-settings, we demonstrate that the new ICF framework has an enormous potential to successfully address the three typical severe problems as mentioned above. Especially, extensive experiments on monthly US real estate price dataset show that our ICF framework has gained significant forecasting performance when a state-of-the-art method, called Neural Hierarchical Interpolation for Time Series (N-HITS), is incorporated, even when we experimented the model with one of the most volatility periods of real estate market in the past decade. The N-HITS method with clustering has outperformed compared to N-HITS without clustering as well as RNN, LSTM, and GRU methods.

Nanoparticles Based on Graphene Oxide for Phototherapy of Hepatocellular Carcinoma

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Phototherapy is a non-invasive therapeutic method with great potential for treating cancer. It has emerged as an alternative to conventional cancer therapies. In phototherapy, specific wavelengths of light activate photoactive agents called photosensitisers (PSs). PSs convert electromagnetic radiation (ER) into chemical or thermal energy, destroying cancer cells. With the application of nanotechnology in cancer therapeutics, it became possible for different nanoparticles (NPs) to be used as PSs in phototherapy. Due to their unique properties and multifunctionality NPs can be designed to carry various drugs along with PSs, thus providing a platform for combined chemo-photothermal therapy. Among NPs, graphene oxide (GO) is a promising nanomaterial because of its 2D structure, easy functionalisation, low cytotoxicity, and good optical properties. There are data in the literature that GO possesses high near-infrared (NIR) light absorbance and biocompatibility and can be used as a photothermal agent for potential photothermal therapy [1].

In this study, we have employed a laser emitting ER at different wavelengths in the UV-Vis-NIR range of the electromagnetic spectrum (343 nm, 515 nm, and 1030 nm) and have evaluated their effect on the viability of hepatocellular carcinoma cells (HepG2) treated with nanographene oxide (nGO) and PEGylated graphene oxide (GO-PEG) NPs. The aim was to investigate the effect of UVA/B (343 nm), green light (515 nm), and NIR light (1030 nm) on the activation of GO-based NPs by suppressing cancer cells' metabolic activity and the viability of HepG2 cells. Further, the current exploration allows us to optimise the physical parameters of the irradiation by exposing the cells to a laser beam with two different power densities (0.1 and 0.2 W/cm²) for 5 and 10 min. The findings demonstrated that the power density of 0.2 W/cm² led to a more significant reduction in the metabolic activity of HepG2 cells, whereas the time exposure did play no significant role. Surprisingly, the laser beam at 1030 nm (0.2 W/cm², 10 min) increased the cells' viability in control



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and GO-PEG-treated groups of cells. Further investigations are required to understand which power density, wavelength, and time exposure ensure better targeting and destruction of cancer cells.

Acknowledgements

The work is funded by the Bulgarian Science Fund, Grant Number KP-06-N31/15.

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Chitosan-Based Nanomaterials as Promising Bionanopesticides: An Approach of Understanding the Mechanism behind Their Antifungal Activity

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The development and future applications of so-called nanobiopesticides provides promising resolutions of important contemporary agricultural problems: the overcome of antifungal resistance and the reduction in usage of over the counter highly toxic pesticides. At the same time, nanobiopesticides can be safe for plants and even exhibit growth stimulating activity on crop production.

In our studies, we present newly synthesized nanomaterials (NMs) – chitosan (CS) nanoparticles (NPs) and chitosan-based nanocomposites (NCs) with several oxides (SiO₂, ZnO and CuO). We determined certain physicochemical properties of these NMs such as size, surface charge and morphology making them a promising candidate for bionanopesticides. The phytopathogens that we examined their activity on, are *Alternaria solani* and *Fusarium solani*, the inducers of infectious diseases on one of the most economically important plant species – patotos, tomatoes, bells and beans. Agar diffusion and microdilution methods were employed for antifungal activity evaluation. All tested NMs exhibited a high antifungal potency with *F. solani* being most sensitive to pure CS NPs and *A. solani* to CS-based NCs. A set of experiments were conducted to elucidate the molecular mechanism, through which the NMs exert their antifungal activity. Laurdan fluorescent spectroscopy was used for evaluation of membrane order alterations. The obtained results showed, that the tested NMs can induce changes in the lipid organization by either fluidizing, or ordering of the fungal membrane. The largest quantitative changes in the membrane order on *F. solani* were induced by CS-CuO NCs, whereas on *A. solani*, were by CS-based NCs. By analytical assays,

we established that NMs were able to induce oxidative stress in both fungal species. High levels of different oxidative markers were measured under NMs treatment: malondialdehyde (MDA), superoxide dismutase (SOD) and protein carbonyl content. Briefly, the NMs antifungal activity is of high potency because they are prone to generate membrane lipid peroxidation, protein oxidation and activation of cellular antioxidant defense.

This study offers newly synthesized NMs with strong antifungal activity. Furthermore, it provides a comprehensive description of the molecular aspect of their action. The obtained results are promising for their future agricultural applications as an effective and safe bionanopesticides.

Acknowledgements

This study was financially supported from the National Science Fund of Bulgaria by Grant KP-06-H58/6/2021 (Consumables to carry out Laurdan fluorescence). The authors thank the Bulgarian Ministry of Education and Science for support: Scientific Infrastructure on Cell Technologies in Biomedicine (SICTB) D01-178/2022 and “National Center for Biomedical Photonics” D01-183/2022, part of Bulgarian National Roadmap for Scientific Infrastructures 2020-2027. DB thanks the Bulgarian Ministry of Education and Science, National Research Program “Young scientists and postdoctoral students – 2”, Module “Young scientists” for financial support on her project entitled “Biological Activity of Chitosan-Based Nanomaterials with Potential Biomedical and Agrobiological Applications”.

Tumor-Suppressing Impact of Iscador on Breast Cancer Cell Lines with Different Metastatic Potential

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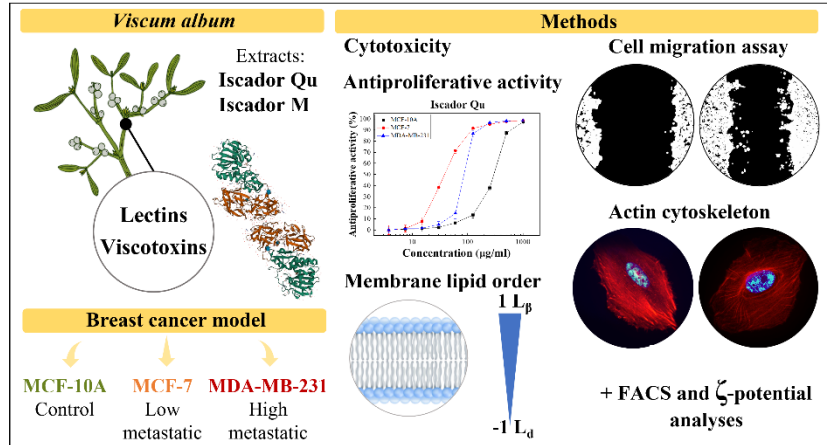
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The study investigated the impact of plant based drugs Iscador Qu and Iscador M on phototoxicity, cytotoxicity, antiproliferative activity, cell surface properties, membrane lipid packing, cytoskeleton organization, and migration in breast cancer cell lines with varying metastatic potential: MCF-7 (low metastatic), MDA-MB231 (high metastatic) and MCF10A (control). Phototoxic effects were not observed for the tested Iscadors. The antiproliferative effect of Iscador was dose-dependent and correlated with the cell lines' metastatic potential. Iscador Qu and M exhibited a higher selectivity index for the low metastatic MCF-7 cell line compared to the high metastatic MDA-MB-231. Iscador Qu demonstrated greater selectivity for both cancer cell lines than Iscador M. Regardless of the Iscador type, the malignant cell lines experienced a decrease in F-actin fibril number and thickness. Iscador treatment had the most significant effect on the migration potential of the low metastatic MCF-7 cell line. Both Iscador species led to a slight increase in early apoptosis in MCF-7 and MDA-MB-231 cell lines compared to control cells. Changes in zeta potential and membrane lipid order were observed in the low metastatic MCF-7 cell line but not in the high metastatic MDA-MB-231 cells. These findings highlight the potential of Iscador as an antitumor agent, particularly for the low metastatic cancer cell line MCF-7. Iscador Qu demonstrated greater potency than Iscador M. Further investigations are needed to fully understand its mechanism of action of this plant based drug.



Acknowledgements

The authors thank the Bulgarian Ministry of Education and Science for support: Scientific Infrastructure on Cell Technologies in Biomedicine (SICTB) D01-178/2022 (Flow cytometry measurements) and National Center for Biomedical Photonics D01-183/2022 (Zetasizer Nano S measurements), part of the Bulgarian National Roadmap for Scientific Infrastructures 2020–2027. This work was partially supported by the Bulgarian Ministry of Education and Science under the National Research Programme “Young scientists and postdoctoral students – 2” (A. Nesheva) approved by DCM 206 / 07.04.2022.

Intercriteria Decision Making Approach for Analysis of Datasets of Blood Serum Indicators for Multiple Myeloma

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Multiple myeloma (MM) is malignant B-cell disease with heterogeneous molecular and genetic nature, diagnosed on the basis of characteristic molecular markers (monoclonal immunoglobulins and free light chains, called M-proteins) and a number of invasive tests. This heterogeneity is also reflected in the thermal stability profiles of the blood serum proteome, as evidenced by us employing differential scanning calorimetry (DSC) [1]. This biophysical technique is classically applied to study and thermodynamically describe the stability and conformational transitions of biomolecules in solution, but recently also gains popularity in characterizing complex biofluids such as blood plasma/serum, cerebrospinal fluid, synovial fluid and saliva. The resulting calorimetric profiles (thermograms/scans) are composed of overlapping thermal transitions corresponding to individual plasma proteins. Typical DSC scan of blood serum, in particular, can be reproduced by the sum of the denaturation transitions of the 16 most abundant serum proteins, among which albumin (HSA) and immunoglobulins (Igs) have the highest contribution and therefore are clearly observed [2]. The DSC profiles are affected not only on the plasma/serum proteins content and conformation but also on various factors that moderate their stability (ligand binding, macromolecular complex formation, mutations, chemical changes, misfolding, etc.). For the case of secretory MM, the DSC scans depend on the type and concentration of M-proteins, while for non-secretory MM the factors affecting the DSC profile are less known.

Due to the complex nature of the MM serum DSC profiles, advanced mathematical and analytical methods are needed in order to extract information with diagnostic potential. In this work, we present the application of InterCriteria analysis, initially developed by Atanassov [3] for exploring a database composed of calorimetric and biochemical data generated for both secretory and non-secretory MM cases, in comparison to Pearson's and Spearman's linear correlation analyses. The utilized approach reveals specific interrelations between the calorimetric and biochemical

parameters of blood serum, beyond the linear correlations, which helped us decipher the nature of the shifts in the thermal stability of the major MM serum proteins [4]. Thus, the proposed approach is useful for the identification of novel biomarkers for MM diagnostics and monitoring.

Acknowledgements

This work was supported by the Bulgarian Ministry of Education and Science: “National Center for Biomedical Photonics” D01-183/2022, part of Bulgarian National Roadmap for Scientific Infrastructures 2020–2027 and Bulgarian National Science Fund under project Ref. No. KP-06-N-22/1/2018 "Theoretical Research and Applications of InterCriteria Analysis". Research equipment of Research Infrastructure for Advanced Studies of Biomolecules, Biomembranes and Biosignals (BioMMS) was used in the study.

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A Data Analytics Approach to the Investigation of Blood Donation Practice and Its Associated Factors in Pleven Regional Centre of Transfusion Haematology, 2017–2022

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Background: We have adopted a data analytics approach to study the blood donation practices in one of the large regional centres of transfusion haematology in Bulgaria, the Pleven RCTH. We analyze a dataset retrieved from the RCTH's information system, comprising the records of 52296 blood units donated in Pleven in 2017–2022. Pleven is the 7th largest city in Bulgaria, provincial administrative centre and hosts one of the 6 medical universities in Bulgaria. Pleven RCTH ensures blood diagnostics and processing for Pleven and five other provinces of Central North Bulgaria (Gabrovo, Lovech, Razgrad, Ruse and Veliko Tarnovo), and is the regional leader with 42% of all registered blood donations.

Aims: Our aim is to characterize the state-of-the-art and recent trends in blood donation activity in Pleven Province. In addition, working with available data from the period before and during COVID-19 allows discussion from the perspective of a global pandemic that has affected both demand and supply of blood and blood products.

Methods: An atomic approach towards data has been adopted early at the research design phase, thus enabling detailed data stratification and a sophisticated inside view. A data cleansing procedure has been applied to ensure data correctness and elimination of incomplete or incorrect records, followed by a data anonymization procedure in compliance with EU GDPR 2016/679.

Results: The findings from our data analytics approach were grouped with respect to the following four aspects.

- 1) General statistics. For the investigated period, 52296 donation acts were registered, of which 14707 by females (28.1%) and 37589 by males (71.9%), with 22074.5 litres of collected blood.

The annual data about donation acts and individual donors are given. Average donor's age is 40.0 years old, average 39.6 for males and average 42.0 for females.

- 2) Frequencies of ABO and Rh blood group distributions. Based on the total blood collected in Pleven for 2017-2022, the ABO system blood group distribution has been identified as: O: 17644 (33.74%), A: 21777 (41.64%) AB: 4177 (7.99%), B: 8694 (16.62%). Further considering the frequencies of the Rh(D) antigen gives: O(-) 2331 (4.46%), O(+) 15313 (29.28%), A(-) 2916 (5.58%), A(+) 18861 (36.07%), AB(-) 513 (0.98%), AB(+) 3664 (7.01%), B(-) 1117 (2.14%), B(+) 7577 (14.49%). The frequencies are further available on annual basis. The average frequency of the Rh(D) antigen is 13.15% (negative) to 86.85% (positive), with the frequencies further available per blood group: O: 13.2% / 86.8%, A: 13.4% / 86.6%, AB: 12.3% / 87.7%, B: 12.9% / 87.1%.
- 3) Individual donors. Thanks to the recorded donors' unique citizen numbers, it is possible to outline the number of individual donors: 30199: 71.7% males, 28.3% females. Of all, 69.7% were one-time donors in the studied period, 15.6% donated twice, 6.3% – 3 times, 3.2% – 4 times, 4.2% donated 5–9 times, 0.9% donated 10–19 times, 0.2% donated 20+ times. Comparing these figures with the Bulgarian National Statistical Institute's data for the population of Pleven Province in years 2017–2022, we determine approximately 36.8 donations per 1000 people (34.4/1000 in 2017, 37.8/1000 in 2018, 37.7/1000 in 2019, 35.7/1000 in 2020, 38.3/1000 in 2021, 40.1/1000 in 2022).
- 4) Voluntary donation. With respect to the purpose of donation, Pleven CTH features 11.9% voluntary donation (6204 units), and 87.3% family/replacement (46088 units). The voluntary individual donors amount to 3761, of whom 64.9% were one-time donors, 18.9% donated twice, 9.5% – 3 times, 3.7% – 4 times, 2.7% donated 5–9 times, and 0.2% donated 10–16 times. Noteworthy, while females donate approximately 2.6 times less than males, when it comes to voluntary donations they donate 1.5 times more: average 10.5% of all donations by men, and 15.5% of all women's are voluntary. The ABO system blood group frequencies in voluntarily donated blood is similar to those in all donated blood units: O(-) 3.63%, O(+) 29.01%, A(-) 4.96%, A(+) 37.43%, AB(-) 1.05%, AB(+) 7.24%, B(-) 2.05%, B(+) 14.64%.

Summary / Conclusions: The presented data and statistics show the current state and allow tracing the recent 6-year trends in blood donation practice in Pleven Province, Bulgaria. A larger benchmark study among all provinces covered by Pleven RCTH will further outline the specifics of the Central North Bulgaria with respect to its transfusion capacity, strengths and weaknesses that need to be addressed. The results of the research will benefit both local and national specialists and policy makers in the area of transfusion haematology. With the achieved level of detail, the prospective next step in this authors' investigation will be analyzing the presented data using the recently proposed method of InterCriteria Analysis, based on intuitionistic fuzzy sets and index matrices.

Acknowledgements

The authors V. A., N. A. and I. U. acknowledge the support provided under Grant KP-06-N22/1 funded by the Bulgarian National Science Fund.

Computer Aided Diagnosis of Cardiac Arrhythmias Based on Machine Learning and Deep Neural Networks: A Project of the Bulgarian National Science Fund

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Artificial intelligence (AI) is the technology of the future, becoming a generator of innovation in modern industrial society. It needs high-performance models and computing resources to scale up intelligent technologies that make their own precise expert decisions and have the ability to self-learn through experience.

We present the planning and current developments on a project related to the application of AI technologies in support of cardiovascular disease diagnosis under grant number КП-06-H42-3 of the Bulgarian National Science Fund in the Competition for financial support of basic research projects – 2020, Main research area: "Mathematical sciences and informatics". Currently, the project (2020-2024) is in the beginning of its second period of funding.

The project presents fundamental research in the fields of mathematics and computer science, biomedical engineering and medicine. The topic is related to applications of machine learning and deep neural networks (DNN) in computer-aided expert systems in cardiology. The objectives are: (i) to design, train, optimize and test novel deep machine learning algorithms using big clinical electrocardiographic (ECG) databases; (ii) to handle the self-extracted information in DNN hidden layers; (iii) to expand the application of AI in emergency medicine, screening and ambulatory programs through accurate computer support for early diagnosis of heart rhythm pathologies. The development of state-of-the-art information products and artificial intelligence engineering

solutions, using up-to-date information technology with a large computational resource, have provided innovative results, so far published in prestigious scientific journals with open access and impact factor [1-7], impact rank [8-11], indexed in Scopus [12-14]. The project activities are arranged in four work packages, as follows:

- WP1: DNN applications for analysis of life-threatening cardiac arrhythmias; Alignment with current recommendations for cardiopulmonary resuscitation (CPR) and the use of automatic external defibrillators in out-of-hospital cardiac arrest. Important results disclose optimizations of DNN architectures and hyper-parameters [4, 8], ECG analysis during continuous CPR without alignment to the start and stop of chest compressions and insufflations [1].
- WP2: Applications related to the ECG preprocessing: Developments of new digital filters [3, 13, 14] and denoising DNN autoencoders [9]; software tools for ECG annotation [10] and ECG generators [12]; DNN embedded in microcontroller systems.
- WP3: Collection of a clinical annotated ECG database in long-term (24 h) Holter-ECG monitoring in a registered clinical study, currently including more than 100 patients with rhythm and conduction disorders; Investigation of a new diagnostic method based on EchoVIEW images with an expert revision and DNN.
- WP4: DNN applications for precise measurements of diagnostically useful ECG parameters; Classification of rhythm and conduction disturbances in multichannel ECG recordings; Comparative analysis of conventional methods with machine learning and deep neural networks. Important results are already published for ECG parameter estimation with InterCriteria Analysis [7]; ECG parameter ranking and explanatory analysis of the decision-making process in DNN [2, 5]; effective atrial fibrillation detection by DNN optimization [2, 5]; risk stratification of atrial fibrillation patients after catheter ablation [11]; classification of 24 rhythm pathologies in a comparative study of classical criteria and DNN using ECG scalograms from wavelet transforms for extraction and classification of diagnostic information in 12-lead ECG [6].

Acknowledgements

This work was supported by the Bulgarian National Science Fund, grant number КП-06-H42/3, “Computer Aided Diagnosis of Cardiac Arrhythmias Based on Machine Learning and Deep Neural Networks”.

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Impedance Balance in Ground-free Biopotential Recording

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Background and Aims: In biopotential sensing, the use of surface electrodes is a standard practice for recording of the electrical activity of different human systems for medical diagnosis. The electrode impedances and the amplifier input common-mode impedances form an impedance bridge. Due to electrode impedance instability over time, the bridge tends to be imbalanced and produces differential power-line interference (PLI) which is amplified together with the useful biosignal. This study aims to present a powerful concept for automatic impedance bridge balance and canceling the PLI.

Methods: The approach processes the differential (V_d) together with the common-mode (V_{cm}) input signals (Fig. 1).

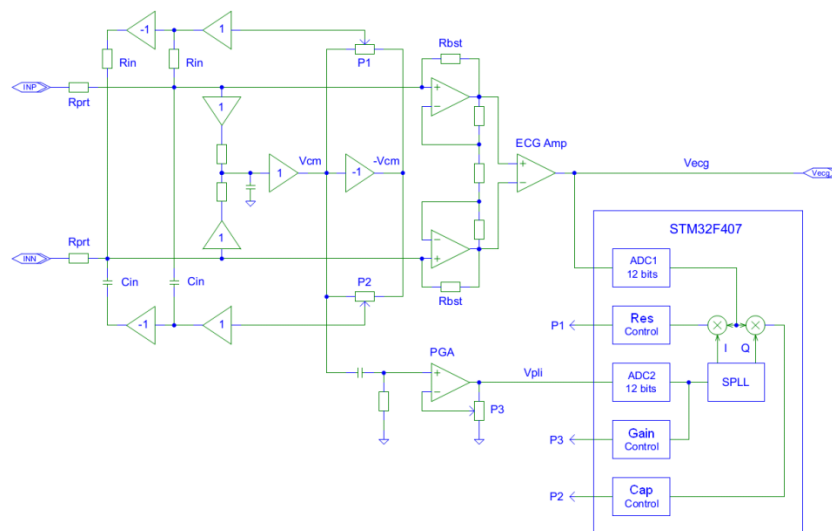


Fig. 1. Simplified schematic of a ground-free ECG amplifier with impedance balance.

The amplified differential signal is $Vecg$. Referred to the input, it consists of two components: the useful biosignal $Vecg/Ad$, and the common-mode noise $V_{cm}/CMRR$. Since the common-mode V_{cm} signal is mainly PLI, it can easily be used for software PLL synchronization to the line frequency [1]. After the SPLL is synchronized, the microcontroller (MCU) performs quadrature amplitude

demodulation of the PLI components present in the output signal V_{ecg} . The demodulated in-phase and quadrature errors are low-pass filtered and integrated, and the results control two high-resolution digital potentiometers P1 and P2. These potentiometers are enclosed in two software servo loops for in-phase (resistance) and quadrature (capacitance) impedance control.

At a steady-state condition, the wipers of P1 and P2 are automatically set at positions for minimizing the output PLI in the range of ± 1 LSB. In other words, the impedance-balancing approach generates an input noise component with an opposite sign to the penetrated noise $V_{cm}/CMRR$.

Thus, the common-mode noise $V_{cm}/CMRR$ is canceled, and the impedance balancing system virtually behaves like a system with infinite CMRR [2, 3].

Results: Experimental results for the real-life operation of an in-house developed breadboard according to Fig. 1 are further illustrated. Fig. 2 presents ECG signals, which are acquired with a non-isolated amplifier and via two types of electrodes placed on the chest in the position of Lead I, i.e. disposable Ag/AgCl electrodes (left) and electrodes made from conductive rubber (right). The two control signals for capacitive and resistive impedance balance (middle plot) are used for effective cancelation of the PLI in the recorded ECG (zoomed part shown bottom trace) after a transition process lasting a few seconds.

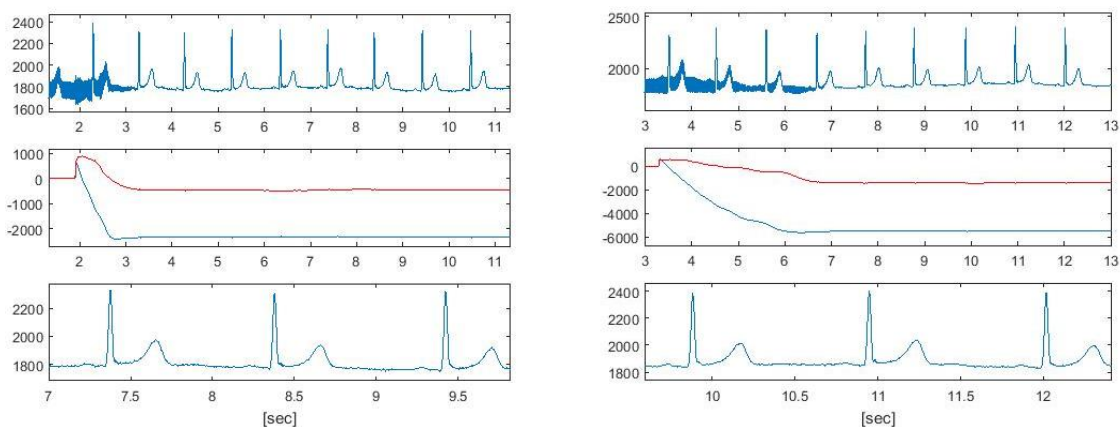


Fig. 2. PLI cancelation. I trace: V_{ecg} , II trace: Control signals for P1 and P2,
 III trace: Zoomed V_{ecg} when the control signals are settled.

Conclusions: The impedance balancing approach shows that adding the common-mode voltage V_{cm} with automatically adjusted amplitude and phase to the differential input signal cancels the common-mode interference. The described impedance balancing approach automatically synthesizes the interference and subtracts it at the amplifier inputs, producing clear V_{ecg} . It cancels the $V_{cm}/CMRR$ input noise component and makes the system to behave like a system with infinite CMRR. The impedance balance is done for the PLI frequency, so the approach acts as a distortionless



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PLI filter. It is applicable to all permanent biosignals, taken with electrodes from the body surface, such as ECG, EEG, EMG, EOG, etc. The approach can be implemented as a part of new ground-free designs, or as a separate module attached to the existing devices to make them to operate without a common-mode reference electrode. It is also applicable to the devices with driven-reference-electrode, where it will function as a distortionless PLI filter.

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In silico Analysis of Selected Hydroxyanthraquinones from *Rubia* spp. for Their Ability to Interact with the Bacterial Enzyme DNA Gyrase

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The increased use of polyphenols nowadays poses the need for identification of their pharmacological targets. Recently, structure similarity-based virtual screening of DrugBank outlined pseudopurpurin and other hydroxyanthraquinone derivatives from *Rubia* spp. as similar to gatifloxacin, a synthetic antibacterial agent from fluoroquinolones' group [1]. This suggested the bacterial DNA gyrase as their potential pharmacological target.

In this study structure-based *in silico* analyses were performed to further elucidate the ability of selected hydroxyanthraquinones to interact with the bacterial enzyme DNA gyrase. The docking in MOE software (v.2022.02, <https://www.chemcomp.com>) outlined pseudopurpurin as the most promising compound in the series. To account for movement of water molecules present in the active sites of the wild type and A90S mutant forms of the gyrase complexes, docking in GOLD (v.2022.2.0; <https://www.ccdc.cam.ac.uk>) was performed. It confirmed the ability of hydroxyanthraquinones to assume the binding modes of co-crystallized fluoroquinolones, gatifloxacin and moxifloxacin. The molecular dynamics simulations outlined differences in the binding strength of moxifloxacin, gatifloxacin and pseudopurpurin.

Our results point out hydroxyanthraquinones of *R. cordifolia* as promising lead structures with antibacterial activity. Further *in vitro* studies are in progress to validate their potential to inhibit the DNA gyrase, including also an antibacterial effect on *Mycobacterium tuberculosis* strain H37Ra.



Acknowledgements

This work is supported by the Bulgarian Ministry of Education and Science under the National Research Program "Healthy Foods for a Strong Bio-Economy and Quality of Life" approved by DCM#577/17.08.2018. The authors acknowledge the networking support by the COST Action CA21145 "European Network for diagnosis and treatment of antibiotic-resistant bacterial infections (EURESTOP)". PA, IL, TP and IT thank the National Science Fund of Bulgaria (№ КП-06-КОСТ/3/23.05.2023).

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Experimental Investigation of Different Control of a Prototype of an Active Elbow Myo-orthosis

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An elbow orthosis can help people with a disability in the elbow joint to improve their mobility. It is believed that when a technical rehabilitation tool is driven by the muscles' own electromyographic (EMG) signals, which reflect the human intention to move, it helps to form new neural pathways, to reorganize and self-train the central nervous system. This brain's ability for functional reorganization is called "neuroplasticity". That is, the creation of an active myo-orthosis, driven by EMG signals, easy for patients' usage, will provide daily self-rehabilitation, which will maintain muscle tone, support the performance of movements otherwise impossible for the patient, prevent complications from lack of movements such as muscle atrophy and joint stiffness, and will also help to restore control of movements by the central nervous system.

The aim of this study is to test both feed-forward control and EMG control of a prototype of an autonomous elbow orthosis. The EMG control one is realized according to the start/stop (threshold) method, which is characterized by better noise resistance and stability. The recordings of EMG signals of *m. biceps brachii* and *m. triceps brachii* were done using "Myoware v2.0" electromyographic sensors, with an additional individual correction of the gain of the analog tract of the sensors. Digital processing of the received signals was carried out using a microcontroller platform "OpenCM 9.04". The signal analysis includes the following steps: digitization of the received analog signal, calculation of the effective value of the signal (RMS) on chosen time segments, additional filtering of the received RMS signal, and a threshold detector that controls the activation of the orthosis. The motor control of the orthosis was implemented by the OpenCM 9.04 controller using the available here library functions. The orthosis control work was examined by 7 volunteers, performing flexion-rest-extension at several speeds with or without electromyographic feedback.

The measurement results showed that the recorded EMG signals successfully activated the orthosis and precisely followed the set trajectory. The device has also shown sufficient functionality, convenience, and safety for autonomous use.



Acknowledgements

This study was supported by the Bulgarian National Science Fund, Grant No. KP-06-M47/6. The work was also supported by Grant No. BG05M2OP001-1.002-0011-C02 financed by the Science and Education for Smart Growth Operational Program (2014-2020) and co-financed by the European Union through European structural and investment funds.